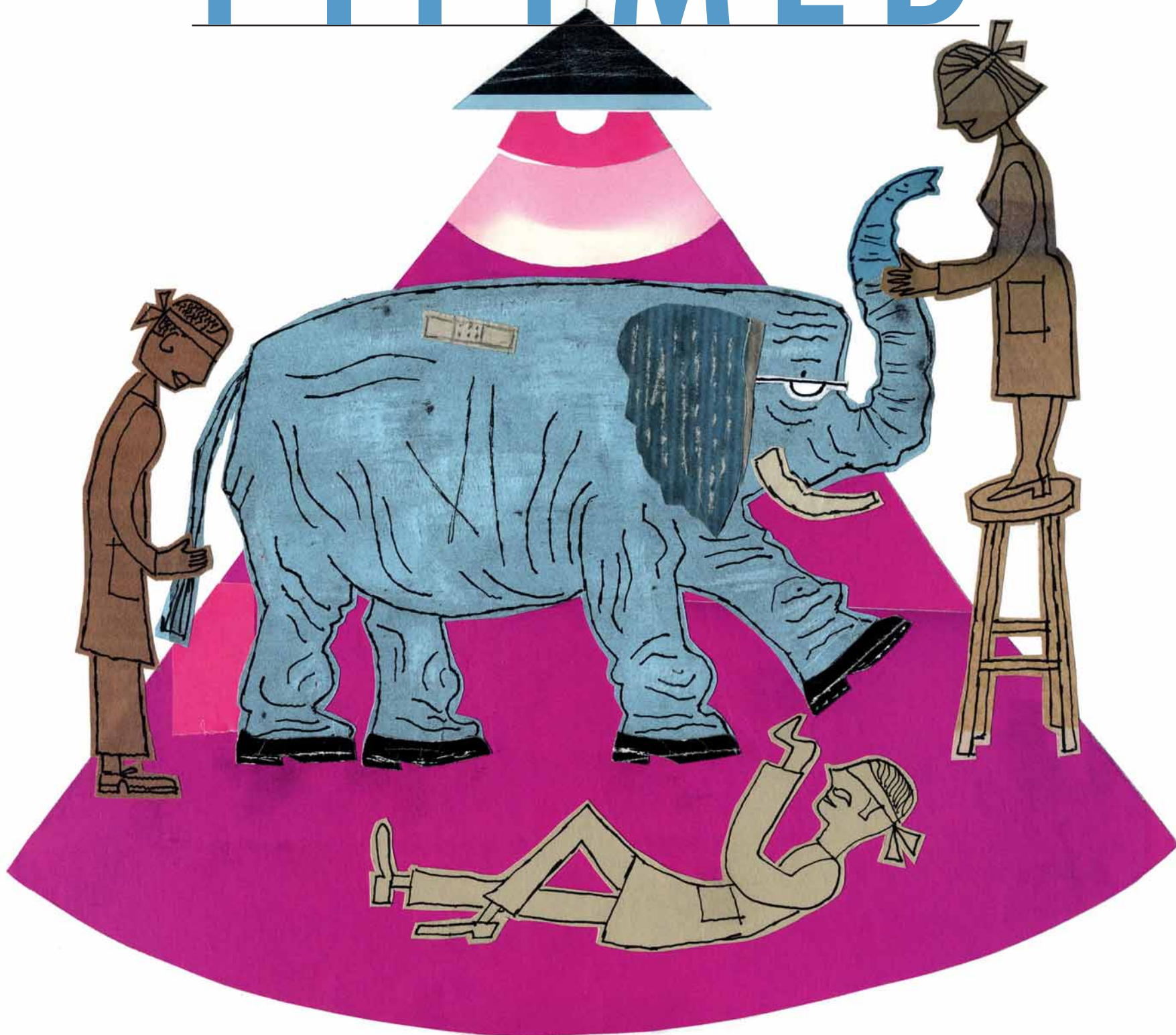


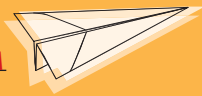
UNIVERSITY OF PITTSBURGH SCHOOL OF MEDICINE | WINTER 2010/11

PITTMED



“EACH WAS PARTLY RIGHT
ALL WERE IN THE WRONG”

TOO OFTEN, TREATING OLDER ADULTS IS A GUESSING GAME



LONG LEGACY OF GREAT CARE

Dr. Al Drash, profiled in the Spring issue, was a wonderful person and a wonderful doctor.

Regarding the treatment of diabetes, only Dr. Best and Dr. Banting, who discovered insulin, did more to benefit patients with diabetes. Dr. Drash's multi-institutional study provided the information and proof that close control of diabetes is important in prevention of the complication of diabetes mellitus. Until that study was done, we did not know if close control of diabetes was important. To me, this is the second most important advance in the treatment of diabetes.

I would like to add that children with diabetes at the Children's Hospital of Pittsburgh were getting very good care even before Dr. Drash arrived. Dr. Danoski and Dr. Kenny were caring for these children, with the help of residents under their supervision.

Thomas J. Martin (MD '60)
Williamsport Regional Medical Center

HATS OFF TO GITLIN

The David Gitlin story ["Bricks That Fell Upward," Fall 2010] was very well done, and I was very happy to contribute. By the way, I trained Bert Lubin in hematology. This is such a small world.

I am sure that Jon [Jonathan Gitlin] is very pleased. Yours was a fine tribute to an extraordinary physician scientist.

David Nathan
President Emeritus,
Dana-Farber Cancer Institute
Robert A. Stranahan Distinguished
Professor of Pediatrics and
Professor of Medicine,
Harvard Medical School

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PITTMED

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Med students kick up some dirt.



CONTRIBUTORS

MELINDA WENNER MOYER ["Autoimmunity's True North?" and "Tracings in the Brain"] spent three years working at a British biotechnology firm before she had her epiphany. One day during her daily ritual of reading the magazine *New Scientist* during her commute, she realized that she'd rather be the one writing those stories. One master's degree later (which she earned from New York University in science, health, and reporting), and she started writing for the likes of *Scientific American*, *Popular Science*, and *Popular Mechanics*, as well as *O, The Oprah Magazine* and *Glamour*. The diversity keeps things interesting. "I'm never, ever bored," says Wenner Moyer.

KAREN SCHOEDEL is a pathologist. And a heavy metal guitarist. And a diorama maker. Schoedel, who's been at Pitt since starting her first of four residencies in 1987, crafted the one-inch-to-one-foot scale model of UPMC Presbyterian's gross pathology and "frozen" labs pictured in "The Rarely Seen Physician."

The hobby came to be by accident: "My mother brought a dollhouse here [for my newborn daughter] that I'd stopped working on in 1974. I wanted to insert a staircase, but I didn't know how to do it." She took lessons, finished the house, and then began making pathology miniatures. "They're time capsules," Schoedel says. "Fifty years from now, people aren't going to be reading my papers, but they'll look at this [model] and say, 'So that's how they did it back then.'"

COVER

The ranks of the elderly are swelling, and doctors will be challenged on how to treat these complex cases. (Cover: Catherine Lazure © 2010.)



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FEATURES

How Little We Know

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Geriatric medicine is a field begging for exploration as the ranks of the elderly swell.

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A young Pitt researcher suggests that scientists may be looking in the wrong place to find a cure for type 1 diabetes.

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Three Pitt med students were granted the opportunity to travel abroad and grapple with the diseases and conditions affecting the bottom billion.

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The Rarely Seen Physician

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Pitt pathologists are bending time, closing distance, fixing errors before they happen, and delving deeper into the cell to turn a traditional discipline into something new.

BY JOE MIKSCH

PITTMED

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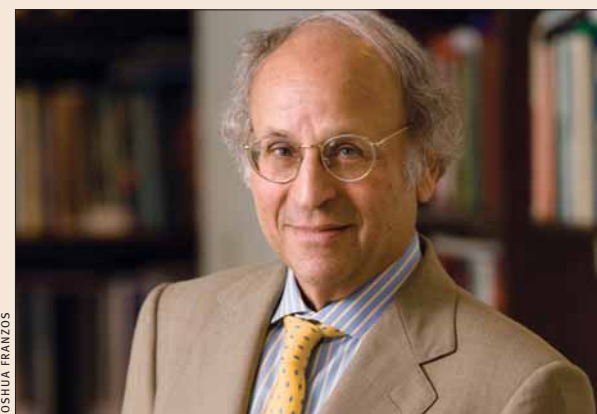
Science, in the very act of solving problems, creates more of them.
—Abraham Flexner

In 1950s Texas, Pitt alumnus Robert Egan (MD '50) spent countless hours perfecting a technique to detect masses in women's breasts by X-ray and sharing his knowledge with other physicians. Decades after Egan's noble efforts, we are in the middle of a confusing and very public debate regarding who should have routine mammograms.

I suggest that it is dyssynchrony between technology and biologic truth that drives this debate.

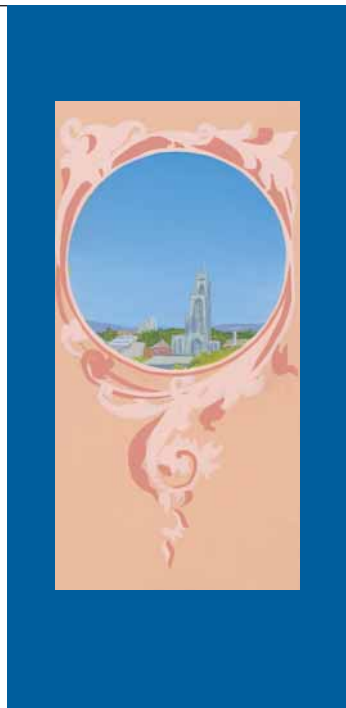
As we attempt to address profound questions in science, we often spur the development of new technologies. Some of these technologies, e.g., gene sequencing, seem to match, in time, the emergence of scientific insight and its application to diagnosis and/or treatment. This is scientific "zeitgeist." Other technologies may outpace our intellectual ability, at a point in time, to fully grasp their implications. This seems to be the case with mammography. Prescribing routine mammograms for women 40 and older made sense when we thought that all breast cancers behaved similarly and had to be eliminated at the earliest possible time to avoid metastases. Recently, however, we have come to realize that there is a broad spectrum of breast cancer behavior even if the cells look identical in the microscope. In fact, there seems to be a bell-shaped curve: At one end are tumors having early and aggressive metastatic capability; at the other end, little or no metastatic risk. The majority of breast cancers fall in between. In the highest-risk group, the tumor cells may metastasize even before they are detectable by mammography. Dr. Egan attempted to help doctors answer this question, *Who needs to be treated for breast cancer?* The more we learn, the more we realize we need to first determine, *Who is at risk?*

What has our 50-plus-year insight into the structure and function of DNA told us about who is at risk of disease? Now we understand that mutations in the *BRCA* genes will commonly eventuate in aggressive breast or ovarian tumors. But we can claim such genetic certainty with only a small fraction of most diseases. Even with the rapid advances and reduced cost of whole-genome sequencing, in the case of many diseases, including cancer, we are still years away from being able to identify who is truly at risk of morbidity and mortality and who is not. *BRCA* is the low-hanging fruit, but disease expressivity likely depends not only on mutations and single nucleotide polymorphisms (variations), but on the dynamics, compartmentalization, half-life et al. of messenger RNA and its micro-RNA inhibitors; protein-protein interactions; membrane dynamics; and other molecular risk factors. This understanding of personal risk will ultimately depend on further advances in technology and on ultrasophisticated computational and systems biology. At present, in the case of breast cancer, screening will likely benefit some women, but we do not yet have any way of identifying those women, other than in the case of *BRCA* mutations. Our efforts should be focused on further developing the technologies and computational methods that will tell us who should be screened frequently and who needn't be. Hopefully, technology and scientific insight will merge (another zeitgeist). Even so, if we had that knowledge today, there would still be women with the tiniest of tumors who nonetheless are at serious risk of metastases. Sadly, their cancers may not be curable (at least at present), no matter how early we identify them. The "mammography wars" may well offer a lesson for much, if not all, of human illness.



JOSHUA FRANZOS

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



*Devoted to noteworthy happenings
at the medical school*

PITT TO BUILD CELL-LINE BANK

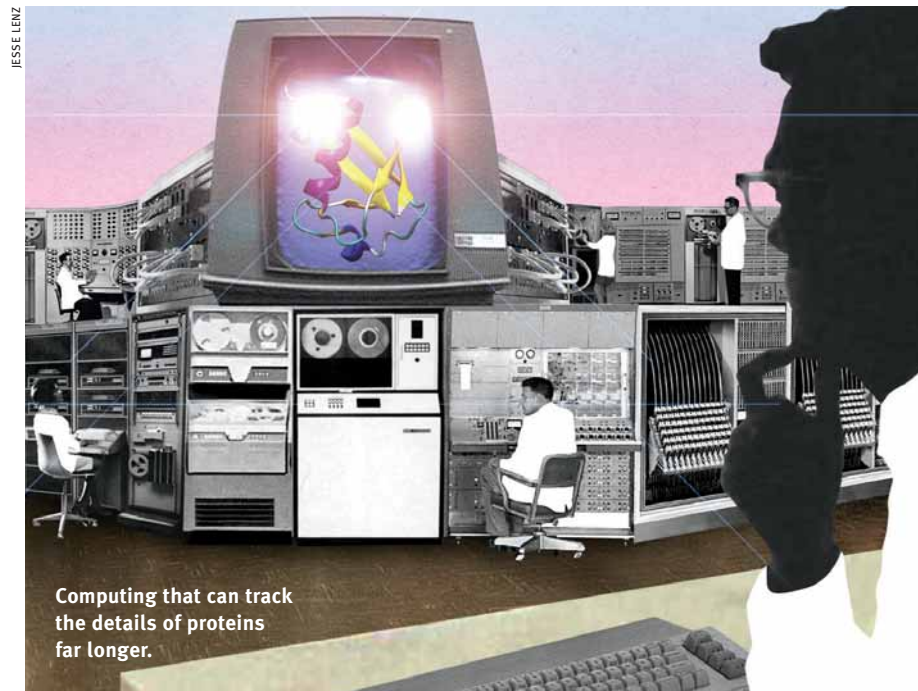
Our cells are always tuning up and repairing the DNA they carry around. When they fail to attend to this maintenance, bad things can happen, like cancer and many other diseases. Now a team led by Pitt's Robert Sobol will give researchers important tools for understanding these deficiencies.

Scientists have identified about 165 genes as "bona fide DNA-repair genes," as Sobol, an assistant professor of pharmacology and chemical biology, puts it. "All tumors are going to be defective in one of these genes down the line," notes Sobol, who is based at the Hillman Cancer Center.

The National Institutes of Health has earmarked \$2.5 million for Sobol's lab and Trevigen, a biotechnology startup, to be used to build a bank of cell lines depleted of DNA-repair genes. The partners will attempt to create a cell line for each gene and make the bank widely available to researchers. Sobol's lab will weaken the abilities of DNA-repair genes with RNA interference "knockdown" technology, which limits a gene's ability to express itself. "The research community will use these cell lines in more ways than we can probably imagine," he says. —Erica Lloyd

FOOTNOTE

Pitt plastic surgeon Ernie Manders thought his patient was a bit fishy. Or, rather, mollusc-y. Manders—along with Pitt colleagues Christine Fisher and Galen Wachtman—helped make a dead and damaged squid presentable for display at the Charleston Marine Life Center in Oregon. Manders had been studying the regenerative abilities of certain invertebrates at the Oregon Institute of Marine Biology, and the institute's director got him hooked on the idea of doing the surgery.



Computing that can track the details of proteins far longer.

A Whole Millisecond?

A millisecond (i.e., a thousandth of a second) isn't a lot of time—unless you are trying to map, say, the complex origami that folds amino acid chains into proteins. If that's the case, the millions of calculations required to track such atomic-level choreography might stop you long before the millisecond mark. Fortunately, now, there's Anton. This new supercomputer—named for 17th-century Dutchman Anton van Leeuwenhoek, one of the fathers of microscopy—will spend the next year at the Pittsburgh Supercomputing Center (PSC), on loan from its designer, New York-based D.E. Shaw Research.

Previously, even the most powerful computers could track only about a microsecond (a millionth of a second) of protein movement. "But the time scales of biologically interesting things typically start in the millisecond range and longer," says Markus Dittrich, a senior scientific specialist at PSC. Anton's hardware runs molecular dynamics exclusively, allowing it to keep tabs on the details of those interesting biological moments.

Anton will support projects submitted by scientists from across the United States, including faculty from the School of Medicine. Dittrich reports that, thanks to a \$2.7 million grant from the National Institutes of Health, the center has set up a "pretty beefy" data storage unit and analysis cluster for Anton data. "There may be much more hidden in the data," Dittrich says, for scientists to mine. —Keith Gillogly & Kelsey Ballance



CAMI MESA

A&Q

Johnny Huard on PRP: Dope or nope?

In 2009, a little-known technology made headlines when it helped Pittsburgh Steeler Hines Ward—who'd been benched for weeks after spraining his MCL—back onto the field in time to play in Super Bowl XLIII. A small amount of Ward's blood was drawn, centrifuged down to a concentrate known as platelet-rich plasma (PRP), and then injected into Ward's injured knee. For two decades, PRP has been used by surgeons to speed healing, but this high-profile case got people thinking. Could PRP be used to boost athletic performance?

In May, Johnny Huard—the Henry J. Mankin Professor of Orthopaedic Surgery Research and director of the Stem Cell Research Center at Pitt—met with his fellow members of the International Olympic Committee in Lausanne, Switzerland, to discuss the ethics of PRP use in athletic medicine. The committee hopes to release a consensus paper with their recommendations this fall.

On the committee's objectives

The paper will address several issues. There's the basic science of PRP, the standard procedures for administering it, its uses in tissue repair, its potential adverse effects. And then the big questions: Could PRP be used to enhance athletic performance, and if so, would that be considered cheating? Also, how do we regulate against that—or even test for it—since these would be [one's] own cells?

On his role

As a basic scientist, my role is to ask, "What is the mechanism of PRP action?" We really don't know how it works. It's been used in the clinic for years. Surgeons don't need special permission to do it, since these are [the patient's] own cells, and many surgeons say PRP is helping their patients recover faster. But there's still a lot we don't know about it. Just last year, the literature showed that it can induce arthritis.

His question for us

Should PRP be considered doping? With the committee, the jury is still out. Personally, I think it takes more than just strength and stamina to make a great athlete. There are also instinct and the mental aspect of the game. So it's not like PRP is going to turn a bad athlete like me into a gold medalist. —Interview by Elaine Vitone

Faculty Snapshots

Freddie Fu (MD '77, Res '84), chair of Pitt's Department of Orthopaedic Surgery, was recently named a Distinguished Service Professor of Orthopaedic Surgery. While seven other professors in the School of Medicine hold the esteemed Distinguished Service title, Fu is the first from Pitt's Department of Orthopaedic Surgery.

Fu says it's his highest honor and a testament to the quality of his staff and faculty. "I don't think it's a personal award. It's more of an accomplishment of the whole department," he says, adding that he hopes the award will bring further recognition to the field.



Fu

Sally Wenzel, director of the Asthma Institute at UPMC and Pitt professor of medicine, received the American Thoracic Society's 2010 Recognition Award for Scientific Accomplishments. Wenzel was one of the first doctors to recognize that asthma is not a single disease, as commonly believed. After this acknowledgment of her lifelong scientific achievement, Wenzel says she "can't possibly take a break."



Wenzel

The American Thoracic Society started more than a century ago as a forum for the study of tuberculosis. Today it focuses on a variety of pulmonary diseases and disorders. Its long-standing award for scientific research is one of the most competitive and acclaimed in the field.



Puhalla

Shannon Puhalla was one of only 16 physicians nationwide recently presented with a 2010 Career Development Award from the American Society of Clinical Oncology. The award, which is granted to up-and-coming physicians, also comes with \$200,000, given throughout three years. Pitt's Puhalla, an MD assistant professor of medicine, studies breast cancer. She's using the funds to conduct a clinical trial using traditional hormonal therapy and a drug that targets cancer stem cells. She hopes the drug can help reduce the need for invasive surgery and full mastectomies. "Instead of going straight to surgery, we're going to give patients hormonal therapy and this experimental drug first," she says. —KG

CLASS OF 2014 CHEAT SHEET

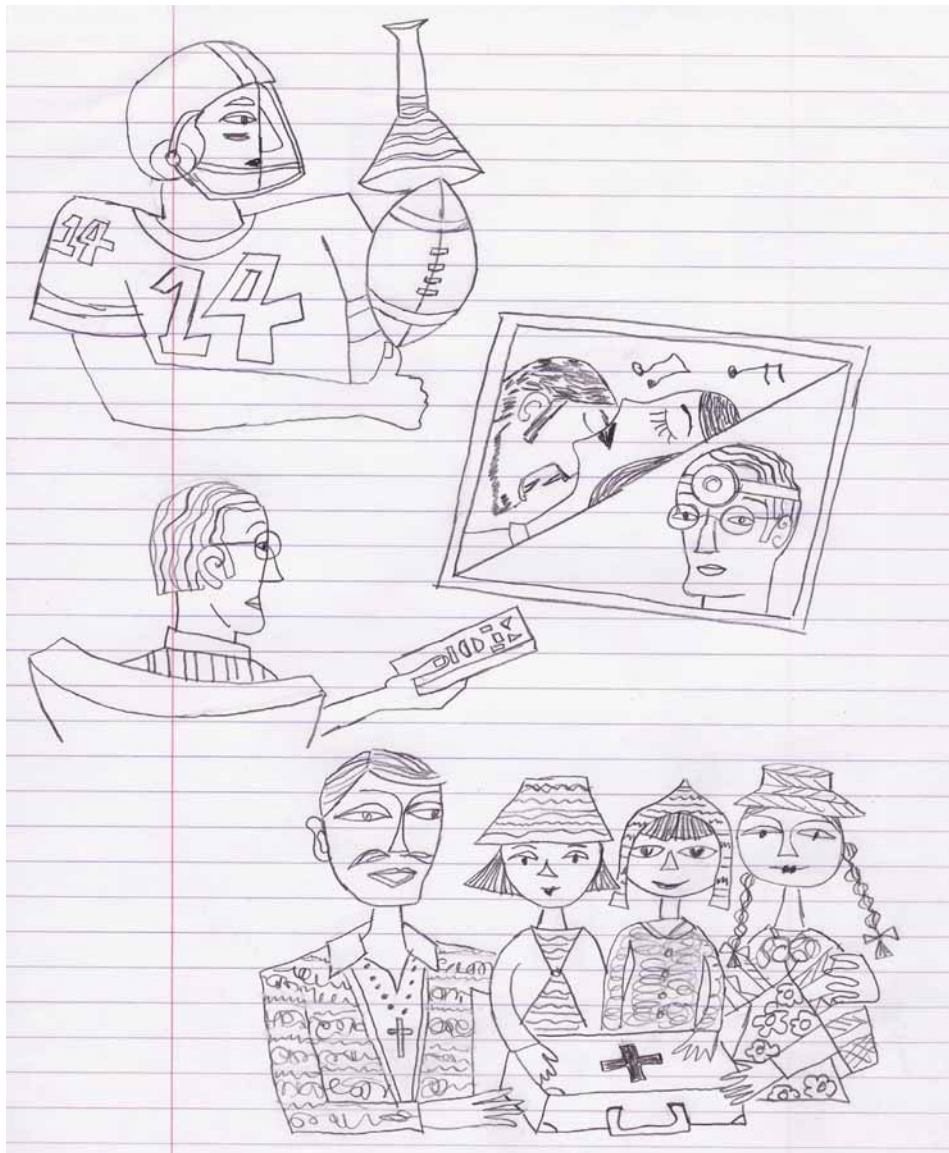
A handful of newcomers to Pitt med—members of the Class of 2014—stood out among the typically diverse and talented new matriculants.

When Ben Rothrauff was a freshman at Northwestern University, he balanced the rigors of playing defensive back in Big Ten football with an 8 a.m. organic chemistry class. The result was a new appreciation for studying as well as an interest in orthopaedics—call all those injuries a kind of “field experience.”

Ian Joel started playing music at age 4, and by 13, he was composing. He went on to write the theme for *Eve’s Blood*, a made-for-TV vampire flick. Although Joel had planned on pursuing a career in music, he ultimately chose medicine for its potential “real, positive impact.”

Cynthia Grady’s family in her native North Carolina was often expanding—she had “eight or 10” foster cousins. Her family established a human services organization that creates group homes and other programs for adolescents. Caring for others was part of a family tradition that Grady intends to honor in her medical career.

Jeremy Kauffman studied theology in college and originally planned on entering the ministry. After he graduated, he traveled to Peru with a Christian organization that offered social work and health care services to homeless children. The experience inspired him to pursue a career “to help people tangibly, as well,” he says. —KG



CATHERINE LAZURE

Hong Kong Partnership

The University of Pittsburgh’s Rocky Tuan has led the School of Medicine into a partnership with the Chinese University of Hong Kong. The collaboration, he says, will allow the two biomedical research powerhouses to collaborate in unraveling the mysteries of stem cells, partner to seek grants, exchange faculty and students, and host annual conferences on stem cells and regeneration.

Professor Tuan is director of the Center for Cellular and Molecular Engineering in the Department of Orthopaedic Surgery in the School of Medicine and executive vice chair for orthopaedic research at the University.

He is also a native of Hong Kong. It happens that Tuan is a friend and former classmate of the director of the newly established School of Biomedical Sciences at the Chinese University of Hong Kong, one of the top schools in Asia. The two also worked together at the National Institutes of Health.

“We chatted before he took off [for Hong Kong], and I came to Pittsburgh,” Tuan says. “We thought, *Wouldn’t it be nice to work together after we get settled?*” They did, and a memorandum of understanding formalizing the ties between the two institutions was signed in the spring. —Joe Miksch

A DRUG REPURPOSED

Among genetic diseases, alpha1-antitrypsin (AT) deficiency is fairly common—one in 3,000 live births. It leads to the accumulation of a misfolded protein (ATZ) and liver disease. AT deficiency is the cardinal genetic cause of liver transplantations in children.

David Perlmutter, an MD and the Vira I. Heinz Professor and Chair of the Department of Pediatrics in the University of Pittsburgh School of Medicine, as well as physician-in-chief and scientific director of Children’s Hospital of Pittsburgh of UPMC, is hopeful that doctors will be able to combat AT deficiency and reduce the need for liver transplantation in AT-deficient children by teaching an old drug new tricks.

Carbamazepine, an antiseizure drug, seems to reverse the accumulation of ATZ and hepatic fibrosis, partially by enhancing autophagy, a cellular digestion and recycling pathway. A phase I clinical trial of carbamazepine as an anti-ATZ drug is about to begin. Perlmutter’s collaborators include Pitt’s Tunda Hidvegi, PhD assistant professor of pediatrics and lead author, and George Michalopoulos, MD/PhD professor and chair of the Department of Pathology. Their findings were published in the July 9 issue of *Science*. —JM



CAMI MESA

OLD MEDS

For 60 years, Frank Critchfield (MD '47) has collected antique apothecary accoutrements, haunting auctions and stopping at every mom-and-pop pharmacy he passed in his travels across the United States and Europe. Last fall, Critchfield donated the whole lot to the School of Pharmacy's Elmer H. Grimm Sr. Pharmacy Museum. His gift of nearly 80 items was appraised at more than \$10,000 and includes apothecary jars, measuring tankers, medicine dispensers, a scale, and a brass mortar and pestle. Also featured are items from black bags of yore: several glass blood-letting collectors of unknown origin and two ivory "doctor's ladies" from China dating as far back as the 17th century. In those days, it wasn't proper for a Chinese woman to disrobe for her doc, the 92-year-old ob/gyn explains. So she'd use a nude figurine to point out where it hurt. How's that for health care's modest history? —EV

Name Dropping

In October, the University of Pittsburgh hosted a cavalcade of stars at Science 2010, its annual celebration and showcase of scientific achievement. This year the title was *Transformations*. Among the University's out-of-town guests:

Ann Graybiel is a PhD and the Walter A. Rosenblith Professor of Neuroscience at the Massachusetts Institute of Technology. She gave the 2010 Mellon Lecture. Since the early 1970s, Graybiel has explored the architecture of the basal ganglia and the function of that brain region's neurotransmitters. Graybiel was the first to establish a mechanism for directed neurochemical control of complex brain circuits. Her talk was titled, "Our Habitual Lives: How the Brain Makes and Breaks Habits."

Mark Roth, a 2007 recipient of a MacArthur fellowship, delivered the Klaus Hofmann Lecture. He is a PhD cell biologist at the Fred

Hutchinson Cancer Research Center in Seattle. Roth made his reputation as a researcher of suspended animation. His presentation focused on the prospect that a combination of inhaled or injected hydrogen sulfide and cooling of the body can induce a state of suspended animation that is helpful in stabilizing injured people en route to the hospital.

Stephen Elledge was the 2010 Dickson Prize in Medicine lecturer. Elledge, a PhD and the Gregor Mendel Professor of Genetics and Medicine at Harvard Medical School, won the 2005 Genetics Society of America Medal for outstanding contributions to the field of genetics. His address delved into the intricacies of DNA damage response. Elucidating this, Elledge says, will be key to treating a slew of diseases, including cancer. "Understanding how these pathways sense the DNA damage caused by cancer chemotherapies allows us to develop more potent chemotherapies and target them to the right kinds of cancer," he said at the event. —JM



SCI PREP

At the Pittsburgh Science and Technology Academy (SciTech), a student is kind of like a stem cell—you know, those undifferentiated proto-cells that can give rise to brain, bone, or fingertip. The ones that can become anything—given the proper environment.

The differentiation takes place especially early at SciTech. These packets of potential narrow their foci as 10th-graders, when they can choose to concentrate in biology, computer science, engineering, or environmental science. The public school opened last year in the Frick building on Fifth Avenue and Thackeray Street.

SciTech teacher and School of Medicine alum Edwina Kinchington (Pharmacology PhD '97) has spent the past year honing the academy's Body & Behavior track with lead curriculum developer Stephen Pellathy, who earned his physics PhD at the University of Pittsburgh last year.

Those aren't the only ties SciTech has to Pitt. It seems natural that the school, embedded in the academic oasis of Oakland, would forge a relationship with its university neighbor. Pitt's Margaret McDonald, associate vice chancellor for academic affairs, health sciences, and David Malehorn,

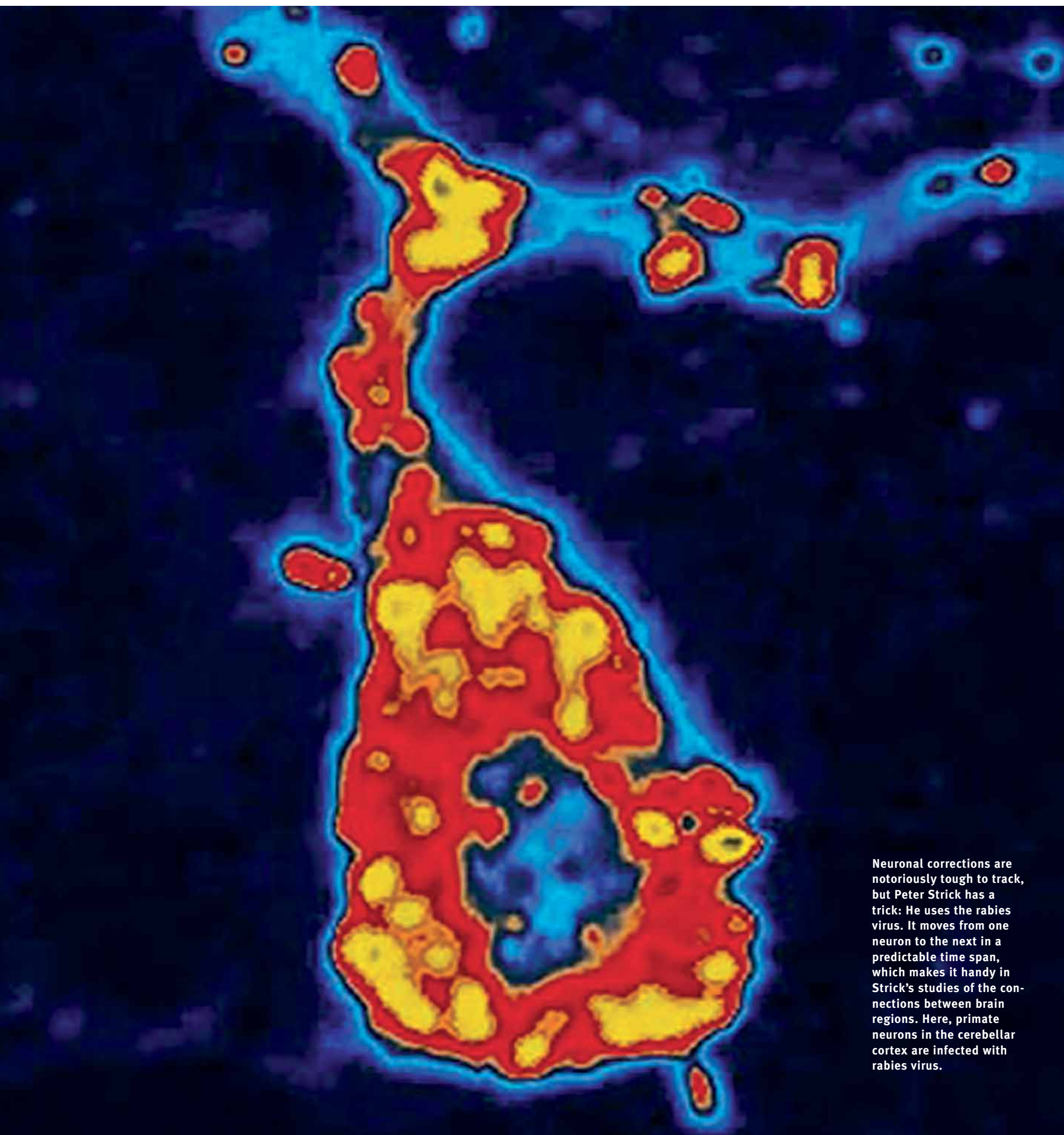
research assistant professor of pathology, served on the school's advisory committees from its planning stages through its opening. And SciTech's bimonthly Science Forum brings students to the School of Medicine for interactive presentations by local scientists.

"We essentially want to arm our students with as much real-life scientific knowledge as possible," says Kinchington—who was the architect of SciTech's life sciences laboratory, which, she says, rivals its counterparts in Pitt's Biomedical Science Tower. In addition, she notes that nearly half of SciTech's ninth graders listed Body & Behavior as their top-choice track last year.

At the beginning of the school year, Kinchington helped students get to know their new toys by organizing a scavenger hunt requiring a hypothesis for each item's function. "I'd imagine this might be used to mix chemicals, possibly to separate them," says SciTech student Sam Rest, referring to a microcentrifuge. Rest says he'd eventually like to attend medical school and become an ophthalmologist.

—By Ben Korman

—Photo by Martha Rial



Neuronal corrections are notoriously tough to track, but Peter Strick has a trick: He uses the rabies virus. It moves from one neuron to the next in a predictable time span, which makes it handy in Strick's studies of the connections between brain regions. Here, primate neurons in the cerebellar cortex are infected with rabies virus.

TRACINGS IN THE BRAIN

RABIES HELPS SCIENTISTS UNDERSTAND
HUMAN DEXTERITY AND PARKINSON'S

BY MELINDA WENNER MOYER

There's no easy way to peer inside the brain and study its complex, intermingled circuits. But Peter Strick, University of Pittsburgh professor in the Departments of Neurobiology and Psychiatry and codirector of the Pitt-Carnegie Mellon University Center for the Neural Basis of Cognition (CNBC), has a trick: He employs viruses. With their help, he recently discovered a division in the human motor cortex that could explain why we exhibit more finely tuned movements than other animals. He has also uncovered a surprising connection between two brain regions that solves a mystery about Parkinson's disease.

For decades, neuroscientists studying how neurons connect to one another have had to rely on tracers "that were good, but not optimal," says Strick. A dye injected into a neuron might reveal the immediate neuron it connects to, but it loses its potency before revealing the next neuron in line. But "that's not the way the brain works," Strick explains. "It's not just who speaks to the neuron and who the neuron then speaks to. These brain areas are parts of circuits."

Deciphering these circuits, Strick says, is the first step toward understanding how humans acquire complex skills. Our ability to learn to play a Chopin waltz—granted, after lots of practice—"is so fundamental to who we are, and is what differentiates us," Strick explains. "We start by asking what the [brain's] road map is. And viruses are a wonderful way of working out that road map."

Strick's virus of choice is rabies, which

moves from neuron to neuron. What's useful about rabies is that it replicates in each neuronal cell body, so it doesn't fade over time. It also moves backwards, tracing a path from, say, a muscle cell, through multiple neurons, eventually reaching the cerebral cortex.

A couple of years ago, Strick and collaborators injected rabies into the shoulder, elbow, and finger muscles of rhesus monkeys and gave the virus enough time to infect neurons two steps back toward the brain. (The virus does not cause these animals any pain or distress.) Strick saw that the virus was able to reach the animals' brains by traveling through a motor neuron and then a special neuron in the spinal cord. It had infected the motor cortex, the portion of the cerebral cortex responsible for planning and executing movement, but only on the right side. When he injected the virus into the same muscles of different rhesus monkeys and gave the virus enough time to infect not two but three steps back, he also saw the virus in the left half of the motor cortex. It had traveled along two motor neurons on its journey.

Earlier work by other researchers revealed that humans and rhesus monkeys—but not cats and rats—have some brain-to-muscle connections via just one neuron. This finding suggests that these "express" connections emerged more recently in evolutionary history than the less direct ones and might be responsible for complex movements. Strick's study, published in 2009 in the *Proceedings of the National Academy of Sciences (PNAS)*, suggests that these new and old connections are also physically separated in the brain. The

"new" motor cortex most likely coordinates finely tuned movements, and the "old" cortex is probably responsible for crude movements. It's likely that "the old motor cortex gets our movements within the right range, and then the new motor cortex supplies the elegance and all of the adaptability and flexibility," he says.

Strick and his colleagues have also used rabies to discover new connections between brain regions. In a May 2010 *PNAS* paper they showed that the cerebellum, a brain region involved in motor control and motor learning, communicates with the basal ganglia, a group of forebrain regions involved in movement and habit formation. Malfunctions in the basal ganglia are also thought to be responsible for producing tremors in patients with Parkinson's disease.

Earlier research by other scientists had shown that Parkinson's patients have abnormal activity in the cerebellum, but no one knew why. When Strick's colleagues injected rabies into the cerebellums of cebus monkeys, he saw that they connected to the basal ganglia by way of two neurons.

"It's not a direct connection; that's why it wasn't seen with conventional tracers," he says. Strick believes that the basal ganglia are sending abnormal signals to the cerebellum, which in turn is either trying to correct for them or is relaying them. If the latter is true, the cerebellum may be more directly responsible for Parkinson's tremors, a finding that could have important implications for treatment. The cerebellum "could either be the problem or the solution," Strick says. ■



Ikeda



Hermann



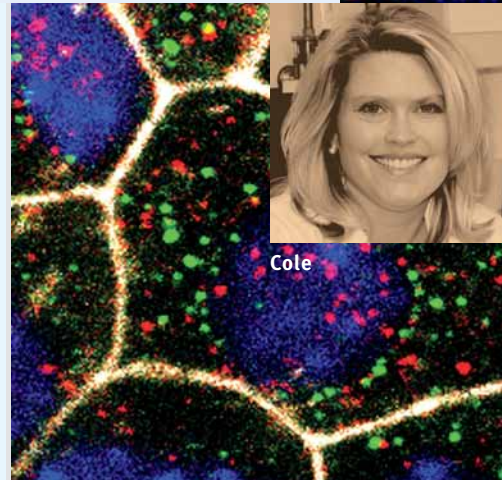
Cole



Turnquist



Halder



SCIENCE IMAGES COURTESY M. BUTTERWORTH

THE BIG LEAP

YOUNG PITT
SCIENTISTS START
OUT STRONG
BY TIFFANI EMIG

Say you've made it through the stress of a doctoral program, postdoctoral work, and a rigorous interview process. You're almost there, right? Once you land your first faculty position, you can finally enjoy the reward you've been working toward: your very own research.

Not so fast. When it comes to starting an independent research career, the first step can be an overwhelming leap.

"Most people ... are expected to generate funding fairly rapidly once they arrive," explains Michael Butterworth, a PhD assistant professor in the Department of Cell Biology and Physiology in the University of Pittsburgh School of Medicine. "Setting up your own lab is a daunting enough experience—to have to then get a grant [application] out the door in the first few months is very difficult."

Butterworth officially started his lab in April of 2010. He studies the regulation of channels that transport salt in the body and the mechanisms responsible for trafficking these channels within cells of the kidney and the airway—work that might eventually have implications for hypertension and cystic fibrosis. Butterworth's transition to independence was slightly smoother than average, thanks to a new award from the National Institutes of Health (NIH).

On average, most PhDs don't win their first NIH Research Project Grant (aka R01 grant) until age 42; for MDs and MD/PhDs it's 44. To help up-and-coming investigators start their careers sooner, in 2006 the NIH intro-

duced the Pathway to Independence awards, or K99/R00 awards. The two-phased award serves as a bridge between a candidate's postdoctoral career and an independent research position.

The first phase, the K99, allows the scientist to work closely with a mentor as a postdoc for up to two years and provides up to \$90,000 of funding. The goal is to work with a well-respected senior advisor to develop a solid research plan and, equally important, build confidence and skills as a researcher. At the end, the candidate has the option to apply for the second phase, the R00 award; it provides three years of funding worth up to \$250,000 for the candidate's independent research.

For PhD Michele Okun, one of the first Pathway to Independence grant recipients nationwide, having the time to develop skills before starting her research has been a big help. "It took some of the stress off," she says. "I thought that was a much better approach." A Pitt assistant professor of psychiatry in her second year of the independent phase, Okun studies how disturbed sleep affects the immune system in the early stages of pregnancy. She has already found promising connections that she hopes will eventually help reduce such complications as preeclampsia and preterm birth.

When the NIH first introduced the awards, the Office of Academic Career Development for the Health Sciences began promoting them and helping students through the application process. Getting a jump on things, it seems, has paid off. Pitt is establishing itself as a

Among those in Pitt's growing roster of Pathway to Independence awardees: Youko Ikeda, Heth Turnquist, Brian Hermann, Indrani Halder, and Marsha Cole. Not pictured: Michael Butterworth, Michele Okun, Cory Robinson, Alejandro Soto-Gutierrez, Hong Wang. The cellular images (top, human; bottom, mouse) are from Butterworth's studies. He's probing how epithelial sodium cells are regulated in the airway.

national leader in attracting these awards. In the first five years the grants have been offered, the School of Medicine has snagged an impressive 10 K99s, and other Pitt schools have received an additional five awards. Pitt currently ranks among the top tier of educational institutions in number of active K99 recipients.

Pitt's done well to keep their awardees, too. Though the NIH encourages researchers to move to new institutions between their K99s and R00s, both Okun and Butterworth lobbied successfully to stay at Pitt. In addition, one K99 awardee and two scientists with R00s have chosen to come to Pitt from other institutions.

Darlene Zellers, director of the Office of Academic Career Development, will study Pitt Pathway to Independence recipients to track outcomes and understand how the grants work in practice.

For Okun, choosing to launch her career at Pitt, starting with her postdoc, wasn't much of a leap. The School of Medicine's nationally renowned research labs were a big draw.

"I asked a senior colleague at Michigan who does similar work as I do, 'Where do I need to go?' And it came right out—'Pitt.'" ■

A CLEAR AND PRESENT DANGER

COURTESY HUBEL LAB

Spindle-shaped blood cells that may help rebuild the vascular system are more prevalent in women with normal pregnancies (right) than in women with preeclampsia (left).

PREECLAMPSIA IS LINKED TO HEART DISEASE, BUT WHY?

BY REID R. FRAZIER

Preeclampsia, the most common of the serious pregnancy complications, could be thought of as the Great White of childbirth. Obstetricians and midwives keep a keen eye out for its signs—namely, high blood pressure and protein in the urine after the 20th week of pregnancy—because when preeclampsia strikes, it can spell disaster. It is a major cause of maternal morbidity and mortality worldwide, occurring in about 5 percent of pregnancies. In preeclampsia, the mother's inability to deliver blood, oxygen, and other nutrients can lead to hypoxia for the fetus. The only known cure is to deliver the baby, either by induced labor or caesarean. Fetuses in these pregnancies have a five-fold increased risk of stillbirth.

The seizures that overcome some preeclamptic women were described in the first century, yet to this day, no one knows exactly what causes preeclampsia, or even if it's one single disease or several that present with similar symptoms.

"Where the disease starts is really still a mystery," says Carl Hubel, University of Pittsburgh associate professor of obstetrics, gynecology, and reproductive sciences, and of environmental and occupational health.

Hubel and other Pitt researchers are beginning to piece together what exactly preeclampsia is, in part by looking at what happens to preeclamptic women after they

give birth, sometimes decades later.

Pitt's Janet Catov, assistant professor of obstetrics, gynecology, and reproductive sciences as well as of epidemiology, found mothers who had elevated levels of lipids, a risk factor for heart disease later in life, had a two- to three-fold increase in the risk of preterm birth, which can include preeclampsia.

The link with heart disease stirs up a greater question: Does preeclampsia cause heart disease, or does it simply unmask an underlying deficit in these women? Sorting out this question is complicated by the fact that many of the risk factors for preeclampsia—e.g., obesity and high blood pressure—are the same for heart disease. Chicken, meet egg.

Add to this picture the extreme metabolic changes that occur during pregnancy—a woman's cholesterol and triglycerides increase by 50 to 300 percent as her body builds new blood vessels and a whole new organ, the placenta. She is slightly insulin-resistant, storing more sugar for the fetus. "At midpregnancy, a woman's lipids and her glucose and insulin levels look like someone with moderate heart disease—and all of that is totally normal," says Catov.

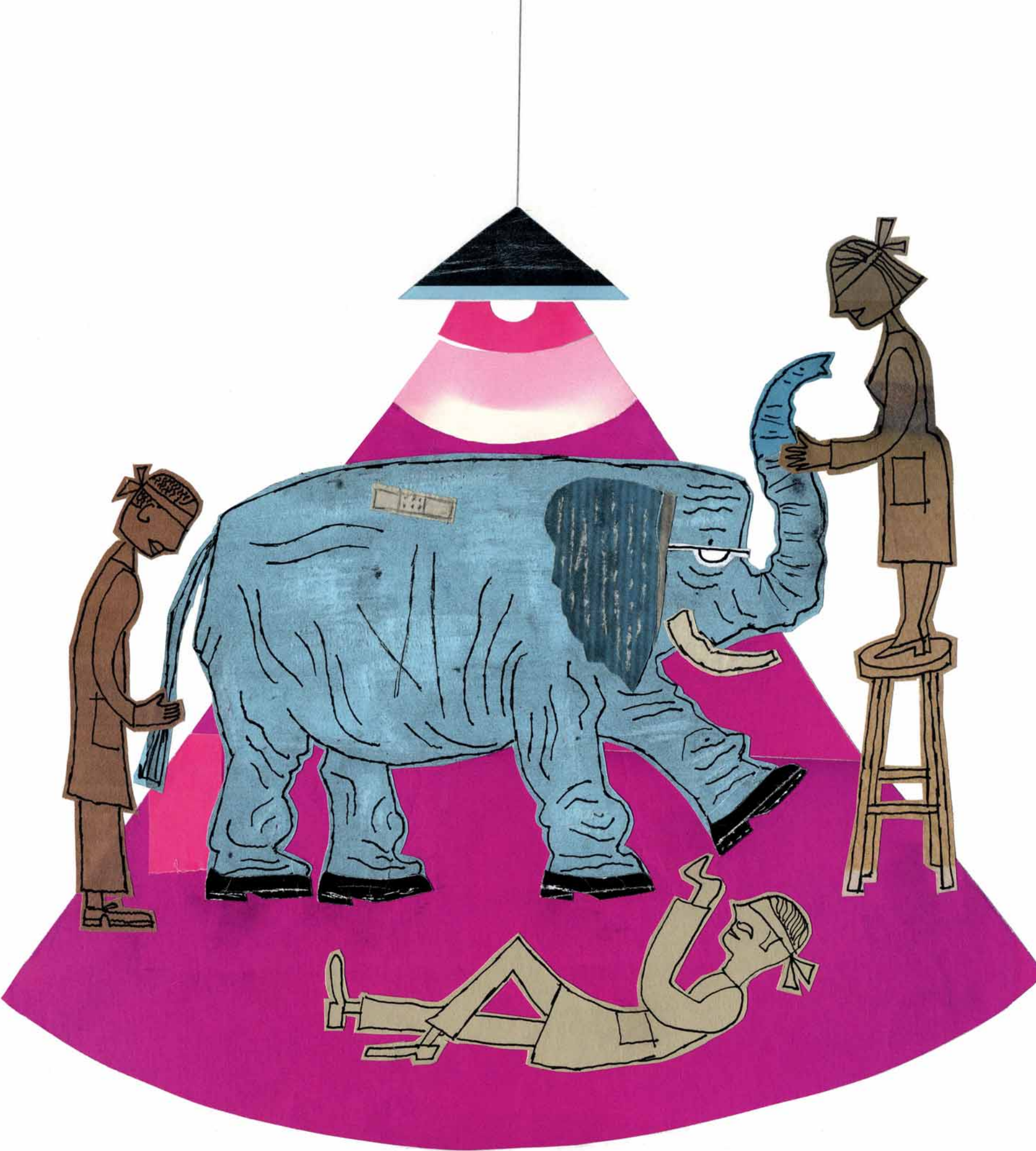
So what exactly determines which women will suffer from preeclampsia?

Hubel and his collaborators are looking at the blood of pregnant women to try to find out. Senior scientist and founding director

of the Magee-Womens Research Institute James Roberts showed in the 1980s and '90s that deficiencies in the vascular endothelium, which helps regulate blood flow, were a major feature of preeclampsia. Hubel has since found preeclamptic women have fewer endothelial progenitor cells (EPCs)—a kind of stem cell that helps replace dying or damaged blood vessel cells—than women experiencing normal pregnancies. These cells are crucial in secreting growth factors and other agents critical for vascular function.

Researchers at Harvard University recently discovered that the placentas of preeclamptic women produce an overabundance of circulating targets for the growth factors that produce EPCs. Normally, the growth factors would bind onto targets on the cell membrane; instead, Hubel and his colleagues theorize that the growth factors bind with circulating targets dispersed throughout the bloodstream. If the growth factors get bound up on dummy targets, these women might not produce enough EPCs, ushering the storm of vascular and placental setbacks that characterize preeclampsia.

He cautions that these developments may be fruit of the same rotten tree—perhaps EPC and growth-factor target levels are a consequence of preeclampsia, not the cause. Bit by bit, however, researchers are beginning to make out the broader outlines of the disease. ■



GERIATRICS IS A FIELD BEGGING FOR EXPLORATION
AS THE RANKS OF THE ELDERLY SWELL

BY SHARON TREGASKIS

HOW LITTLE WE KNOW

As an undergrad in Boston, Cathy Cheng volunteered as a companion to elderly residents in a local nursing home frequently cited for poor quality of care. By the time she'd earned her bachelor's degree, Cheng was running the program that matched college students with their older neighbors and had doubled the number of young people involved. "I didn't have the privilege of having my grandparents live in the same country as I did," says the 25-year-old, now a fourth-year student at the University of Pittsburgh School of Medicine, "and they all passed away before I turned 21."

When she enrolled in medical school, the Chicago native knew her career would one day feature work with an aging population. As a first-year, she joined Geriatric Experiences for Medical Students (GEMS), a Pitt program that pairs medical students with elderly Allegheny County "buddies" and complements their one-on-one visits with debriefing sessions guided by faculty from the Division of Geriatric Medicine. Cheng was paired with a 91-year-old retired pharmacist—and despite the student's growing portfolio of experience with older adults, the relationship was still illuminating.

The drive to isolate problems in research and treatment of the elderly is self-defeating. Consider the parable of the blind people examining an elephant: Each comes away with only a partial understanding of the whole, because each touched only a tusk or the trunk, the ears or the tail.

ILLUSTRATIONS | CATHERINE LAZURE

"He was more on top of the meds than I was and could tell me exactly what each of his prescriptions was for," says Cheng, who had expected to provide her buddy with assistance on both fronts. The man had limited vision, hearing, and mobility. And while his sons visited and read for him, he remained largely independent, living alone in his apartment and preparing his own simple meals using a microwave. "He remained active in his faith and, until his death, served as president of his congregation in Squirrel Hill," says Cheng. "He was a very lucid person."

In the pantheon of medical specialties, geriatric medicine lacks the glamour, adrenaline, or status of such fields as emergency medicine or transplantation. Yet Cheng and her peers are finding that the field more than compensates. Not only is geriatrics ripe with opportunities to make meaningful personal connections with patients, it's also largely unexplored intellectual territory.

Geriatric patients pose unique challenges for physicians, whose early training focuses disproportionately on young adults. Perhaps

counterproductive for other conditions."

Physicians who haven't already become familiar with the unique needs of an aging patient population don't have a lot of time to come up to speed.

In January, the first of America's 78 million Baby Boomers will mark their 65th birthdays. Nationwide, just 13 percent of the U.S. population has passed that milestone; yet over the next 25 years, almost 75 million people will enter the Medicare rolls. By 2050, Americans over the age of 65 will make up more than 20 percent of the population.

Geriatricians have been saying for decades that their own numbers aren't keeping pace with the tsunami of demand the Boomers will create. (Students who are interested in the field may even be "distracted away" by physician mentors who denigrate it, notes Studenski.) Fewer than 8,000 of this nation's 900,000 physicians are trained geriatricians—one for every 2,500 Americans over the age of 75. As the Boomers age and many current geriatricians anticipate their own retirement, that ratio is only getting worse.

faculty and students aspiring to the field, the two-week course introduces the geriatric syndromes of dementia, falls, and incontinence; addresses geriatric pharmacology; and tackles the ethical issues associated with assessing decision-making capacity. A field trip to a long-term care facility and a case-study project incorporating surgical, medical, psychiatric, and social issues round out the course. Nursing and pharmacy students also take the class. (It was recently expanded, thanks to support from the Jewish Healthcare Foundation of Pittsburgh and the Josiah Macy, Jr. Foundation.)

"We're able to get [students] really thinking about how older people are different from younger adults," says Susan Hardy (MD '96), an assistant professor of medicine. "By the third year, they've mostly seen older adults who are clearly sick. I think it's good for them to see patients in the nursing facility when they're doing well: up and dressed, wearing their makeup, and thrilled to be hosting medical students. We're not—in one week—going to make these students into geriatricians, but we do make them more aware of the special issues associated with dealing

"With old people, you have anywhere from two to 12 concurrently present diseases. That is further confounded and complicated by the fact that there are changes occurring in every organ of the body due to aging."

the most immediate is the necessity to simultaneously treat multiple conditions.

"With old people, you have anywhere from two to 12 concurrently present diseases," says Pitt's Neil Resnick, the Thomas Detre Professor of Geriatric Medicine and chief of the Division of Geriatric Medicine. "That is further confounded and complicated by the fact that there are changes occurring in every organ of the body due to aging. You have to factor in that all of their organ systems have changed with age, and those changes impact the way the [condition] presents, its natural history, and response to treatment."

"Diseases do not occur one at a time in an older person," says the University of Pittsburgh's Stephanie Studenski, director of research for the division and director of Pitt's Claude D. Pepper Older Americans Independence Center.

"You may have diabetes alone in a 25-year-old, but in an 80-year-old, you have arthritis, congestive heart failure, and diabetes. There is extensive literature to suggest that medications and treatments for one condition may be

In 2003, just .9 percent of the residents who graduated from U.S. medical schools enrolled in geriatric fellowships. Five years later, that number had dropped to .7 percent. If that trend persists, by 2030—when the youngest Baby Boomers become Medicare-eligible—there will be just one geriatrician for every 4,254 older Americans.

Yet physicians of all stripes—even, perhaps, pediatricians seeing a growing number of grandparent caregivers for their young patients—will have to accommodate the needs of older people. At Pitt, faculty and students have designed a host of programs to ensure that all physicians trained here have had an introduction to the essentials of clinical care and research for elderly patients. "We need to incorporate aging into what health care providers learn as a routine," says Studenski.

Pitt now requires its third-year med students to take a team-taught course that includes small-group discussions and lectures by faculty from the Divisions of Geriatric Medicine and Geriatric Psychiatry.

Developed by a committee of geriatrics

with older adults."

Before enrolling in medical school herself, Studenski trained during the mid '70s as a nurse in Kansas. A patient she encountered during that time continues to shape her approach to geriatric research and care. Flown to the hospital from an outlying rural area, the 97-year-old was agitated and aggressive, swinging her purse so violently it was difficult for staff to approach her. As the woman's delirium eased, Studenski and her colleagues began to learn more about her.

A native of Scandinavia born as that region roiled with unemployment, the patient had emigrated to the United States, crossed the Great Plains in a prairie schooner, and homesteaded ever since. Until the episode that introduced her to Studenski, the woman had lived independently, most recently with her 95-year-old sister.

"I was struck by how easy it was for old people to look like they had no capacity or potential when they get sick and are away from people who know them," says Studenski. "It made me treasure what people have to offer. That can be invisible when they get sick and you don't know who they are."



While medicine often promotes compartmentalization of organ systems, geriatricians learn to think differently. "These systems are all interacting," says Pitt's Stephanie Studenski.

For Hardy, an expert in mobility and recovery from disability among frail older adults, the elderly patients she encountered during her third-year Pitt clerkships—in surgery at the VA Pittsburgh Healthcare System, in geriatric psychiatry, and in the urogynecology clinic—sealed her interest in geriatric medicine. “I just found that I loved taking care of older adults,” she says. “They were really interesting and fun to talk to and intellectually challenging because they had lots of problems.” And the more she saw as a physician, the more she wanted to know as a researcher.

“I discovered that for so many of the questions I had about how to best care for elderly patients, there weren’t answers,” says Hardy.

women, biofeedback helps. Unlike drugs, which can interact negatively with pharmaceutical treatments for the other conditions older patients often have, the noninvasive biofeedback approach is side-effect free. During training sessions, electrodes placed on the woman’s skin monitor the electrical impulses generated by muscles in her pelvic floor; a display monitor prompts her to contract the muscles, then translates the associated electrical impulses into visual cues.

“I think it’s kind of fun for patients—” says Cheng, “seeing whether they’re moving the muscles the way they should be.”

Over time, a woman can use those visual cues to regain control over the critical muscles of her bladder and the associated synaptic

subjects without bladder control problems experienced deactivation in certain brain regions while their bladders were filling, those with severe urge incontinence had precisely the opposite experience.

Now copresident of Pitt’s student-run Geriatrics Area of Concentration—a four-year certificate program that combines coursework, independent research, and public service—Cheng has remained involved in the Continence Research Unit’s work. She and her colleagues are examining how mental health history plays into an older woman’s ability to use biofeedback to increase bladder control. One third of women with urge incontinence also suffer from depression. Doctors don’t yet know whether the stress of embarrassment and social isolation related to

“What’s going on underneath that’s making the body less capable of self-correcting?”

“There wasn’t a whole lot of evidence about older people. We needed answers about how best to take care of older people, keep them functioning and [enjoying] a high quality of life.”

Hardy earned a PhD in investigative medicine at Yale before returning to join the Pitt faculty. She came to the right place: *U.S. News & World Report* places the medical school and UPMC among its top 10 geriatrics sites. And Pitt is the only university with John A. Hartford Centers of Excellence in both geriatric medicine and geriatric psychiatry.

Every day throughout the summer between her first and second years at Pitt, medical student Cathy Cheng settled into a lab in the Geriatric Continence Research Unit at UPMC Montefiore, turned on her laptop’s statistical software, and sifted through the medical histories of 175 women afflicted with urge incontinence. At night many wet their beds or incontinence pads. During their waking hours, the urge to urinate would send them rushing for the toilet with barely enough warning—sometimes once and sometimes a dozen times. “People have this perception of urinary incontinence being a normal part of aging,” says Cheng, whose work was funded by a National Institutes of Health training grant. “It’s not.”

Doctors know that the condition—also called overactive bladder—emerges when the brain’s control over the urinary system goes haywire. They don’t know what causes it or the mechanisms involved. For many elderly

connections. With practice, she can reclaim her continence. And more important, she can resume her social life with confidence. Many women confine themselves to home rather than risk an embarrassing accident in public.

Back in the summer of 2008, Cheng’s data collection and analysis supported the efforts of her mentor, geriatrician Stasa Tadic (Res ’04, Fel ’06), an assistant professor of medicine (who did a geriatric fellowship at Pitt), and Tadic’s Pitt collaborators—Geriatric Continence Research Unit codirectors Neil Resnick, PhD engineer Werner Schaefer, and Derek Griffiths, a PhD physicist—to assess what happens in the brain during urge incontinence. A nurse used a catheter to fill and empty each woman’s bladder with sterile water as a functional magnetic resonance imaging (fMRI) scanner monitored the volunteer’s brain activity.

By tracking the women’s brain patterns at the moment when each indicated the urge to urinate, the scientists could monitor which regions are activated by the sensation and confirm the validity of fMRI as an investigative tool to study the mind-bladder connection. In January 2010, *The Journal of Urology* published the group’s finding that the most active regions in the women’s brains during the experiment were in centers that register sensation, process emotional experiences, and make decisions. The intensity of those activity patterns correlated with the severity of a woman’s incontinence as measured by a daily journal and measurements of leaked urine. The group also found that though research

incontinence precipitates a mental health decline or whether depression or some other neurological phenomenon triggers the incontinence.

Yet Cheng and the other researchers were able to determine this: “Having a history of depression predicts how well you do with biofeedback,” she says. “Elderly women with a history of depression have a diminished degree of improvement compared to those without a history of depression.”

Without a holistic view of the patient’s mental and physical well-being, a physician could miss a lot, says the student. “As clinicians we have to ask, ‘How are you feeling? How is your mood? Have friends passed away recently?’ We have to take the time to figure out their social situation, whether they’re having trouble getting to the bathroom. ... People are embarrassed, and often they don’t volunteer the information because they think it’s a normal part of aging.”

Physicians stand a far better chance of helping their patients combat urge incontinence when they tackle the problem as more than a physiological phenomenon, says Cheng. “We should treat depression first for the biggest bang for our biofeedback buck.”

That approach is sure to get a boost with the July 2010 appointment of psychiatrist Charles Reynolds—longtime director of Pitt’s John A. Hartford Center of Excellence in Geriatric Psychiatry and one of the world’s leading experts in late-life depression—to head the Institute on Aging, a partnership between UPMC and the University. Founded by Resnick and Pitt professor of psychiatry Richard Schulz seven years ago, the institute integrates teaching, research, and

service in the field of gerontology. It boasts a multidisciplinary network of researchers from 16 undergraduate and professional schools on the Pitt campus and offers seed-grant funding for scientists; a certificate in gerontology for students across campus; and working groups to reduce hospital readmission, enhance access to palliative care, and promote programs in healthy aging.

"It really helps to have multiple areas of competence" to address issues faced by older adults, says Studenski, who serves as the institute's associate director of research. "It's rarely one organ system or problem—they're almost always multifaceted problems that take a team to figure out."

In her own efforts to predict falls—a central element of Studenski's investigation of balance, mobility, and functional independence—the professor has collaborated with epidemiologists, statisticians, physical therapists, and radiologists, among others. "I'm the 21st-century equivalent of the Jewish matchmaker," she says. "Building teams is a big part of my life."

As faculty advisor to the Geriatrics Area of Concentration, Studenski also helps students wrap their minds around how basic physiology actually changes with the aging process.

"The ability to self-correct becomes creakier and more full of failures," she says. "Things don't work as well as they used to."

While medicine often promotes compartmentalization of organ systems—I'm a nephrologist, you're a cardiologist, she's a neurologist—geriatricians learn to think differently. "You can't just have separate boxes for kidney, heart, and brain," says Studenski. "These systems are all interacting, self-correcting each other. You don't want to make the heart better and the

kidney worse, but that happens all the time in medicine."

For geriatric patients, whose organ systems are less resilient to such insults, the risk can be significant. Studenski notes that doctors and scientists need to move beyond diseases and start asking, "What's going on underneath that's making the body less capable of self-correcting?"

Ultimately, she says, the very way investigators think about the elderly needs an overhaul. "I'm particularly excited about developing scientific processes that thrive on interactions among [biological] systems and processes," she says. "It makes the science really exciting and relevant."

Consider the parable of the blind people examining an elephant: Each comes away with only a partial understanding of the whole because each touched only a tusk or the trunk, the ears or the tail. As the poet John Godfrey Saxe noted, *each was partly in the right/ And all were in the wrong!*

"The drive to isolate problems is self-defeating," Studenski says. Yet in the past 50 years, medical research has hinged on an experimental method that divides and conquers, investigating heart disease only in research subjects without confounding diagnoses; depression or dementia only among people without simultaneous physiological problems; incontinence only in patients who have no other complaint. The resulting insights often have limited relevance among older adults.

But generating the insights most desperately needed by clinicians treating older patients

isn't easy. For example, because of high rates of death and disability, doctors who study the elderly are likely to find it difficult to keep a stable pool of study participants; that can lead to big data gaps. "In the geriatric population, a large number [of participants] may cease to be able to come to the clinic," says Hardy. "Researchers may not be aware of what a problem it's going to be, or they're too aware of what a problem it's going to be and so they don't study them for fear of losing track of them." (There are ways of designing studies to get around such issues, Studenski and Hardy note in a 2009 article for the *Journal of the American Geriatrics Society*.)

And yet, no matter how much research geriatricians do, or how well they do it, some mysteries will almost certainly remain. Studenski's father died just a few years ago, at the age of 93. Despite his longevity, he took a contrarian approach to healthy living.

"[He] hated fruits and vegetables, smoked, was totally sedentary, and hated exercise," recalls his daughter, who has invested significant effort in developing and testing an exercise program for postmenopausal women based on the video game DanceDance Revolution (she had tech support from "digital natives," as her medical students' age group is known by demographers).

"There's something about will power and determination that influences how people deal with late life," says Studenski. "[My father] was a very resilient man; you don't get to see that so much in young people. Until you hit the rough parts of the road, you don't know how you'll deal with them." ■

A NEW KIND OF LOVELINESS

**What do we do
with leftover cake?**

**We have some next day
for breakfast—
that's what we do—**

**...and for lunch too
and the next day the same
until none remains**

**We've consumed
each crumb**

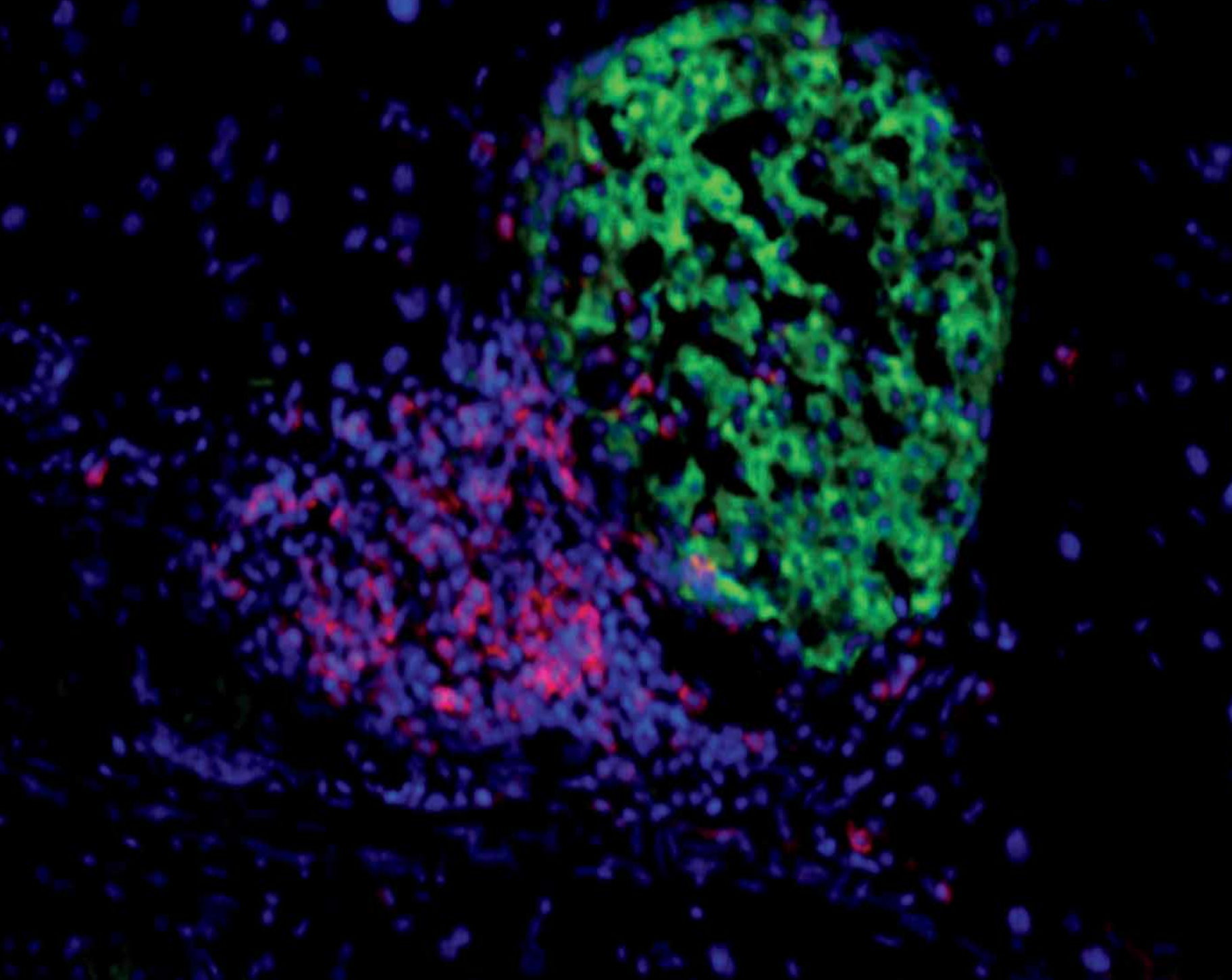
View to a Dream

**The view out the window is new
the old plum tree half dead,
once a thing of beauty
with white blossoms in spring,
cut down yesterday,
down to the stump**

**Now, behind the garage
above the roof, we see the oak
with orange-reddish leaves
which reminds us:
beyond beauty lost,
a new kind of loveliness.**

Dorothy Holley, who loved wild hats, colorful socks, gardening, and the taste of ripe raspberries, began writing in earnest in her 80s. That's when she published her four books of poetry, offering us "delicious morsels of a full, observant life," as one reviewer noted. Holley—a great-grandmother to three, grandmother to eight, and a mother to five, including Pitt professor of medicine Beth Piraino (Res '80, Fel '82)—died on June 6 this year at the age of 87 of complications from a broken hip. These poems appeared in her last book, *Dream Quartet* (© 2009). —Erica Lloyd

AUTOIMMUNITY'S



THE OVERLOOKED THYMUS

BY MELINDA WENNER MOYER

TRUE NORTH?

Ask a handful of biomedical scientists which organ plays the leading role in type 1 diabetes, and most will name the pancreas. After all, the disease, which afflicts some three million Americans, develops when the body erroneously attacks the beta cells of the pancreas—leaving them unable to produce insulin, the essential hormone that removes sugar from the blood. Because the pancreas is where the dirty work of diabetes unfolds, it is, as would be expected, where most researchers focus.

This cannot be said of Yong Fan, a research assistant professor in the University of Pittsburgh's Department of Pediatrics, and his mentor Massimo Trucco, Hillman Professor of Pediatric Immunology and an MD professor of pediatrics, pathology, human genetics, and epidemiology at Pitt who heads the Division of Immunogenetics at Children's Hospital of Pittsburgh of UPMC. But then, one might not call them typical diabetes researchers. Fan, who hails from China, has a background in developmental biology, which few diabetes researchers do. And Trucco, who is Italian, wears the same uniform every day (black jeans and a black shirt), has a guttural laugh that slips out frequently, and exudes a keen wisdom: He seems to know that where the human body is concerned, things are not always how they first appear.

A young researcher demonstrates the importance of the thymus in treating type 1 (juvenile) diabetes. Here we see what happens when Pitt's Yong Fan engineers mice so that the thymus doesn't recognize important insulin-producing cells. Immune cells (red) attack the pancreatic cells.

IMAGE COURTESY FAN AND TRUCCO LAB

Fan and Trucco are marching in the vanguard of what might be called a diabetes revolution. It is their belief that many of the disease's unsolved mysteries can be rectified not by looking at the pancreas but at the thymus, a small immune organ found in the center of the upper chest "that generally, in clinic, nobody cares about," Trucco says. In a study they published in September 2009 in *The EMBO Journal*, Fan and Trucco showed that mice that are genetically resistant to type 1 diabetes nevertheless develop the disease in only three weeks—about nine times faster than usual—if they are born without the ability to make insulin in the thymus, even if their pancreatic beta cells can produce plenty of the hormone.

It is an astonishing finding—"against prevailing dogma," according to a 2010 commentary published about it in *Pediatric Diabetes*—and it illustrates something that Trucco says he has come to understand about diabetes over the years: "The more we study the disease, the more we understand that it is more complicated than we wanted it to be," he says. Fan and Trucco's findings suggest why a diabetes cure has been so difficult to find—researchers may have been looking in the wrong place. But now they may have identified diabetes' true north.

Fan hasn't always been passionate about the thymus. Prior to 2002, he, too, was focusing on the pancreas—more specifically, he was trying to coax stem cells to develop into pancreatic beta cells in hopes of using them as replacement cells in diabetes patients. But he was starting to grow wary of his approach, because he knew that "no matter how many [beta cells] you make, once you put them in the patient, the body will destroy them," he explains. "I realized the more fundamental question was unresolved: We needed to crack open what actually was causing this autoimmunity," meaning the tendency for the body's immune cells to attack its own tissues.

One day at around the same time, Trucco invited Constantin Polychronakos, a pediatric endocrinologist at McGill University, to give a talk to his lab members. In his presentation, Polychronakos mentioned his own discovery that low levels of insulin were produced in the thymus. This "was a total surprise to me," Fan says. The thymus, Fan knew, was the immune organ that produced T cells, specialized white blood cells responsible for fighting infections. (They get their name because they come from the thymus.) Polychronakos went on to sug-

gest that insulin might be a kind of classroom tool used by the thymus to "train T cells to be useful," Fan recalls.

It made sense. T cells mercilessly fight intruders, but how do they learn what belongs in the body and what does not? Somehow, the immune system must explain to developing T cells that the proteins and hormones produced by the body should not be destroyed. Low levels of many of the body's proteins are produced in the thymus, and it was Polychronakos' belief that T cells were being introduced to these proteins—such as insulin—in a biological meet-and-greet designed to show them that the proteins were friends, not foes. If any rogue T cells did not get the drift—if they attacked the friendly proteins they met in the thymus—they would be killed before they left the thymus and did serious damage.

The idea immediately piqued Fan's interest. "I said, 'Wow, this is interesting,'" he recalls.

If insulin is being produced in the thymus in order to train T cells not to attack insulin-producing cells—i.e., pancreatic beta cells—then perhaps type 1 diabetes develops in people who are not producing enough insulin in the thymus. In 1997, Polychronakos had shown that people who produce less bodywide insulin as a result of genetic abnormalities are more likely than others to develop type 1 diabetes. Perhaps, Fan thought, too little insulin production in the thymus was actually the culprit. Without it, T cells aren't primed to leave insulin alone. Then, when they are released into circulation and "pass by the pancreas and find cells producing insulin, they kill those cells because they believe that they are foreign," Trucco explains.

To find out whether he was right, Fan set out to engineer mice that could not produce insulin in the thymus. First, he bred mice so that the predominant insulin gene in all of their cells was flanked by two short genetic sequences called loxP sites. Then he engineered a second group of mice so that they contained a gene called *CRE* that excises any gene found in between two loxP sites, effectively removing it from the genome so that it cannot be expressed. In front of the *CRE* gene, he placed a master controller gene that switches *CRE* on only in the insulin-producing cells in the thymus.

In his final step, Fan bred the two groups of mice together, producing baby mice that contained both the *CRE* gene and the two loxP sites flanking the insulin gene. The end result:

CRE cut the insulin gene out of the mouse genome, but only in the insulin-producing cells in the thymus, leaving insulin production everywhere else in the body—including the pancreas—untouched. In effect, Fan had engineered mice that could not produce thymic insulin, but who could produce insulin elsewhere.

Then Fan and Trucco watched what happened. Typically, 80 to 90 percent of female mice with a genetic predisposition to diabetes develop the disease within 20 weeks, with progression in males being slower. But in this case, within three weeks, every single one of the male and female mice who could not produce insulin in the thymus developed severe, fatal diabetes. Fan had shown that the thymus was arguably as important for diabetes development as the pancreas.

For the many researchers who study diabetes, Fan and Trucco's findings are a wake-up call. For one thing, they shed light on the importance of central tolerance—the schooling of T cells in the thymus to prevent them from attacking self-made proteins—and reveal at least one important way it can go awry. "It opens avenues to explore how T cells escape central tolerance, resulting in autoimmunity," says Anil Bhushan, a cell and developmental biologist at UCLA.

And if the disease starts in the thymus, then the organ may be a far better target for a cure than the pancreas. The game, as Trucco puts it, then becomes trying to find a way to help people whose thymuses don't express enough insulin to start expressing it.

That said, if the problem is only discovered after rogue T cells have already attacked the pancreatic beta cells, then additional treatments may be necessary to replace them, since beta cells don't naturally regenerate. That problem may also be solved at Pitt: Earlier this year, Andrew Stewart, chief of the Division of Endocrinology and Metabolism in the School of Medicine, showed that when human beta cells are engineered to produce high levels of certain regulatory molecules, they can regenerate continuously for four weeks when transplanted into diabetic mice.

Trucco and Fan's findings also help explain something that has perplexed scientists for years: Some children develop type 1 diabetes at a very young age despite not having a known genetic predisposition to the disease. Perhaps their problems can be traced to the thymus.

Fan and Trucco's discovery could shed light on the root causes of other autoimmune diseases. After all, thymus cells don't just express insulin—"Twenty to 30 percent of the genes in our [bodies] are expressed in this cell population," Fan explains. Like insulin, these other proteins teach developing T cells that they are not enemies. It's possible that if these other proteins aren't produced in large enough quantities, different autoimmune diseases—such as rheumatoid

arthritis, multiple sclerosis, and lupus—might develop. It makes sense, especially considering that people with type 1 diabetes often have other autoimmune diseases, too. Perhaps they suffer from a central thymus defect that could be treated by increasing thymic gene expression on a global level. Trucco and Fan are now engineering mice so they are unable to produce other proteins in the thymus, to see whether they develop other autoimmune diseases.

For Trucco, the discovery is gratifying on an even deeper level. He has long believed that although biology is full of surprises, everything happens for a reason. But try as he might, he could not find an explanation for why the T cells of patients with diabetes suddenly started attacking the body instead of defending it. Now he finally has one.

"I knew there must be some sort of logic," he says, then paraphrases Shakespeare. "There must be reason in this madness." ■

FATTY ACIDS AMPED

In biology, free radicals have the reputation of a no-good street gang. They sneak around the body, brimming with incessant energy, doing damage here and there for seemingly no reason at all. When too many of them troll around for too long, bad things can happen. But Bruce Freeman, UPMC Irwin Fridovich Professor and Chair of the Department of Pharmacology and Chemical Biology in the School of Medicine, has seen unique potential in these historic hoodlums. Now, he thinks free-radical reaction products might even have what it takes to beat type 2 diabetes.

Freeman didn't always have a soft spot for free radicals. In 1990, while at the University of Alabama at Birmingham, he published a seminal paper—among the most frequently cited papers in biology—revealing the major pathway by which free radicals cause tissue injury. But when he started testing the effects of these free radicals in animal models, he found that one free radical in particular, nitric oxide, didn't always cause damage. When it interacted in the body with fatty acids like oleic acid—the major component of olive oil—the free radical actually *reduced* inflammation rather than causing it.

"It was heretical," Freeman says of the discovery. Since then, he has published paper upon paper showing that these nitro-fatty acids, as they are called, can in fact limit and even heal tissue injury. The nitro-fatty acids are what Freeman refers to as electrophiles, molecules that interact with electron-rich molecules and thereby initiate signaling cascades and gene expression profiles that attenuate stress in the body.

"There are about 300 to 500 major genes whose expression is modified by electrophile levels," Freeman explains.

Recently, Freeman's team uncovered a link between these nitro-fatty acids and type 2 diabetes. The acids, the researchers discovered, bind to a cell receptor called PPAR-gamma that is well-known in the diabetes world. Diabetes drugs like Avandia work by binding to PPAR-gamma in a way that activates a host of biochemical cascades modulating insulin resistance and sugar metabolism. Problem is, some of these cascades also spark water retention and fat production, causing serious weight gain, a common diabetes drug side effect. But when Freeman studied how nitro-fatty acids interact with PPAR-gamma, he discovered that they bind dif-

ferently, via a covalent bond. He wondered: *Was it possible that by binding differently, the nitro-fatty acids might turn on all the good cascades—improving insulin sensitivity and glucose metabolism, and thus treating type 2 diabetes—without eliciting the unwanted side effects?*

To find out, the researchers synthesized nitro-fatty acid in the lab and administered it to obese, insulin-resistant rats for four weeks. Within just four days of starting, the treatment normalized their blood-sugar levels and significantly reduced their insulin levels, a change that did not occur in mice that had been given naturally produced fatty acids, such as those found in olive oil. Most importantly, though, the mice he treated did not gain any weight. Compared to existing diabetes drugs, the nitro-fatty acids seem to cause "less stimulation of fat metabolism, less weight gain, and less fluid retention," he says. Freeman and his colleagues, who include Pitt's Francisco Schopfer and Chiara Cipollina, published their results in April 2010 in *The Journal of Biological Chemistry*.

Certainly, some fatty acids—such as omega-3 fatty acids—have anti-inflammatory effects of their own, which is why we're told to eat lots of fish. But his work suggests that when these fatty acids interact with nitric oxide (or other oxygen-centered free radicals), they become even further activated. "What's really impressed us is if we modify the fatty acids chemically to make them electrophilic, there's a very significant increase in their anti-inflammatory capability," he says.

These molecules don't just have implications for type 2 diabetes, either. Since 2009, Freeman has shown in rodent models that nitro-fatty acids attenuate atherosclerosis, inflammatory bowel disease, hypertension, and the damaging inflammation that develops after heart attacks and cardiac arrest. Now he is turning his attention to heart failure: "We're predicting we'll have a significant impact," he says.

Ultimately, Freeman hopes to manufacture large quantities of these molecules using synthetic, inexpensive strategies. He has started a biotechnology company, Complexa, to commercialize the concept and is currently testing the compound in different animals for safety. "What we'll be doing is increasing the concentrations of the activated form of unsaturated fatty acids to levels greater than we would otherwise achieve through dietary strategies," he says. —MWM



Meg Quimper received a travel scholarship from Pitt's Center for Global Health to conduct global-health research in Malawi. She worked with Project Peanut Butter, a program that provides nutritious, high-calorie peanut paste to children with severe acute malnutrition. TOP: The factory in Blantyre, Malawi, where the fortified peanut butter is produced. LOWER LEFT: At Chikweo Health Center in southern Malawi, families listen as health care workers explain how the clinic runs. LOWER RIGHT: Quimper administers antibiotics to a child enrolled in a study of treatment for an intestinal disease that's widespread in rural Malawi. OPPOSITE PAGE: A child tastes the therapeutic peanut butter for the first time. This therapeutic snack time "could be quite messy, but it was always fun to watch," says Quimper.

Photos courtesy Meg Quimper



WHEN A PATCH OF SHADE IN RURAL
AFRICA REVEALS A CAREER PATH

BY ELAINE VITONE

PASSIONS FOUND

They left before dawn, lumbering through the darkness along the unpaved roads of rural Malawi, a southeast African nation slightly smaller than Pennsylvania. The sun rose, and flatlands rolled on around them for miles in every direction. Some days they drove for three hours before reaching their destination: usually the lawn of a health clinic, sometimes just a patch of shade beneath a baobab tree. Waiting for them in the rising heat of the cloudless summer morning would be a host of hundreds—mothers who'd been carrying their children on their backs for just as long as the team had been driving. Some families had been walking for days.

"There's not really a line at that point," Meg Quimper recalls of those hours in the din of crying babies and the occasional bleating goats and clucking chickens. "It's just a mass. You just get in this rhythm." The mothers undressed their children, and Quimper and her fellow volunteers set up their mobile clinic and assessed each child for signs of malnutrition: either what's known as marasmus—which whittles down the body to mere skin-on-skeleton—or kwashiorkor—a swelling of fluid that puffs out the belly and cheeks. The team checked for anemia and measured the children's weight/height ratios and the girth of their upper arms—one of the first places a human body loses muscle mass when starvation sets in. The workers also checked the children's feet—the easiest place to find kwashiorkor swelling.

"The kids are going crazy, and I can't blame them," Quimper says of that line with a sympathetic smile. "I wouldn't be happy either if I were naked and getting passed around like that in the morning." Her voice turning somber, she adds that



the hardest part was seeing the kids who were too lethargic to be scared, too swollen-footed to walk, too severely malnourished to even hold up their own heads.

Quimper is one of three Pitt School of Medicine students who conducted international health research last summer with the help of travel scholarships from the University of Pittsburgh Center for Global Health. The scholarships are intended to help students address compelling global-health issues, particularly in the developing world. Since its inception three years ago, the travel-grant program has awarded \$120,000 to 37 graduate students in the University of Pittsburgh's six health sciences schools, as well as in its Graduate School of Public and International Affairs and School of Law.

All three of the School of Medicine students who conducted research abroad this summer had been to their sites before. Earlier volunteer or professional experiences in Africa had inspired them and put them on a path toward global-health research. Traveling abroad, away from the comfortable and familiar, has helped them find their passion.

Thuy Bui, medical director of Pitt's Program for Health Care to Underserved Populations, has advised all three students in some capacity. "What they share is a yearning and audacity to tackle big challenges—of logistics, culture, language, resources—to understand the diseases and conditions affecting the bottom billion and the complexities of the necessary interventions," she says.

As an undergraduate, Quimper spent 10 weeks with this same mobile clinic in Malawi. It's part of an organization called Project Peanut Butter (PPB), so named because, after assessing each child, it sends malnourished children home with high-calorie, fortified peanut butter known as Chiponde (the full name is Chiponde Plumpy'nut). On a steady diet of this protein-packed PB, the kids who'd been totally unresponsive their first day at Chiponde clinic are soon "going crazy," just as they should. Most reach a normal weight in eight weeks or less.

"It's pretty amazing to watch and really rewarding," says Quimper. "You see them start running around and acting like kids."

On that first trip, Quimper worked with PPB founder Mark Manary, a pediatrics professor in the School of Medicine at Washington University in St. Louis, on a study of zinc deficiency in rural Malawi. The team established that this problem was prevalent in the

population and, furthermore, that it was most likely caused by the intestinal disease tropical enteropathy.

Although not much is known about the mechanism of the disease, it has been shown to respond to antibiotics. So, this summer—just after Quimper and Manary's first study results were published in *Pediatric Research*—Quimper used her Pitt travel scholarship to return to Malawi and take the work a step further. The team completed a double-blind study to test whether adding antibiotics to the Plumpy'nut would make a better butter—one that speeds recovery—and how cost-effective such a regimen would be. The final data analysis will likely start this spring.

In Malawi, when you get sick and go to a hospital in a rural area or even a larger town, chances are you won't see a doctor. The only MDs in Malawi work in what are called central hospitals, of which there are only four. For the routine medical complaint—be it a sore throat or AIDS—treatment is in the hands of mid-level clinicians (the equivalent of nurse practitioners or physician's assistants).

Mid-level clinicians are in short supply and are largely on their own. There's no supervision, no feedback, and little opportunity even to witness the effects of their work. Typically, patients see whoever happens to be working on a given day at these walk-in sites.

Malawi's mid-level clinicians follow a thick book of guidelines adapted from those of the World Health Organization; the book contains a series of scenarios designed to speak to the majority of the population. "It's sort of an if-then-else construct," says Zach Landis Lewis, borrowing a phrase from computer programmers—which he does often because, well, he is one. He's also a graduate of Pitt's Master of Library and Information Sciences program, which may contribute to his having the well-read, warm, what-can-I-do-for-you sensibilities of a good librarian. These days, Landis Lewis is a fourth-year PhD student in the School of Medicine's Department of Biomedical Informatics.

Following the guidelines consistently, Landis Lewis explains, can be a challenge for Malawi's mid-level clinicians for various reasons. But in the case of AIDS, the challenge is particularly daunting because those guidelines are a moving target. As the population becomes resistant to the first-line drug treatment, the treatment begins to fail more

people. Eventually, it's phased out and replaced by a second, and then a third, and so on.

In 2003, Landis Lewis took a job leading a software-development team in launching an electronic medical records system for Malawi. It was a project of Baobab Health, a Malawi-based nonprofit organization founded by Bui and Gerry Douglas (PhD '09), who are married. Landis Lewis began his work in Pittsburgh, and then, from August 2005 to July 2006, he and his wife, Deborah Landis Lewis (MD '06), lived in Lilongwe, Malawi—she took a year off from med school during which she volunteered at Bottom Hospital, which performs 12,000 deliveries a year with only two consultant ob/gyns.

"Deb's work has definitely been an inspiration to me and others," Zach Landis Lewis says.

With his travel grant, he spent a month back in Malawi this summer doing a feasibility study for what he envisions as the next phase for his program. Perhaps clinicians could receive regular automated feedback, he posited. He met with a few clinicians in Malawi, who welcomed the idea and gave him some suggestions.

For now, Landis Lewis is examining the areas where clinicians have room to improve, particularly in spotting the two most vexing problems with AIDS treatment: management of side effects and treatment failure. Malawi is in the middle of scaling up antiretroviral therapy. The government has about 300,000 people on treatment and aims to eventually treat the entire population of AIDS patients, which is currently about one million.

"As they get more and more people on treatment, they start to do better and better," says Landis Lewis. "Unfortunately, that also means resistance is going to increase. Helping clinicians to recognize that that's happening is going to be very important."

"Zach's work is tremendous," says Bui. "I expect a lot from him in the future."

When second-year MD student Mingyi Huang began his door-to-door survey project this summer in Mityana, Uganda, he decided to skip every other house—he wouldn't need every single family in the district for his data sample, he reasoned. But when people saw him pass them by, they chased after him.

"It's very different from doing a survey here," Huang says with a laugh. "Everyone was just so eager to help."

Huang encountered plenty of this disarming generosity while in Uganda. Even Huang's translator, Noah Kintu, who worked seven-hour days with him four days a week for more than



A few years ago, Zach Landis Lewis developed an electronic medical records system for health care workers in Malawi. This summer, he laid the groundwork for an upgrade to his system: automated feedback for clinicians. **TOP RIGHT:** Landis Lewis (left) at his going-away party in 2006, after he spent a year living and working in Malawi. **TOP LEFT:** A rural district-hospital HIV/AIDS clinic where Landis Lewis observed and interviewed clinicians this summer. **MIDDLE:** A health care worker uses Landis Lewis' system to register patients in a pediatric ward at a district hospital. **LOWER LEFT:** A wall in the clinic where health care workers have taped informational handouts. "These are good indicators of their information needs at the point of care," says Landis Lewis. **LOWER RIGHT:** Entrance to a district hospital.

Courtesy Zach Landis Lewis



a month, had initially assumed he was working for free—and was fine with this. (Huang did, of course, pay Kintu for his services.)

Huang is studying risk factors associated with the spread of malaria, which is easily the biggest public health problem in Uganda. Malaria spreads through the bites of female mosquitoes, infecting each host with one of five *Plasmodium* parasites. Once in the body, the parasite sets up shop in the liver, where it's able to escape the notice of the immune system. Within weeks, the parasite multiplies and leaves the organ, infecting new red blood cells over and over again in waves that cause a cycle of debilitating, flu-like, feverish spells—and in severe cases, fatal seizures.

It's a difficult disease to study. The hours-long fevers course through the body in cycles every few days, and this can go on for weeks. In places like Uganda, where the disease is so widespread and undertreated, it's hard to know when one

infection stops and the next one begins. Many Ugandans can't afford hospital stays or even manage traveling to the hospital in the first place. Drugs are in short supply at the hospitals, which are government-run, and counterfeit drugs are rampant. There is no widely available vaccine for the disease.

Many people told Huang it was not uncommon to be sick four times in one month, and health care workers told him that 80 to 90 percent of the patients they see are malaria cases. Whenever anyone comes in with any possible sign of the disease—headache, fever, abdominal pain, diarrhea, and so on—they're automatically treated for malaria.

"It's challenging," says Huang. "That's why my main goal is prevention."

Huang asked survey respondents about their incidence of malaria and about the steps they take to avoid it—which might include

insecticide, insect repellent, mosquito nets, and what time they close their windows at night (prime time for mosquito feeding).

In particular, Huang targeted the two highest risk populations: children under 5, who have no immunity and suffer the disease's ill effects the worst, and pregnant women—or rather, their fetuses—who are even more vulnerable. Children can suffer brain damage, and in pregnancy, malaria heightens the risk of stillbirth, low birth weight, and birth defects.

Huang is still analyzing the data, but thus far, he does have some startling numbers on incidence. It appears that 65 percent of children age 5 or younger in the sample had malaria within two months of the survey. Huang is spending the fall sifting through his data with the help of Pitt's Clinical and Translational Science Institute. Eventually, he'll compare the incidence of individuals who have contracted

malaria to the prevention methods they use in hopes of uncovering the most effective means of heading off the spread of the disease.

Like Quimper, Huang chose a research site where he had been before. In 2008, as an undergrad, he'd volunteered at a Uganda primary school, where he taught health and nutrition classes. He'd also organized and fundraised for a rainwater harvest system and garden as well as for a concrete floor for the classroom. And he'd made a few friends, with whom he was able to catch up this summer.

"It's really hard," he says. "The more people you meet, the more people you want to help."

When she first came to Malawi, Quimper struggled with not being able to help everyone she met, too. Some mothers would follow the Chiponde regimen to the letter, but two months later, the kids were still malnourished. That meant something else was wrong, too—most likely, they had AIDS.

Antiretroviral medications are free for children, but when Quimper was in Malawi this summer, there were no HIV tests available in the country. The government won't issue the therapy without a positive test.

"I guess you kind of expect this sort of thing to happen in a very resource-poor setting," she says. Yet, Quimper adds, it's hard to

know when such obstacles will show up.

Manary, Quimper's Project Peanut Butter mentor, encouraged her to focus on nutrition. That was the problem they'd set out to solve, and the problem they had a better handle on than others did. "That's something I learned from him," says Quimper. "You kind of pick a problem, and you do what you can about that. You can't worry about everything else—or you're not going to accomplish what you set out to do." Another lesson she learned from her global health research: Set out to do what you're passionate about.

One day at Chiponde clinic, a mother brought her child—a skinny 2-year-old—in at 7 a.m. and left him there all day. He was malnourished, and his fingers had been broken and healed askew. Throughout the day, Quimper and her fellow volunteers kept an eye on him as best they could, all the while wondering what kind of monster of a mother would leave him like that. When the mother came back at the end of the day, the nurses laid into her.

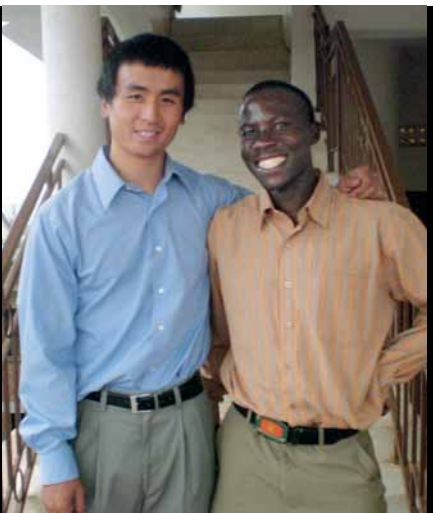
"The mom was stoic," Quimper recalls, "just not responding. And then she just started crying and told us what she was going through."

The woman's husband had died, and she'd been taken in by another man. This stepfather was the one who had broken the child's

fingers—because the child had wet the bed. The stepfather had forbidden her to take the baby to Chiponde clinic, so the mother had lied and said she was taking him to her sister's so she could go work in the fields. She'd figured the Chiponde volunteers would watch him, and they did.

Realizing that this mother was so desperate that this was her best option—to marry a man who beat her child, because she had no rights—was one of many moments that resonated for Quimper. Through her summer project, she has learned the importance of listening, of keeping an open mind. And just as Manary had decided it was unconscionable to allow severe acute malnutrition—a very preventable condition—to be the most deadly killer of children under 5 worldwide, Quimper is finding her own calling in women's health and rights.

Bui sees a lot of similarities between the Pitt med's three scholarship recipients. Each of them returned to Africa to implement a new idea, she points out. "They are all rather quiet, gentle people but ... so effective. They have the personality that breeds tolerance, flexibility, resilience, and ingenuity—important qualities for success in low-resource settings. I believe that the small investment made by the Center for Global Health and the University is already life-changing and will have lifelong career impacts for each of them," Bui says. "That's the best rate of return one could ever ask for." ■



Mingyi Huang is studying malaria in Mityana, Uganda. After conducting door-to-door surveys last summer, he's now comparing individuals' reported incidence of malaria against their prevention methods. ABOVE: Huang (left) with his translator and good friend, Noah Kintu. RIGHT: The chairman of the village of Nakibanga guides the team along a footpath that leads to the home of a survey respondent.

Courtesy Mingyi Huang



It's just like a real gross pathology lab, only smaller. In this diorama, pathology assistants and a pathologist go about their business getting tissue samples ready for microscopic review.

FEATURE



THE RARELY SEEN PHYSICIAN

**PATHOLOGISTS
ARE CHANGING MEDICINE**

BY JOE MIKSCH

DIORAMA BY

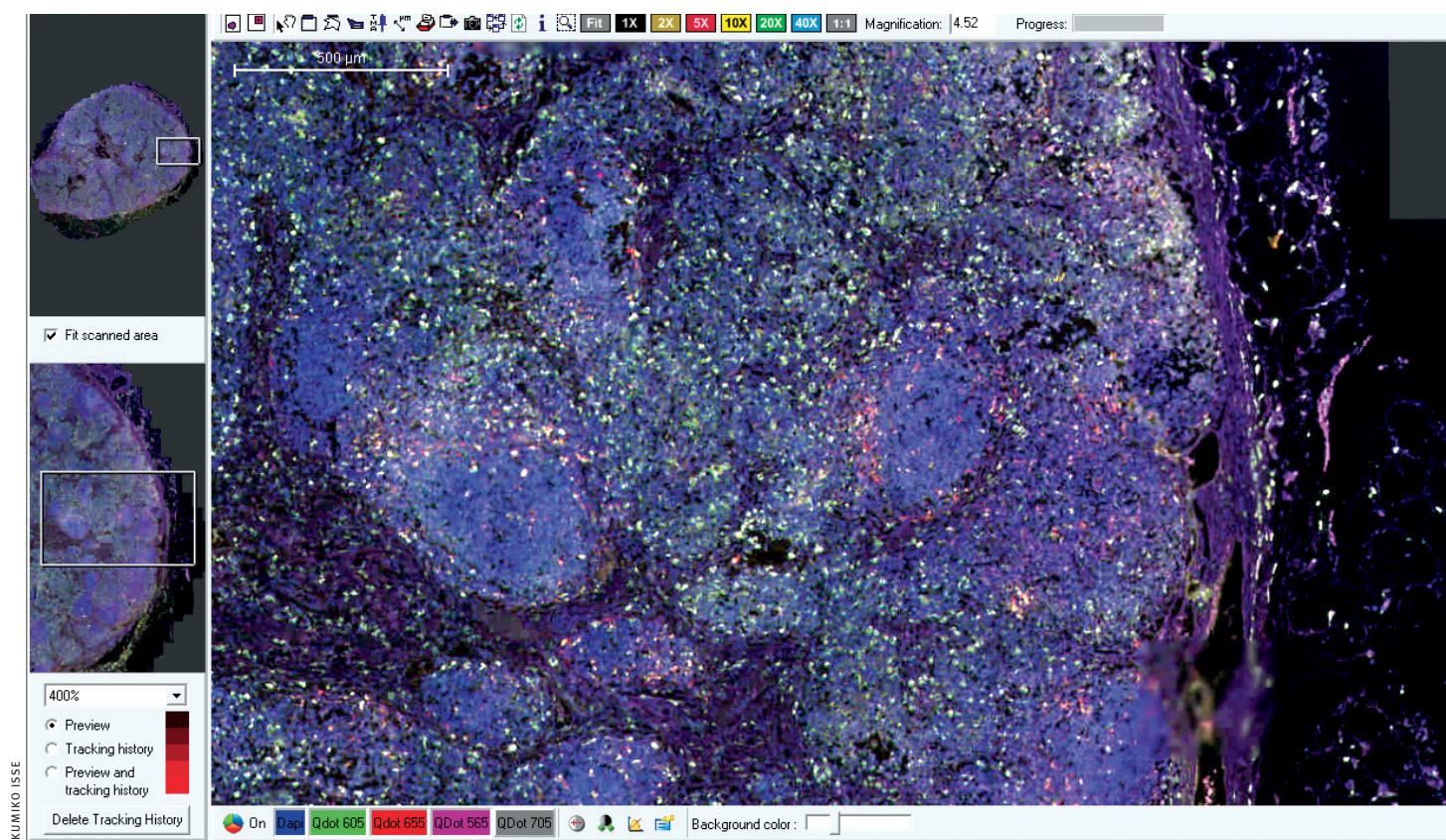
KAREN SCHOEDEL

PHOTOGRAPHY BY

JIM JUDKIS

On a map, Palermo, Italy, on the island of Sicily, appears to be about 4,800 miles from Pittsburgh. To Anthony Jake Demetris, an MD professor of pathology and the Thomas E. Starzl Professor in Transplant Pathology in the School of Medicine and director of the Division of Transplantation Pathology at the Thomas E. Starzl Transplantation Institute at the University of Pittsburgh, it's as close as the nearest computer. Demetris is in the business of making the ocean between the cities irrelevant, at least to pathologists and patients in Palermo.

Demetris and other pathologists rarely see patients; rather, they see biopsies. Their professional worldview begins at a



Technology allows pathologists to zoom in and out on an image, in this case a slide of a lymph node biopsy, just as if they were using a microscope.

microscope. Yet the work they do is at the core of the practice of medicine. Masters of diagnosis, these men and women peer at glass slide after glass slide festooned with a slice of paraffin-preserved tissue. Is that cancer? About how many abnormal cells do I see? How much of biomarker X is in this sample?

What they decide guides treatment, and those decisions can determine whether a patient improves or declines. This traditional aim, figuring out just what's going wrong in the body, is immutable. However, the ways in which anatomic pathologists practice their art and craft are changing, and Pitt's own people have sparked many of these important transformations.

For more than a decade, the School of Medicine and UPMC have had a presence in Palermo in the form of ISMETT, a hospital that specializes in adult and pediatric abdominal and cardiothoracic medicine and surgery as well as multi-organ transplantation.

Of course, ISMETT has pathologists. But when the facility first opened, Demetris says, "They were getting ready to do organ transplants and biopsies. Now, we had trained pathologists over there, but it was just a few

years' training period. Our entire team felt better if there could be some sort of link between Pittsburgh and Palermo."

There wasn't a Pittsburgh/Palermo link at the time, but they created one and called it "telepathology." In the beginning, telepathology was a valuable tool, albeit a primitive one. Not because of a lack of brainpower, but because of the limits of extant technology.

A patient in Palermo is about to undergo a biopsy. He's prepped, the tissue is excised, a lab tech affixes the sample to a slide, and a pathologist in Pittsburgh is ready for a consult. But it's pretty expensive, not to mention time-consuming, to fly a doc overseas ...

"So," says Demetris, "what we did was have a camera mounted to a microscope [in Palermo]. They'd take a snapshot and send it to us via e-mail." The problem was that this picture was far from the big picture.

"The thing that's inconvenient about it is twofold," Demetris says. "One, you don't have all the other information [in the patient's chart] that goes along with it and, two—you know how you can move around a slide on a microscope?—well, working with snapshots, our view is limited to what the sender sends."

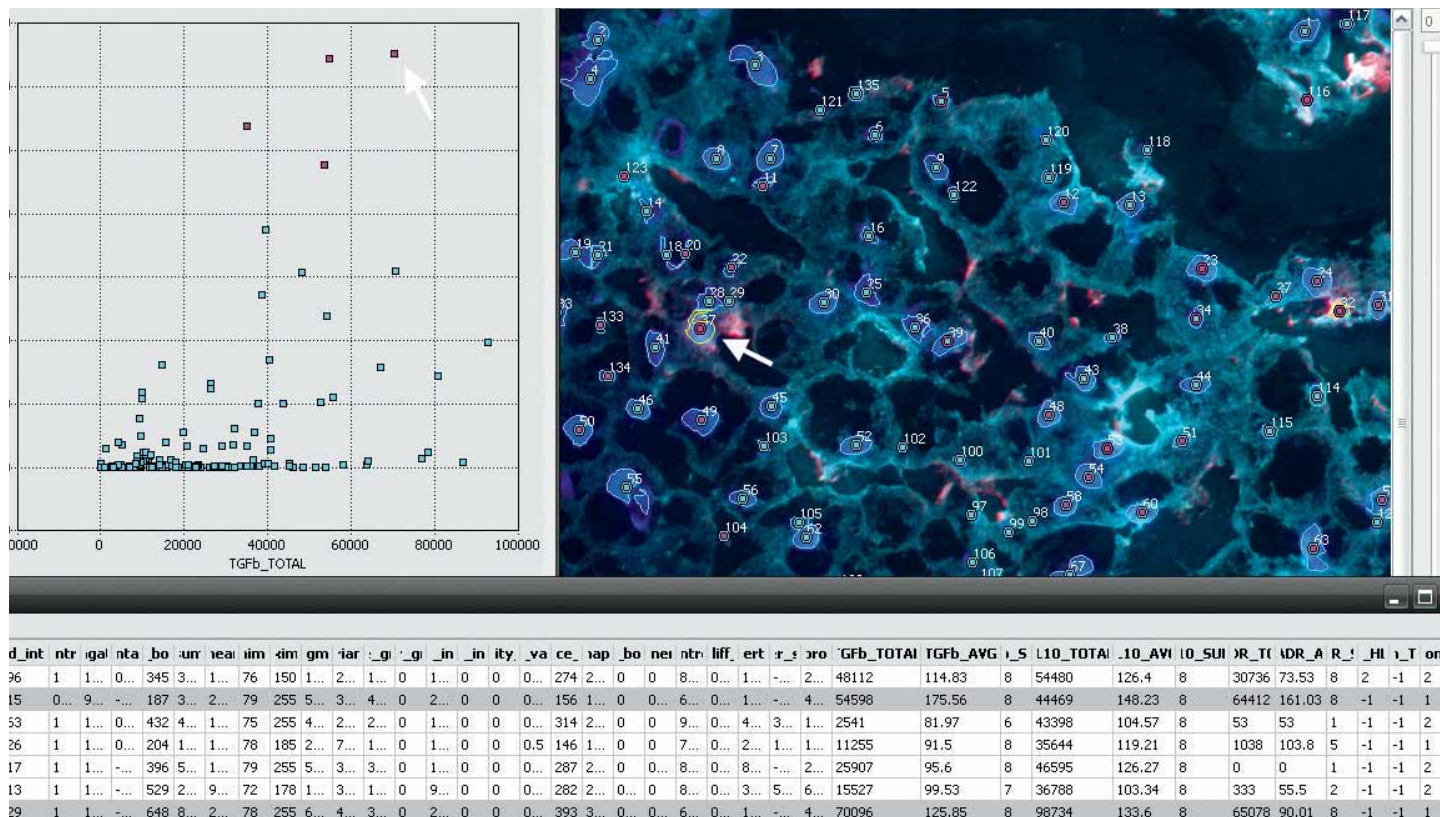
Thus necessity became a mother for the nth time.

Demetris and colleagues crafted software that allowed docs in Palermo to paste several images, as well as patient data, into a message. This "store and forward" pathology was an improvement, sure, but not enough of one. Soon thereafter, the Pitt/Palermo team rigged a microscope at ISMETT with tiny motors and gears and, using readily available software, was able to manipulate the scope's field of vision over the Internet.

"That's actually old technology," Demetris says of something just a few years into its life. "It became cumbersome. It took too long to review slides." The work got done and got done well, he adds, but something faster was needed.

The team decided to scan and digitize such slides, taking thousands of pictures and quilting them together with software. The resulting mosaic represents an image of the entire sample that, thanks to the dizzying detail captured by the thousands of little images, can be manipulated so that a Pittsburgh pathologist can look at it from any perspective he chooses.

"It's kind of like the technology used for



Telepathology uses a computer like a microscope and also takes advantage of the machine's powerful data analysis capabilities. Software allows pathologists to isolate individual cells in a tissue sample and show exactly what's going on inside them.

Google Earth," Demetris explains. "You find a city and then you zoom in on a house or something. It's the same principle with a [digital] slide. The slides are put on a secure server, and you go to a Web site that contains the patient's information and that image. You can go right in like you're practicing pathology right in Palermo."

So the biopsy is taken, a diagnosis of liver disease is made, transplantation is indicated, an organ match is found, and surgery is performed. And all of this with the Palermo patient probably unaware that a pathologist had any role in the process, let alone that the pathologist did his work in Pittsburgh.

In 2007, a 43-year-old woman—we'll call her Rosa Costa—visited ISMETT after a nuclear magnetic resonance (NMR) test at another Italian hospital showed that there was a lesion on her liver. What kind of lesion, though, was unclear to her doctors and to the radiologist who examined her NMR scans.

At ISMETT, doctors went into the lesion with a needle to sample a portion of the tissue for a pathologist to examine. They hoped the

resulting histology could provide some definitive answers.

Marta Minervini, an MD, was chief of pathology at ISMETT at the time. (She has since arrived in Pittsburgh to take a post as an assistant professor of pathology.) Minervini examined the slides, reviewed the images from radiology, and became pretty sure she was looking at an adenoma, which, she feared, had

"It's kind of like the technology used for Google Earth. You find a city and then you zoom in on a house or something. It's the same principle with a [digital] slide."

the potential to develop into malignant hepatocellular carcinoma. Such a cancer could kill a person in just a few months without surgery. But Minervini wasn't certain what to conclude. A surgical resection of the lesion would give an even clearer picture; but was it necessary?

Clinicians, naturally, want as much certainty as possible before they decide whether to order surgery. Opening the body, no matter the skill of the surgeon, is always a risk

(and costly).

"I didn't have any other colleagues over there, but I wanted a second opinion," Minervini recalls. "I was working alone and considered it a difficult case. That's why I decided to post it, to send it to Pittsburgh for a second opinion."

Minervini's report—a narrative accompanied by histological and radiological images—noted that the lesion was fed by a number of aberrant arteries. *Some findings are more compatible with hepatocellular adenoma* [a potential malignancy], she wrote, *while others are more suggestive of focal nodular hyperplasia* [a kind of benign tumor].

Then she clicked "send." Less than 24 hours later, the response came from Demetris.

I agree that the interpretation of this case is difficult, he wrote. After suggesting further histological tests, Demetris came to this conclusion: *In the meantime, I would probably recommend that the liver be resected . . .*

Given the very real risk of a malignancy, Costa's clinicians decided to remove the lesion. "There was a reasonable conclusion that this

lesion had to be removed from the patient because it could be evolving into something worse,” Minervini says.

The practical benefits of the Pittsburgh/Palermo connection are obvious—readily available expertise from the other side of the world in real time. And telepathology can make a difference closer to home, as well. In a hospital system like UPMC’s, not every hospital necessarily has a pathologist from every subspecialty. Yet the long-term implications of this scanner technology are much, much larger.

“This,” says Demetris, “will revolutionize pathology. It’s already starting. With the help of engineers, and mathematicians, and software designers, you name it, we’re getting bigger and better, and I think someday the field would be better named ‘diagnostic medicine.’ We’re adding so much information to what we do.”

The one thing that pathologists have always been good at, Demetris says, is absorbing and interpreting tons of visual data. With education and training, he says, a good pathologist can quickly and accurately see patterns in slides. “But in terms of patient care,” he adds, “it sometimes irritates other specialists (such as a cardiologist

remarked, “The reason I’m here is that we were one of the earliest adopters of this technology. The images you get from whole-slide imaging aren’t as good as a microscope right now, but [the technology is] pretty darn close, and I think it will eventually surpass the microscope.”

As it happens, Pitt and UPMC, in partnership with GE Healthcare, are doing their level best to make sure this happens by December. A joint venture called OMNYX, with offices adjacent to PNC Park, is about to roll out software and digital scanners that will make packing and mailing glass slides between distant pathologists a thing of the past.

Anil Parwani, associate professor of pathology and director of the Division of Pathology Informatics, is one of several School of Medicine faculty members consulting with OMNYX.

While scanning and digitizing pathology slides isn’t a technology that’s only being pursued in Pittsburgh, Parwani, an MD/PhD, says that OMNYX is building a better—perhaps the best—digital pathology mousetrap.

“We’ve been scanning glass slides here for a long time; maybe five or six years now,” Parwani says. “When [GE] decided to partner with an institute, they chose us because of

“We’ve built into the system a lot of things you can do with the image after it’s acquired,” Parwani says. “You can take pictures, you can measure things, you can run algorithms to quantify the intensity of a biomarker. All these things will enhance the pathologist’s work flow, making it more efficient, making it more robust.”

Most of this progress, Parwani says, has been made in the past two years, and the commercial launch of OMNYX’s products is nigh. The company recently showed off its wares at the College of American Pathology conference in Chicago. Pathology departments worldwide should be able to purchase both the OMNYX scanner and software by December.

Pathology is an interpretive specialty, so it’s quite possible for two pathologists to draw two different conclusions from the same slide. Today, though, pathologists are implementing quantitative tools and objective measures—to reduce the “interpretation gap.”

Traditionally, pathologists have reviewed their work after the fact at periodic departmental review sessions. At these meetings, a few cases are selected and discussed, and group members try to reach consensus on just what it is they’re seeing.

But if it turns out that, say, a population of cancer cells was missed or amyotrophic lateral sclerosis was misdiagnosed, the patient is already either being treated for a disease he doesn’t

have or is not being treated for something that is afflicting him. Retrospective, blind reviews show that errors are made in as many as 6.7 percent of cases.

About two years ago, Parwani and others pilot tested a computer program they’d designed that allows for proactive quality-assurance reviews of pathology slides. About six months ago, it was implemented in all UPMC hospitals. It’s now commercially available and used throughout the country.

The system works like this: A pathologist has spent the day working on his cases. He’s seen the slides, reviewed the patient data, and made his report. As he goes to electronically file the case, suddenly, and at random, this message comes across his screen: “This case has been selected for quality assurance review.” He can’t enter the report into the system.

“At that point,” Parwani says, “the case will be removed from the work list and sent to a second pathologist who has been pre-assigned

The one thing that pathologists have always been good at, Demetris says, is absorbing and interpreting tons of visual data.

or oncologist providing care), because they’ll say ‘This is only semiquantitative.’ We’ll say, ‘There’s a moderate amount of X, about 50 percent,’ and they want to know if it’s 52.3 percent.”

When a lab worker scans a slide and hands over data to the software developed here at Pitt, the pathologist’s interpretive skills are joined with the computer’s ability to quantify. And this arrangement, known as digital pathology, has broad implications for patients.

“We can now easily quantify the amount of a biomarker,” Demetris says. “In women who have breast cancer, an important predictor of outcome is the expression of estrogen and progesterone receptors. We have programs, they’re not quite mainstream, where you can stain the tissue and then [the program] will tell you how many cells or what percentage of cells are positive.”

On the phone from Boston, where he was giving a talk on telepathology, Demetris

our experience and our understanding of this technology.”

OMNYX, Parwani says, manufactures scanners—at a plant in New Jersey—that are about five times faster than anything else out there. That’s great, he says, but what makes OMNYX likely to be a successful commercial venture is its software.

“The [software] is integrated with whatever computer system you already have in place, so you don’t have to go to several different systems to get all the information,” he says. “Everything, including all the patient information, is [right there], and being able to look at the image and this information simultaneously is a very positive thing.”

The 500-megabyte images OMNYX’s scanner captures can be manipulated in all manner of ways on the computer screen, just as glass slides can be manipulated under a microscope. A pathologist can zoom in, zoom out, and scroll over to another segment of the slide.



Miniature pathologists examine slides in the frozen section lab.

to look at all the quality-assurance cases. This pathologist will get the glass slides and the report and will write his comments in the computer system.” The system flags about 8 percent of each pathologist’s cases.

The quality-assurance pathologist then has 24 hours to review the case. If the two pathologists agree, great. If they don’t, they work together or with other colleagues to reach a consensus. Parwani is the senior author of a 2010 *American Journal of Clinical Pathology* paper on this system. In the paper, Parwani et al. report that minor disagreements (those with an academic interest to pathologists, but with no impact on patient care) were found in 2.2 percent of the reviewed cases and a mere .07 percent of cases resulted in a moderate disagreement (meaning the issue may be of some clinical importance but is highly unlikely to impact the patient).

Parwani thinks that the mere fact that a

case may be flagged for review causes pathologists to pay even more attention to their work, reducing errors proactively. “The number of amended reports has decreased,” he says, since the quality-assurance system has been in place. “I think this is really improving the quality of our work.”

Thyroid cancer is relatively rare; there are about 40,000 new cases diagnosed annually in the United States. On the other hand, thyroid nodules, a possible indicator of thyroid cancer, are very common. “The question is,” Pitt pathologist Yuri Nikiforov says, “Is the nodule benign or malignant?”

At most hospitals, the first step in thyroid cancer diagnosis is removing a population of thyroid cells by needle and testing them in a cytology lab. “This is a very accurate test,” Nikiforov says, “but it has intrinsic

limitations. It can only establish a conclusive diagnosis of whether [the nodule] is benign or malignant in about 70 percent of cases. In the remaining cases, cytologists have to say, ‘It’s indeterminate. That’s the best we can do.’”

There’s one way to hedge your bet here, and that’s to remove the thyroid lobe. Surgeons then send the excised lobe to a lab, where pathologists can make a definitive diagnosis after examining the tissue under a microscope.

If the pathologist determines the organ is cancer-free, that’s great, of course, but it’s not a free pass, as Pitt’s Marina Nikiforova explains:

“There [can be] a lot of complications if a thyroid is removed. The patient will need hormonal therapy, and the surgery itself is not benign; it can have many post-surgical complications,” including nerve injury and a loss of voice.

Of course it’s not welcome news if the nodule is malignant, for obvious reasons. And

that unpleasant news can get worse. Once a malignancy is diagnosed from an excised thyroid lobe (there are two of them), a surgeon has to go back in and get the other one. And this second surgery can present many of the same complications as the first.

Yuri Nikiforov and Marina Nikiforova are husband and wife. He is an MD/PhD professor of pathology who leads the Division of Molecular Anatomic Pathology, and she is an MD associate professor of pathology. Each is a codirector of the Molecular Anatomic Pathology Laboratory.

The Nikiforovs continue to refine and improve a test they've developed that has taken much of the guesswork out of thyroid cancer diagnosis and led to the reduction of unnecessary surgery.

"Basically, what this test does is look for a panel of seven known mutations" that indicate malignancy, Nikiforov says. "We take all these indeterminate cytologies and split them into benign and malignant."

Every thyroid patient at UPMC hospitals is given the test, and UPMC is the only hospital system in the country where it's available to all. While the molecular test isn't perfect—"The seven mutations we test for, they account for 75 percent of all thyroid cancers," Yuri Nikiforov says—it does allow

Reading that 2008 MRI report, amid all the information on her osteoarthritis, Matute learned that she had a small nodule on the right lobe of her thyroid. "Even my physician didn't see it at first," she says. "It said, 'Incidentally.' It said, 'Incidentally, there is a 2-centimeter nodule.'"

Although not a cause for panic, this is an "incidentally" that's surely a cause for concern.

Matute decided to go to UPMC Presbyterian for further tests—fine-needle aspiration (FNA) at first. Doctors would drive a needle into the nodule, excise some cells, and then test the cells to see if they were malignant or had a likelihood to become malignant. Yet, pathologists found, the doctors hadn't extracted quite enough cells for a reliable cytology test. However, there were enough thyroid cells for the test developed by the Nikiforovs.

The test revealed mutations—enough to suggest that there was an 85 percent chance that Matute's cells were malignant.

"I was given the option of going in for another FNA. But why should I have another needle stuck in my neck—it's painful—if I don't have to?" Matute says. "I decided to get surgery."

Her thyroid was removed in May 2008, and the post-op examination found that the

once the map of the human genome was first published in 2001. Having assembled the massive jigsaw puzzle that is the human genetic code, scientists went about tracing how mutations correlate with disease states.

The husband-and-wife pathologists spend a lot of time sifting through the human genome to find out why, among other things, certain cancers respond to treatment while others, which look the same under the microscope, do not.

This work has given them a unique perspective on the future of pathology and medicine.

"Pathology is where we make distinctive diagnoses," Yuri Nikiforov says. "But when we distinguish certain types of cancer, we'll say, 'This is colon cancer,' and treat it." But not all colon cancers are created equal. "Yes, this is colon cancer," he continues, "but there are different genes that these cancers possess and different drugs that act on different genes. We need to find out which cancers have which subabnormalities, and why these subabnormalities occur to let us better know how to treat this disease.

"For sure, cancer is a genetic disease," he continues. "It's considered that multiple genetic abnormalities need to cumulatively occur in order for a cancer to develop, and in some cases, we know zero of these mutations.

"Take colon cancer," he says. "Now we know of seven or eight mutations. Eventually, I think, we'll find about 20." One person's colon cancer could have eight of the 20 mutations, and another's may have a different eight of the 20. Others still can and will have different combinations of all these possible mutations. Knowing what the mutations are provides a robust set of therapeutic targets.

"So we develop drugs to treat each of the individual 20," Yuri Nikiforov says. "Then, depending on the combination of the mutations in a patient, we can find a very good combination of drugs. We'll have a general group of therapies for this disease, but depending on the specific genetic makeup, we'll be able to assemble a therapeutic regimen specific for the patient."

But the true age of personalized medicine is not quite upon us, Yuri Nikiforov notes:

"When the human genome project was finished, everyone said, 'In 10 years, we'll have personalized medicine.' That's not going to happen. That was overly optimistic. But, it will happen. It's only a matter of time and resources." ■

"What is pathology?... Now it's not only diagnostic, it's providing treatment strategies."

pathologists to assess whether three-quarters of those indeterminate cytology cases are benign or malignant. "We still need to find the mutations for the rest of those cancers," Yuri Nikiforov says.

The test helped Sandra Matute (we've changed her name), a retired physician in the North Hills of Pittsburgh, quickly make some decisions about her own health.

In March of 2008, Matute went to get an MRI. Her neck had been hurting, and she knew that she had osteoarthritis, so the MRI was a way to see what was going on with her bones.

Besides being trained as a physician, Matute also earned a PhD in public health from the University of Pittsburgh and was an adjunct faculty member here—so she was interested in reviewing her medical reports on her own. "I always get a copy of the reports for myself," she says.

nodule indeed was malignant. She recovered well, without complications. Today, Matute says, she's doing fine. So much so that she's about to embark on a trip to China.

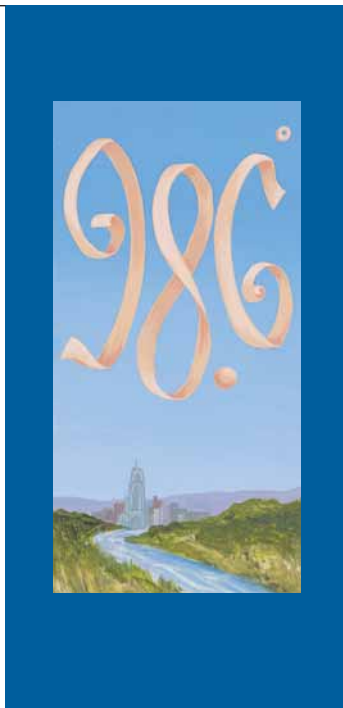
"This test saved me time, saved me pain, and got the cancer out," she says.

Improving diagnosis, presenting targets for therapy, cutting costs, saving lives, and making the information necessary to do all that available in an instant and at just about any location. None of this makes pathologists any more visible to patients. And really, fundamentally, it doesn't change the core of pathology; it adds to it.

"What is pathology? Well, it's still a diagnostic specialty," Yuri Nikiforov says. "But now it's not only diagnostic, it's providing treatment strategies."

The Nikiforovs are practitioners of molecular pathology, a field that came into its own

*People and programs
that keep the school
healthy and vibrant*



THE LONG GIFT

BY JOE MIKSCH

When World War II was afoot, J. Fraser Jackson was bunking in the Cathedral of Learning, doing a hitch in the Armed Services Training Program's medical unit, while earning his MD at the University of Pittsburgh School of Medicine.

After graduation and a three-year residency at West Penn Hospital, Jackson (MD '44) returned to his hometown of East Liverpool, Ohio, where he worked long days and full weeks for 52 years tending to the medical needs of his community.

Jackson retired from what he says was his one true calling in 2002. Only 350 people were at his retirement party, but that's only because there wasn't room in the hall for the others who wanted to honor him. He's the kind of man who, prior to hanging up the stethoscope, called each and every one of his patients to apologize for retiring.

As consistent as he was as a physician, he's been equally consistent in his dedication to his alma mater. Since 1970, Jackson and his wife, Irene, who trained as a nurse in Pittsburgh hospitals, have donated \$1,000 a year to the School of Medicine. It's the longest-tenured annual donation of such a significant sum in the School of Medicine's history.

Actually, Jackson suspects his giving may date back even further than four decades, but the records only go back so far.

"Having gone to Pitt medical school, I

owe them all I have for my career in medicine," the 91-year-old says. "The day I found out that you could give, and have that deducted from your income tax, was the day I decided to do it. And I'll keep giving until the day I die."

The annual gift, Jackson says, is obviously intended to help the School of Medicine. But it's more than that, he adds: It represents a regular opportunity to recall and thank the school and the people who gave him such a fulfilling career.

"I think of all the wonderful professors, all the doctors that I idolized, and what wonderful men they were," he says.

"There was Paul Steele, who was head of orthopaedics at the medical school and Allegheny General Hospital. He was the man who had the most effect on my life at that time." Jackson then rattled off more names of those who educated and molded him, like his own doctor, 1919 Pitt med graduate Albert Michaels; Davenport Hooker, Pitt professor of anatomy; and Pitt's James Heard, who was chief of medical services for several Pittsburgh hospitals in the first half of the 20th century.

"I thought of all of them as giants," Jackson says.

"I always wanted to be a family doctor—that was my ambition. These men inspired me, as did my uncles, who were physicians and surgeons, and my mother and sisters, who were all registered nurses."

Irene and J. Fraser Jackson will be honored in February at a special donor reception. The Jacksons will be singled out for their long-standing support.

Jackson says his gifts reflect his belief that the School of Medicine is "one of the best in North America. You have these Ivy League schools, and Pitt's right up there with them."

He adds that if he had it to do all over again, he'd most assuredly choose Pitt med. ■

COURTESY D. DESJARDINS



J. Fraser and Irene Jackson have given to the school's annual fund for at least 40 years.

BOOSTER SHOTS

When Sandy Gerson Snyder's mother, Sadie Gerson, died of colon cancer at age 51, the daughter mourned. Then she chose to act. In December 2009, Gerson Snyder made a donation to the University of Pittsburgh School of Medicine to establish the **Sadie Gerson Distinguished Scholar Award**. This fall, Pitt's **Robert Schoen**, an MD/MPH, became the award's first recipient. Schoen, a professor of medicine and epidemiology, has made a name for himself by seeking ways to detect colon cancer early in its course.

Schoen says he's honored to be the inaugural recipient of the Gerson award. "I see the award as recognition for the numerous researchers and research studies at Pitt that are seeking to ameliorate and mitigate the scourge of colorectal cancer."

Richard Raizman (MD '71) and his wife, **Dorothy** (a Pitt JD grad), were brought up in a tradition of giving. Before Richard's death from neuroendocrine cancer in 2009, the Raizmans established a scholarship fund at the medical school and contributed to the creation of Pitt's vaccine research laboratory. Richard also gave of himself, his wife notes, working in India with the Tibetan refugee community.

As Richard battled cancer, he was aided by what he and Dorothy felt were "remarkable" surgeons at UPMC, "whose unique combination of skill and humanism gave him precious years in the face of a relentless disease," Dorothy says. Before Richard's death, the Raizmans committed to establish a chair in the Department of Surgery to honor and acknowledge these men. —JM

FOR INFORMATION ON GIVING TO THE SCHOOL:

Deb Desjardins, 412-647-3792 or
ddeb@pmhsf.org



Paul Rogers lets students make mistakes in a safe setting. His critical care simulation course has the highest enrollment of any Pitt med elective.

PERCHANCE TO TEACH

INTERVIEW BY MAUREEN PASSMORE

As a medical educator, Paul Rogers isn't in a class by himself, but as the University of Pittsburgh's first recipient of the Robert J. Glaser Distinguished Teacher Award from the Alpha Omega Alpha medical honor society and the Association of American Medical Colleges, which selected the MD for this national award in 2008, he clearly stands apart.

Rogers, the Ake and Inger Grenvik Professor of Critical Care Medicine and Education, is also director of the School of Medicine's Multidisciplinary Critical Care Training Program, a founding member of its Academy of Master Educators, vice president of the VA Pittsburgh Healthcare System, and director of the surgical care unit at the Veterans Affairs Medical Center. His critical care simulation course has the highest enrollment of any elective course in the School of Medicine.

Here he reflects on what he does so well.

Where did your path in medical school education begin?

I had no idea that education would end up being such a large part of my job. When I started here in 1987, the chair of our department asked if I would develop a fourth-year elective in critical care medicine—one didn't exist at that time. I had no idea how to go about teaching. I learned from several of my mentors here how to create a curriculum so that it fit adult learners and wasn't a typical didactic session. I sort of lucked into this role because, back in the early '90s, the anesthesia department got [Pitt's] first human simulator, and I thought it would be a great tool to use with teaching.

We could create rare, life-threatening situations that students could go perhaps their whole careers in medical school and never see until they're expected to manage such situations as interns. There's a difference between sitting in a classroom, taking notes, and watching a PowerPoint presentation and actually being in a simulated crisis situation where the mannequin can reproduce physiology so that, if you're doing the right management, it will respond appropriately. When I first started, I was teaching maybe 20 to 25 students a year, and now I teach 120 or more per year. We cover things from patients with critical illnesses to more common cases, and the students learn communication skills

and motor skills with various pieces of equipment. It's very lifelike. The more they practice, the more confident they are in any situation, and that's what medical education should be about—training in a manner that's safe for our patients and that doesn't allow students to get into trouble. I just wish we'd had it when I was in my training.

What do you think makes you successful as an educator?

I just remember how I wanted to be treated as a student, and I try to hang on to those values of respecting the students, respecting their time, wanting to see them succeed, and not wanting them to fail at all. I can remember some of the things that happened to me, and I want to make sure these students don't end up in the same kind of situations. Most of the scenarios we simulate in class happened to me at some point in my training.

What are some of the challenges facing medical education today?

One is finding the time to be able to teach. Actually, the University of Pittsburgh has some unique opportunities that have allowed me to be a successful teacher. The dean's educational credit units reimburse departments for the hours their faculty members teach. So, I get freed up for an hour a day. Another thing that is a challenge, but that Pitt does well, is recognizing and promoting people based on teaching effectiveness. When I started here, people told me that I'd never be promoted if I wanted to teach. Now, with the educational track, if you create curricula and have a means of evaluating their effectiveness, you can be recognized for that here. They've created the Academy of Master Educators to recognize good teachers. I gave a talk at the Society of Critical Care Medicine [in 2009] on the importance of valuing the teacher in the academic setting, and most people who spoke with me did not have the same situation I have. I was hearing more people speak of teaching out of obligation at the end of their shifts; it's not woven into the fabric of their day. Not everyone is so lucky.

Have medical students changed since you first started teaching?

I don't think so. They all have a great fear that suddenly, at the end of the fourth year, they won't know all there is to know. And I tell them that's okay; they'll be learning the rest of their careers. The only thing they have to remember is that there are people around them who know more than they do, and they should feel free to go to those people and ask for guidance.

Do any particular teaching moments stand out for you?

I hear a lot from former students that they've found themselves in real-life situations where none of the other interns knew what to do and hadn't experienced anything like it before, but they did because we had gone over it in the simulations. I'm very fortunate because I don't have to convince students that they need to learn these basic management skills. I know that it works because I get plenty of e-mails from people saying how they had to deal with someone who had, say, respiratory distress, and all the stuff we talked about in class came back because we had practiced it so many times.

What are your goals now as an educator?

Well, I used to say that I'd retire when I was 50—but 50 got here in a hurry! What I would like to do, and have had opportunities to do, is mentor junior faculty so that when I do retire, this method of teaching continues. It's a style that anybody who wants to put time into being an educator can do. They just have to be given the resources and opportunity. I have a pact with students not to embarrass them; my goal is to let them make mistakes in an environment where it doesn't hurt anyone. They tell me that they want to see the consequences of their decision-making played out, so they can see what happens if they don't manage patients' care correctly.

So, I tell them on day one that this is their opportunity to show me what they don't know, and they need to feel comfortable getting up and making mistakes because it's a much better place to make a mistake than in the real world.

If you think about being able to teach one person to do something better than you did when you were an intern, it is a rare opportunity. The chance to teach 100 or more people to do something better is an honor. ■



CLASS NOTES

'60s

Three months into his freshman year at Cornell University, **Maurice Mahoney** (MD '62) realized his intended major, chemical engineering, was a mismatch. "I wanted to be able to shift directions, shift emphasis," he says. So, he pursued a career in academic medicine. Now in his 40th year on the faculty at the Yale School of Medicine, Mahoney is professor of genetics, pediatrics, and obstetrics and gynecology, director of clinical affairs, and executive chair of the school's human research protection program (which allowed him to dust off his JD—yes, in the '90s, he studied law, too). Although his responsibilities are now "more diverse than ever," Mahoney still finds time to run with another crowd: triathletes. He says he prefers triathlons to his old hobby of half marathons. "I suppose because on the bike, you get to just sit for a while," he says.

'70s

At the bedside of a critically ill patient, every syllable and pause has gravity. As a specialist in hematology and oncology, **Eric Kraut** (MD '76) has become a firm believer in the "tremendous power" of language. Ten years ago, he published in *The Oncologist* "At the Edge of Suffering," a poem about his struggle to find the right words for a patient, a 33-year-old woman with leukemia. In March 2010, Kraut was honored with the Earl N. Metz Distinguished Physician Award by Ohio State University Medical Center's Department of Internal Medicine, where he is a professor and director of benign hematology. Kraut relished writing his speech for the ceremony. "It was a great opportunity to reflect not only on the impact I've

had on other people, but on the impact others have had on me." In his talk, he tipped his hat to his mentors, including Arthur Sagone (MD '63), a former Ohio State professor of medicine.

'80s

At age 17, **Patric McPoland** (MD '80) hostelized across Europe. After his first year at Pitt med, he hitchhiked to California. And in the '90s, he served in the Navy as a commander in Operation Desert Storm. This July, McPoland—who's now a civilian dermatologist based in West Palm Beach—set out on another sea excursion. He provided general medical care in Indonesia on the USNS *Mercy* as part of Pacific Partnership 2010, an annual humanitarian-assistance deployment to Southeast Asia and the Western Pacific. On the *Mercy*—which served as a disaster-relief training center for physicians and a floating hospital for patients in Indonesia, Vietnam, Cambodia, and Timor-Leste—McPoland and fellow Pitt med alums **Alan Lim** (MD '91), **Scott Flinn** (MD '88), and **Arturo Torres** (MD '06) were part of a diverse, international contingent of specialists delivering treatment to regions lacking basic medical care. "It was as intensely colorful as any adventure I've ever had," McPoland says.

As a pediatrics resident at Children's Hospital more than 30 years ago, **Clydetta Powell** (Pediatrics Resident '79, Child Neurology Fellow '82) first used a helicopter to reach sick newborns in the more remote areas surrounding Pittsburgh. This January, Powell—now a medical officer for infectious disease in the U.S. Agency for International Development (USAID)—braved the skies once again, this time transporting trauma victims over Haiti's earthquake-ravaged terrain. As the sole pediatric neurologist on the USNS *Comfort's* relief mission from January to mid-February, Powell worked 19-hour days, treating earthquake-related neurological injuries (such as spinal cord trauma) as well as unrelated conditions



Powell (middle) with colleagues during the USNS *Comfort's* relief mission to Haiti early in 2010.

(including tuberculosis). In May, she and fellow *Comfort* neurologists published a paper in *The Lancet Neurology* outlining the importance of neurology and its subspecialties in disaster response.

As a doctor in pediatrics, **Scott Serbin** (MD '82) became dissatisfied with the pace of his job, "running, running all the time." But instead of quitting his practice, he transformed it. Five years ago, Serbin opened a pediatric concierge practice. Appointments can be scheduled nearly any time parents request, and Serbin only makes house calls. Serbin says he "didn't suddenly become a better doctor by switching to this style of medicine." But he did finally have the time to wait for a sick child to stop crying—an advantage that's helped him better connect with his patients.

John McConaghy (MD '89), now a professor of family medicine at Ohio State University, has won his department's teacher of the year award six years in a row. The secret to good teaching, he says, is simple: Love what you do. "It's very rewarding watching the young students of medicine grow and mature. We often think of them as our children."

In addition to his performing teaching and clinical duties, he chairs quality and patient safety for University Hospitals East—and keeps up with his actual children. His two teenagers play three sports each, and between all those games, "Dr. Mac" squeezes in scoutmaster duties for his son's Boy Scouts troop. "You've got to enjoy it while it lasts," he says. "You're only young once."

'90s

In July, **Richard Pan** (MD '91), associate professor of pediatrics at UC Davis Children's Hospital, received the 2010 Physician Humanitarian Award from the Medical Board of California for his dedication to caring for underserved patients in the Sacramento area. Pan is founder of Communities and Health Professionals Together, which connects resident physicians with disadvantaged communities, and cofounder of Healthy Kids Healthy Future, which has provided health, dental, and vision coverage to more than 65,000 California kids.

Pan's experience has taught him that there's a lot more to health than health care, he says. For example, he can tell patients and their families to eat healthfully, but what

if there are no nearby grocery stores with fresh fruits and vegetables? “If my goal is to improve health, I need to understand what drives health,” he says. In November, Pan, a Democrat, won a seat in the 5th Assembly District of California.

'00s

In May, **Michelle Clayton** (MD '00), a child abuse pediatrician at Children's Hospital of the King's Daughters in Norfolk, Va., was honored as the 2010 Influential Woman of the Year by Virginia Lawyers Media. The award recognizes the outstanding efforts of women in all fields who are making notable contributions to their chosen professions, their communities, and society at large.

Having performed hundreds of consultations with police, social service officials, and prosecutors, Clayton instructs physicians and investigators on injury patterns and other aspects of abuse assessments. Child abuse is more common than many believe, she says. At her hospital alone, the staff sees more than 1,000 child abuse cases a year—and, of course, not every abuse case gets reported. Yet most abused children Clayton sees don't seem to need any more emotional comforting than other patients. “Children always amaze me with their strength and resilience,” she says. “They're a joy to work with.”

Throughout his otolaryngology residency with the University of Cincinnati, **Gordon Sun** (MD '06) has noticed that the head-and-neck-cancer patients he sees in the VA hospital seem to be diagnosed later than his other patients with the same disease, making treatment a much tougher road. Many of his colleagues have noticed the pattern, too, but at this point, “It's purely observational,” notes Sun, who is now chief resident. “No one has ever studied this systematically.”

Starting next July, Sun will try to find out what's happening with these patients as a University of Michigan Clinical Scholar. For his two-year fellowship, which is sponsored by the Robert Wood Johnson Foundation, Sun will compare incidence, staging, and outcomes of U.S. veterans to those of nonveterans; if there's a disparity, he'll also investigate possible contributing factors. Sun hopes his project will inform policy. “Perhaps outreach and treatment programs can be developed to better accommodate the veteran population,” he says.

—Keith Gillogly, Ben Korman, and Elaine Vitone



ABOVE: Clayton. BELOW: Sun



THE WAY WE ARE CLASS OF '56

In the days of the draft, some Class of '56ers figured they'd fare better by enlisting. **Gerald Johnston** was commissioned in the Army his last year at Pitt and later served as chief of medicine in Uijeongbu, South Korea, setting for the 1970s sitcom *M*A*S*H*. When he returned to the States, Johnston went on to head Army nuclear-medicine programs in Honolulu and San Francisco and later at the National Institutes of Health. He then spent the last 18 years of his career at the University of Maryland before retiring in 2009.

Recently, Johnston served with Global Medicine in Tasmania. Service seems to come naturally to docs of his ilk. “People who work in medicine in the military for a dollar a day are the ones who have a calling rather than an eye on the bank account,” he says.

Bob Dille went the Air Force route. His research on some of the earliest prolonged B-52 missions won him a Guggenheim Fellowship to Harvard School of Public Health. While in Boston, he was tapped to direct the new Civil Aeromedical Research Institute in Oklahoma City. He accepted and stayed for 22 years. Dille has lectured on six continents on the evolution of aviation medicine and physiology. He wrote chapters for three editions of *Fundamentals of Aerospace Medicine*, the field's flagship textbook, as well as 240-some-odd articles.

Dille finished his military career in the National Guard, and then when he was 60, his provost marshal sent him to jail ... as medical director of Oklahoma's Department of Corrections. Dille later became a surveyor for the national commissioner on correctional health care. He retired five years ago.

Like Dille, **Philip Migliore** served as a flight surgeon. He was stationed in San Antonio for part of his residency, then finished in Pittsburgh before returning to Texas for a pathology fellowship at MD Anderson Hospital in Houston. He then moved to Baylor College of Medicine and Methodist Hospital, where he stayed for 30 years. During that time, he was chief of clinical chemistry for the Methodist Hospital Labs and served as research director of Baylor's Moran Foundation for Research in Pathology. Migliore retired in 2000.

Nineteen out of 89 members of the Class of '56 went into pathology—an unusually high rate for this unsung specialty. Migliore chalks that up to Frank Dixon, who chaired Pitt's pathology department from 1951–1961 and served up plenty of “real-world pathology,” Migliore recalls. “During our Pathology course, autopsy call was required, and we spent many hours studying buckets of hearts, livers, and other organs, diseased or otherwise. This approach to the teaching of pathology was rather unique and is no longer practiced, as far as I know.”

Fellow pathologist **Robert E. Lee** taught at Pitt's School of Medicine and practiced at Presby for more than 55 years before retiring from clinical work. His research is ongoing. Since 1961 he has studied Gaucher's disease and has published hundreds of articles on the subject.

Lee is the historian for the Medical Alumni Association and the person for whom of the School of Medicine's student award for excellence in anatomic pathology is named.

Cyril Wecht, as many are aware, also went into pathology. After completing his MD, he received his JD from Pitt's School of Law in 1962. He later became coroner of Allegheny County and consulted on such high-profile forensic cases as John F. Kennedy, Elvis Presley, and JonBenét Ramsey, among many others.

Wecht has written dozens of books and performed thousands of autopsies. But what he's most proud of is the work he has done as an expert witness in civil lawsuits on behalf of miners' families facing loss wreaked by black lung disease, he says. —EV



Johnston



Dille



Migliore



Lee



Wecht



Detre

THOMAS P. DETRE

MAY 17, 1924–OCT. 9, 2010

In the early 1970s, when Thomas Detre announced that he was leaving a tenured position at Yale to work for Pitt, a colleague scoffed, saying that planes didn't bother to land in Pittsburgh. Detre replied, "They will land when *we* land." True to his word, Detre led the University of Pittsburgh to international prominence as a research university and became a key architect of UPMC.

Detre arrived in Pittsburgh in 1973 to chair Pitt's Department of Psychiatry and to direct the Western Psychiatric Institute and Clinic (WPIC). He initiated an innovative new funding cycle, investing profits from the clinic in patient care, faculty recruitment, and interdisciplinary research, then applying research results to clinical advances. In recruiting, he was so successful that he was known as the coach of the "Pittsburgh Stealers," taking the department from 36 members in 1974 to nearly 150 in 1982. His approach made Pitt's psychiatry department one of the top three recipients of National Institutes of Health (NIH) funding within a decade.

University administrators called on him to serve as the first associate senior vice chancellor for the health sciences—and then, as senior vice chancellor, a position he held until 1998. Under his direction, Pitt ranked 10th in NIH funding in 1997; the University has steadily climbed the rankings within this elite group since then.

"His philosophy of integrating research with the practice of medicine brought brilliant clinician-researchers to the University and altered its scientific landscape," says dean of Pitt's School of Medicine, Arthur S. Levine, who succeeded Detre as senior vice chancellor for the health sciences.

Detre also led what was known as the School of Medicine's Medical and Health Care Division as it evolved into UPMC, which he presided over from 1990 to 1992, and later served as an executive vice president and medical director of international programs for UPMC.

Detre's wife of more than 50 years, Distinguished Professor of Epidemiology in Pitt's Graduate School of Public Health Katherine Detre, who died in 2006, was also a leader in her field. Thomas Detre later married Ellen Ormond, a psychologist at the University of Pittsburgh Cancer Institute.

—Kelsey Ballance

MERRILL J. EGORIN

MAY 25, 1948–AUG. 7, 2010

Merrill J. Egorin, an internationally known researcher and codirector of the Clinical Pharmacology Analytical Facility at the University of Pittsburgh Cancer Institute, was "never too big for small data," says Jan Beumer, his successor at UPCI. "He was all over the data, always asking really basic questions."

Egorin, 62, died five years after he was diagnosed with multiple myeloma. A dedicated professor of medicine and pharmacology, he even used his own cancer treatment as a teaching model for his students. An expert in cancer pharmacology, he accrued a slew of honors, including the 2003 Elliott Osserman Award for Distinguished Service in support of Cancer Research, the 2006 Joseph H. Burchenal Clinical Research Award, and the 2009 American Society of Clinical Oncology Translational Research Professorship. He held memberships or fellowships in five American medical societies, as well as editorship of *Cancer Chemotherapy and Pharmacology*.

Egorin relished his relationships. During lunch, he Skyped with his two children and their families. In his work, he strove to help junior colleagues network with scientific superstars, arrange training opportunities for other doctors, and ensure recognition for everyone, including his technicians.

"If you look at the impact he had on other people, that was what he always focused on. You realize how much he helped us," Beumer says. —KB



Egorin

KENNETH SCOTT MCCARTY JR.

FEB. 11, 1948–OCT. 15, 2010

As a young pathologist at Duke University, Kenneth McCarty collaborated with his father, Kenneth Sr., a biochemist, to research the hormonal aspects and treatment of breast disease. (The intense young man had graduated from college at 18.)

At the University of Pittsburgh School of Medicine, where McCarty alighted in 1993 as a professor of pathology and of medicine, he designed a tool to help physicians make decisions about prostate cancer treatment according to a patient's preferences. While he was the school's assistant dean of graduate medical education, he pursued a passion of his, troubleshooting such issues as resident work hours.

McCarty, an MD/PhD, became the chief editorial advisor of this magazine in 2002, offering careful reads and candid, heartfelt commentary and counsel to keep *Pitt Med* relevant to readers. His love of language and frequent witticisms helped make quarterly advisory board meetings as enjoyable as they were productive.

McCarty's wife of 26 years, Berrylin Ferguson, is also an MD. She recalls that her husband's penchant for finding solutions to problems surfaced very early in their relationship.

"When we first started dating, I had a sailboat that I didn't know how to sail," Ferguson says. This fact was made evident when she capsized the vessel with her future husband on board. "So, he ended up taking sailing classes and became an expert sailor. I think he could have become an expert in anything."

—Joe Miksch



McCarty

IN MEMORIAM

'40s

JOHN P. BRANDT
MAY 10, 2009
MD '43B

JOHN F. FULTON
SEPT. 8, 2010
MD '45

JOHN L. HAPPEL SR.
APRIL 22, 2010
MD '48

JOHN A. ZELNIK JR.
AUG. 18, 2010
MD '48

'50s

LEONARD SCHWARTZ
MAY 11, 2010
MD '52

HERBERT D. MILLER
JULY 15, 2010
MD '54

'70s

DALE A. KUREMSKY
JUNE 27, 2010
MD '70

'80s

GARY PURDUE
OCT. 3, 2010
RES '81

ANDREW EGOL
AUG. 19, 2010
FEL '82

COACH IN SCRUBS ROBERT HIGGINS

BY REID R. FRAZIER

The organ-sharing system in the United States decides which of the 100,000 patients in need of a transplant will get one when an organ becomes available. There aren't enough organs for everyone—each year, 10,000 patients die while on the waiting list—and deciding how best to allocate organs is a difficult task. Should the organ go to the sickest, those on the list the longest, or those who stand to live the longest?

Transplant surgeons disagree on the answer, often vehemently. Getting a group of them to approve a set of guidelines is a little like trying to dodge a herd of linebackers.

Maybe that's why Robert Higgins volunteered for the job. Higgins (Res '90), who served as president of the Organ Procurement and Transplant Network (OPTN) and United Network for Organ Sharing (UNOS) for 2008–09, has presided over some of the more heated debates over organ allocation. A former high school all-American football player who played running back for Dartmouth during the '80s, he's no stranger to a scrum.

Higgins, a Master of Science in Health Administration as well as an MD, fell under the spell of transplant medicine while a medical student at Yale University. He chose to specialize in cardiothoracic transplant—"High risk, high reward," he says. He came to Pitt for residency to learn from its legendary faculty in the '80s and '90s, including Thomas E. Starzl, Henry Bahnson, Bartley Griffith (Fel '78, Res '81), and

Robert Hardesty. In the past decade and a half, Higgins has built up several heart and lung transplant programs around the country. He recently was tapped by Ohio State to direct its Comprehensive Transplant Center, where he is also chief of the medical school's Division of Cardiac Surgery and holds the John H. and Mildred C. Lumley Medical Research Chair.

Throughout his career, Higgins has prided himself on getting everyone in a transplant unit—surgeons, anesthesiologists, social workers, and so on—to work in sync. "I enjoy the challenge of making complex, often complicated environments, work more effectively. I love the idea of building teams." This trait earned Higgins the nickname "Coach" from the nurses at Rush University Medical Center in Chicago. Higgins' organizational prowess recommended

him for leadership on the boards of OPTN and UNOS, says Walter Graham, the executive director of the latter group. One of Higgins' first tasks as UNOS president was to preside over a conference for kidney allocation, one of the field's most contentious issues. Kidneys are by far the most sought-after organ—there is a waiting list of 80,000 for fewer than 10,000 kidneys. Priority has traditionally operated on a "first-come, first-served" basis, but the sickest patients might not show up on the list until they are in the late stages of their disease.

Blacks are much less likely than Whites to get a kidney transplant. "They may not have the resources, they may not have access to sophisticated treatments. In general they're not as well-positioned as others [on the list]," says Higgins. He worked to bring the needs of underserved patients to the attention of the transplant professionals at the kidney-allocation conference. In the end, the committee drafted new rules that gave priority to those who'd been on dialysis the longest, a marker for how long they had been sick. Graham says Higgins shepherded the group through "complex issues that have a lot of emotion behind them."

Jumping into the organ-allocation debate seemed only natural to Higgins.

"You can either be someone on the sidelines—offer an opinion, but never get in the game—" Higgins says, "or you can get in the game and have an impact. I prefer to not be on the sidelines. I'd rather be in the game." ■

THE OHIO STATE UNIVERSITY MEDICAL CENTER



Higgins presided over OPTN and UNOS, the organizations that manage patient waiting lists and donor organ allocations in the United States.

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GOOD SPORTS

Med students have a reputation for being competitive, and not just about exams.

This October, Pitt med first- and second-year students took a study break for some serious rivalry—the annual flag-football gridiron standoff, aka the “Turkey Bowl.” For four years now, each of the two classes has sent a men’s team and a women’s team to pit their grit against the other year’s teams. “It’s really, really competitive,” says second-year student and co-organizer Megan Wolf. “It’s always up for grabs.”

Although nothing more than pride is at stake, the Cost Center field is always lined with other students yelling support. (Upperclassmen refs keep everything under control.)

The event is organized by ProActive!, a student group that promotes balanced lifestyles. In addition to getting some fresh air, the Turkey Bowl lets students get to know some fresh faces.

But mostly, the Turkey Bowl is just old-fashioned, breathless, mud-in-your-cleats fun. Last year, hungry players got together afterward to gobble at Oakland restaurants—the second-years were notably absent, however. They headed home to—guess what—study for an exam. —Kelsey Ballance

PHOTOGRAPHY: VISHAL S. PARIKH (CLASS OF 2013)

C A L E N D A R

OF SPECIAL INTEREST TO ALUMNI AND FRIENDS

For information on an event,
unless otherwise noted, contact
the Medical Alumni Association:
1-877-MED-ALUM, 412-648-9090,
or medalum@medschool.pitt.edu.
Or go to www.maa.pitt.edu.

HEALTH SCIENCES ALUMNI RECEPTION NOVEMBER 9

6 p.m.
"Strength Through Partnership:
How the University of Pittsburgh Is
Serving Our Military and Beyond"
Soldiers & Sailors Military Museum
& Memorial
Pittsburgh
For information:
Pat Carver
412-647-5307
cpat@pitt.edu

2011 WINTER ACADEMY
JANUARY 28
Ritz-Carlton
Naples, Fla.
For information:
Pat Carver
412-647-5307
cpat@pitt.edu
www.winteracademy.pitt.edu

SOUTHWEST HEALTH SCIENCES ALUMNI RECEPTION

APRIL 2
Phoenix, Ariz.
For information:
Pat Carver
412-647-5307
cpat@pitt.edu

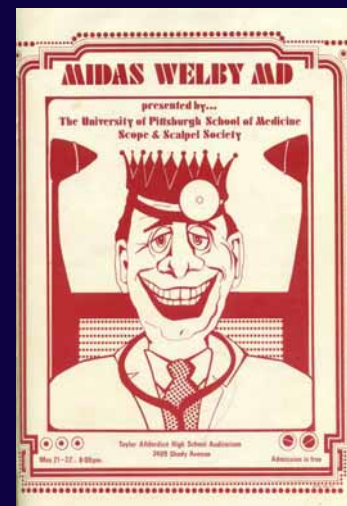
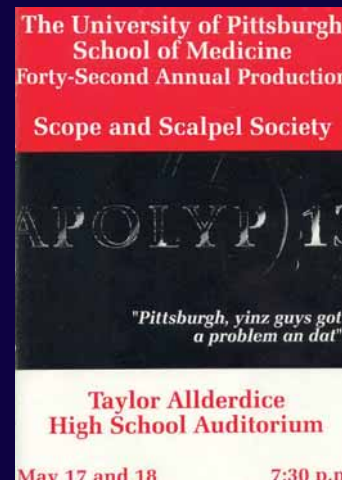
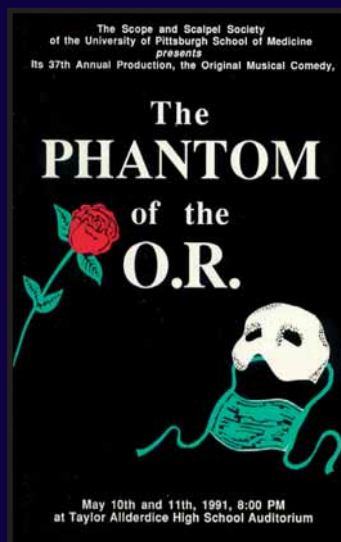
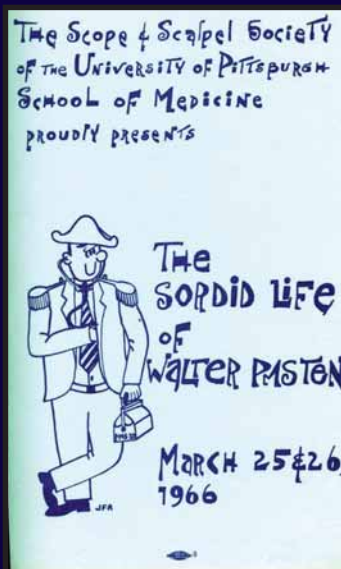
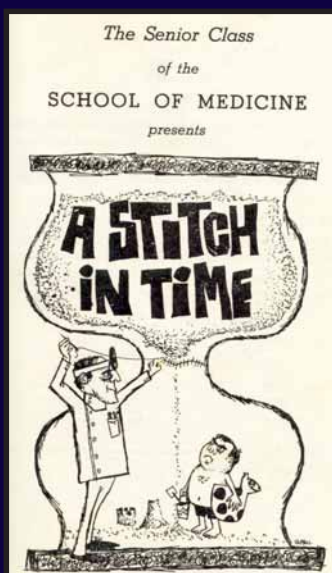
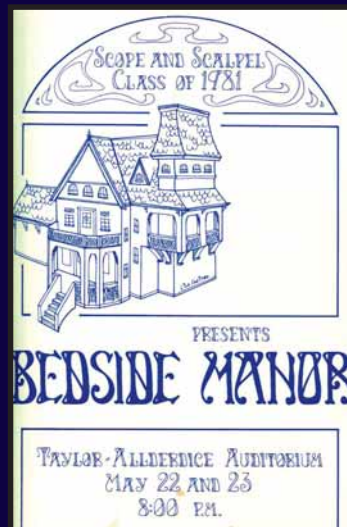
MEDICAL ALUMNI WEEKEND 2011 MAY 20-23

Reunion Classes:

2001	1996
1991	1986
1981	1976
1971	1966
1961	1956

UPCOMING HEALTH SCIENCES ALUMNI RECEPTIONS:

DATES TBA
Cleveland, Ohio
West Palm Beach, Fla.
Los Angeles, Calif.
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FROM TOP LEFT:

1956—*Spring Tonic*
1961—*A Stitch in Time*
1966—*The Sordid Life of Walter PMSTEN*
1971—*C*A*S*H*
1976—*Midas Welby, MD*
1981—*Bedside Manor*
1986—*Miami Slice*
1991—*Phantom of the O.R.*
1996—*Apolyp 13*
2001—*The Sixth Stench*

WELCOME BACK, CUTTER

From the original 1955 production, *PMS IV*, to last year's trip down the pothole, *Cialis's Wonderlands*, the Scope & Scalpel all-student revue has been a farce to be reckoned with. Catch the 57th annual show during Medical Alumni Weekend 2011—and reconnect with the cast of characters from your own Pitt med days.

Medical Alumni Weekend

May 20–23, 2011

For a list of classes having reunions in the spring, turn to our calendar on the other side of this page.

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