UNIVERSITY OF PITTSBURGH SCHOOL OF MEDICINE | SPRING 2008

PITTMED



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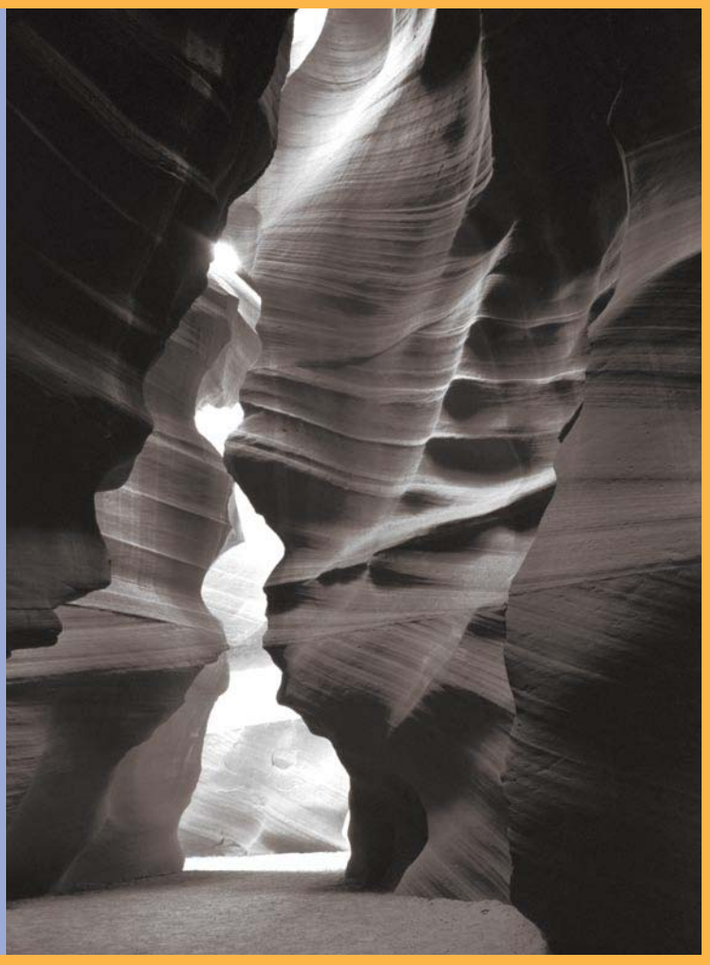
DO FREE LUNCHES INFLUENCE WHAT DOCTORS PRESCRIBE?



WHEN THE DESERT BLOOMS, SOME OF US ARE STILL SHOVELING SNOW.

Whether you live in the neighborhood or just want to try your hand at being a snowbird in Arizona, you are welcome at Winter Academy West. Join Pitt alumni from the schools of the health sciences plus friends of the University for exclusive updates from Pitt's top researchers in the fields of oncology, tissue engineering, and diabetes.

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PRIMATE BUSINESS

I was excited to see the photo of Dr. Fu, Pitt chair of orthopaedic surgery, (Fall 2007) operating on a monkey's knee at the Pittsburgh Zoo. It looks similar to a photo from November 2005 (at left) when I was consulted to perform a bone marrow aspirate on Brass, a 16-year-old red-ruffed lemur who was ill. In addition, Dr. Marian Michaels (Fel '92), associate professor of pediatrics, (the main zoo contact) has been consulted multiple times regarding primates with infections, and Dr. Geoff Kurland, professor of pediatrics, performed a bronchoscopy on a sea lion at the zoo.



Thanks for the great photo.

Peter Shaw, MD
Assistant Professor of Pediatrics
University of Pittsburgh
Children's Hospital of Pittsburgh of UPMC

LOEBER LORE

I very much enjoyed reading the Fall 2007 issue of *Pitt Med*; congrats on such a consistently fine publication. I was especially interested in the article on the Loebers, as I have worked with this dynamic couple. It was a pleasure to see their creative pursuits highlighted alongside their significant professional contributions.

Barbara Strelec, MSL, RN
University of Pittsburgh

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

Pitt Med
400 Craig Hall
University of Pittsburgh
Pittsburgh, PA 15260
Phone: 412-624-4152
Fax: 412-624-1021
E-mail: medmag@pitt.edu
http://pittmed.health.pitt.edu

For address corrections:

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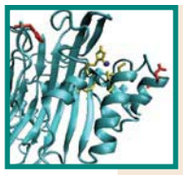
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(J. Miksch)

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VOL. 10, ISSUE 1



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CONTRIBUTORS

ERICA LLOYD ["Elephantiasis Worm Genome Sequenced" and other stories] has been at the helm of *Pitt Med* since its inception in 1999. In 2007, she took a leave of absence to try something different.

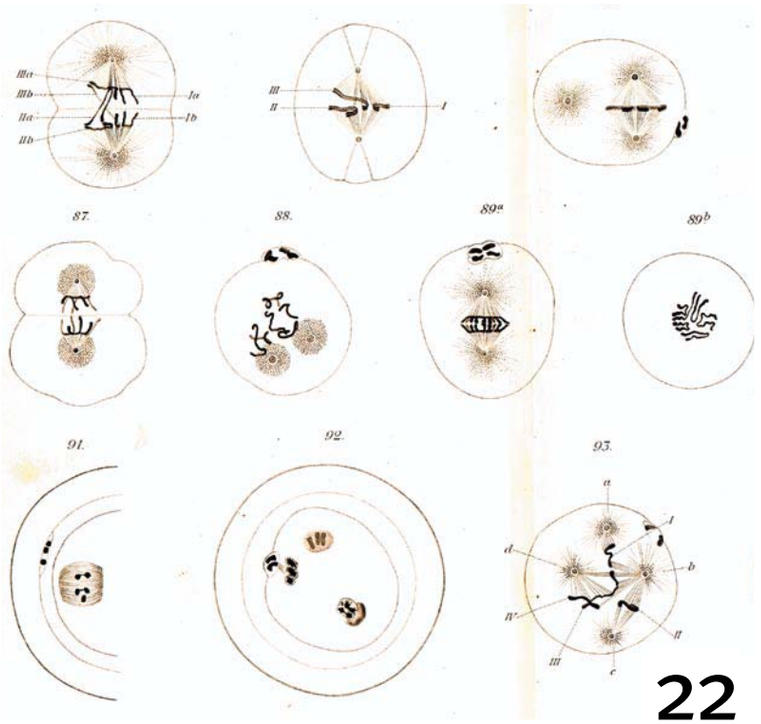
Accompanying an international team of scientists and engineers, Lloyd went to the high arctic for six weeks to report on a NASA/National Science Foundation-funded expedition for *Wired*. Aboard the Swedish icebreaker *Oden*, Lloyd hung around with scientists using free-swimming robots to explore an uncharted bit of ocean floor called the Gakkel Ridge. She also did a bit of skeet shooting, saw polar bears, didn't see the sun set, and marveled at how long *Oden*'s mates could make produce last.

Her piece, published in January, was the basis for a segment on the PBS TV program *Wired Science*. Under Lloyd's editorship, *Pitt Med* has received more than 40 awards for writing, design, and overall quality. She lives in Santa Cruz, Calif., with her husband, Tim, and dog, Zafod.

According to DAVID POHL ["Take-out Medicine"], the best aspect of the illustration process is the initial creative spark, or "turning that idea into the first vision," as he puts it. Pohl works in digital mixed media, enhancing his vibrant images by scanning in textures from his paintings and studio pieces. He creates illustrations for print, web, and TV. When seeking inspiration for his work, Pohl often pages through old encyclopedias stacked in his studio, including a Turkish set from the 1930s. In addition to providing artwork for publications like *The New York Times* and the *Boston Globe*, Pohl teaches installation art to high school students in "Factory 14S," a program at the the Mattress Factory museum.

COVER

Maybe there really is no such thing as a free lunch. (Cover: Chris Everard/Getty Images © 2008.)



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BY CHUCK STARESINIC

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PUBLISHER
Arthur S. Levine, MD

EDITOR IN CHIEF
Erica Lloyd

ART DIRECTOR
Elena Gialamas Cerri

SENIOR EDITOR
Chuck Staresinic

ASSOCIATE EDITOR
Joe Miksch

PRODUCTION COORDINATOR
Chuck Dinsmore

STAFF CONTRIBUTORS
Sarah Evans, Meaghan Dorff, Emily Karam

OBITUARIES CONTRIBUTOR
Macy Levine, MD '43

CIRCULATION MANAGER
Crystal Kubic

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

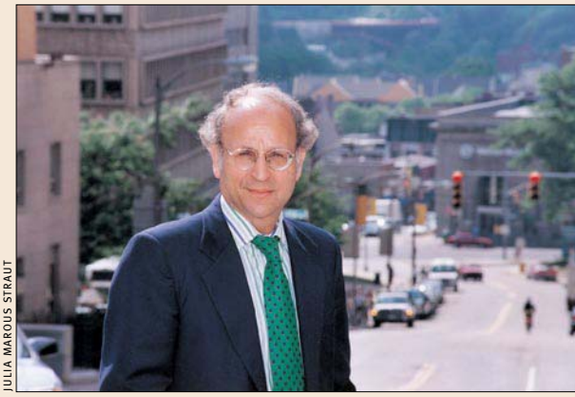
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JULIA MAROUS STRAUT

I would rather discover a single causal connection than win the throne of Persia.
—Democritus

Imagine you have no idea how a stereo works, but you want to understand it. If you took a knob off the receiver and studied it, that might tell you something—about how volume changes, perhaps. It would not explain, however, why beautiful music comes out of the speakers.

It can be a bit like that when studying certain aspects of human biology, Peter Strick noted recently. Peter, a prominent neurobiologist, codirects the University of Pittsburgh and Carnegie Mellon University's Center for the Neural Basis of Cognition. He now also heads our new Institute for Systems Neuroscience. His point about the stereo is that biologists have been focused on studying synapses, cell organelles, genes, proteins, and the like—essentially, small component parts—without necessarily being able to put together how these elements fully interrelate and interact.

Which is not to say that studying individual elements hasn't been valuable. We've clearly learned a lot from analyzing parts. But if we want to understand, for example, behavior, we'll need to understand how neurons in a given neural pathway cooperate and how they are linked together to form circuits and networks. We're learning, not surprisingly, that these systems almost always play roles as important as the functions of individual parts.

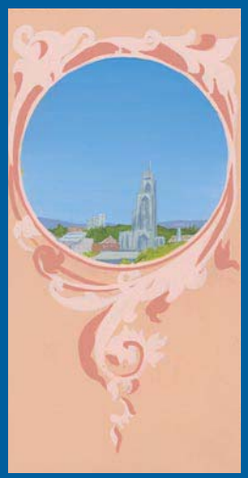
Great discoveries often come hand in hand with new methodologies and technical approaches. In neuroscience, scientists have developed the ability to monitor populations of neurons and their interconnections at levels unheard of 15 years ago. Aaron Batista, a new recruit at the institute, is able to monitor the activities of a hundred neurons at once. He's hoping his work will one day help patients use their own thoughts to control prosthetic limbs.

And no cortical region acts in isolation. By using viruses and other tools, Peter's own lab has managed to trace neural interactions related to behavior to a few orders of connection. He has found that circuits and regions within our brain interact with other circuits and regions with a complexity that would make the entanglements in a Tolstoy narrative seem simplistic.

Another new recruit, Rob Turner, is exploring what happens when these complex interactions go awry—like the chain of dysfunctions that take place in Parkinson's disease. Rob is working with a new model of the disease that allows him to investigate why deep brain stimulation gives some patients relief.

As they delve into these and other secrets of the nervous system, Peter, Rob, Aaron, and their colleagues here and elsewhere are helping to write the next chapter of the history of neuroscience. Nothing fascinates us more than how our brains work—what's hardwired, what's learned, and why even the most powerful supercomputer must still be instructed by us. Virginia Woolf once wrote, "My own brain is to me the most unaccountable of machinery—always buzzing, humming, soaring roaring diving, and then buried in mud. And why? What's this passion for?"

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



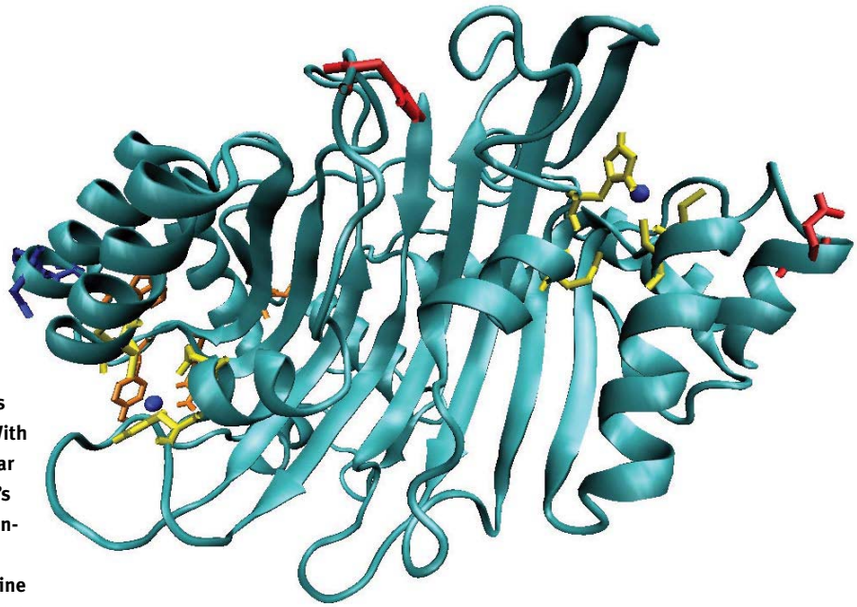
Devoted to noteworthy happenings

at the medical school

Understanding HIV

Scientists have a fairly good understanding of how HIV attaches to its host and gains entry into cells, says Angela Gronenborn, a PhD and the UPMC Rosalind Franklin Professor and chair of the Department of Structural Biology at the University of Pittsburgh.

However, what happens on a molecular and structural level when the virus invades remains a mystery. Sorting that out could lead to new drug targets. With this in mind, the National Institutes of Health bestowed a $16 million, five-year grant upon the School of Medicine. These funds will go toward the University's new Pittsburgh Center for HIV Protein Interactions, led by Gronenborn. The center uses nuclear magnetic resonance spectroscopy and X-ray crystallography (which employs scattered rays to determine the arrangement of atoms) to define protein structures. Other techniques, such as cryo-electron tomography, in which frozen virus is bombarded with electrons, help investigators focus on the interaction between HIV and the cell. Gronenborn hopes to identify moments when the virus becomes vulnerable to drug therapy. ***—Joe Miksch***



When does HIV become vulnerable to therapy?
ABOVE: A human cellular protein model

COURTESY DENISE CHAN AND LIN LIU

BIOFUEL

Ideas fuel biomedical research. So do dollars and cents. Recently released data show that the University of Pittsburgh ranks sixth in the nation in funding fuel, having received $447 million in National Institutes of Health support for the 2006 fiscal year.

In these lean funding times, the University is one of more than 3,400 entities receiving NIH support. Of those, Pitt is fourth in the total number of grants received, with 1,082.

FEEL THE PRESSURE

As of late 2007, there is a negative pressure zone on the University of Pittsburgh's campus, located on the eighth and ninth floors of Biomedical Science Tower 3. This is the new $28 million Regional Biocontainment Laboratory—one of 13 such labs in the country funded by the National Institute of Allergy and Infectious Diseases. Pitt's RBL, part of the School of Medicine's new Center for Vaccine Research, is the second to complete construction.

Open a door to a negative pressure lab and the air will rush in ahead of you. This simple biosafety measure helps to ensure that the dangerous pathogens under scrutiny—including those that cause SARS, dengue fever, and tuberculosis—will not escape on an errant breeze. A host of other safety measures and strict research protocols allows scientists here to work with highly infectious pathogens that occur naturally and also are potential bioweapons.

—Chuck Staresinic



SEAN GRAFF

A&Q

Of Mice and Men with Mario Capecchi

On October 8, the University of Utah's Mario Capecchi (shown above)—along with Oliver Smithies of the University of North Carolina at Chapel Hill and Sir Martin Evans of Cardiff University in Wales—netted the Nobel Prize in Physiology or Medicine. The Nobel Assembly recognized them for work that led to one of biomedical science's most important modern tools: knockout mice, those critters typically bred without certain genes, which are helping scientists understand more precisely how genetics affects health.

Four days later, Capecchi, a PhD and Distinguished Professor of Human Genetics and Biology as well as cochair of Utah's Department of Human Genetics, visited the University of Pittsburgh. He'd arrived to give a plenary lecture during Pitt's annual science festival, Science 2007. *Pitt Med* caught up with him to talk about his work and the future of basic science.

On starting big

We actually thought that we might be able to go all the way. It took us over 10 years to develop the means to do the work. It's not one of these occasions where you come stumbling into it. We had the vision, but it took quite a lot of technical know-how.

On the next generation of Nobelists

I think we're going to see a lot of progress regarding how the brain works. When we're talking, we can pull out a memory in a millisecond, but [functional magnetic resonance imaging] capture times are much slower. My guess is that [someone will improve capture time to] the level that will allow us to really start to understand what it means to pull out a memory.

On funding

This is an absolutely peak time to go into science, but then the ability to get funding is at the lowest spot ever. But funding is cyclical, so that will improve. This is actually a good time for scientists to come in, because by the time they're ready to get a job [the funding will be there].

His question for the scientific community

I think it is important for scientists to communicate with the public, [that's who] we're supporting in science. What can we, as scientists, do to improve communication with the public?

—Interview by Joe Miksch

Faculty Snapshots

Steven Kanter took the helm of the Association of American Medical Colleges monthly peer-reviewed journal, *Academic Medicine*, in January.

Kanter, an MD and vice dean of the University of Pittsburgh School of Medicine, has been a member of the journal's editorial board since 2005. *Academic Medicine* serves as a forum for medical schools and teaching hospitals to address pressing issues in the field.

L. Dade Lunsford, director of Pitt's Center for Image-Guided Neurosurgery, was an honored guest of the Congress of Neurological Surgeons, a recognition bestowed upon one international surgeon a year.



Kanter

Lunsford, an MD and the Lars Leksell Professor of Neurobiological Surgery in the School of Medicine and former neurosurgery department chair, is credited with helping the University of Pittsburgh Medical Center to become the first in the nation to use the gamma knife, a device for performing brain surgery without an incision, in a clinical setting. He was also recently named a 2007 Castle Connolly National Physician of the Year (one of three in the United States) and a University of Pittsburgh Distinguished Professor.



Lunsford

Judith Klein-Seetharaman was named the winner of the 2007 Margaret Oakley Dayhoff Award by the Biophysical Society. She is a PhD assistant professor of structural biology at the School of Medicine.



Klein-Seetharaman

Named for a former president of the Biophysical Society, the award honors women considered to be on the verge of achieving prominence in their fields. Klein-Seetharaman's work focuses on membrane-receptor folding and misfolding and how these processes contribute to disease.



Lewis

The Institute of Medicine has made David Lewis the 19th University of Pittsburgh faculty member to join its ranks.

Lewis, an MD, is the UPMC Endowed Professor of Translational Neuroscience in the Department of Psychiatry and a professor of neuroscience in the School of Arts and Sciences. He has spent his career researching schizophrenia. *—JM*

Think Like a Scientist

When the medical school first started requiring students to undertake a scholarly project four years ago, Vice Dean Steven Kanter had one concern.

"I didn't think it was fair to parachute a student into a lab, then airlift [her] out a number of weeks later," he says. So Kanter called on two University of Pittsburgh profs—Beth Piraino, an MD professor of medicine, associate dean of admissions and financial aid, and practicing nephrologist, and Peter Drain, a PhD associate professor of cell biology and physiology who studies ion channels in proteins related to diabetes. Kanter asked them to figure out how to teach med students to think like scientists.

The result was Methods and Logic in Medicine, a two-semester course that has already garnered national attention. It won an award from the Association of American Medical Colleges for innovation in preclinical education.

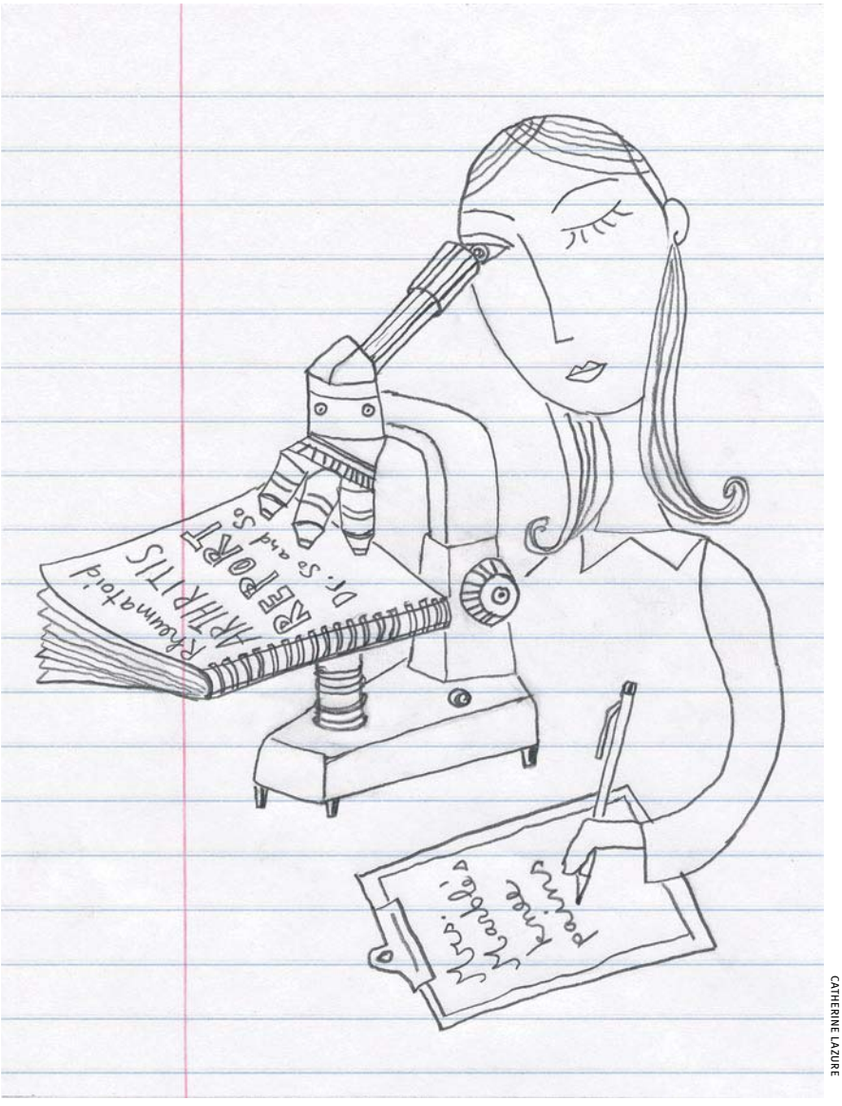
Working in small groups, first- and second-year students select published papers—on rheumatoid arthritis, say, or cytomegalovirus—and critique them. Is the sample size large enough? Are the samples random enough? Is the research question clear?

The course teaches the physicians-to-be how to drill down through the literature to find medical knowledge that can help them treat patients.

"The amount of information you're expected to keep up with as a physician is astronomical," says Piraino. "And you have to figure out how to do that and how to do that critically."

Piraino also brings patients from her own practice into the class. Students take medical histories, then locate research papers to help them propose treatments.

"It reinforces the medical cycle," says Drain. "You begin by defining the patient's problem, investigate it in the medical literature, then bring the relevant knowledge back to your treatment plan for the patient. We're teaching the students to develop this cycle throughout their lives as physicians." ***—Reid R. Frazier***



CATHERINE LAZURE





COURTESY B. BRANSTETTER

A CHIVALROUS LIFE

Barton Branstetter lives in a metaphor. The man's Marshall Township home is, well, a castle.

Branstetter (Res '00, Fel '01), an associate professor of radiology, otolaryngology, and biomedical informatics in the School of Medicine, and his psychiatrist wife, Cara McCandless (Fel '00), built their 7,000-square-foot medieval-style residence in three years and took up castle-keeping in January 2007.

The turreted, drawbridged, and moated structure is modeled on Bodiam Castle in southern England. Every now and again, the couple will have friends over for a grand feast in the great hall or a mock sword fight on the grounds.

"I am involved with medieval recreation because of the romance," Branstetter says. "It was really the romance of living in a castle and leading a chivalrous lifestyle that drew us to it." *—Sarah Evans*

FOR MORE INFORMATION:
www.pitt.edu/~caram/castleindex.htm



DAVID SCHROTT

DANCE REVOLUTION

Ever see those arcade games that show kids dance moves? Stephanie Studenski, professor of medicine, thinks they can get older Americans on their feet, too.

Studenski, a mobility and balance disorders geriatrician who once considered herself a klutz, has lost 47 pounds video-game dancing. "I dance every day and can't stop. I go and go and go," she says. She found the same was true for many of the participants in a National Institutes of Health–sponsored six-week pilot study of postmenopausal women.

It wasn't unusual for Studenski's study participants, who had agreed to dance for 30 minutes, to beg to continue once the half hour was up—they were so eager to get to the next level. These women had been unable to sustain much physical activity in the past.

Studenski suspects a longer study would confirm significant weight loss and perhaps improved physical and cognitive function among participants.

The women chose from hundreds of songs. One sure tune to get those feet moving: Gloria Gaynor's "I Will Survive." "You should see those women dance to that!" says Studenski.

Name Dropping

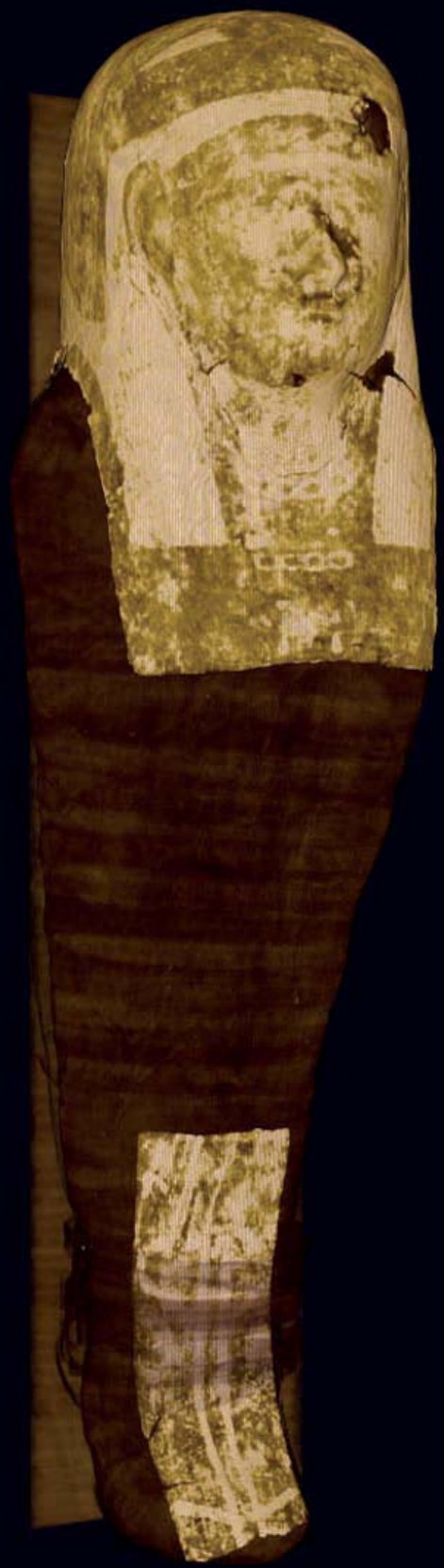
Carol Greider won this year's Dickson Prize in Medicine, the most prestigious award given by the University of Pittsburgh School of Medicine. During Science 2007, Pitt's annual fall science festival, she presented the Dickson Prize in Medicine Lecture on telomerase, an enzyme that maintains telomeres (terminal segments of chromosomes). Telomeres are vital to chromosomal reproduction and stability.

Greider, a PhD, is the Daniel Nathans Professor and director of the Department of Molecular Biology and Genetics at Johns Hopkins University. Her research attempts to understand the roles of telomerase and telomeres in chromosomal instability, cancer, and stem cell failure. She also is a recipient of the Albert Lasker Award for Basic Medical Research.

Laurie Glimcher visited Pitt during Science 2007 as well; she presented the Mellon Lecture. Glimcher is a professor of medicine in Harvard Medical School and the Irene Heinz Given Professor of Immunology at the Harvard School of Public Health.

The MD studies the development and activation of T helper cells, which are vital to the development of protective immunity and play a role in immune system malfunctions that underlie autoimmune diseases.

Mina Bissell delivered the Daisuke Nakada Memorial Lecture at the University of Pittsburgh Biomedical Graduate Student Association's 2007 research symposium in the fall. Bissell, a PhD and Distinguished Scientist in the Life Sciences Division at the Lawrence Berkeley National Laboratory in California, studies how the cell's scaffolding regulates genes in normal tissue and malignant tumors. *—JM*





WHEN I WAS YOUR AGE

Last year, University of Pittsburgh medical student Tanya Lucio started working with a patient who hadn't been to a doctor in 2,300 years.

With a team of experts from the School of Medicine and Carnegie Museum of Natural History, she has been using a CT scanner to investigate the life and death of an Egyptian child mummy.

Lucio, in her second year of med school, has come up with a plausible diagnosis of the disease that led to the demise of the 3- or 4-year-old boy with matted hair—some form of hydrocephalus.

Not every practitioner of Egyptian mortuary science during Dynasty XXX of the Early Ptolemaic period (from 380 to 250 BCE) knew what he was doing, Lucio surmises:

"They dislodged the head during the mortuary process and took a piece of hard papyrus and shoved it down the spinal column to keep the head from lolling around."

The mummy's heart was the only organ not removed during embalming; it shifted to the right side of the chest cavity in the millennia since the boy's death.

Lucio became involved with the project through a School of Medicine/Museum of Natural History elective. She is thinking of becoming a pediatric radiologist or pediatric surgeon. In the meantime, Lucio aims to find out exactly what kind of hydrocephalus afflicted her very old pediatric patient.

—Joe Miksch

—Large photo by Jeff Towers, Inset photo by Sandra Beard

Explorations and revelations taking place in the medical school



Existing treatments for elephantiasis can leave adult worms in the lymph nodes, where they can procreate and live for years.

ELEPHANTIASIS WORM GENOME SEQUENCED

BUT HOW DOES IT SLINK AROUND THE IMMUNE SYSTEM? | BY ERICA LLOYD

When Dutchman Jan Huygen Linschoten spent some time in Goa in the late 16th century, he noted that some locals had limbs "as thick as an elephant's leg." After Linschoten, medical historians find many references to lymphatic filariasis. This tropical disease is often called elephantiasis, though the afflicted typically experience both elephantiasis (thickened and hardened skin) and lymphedema (disfiguring enlarged limbs and other body parts). Infected men and women also can suffer from damaged and swollen genitalia, adding to the stigma of the disease.

The human species hosts more than 300 parasites, and the microscopic worms that cause elephantiasis have probably been living with us well before Linschoten's travels. Bloated limbs on representations of Pharaoh Mentuhotep II from 2000 BCE suggest those who set up house along the Nile have dealt with the disease for millennia. Yet it wasn't until 1877 that scientists realized how the parasitic infection spreads—through mosquitoes that carry the worm larvae.

Now, researchers led by the University of Pittsburgh's Elodie Ghedin have sequenced the genome of *Brugia malayi*, a nematode that causes the disease.

Ghedin, an assistant professor of medicine in the Division of Infectious Diseases, reported on the sequencing in the Sept. 21 issue of *Science*. Her paper suggests areas of the genome that may yield new drug targets for the disease. Probably 40 million people are severely disabled by the disease, the World Health Organization estimates.

No vaccine exists for elephantiasis. Drug treatments often target the larvae or don't kill all the adult worms—leaving procreating worms in the system that can continue to live for several years. Existing drugs also don't alleviate the disfiguring and painful symptoms (though intense hygiene treatments help). There's evidence that the nematode is developing drug resistance as well, Ghedin notes.

She hopes the sequenced worm DNA also will help scientists understand the subtleties of human immunity.

Mosquitoes that carry *B. malayi* larvae in their proboscises spread the disease. When the bugs bite people, the larvae molt in the bloodstream, then wiggle their way into the lymph nodes, where they live and reproduce as adults. One worm can bear 1,000 larvae a day, which swim back to the peripheral blood. There, the larvae might be picked up by a dining mosquito, continuing the cycle.

If the immune system reacts to the parasite, the membrane of the lymph node becomes inflamed and, eventually, injured. The lymphatic system then can no longer carry out its duties—including draining lymph—resulting in the swollen, hardened limbs and other infamous symptoms of the disease.

"The parasite doesn't feel good if you don't feel good," says Ghedin, explaining that *B. malayi* procreates best when it slinks beneath the immune system's radar. Often, adult worms can keep right on reproducing without causing noticeable trouble. Most people hosting the parasite don't get the disease, yet those same people are the most effective at spreading the infection (if they continue to come into contact with mosquitoes).

B. malayi can live for years in humans without setting off an immune response. Oddly, the worms manage to do this while cozying up within the garrisoned lymph nodes, where the body usually mobilizes its response against infection.

"We think the worms are secreting compounds to the immune system so the system ignores them and doesn't reject them," says Ghedin.

The National Institute of Allergy and Infectious Diseases funded the sequencing project. Ghedin's team was based at TIGR, the Institute for Genomic Research (now part of the J. Craig Venter Institute), in Rockville, Md. TIGR is Ghedin's former professional home; she retains an adjunct investigator position there since joining Pitt in 2006.

The sequencing task was not straightforward, Ghedin reports. Among other difficulties, the chromosomes in *B. malayi* were tangled together and couldn't be individually separated. This means the researchers couldn't solve the genome chromosome by chromosome, as the sequencers of the human genome did. Instead, Ghedin's team effectively blasted the genetic material apart, then relied on overlapping sections of DNA molecules to reassemble it, "like Legos," Ghedin says.

"It's still in 8,000 pieces," she says. "But the pieces were large enough that we were able to do all sorts of analyses."

The researchers found thousands of genes in *B. malayi* not yet identified in other organisms. Ghedin is working with Penelope Morel, Pitt associate professor of immunology, to find out whether any of these genes code proteins that allow the nematode to thrive without setting off an immune alarm. (Both investigators are affiliated with Pitt's newly created Center for Vaccine Research.)

Such discoveries might help the millions infected with *B. malayi* as well as millions out of the worm's reach.

"It could be huge if we could determine what proteins the worm produces that can have such a strong impact on the immune system," says Ghedin.

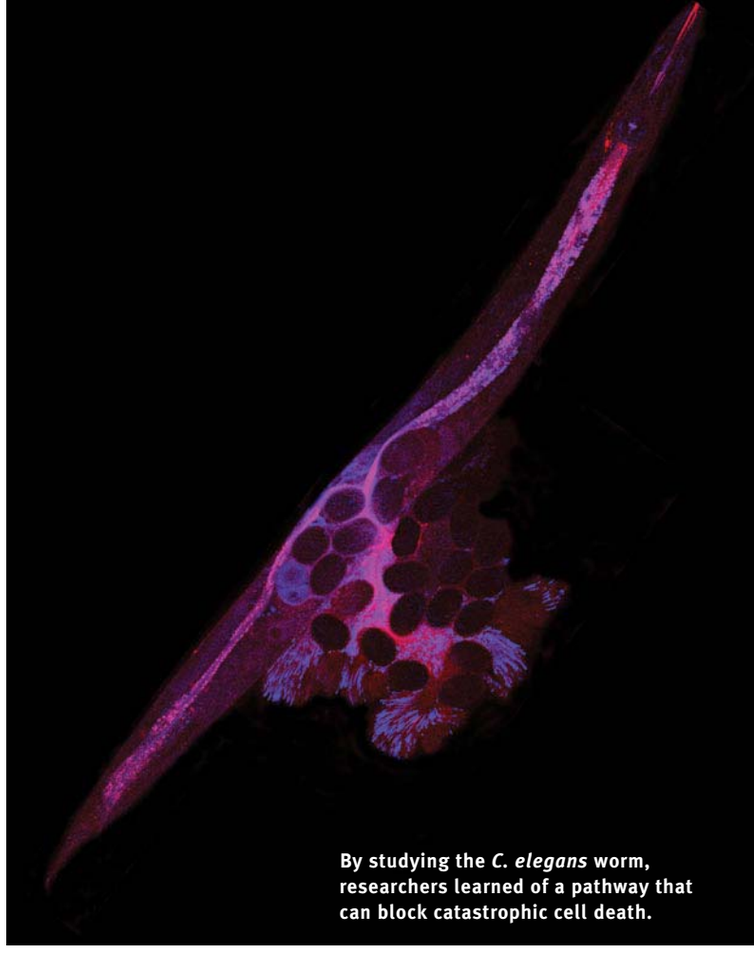
"We could use them in transplantation, to prevent rejection of transplanted organs." She adds that such proteins could also inform our understanding of autoimmune diseases, including diabetes and multiple sclerosis.

Other researchers have already hit upon promising candidate proteins. ■

COURTESY A. SCOTT

AN *ELEGANS* SOLUTION

TINY WORM DEATHS YIELD KEY TO CELLULAR LIFE | BY JOE MIKSCH



By studying the *C. elegans* worm, researchers learned of a pathway that can block catastrophic cell death.

COURTESY C. LUKE

For a biomedical scientist, getting the cover of *Cell* is akin to an emerging rock band landing the cover of *Rolling Stone*. It's a sign, in both cases, that some significant work has been done. Of course, there are some differences between finding a protein that can halt and reverse the sudden and dangerous death of cells and pumping out some edgy alternative rock. But in the realm of professional pride, that's a difference without a distinction.

The Sept. 21, 2007 coverboys, or, rather, coverscientists Gary Silverman and Cliff Luke are investigators at Magee-Womens Research Institute. About five years ago, Luke, a PhD assistant professor of pediatrics in the University of Pittsburgh School of Medicine, was attempting to dislodge a clan of tiny roundworms, *C. elegans*, from the surface of a lab dish. He squirted them with water. Many died a pretty violent death: They exploded.

The assumption shared by Luke and Silverman, an MD/PhD who is chief of newborn medicine in Pitt's Department of Pediatrics and head of the lab in which Luke works, was that the dying worms had some sort of problem regulating cell volume. In short, they thought that the worms' cells were unable to expel water, causing them to burst.

Luke and Silverman were wrong.

A couple of years of investigation have led them to conclude that the dying worms were deficient in a protein called SRP-6, a serine protease inhibitor (or serpin). The scientists had knocked out the gene for SRP-6 (pronounced *serp six*) in the exploding worms but never imagined it would have that effect.

The dying worms didn't have a volume-regulation problem. The worms died before they even had a chance to deal with the hypotonic stress. It was a type of catastrophic, unregulated, and irreversible cell death called necrosis—the same thing that happens to human cells deprived of oxygen through a heart attack—that was decimating Luke and Silverman's worm population.

Perhaps, Luke and Silverman began to think, the lack of SRP-6 got the necrotic process started. And, if that's the case, if there's a rhyme and reason to necrosis, maybe the process isn't unregulated after all. And maybe the labels "irreversible" and "catastrophic" can be cast aside as well if the cellular death march can be reversed.

"It turned out that SRP-6 protects the lysosome," Silverman says. The lysosome is the cell's digestive center and home to powerful poisonous enzymes that are released when it is damaged. "And should the lysosome get injured and leak some of its contents, SRP-6 also plays a role in blocking some of those enzymes that are released," he adds.

The researchers say that's a powerful piece of knowledge.

"We now have a pathway we can attack therapeutically that can potentially save any cell dying by necrosis," Silverman says.

"If you can block that, and even if the lysosomes break apart—which you would think would cause catastrophic, irreversible death—if there's enough SRP in the pathway, the cell survives and the lysosome will reform." He pauses, lowers his voice almost to a whisper, and adds, "That's stunning."

Silverman and Luke, the *Cell* paper's senior and primary authors, respectively, have already embarked upon the search for a SRP-6–related therapeutic agent. In partnership with Pitt's Drug Discovery Institute, they are screening thousands of compounds, looking for a drug that might be able to increase the presence of SRP-6 in cells that have begun to die by necrosis.

Silverman says stroke, heart attack, and various gastrointestinal disorders and neurodegenerative diseases are all potential SRP-6–related drug targets.

As an example, Silverman imagines a man stricken with a heart attack caused by a clogged blood vessel. Today, to prevent his heart from absorbing further damage, emergency room doctors are likely to rush to give him a shot of blood thinner to restore flow to the dying heart cells as quickly as possible. The cells that have already suffered a fatal insult? They're goners and aren't coming back.

"But imagine if you can get enough of a SRP-6–like drug in there," Silverman says. "You could probably protect cells from dying even if it's a very late stage of the game." As fewer cells suffer necrosis, the heart muscle could come away from the insult much healthier than it would without such a drug.

So breaking ground by defining a pathway that kills cells and often kills people, starting the search for new life-saving drugs, and landing the cover of *Cell*, that's got to be pretty cool, right?

"It is," Luke says, laughing. "It really is." ■

PICK YOUR POISON

CO IS GOOD FOR YOU (IN SMALL AMOUNTS)

BY SARA GOUDARZI



GETTY IMAGES

Carbon monoxide. When we think about it, we tend to think of cars coughing up exhaust or maybe a poorly vented kerosene heater. It's a leading cause of fatal poisoning.

Yet the deadly gas is actually produced in small doses by our bodies.

And in minute amounts, carbon monoxide can be therapeutic. If your body produces more of the gas, you're likely to heal more quickly from injuries. Some researchers are hoping to one day administer it to patients in need.

"What I find interesting about carbon monoxide is that it still has a little bit of a shock value that you're using what's really thought of as a lethal gas for beneficial effects," says the University of Pittsburgh's Brian Zuckerbraun, an assistant professor of surgery.

Zuckerbraun is among a handful of researchers actively investigating the anti-inflammatory effects of carbon monoxide. He says his work is heavily influenced by research conducted by Augustine Choi and Leo Otterbein. In the mid-1990s, those scientists were investigating the beneficial effects of heme oxygenase-1 enzymes—which break down to form carbon monoxide as one of their byproducts—for preventing injury from different types of insults.

The two researchers, then at Johns Hopkins University, discovered that blocking the enzymes led to more cell damage.

"I came up with the hypothesis that carbon monoxide was the mechanism by which the enzyme heme oxygenase-1—which was known to be protective and which Dr. Choi and I had studied for years prior—was functioning," says Otterbein.

This idea became the focus of Otterbein's doctoral dissertation and, later, his research concentration when he and Choi moved to Yale University. Shortly after they published a *Nature Medicine* paper in 2000 that showed carbon monoxide had anti-inflammatory effects in mice and in mouse cell cultures, the scientists relocated to Pitt.

At the time, Zuckerbraun, then a surgery fellow, was working on nitric oxide—another gas notorious for its toxicity and later found to be beneficial in small quantities within the body. He soon joined Choi and Otterbein's research efforts.

Now Zuckerbraun runs his own lab, with carbon monoxide as a main area of investigation. (In 2004, Otterbein left Pitt to join the faculty at Harvard Medical School. Choi recently accepted a position there as well.)

Zuckerbraun studies pulmonary hypertension, i.e., high blood pressure in the arteries supplying blood to the lungs.

By the time symptoms of the disorder present themselves, the damage is typically irreversible. Patients end up short of breath from even low levels of exertion and can't perform simple functions such as walking up the stairs.

In end-stage cases, the only treatment is lung transplantation. No therapies are available to reverse the artery thickening that causes high blood pressure.

Zuckerbraun is interested in how carbon monoxide might help those with the disorder.

He's exploring using carbon monoxide to reverse thickening of blood vessels in the lung by encouraging protective genes and restoring damaged cells to health.

The surgeon also investigates how inhaling the gas could protect against injuries of other organs and hemorrhagic shock.

"If you could deliver controlled doses of carbon monoxide, you could potentially prevent inflammation that takes place as a result of the hemorrhage and the consequences of that," says Zuckerbraun.

In cases such as hemorrhagic or septic shock, our tissues don't get enough oxygen. When inhaled in large quantities, carbon monoxide is poisonous—entering the bloodstream where its molecules bind to oxygen-carrying hemoglobin and essentially suffocating the body by starving it of oxygen at the cellular level. Doctors have known that since the 19th-century French physiologist Claude Bernard poisoned dogs to learn about the toxic effects of carbon monoxide.

Yet Bernard had only half the story. The gas doesn't always reduce oxygen levels in tissues. In fact, in some circumstances, it can lead to increased oxygen levels, says Zuckerbraun.

And he and Otterbein suggest it's likely that carbon monoxide is helpful during shock states to limit and regulate oxygen consumption in the setting of decreased oxygen delivery to organs and cells.

Carbon monoxide also acts as a signaling molecule within the cell. "For instance, in Brian's work," says Otterbein, "nitric oxide is deficient in pulmonary hypertension."

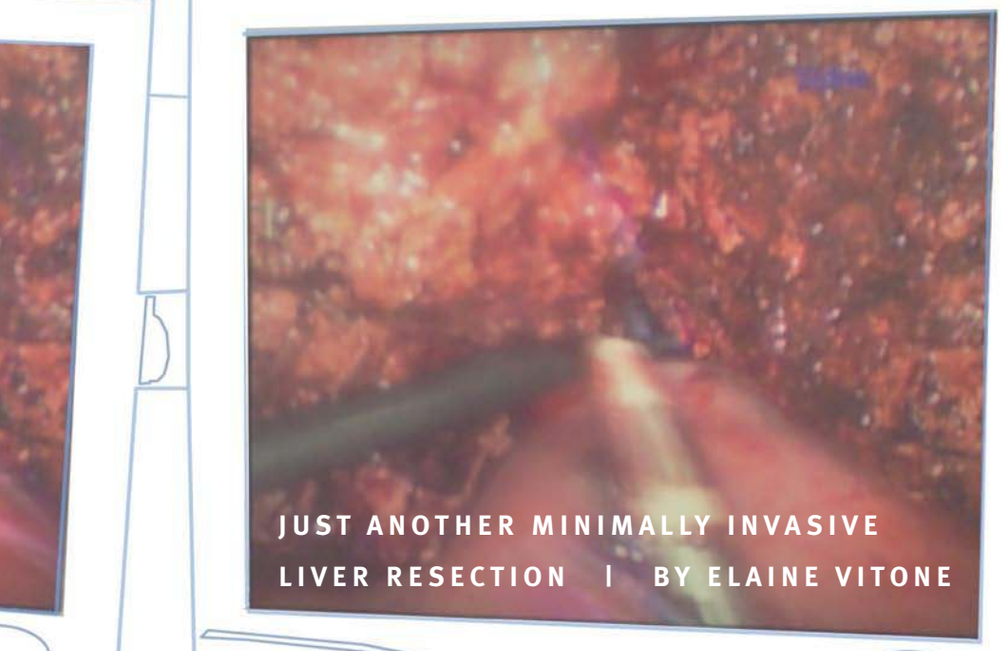
"We need nitric oxide, driven by carbon monoxide, [to decrease the thickness of artery walls].

"So in that case, the target of carbon monoxide is the enzyme that makes nitric oxide synthase. We believe that carbon monoxide influences that enzyme directly to make more nitric oxide."

Pick your poison. Now scientists have shown us two—nitric oxide and carbon monoxide—required to keep people healthy. ■



PUT



JUST ANOTHER MINIMALLY INVASIVE LIVER RESECTION | BY ELAINE VITONE

A BAND-AID ON THAT INCISION

If you were to observe David Geller (Res '96, Fel '98) prepping for surgery on UPMC Montefiore's fifth floor, at first, you might get the impression that he has an imaginary friend.

"Sidney… Sidney?" Geller says, apparently to no one in particular, as he sits at a computer by the door. Masked staff members circle the room arranging instruments and supplies. They chat pleasantly with one another, but no one answers Geller, who is the Richard L. Simmons Professor of Surgery and codirector of the Liver Cancer Center.

"Sidney…" Geller tries again, and this time, the OR's voice-activated software program, SIDNE (Stryker Intelligent Device Network), responds with a ding. With a few short spoken phrases, Geller adjusts the lights, the patient's bed, and the camera that feeds digital still images to the three flat-screen monitors above the patient's head.

ILLUSTRATION | ROB KELLY

"We have a nice stereo in here with surround sound," Geller, 44, says proudly, plugging his MP3 player into the computer. As his Beatles play list begins, you can practically see him smiling through his mask—a gadget guy in hog heaven here in Room 30, which he calls the OR of the future.

Eighty-two-year-old Agnes Ricci (we've changed her name) lies sedated in the middle of the room, all but her stomach covered in blue sterile drapes. Her swollen, Betadine-orange belly looms large.

"That's her CAT scan up on the plasma screen there," Geller tells me. On the large monitor on the wall, he points out the cause of Ricci's condition—a giant, benign liver cyst that covers three-quarters of a cross-section of her torso. "She feels full and is in pain," he says. "She's unable to leave the house. Her bile ducts are quite swollen. She's close to getting jaundiced."

Ricci first learned of her cyst eight years ago, when it was just the size of a lemon. Her surgeon at the time discovered it while operating on her for another condition, and so he drained it—a temporary fix. He knew it would surely reseal and refill. It was the best he could do at the time. He told Ricci cysts like hers were common—as far as he knew, it was nothing to worry about. Besides, attempting to remove it would be too dangerous.

But things are much different here in the OR of the future. Ricci ended up with a 12-inch scar from the open surgery she had eight years ago—which left this cyst. Today's laparoscopic surgery to remove it will leave Ricci with merely a 12-millimeter incision just below her navel.

Surgical fellow Jason Heckman assists Geller in threading through the hole a laparoscope with a light and camera at the end. Then Heckman holds it steady in his left hand. Ricci's stomach glows—illuminated from the inside out, like ET's chest. George Harrison's voice drifts through the room: *Here comes the sun. And I say it's all right.*

High-resolution footage of the giant, tan, water-balloon-like culprit fills the screens. The cyst has made itself at home in Ricci, spreading scar tissue and connecting itself to her colon, duodenum, and gallbladder.

Through four additional, 5-millimeter holes in Ricci's skin, Geller inserts rods tipped with tiny metal tools. Many of these graspers, scissors, hooks, staplers, and other cutting, cauterizing, and hemming instruments Geller and Heckman refer to with pet names like "the duckbill" and "the alligator." Their bills and jaws only measure an inch or two, but they look much bigger on the monitors.

Geller pierces the surface of the cyst wall.

He drains the cyst of its contents—3.8 liters of dark-brown bile the color and consistency of café mocha. Siphoned through a tube, it spills out into a large, clear-plastic container at Ricci's side.

With graspers, Geller holds open what looks like some beastly maw. It's a swamp in there, all spongy, slimy, and dark brown. "Sidney… Sidney… digital capture," he says, taking a quick snapshot for the Riccis. (Yes, many families do actually want these souvenirs.) He then sets to work on suctioning that last thick, mud-like sludge out from the inside of the cyst. "Hard Day's Night" plays on the stereo, as if on cue.

In the next hour, Geller carefully cuts and burns around the cyst to sever its connections with Ricci's body. He then cuts most of the loose flap of cyst wall out, all in one large piece. In his final, climactic move, he uses a long, blunt, gray instrument dubbed "the silver bullet" to pull out the cyst-wall piece through the 12-millimeter laparoscopic incision, then places it on a tray at Ricci's feet. It's innocent-looking enough now—about 5 by 3 inches—and shaped vaguely like Illinois.

Geller first started here at Pitt as an intern in 1988, back when liver surgeries were "big, gross, and bloody." If you'd have told him 20 or even 10 years ago that he'd be performing laparoscopic surgery on cysts and tumors of the liver—that large, infamously bleeding-prone organ that surgeons consider one of the most intimidating to work on—he would've laughed. And yet here he stands, wrapping up lap liver number 184, sewing five tiny incisions and covering them with ordinary Band-Aids. Another successful, virtually bloodless procedure. All in a hard day's night.

"Here it comes. It's huge. We can do this. We can take out half a liver laparoscopically. It's like delivering a baby."

That evening, at the Liver Cancer Center on the third floor of the Kaufmann Building, Geller clicks away at his computer, opening a series of video clips from previous surgeries—success stories unfolding on-screen before us.

"Watch this—it's a young woman your age [around 30]," he says. "She sent us her records, and I told her, 'I can cut this out [laparoscopically].' She flew up from Florida. There's my hand in there. Yes, this is still a laparoscopic surgery, but it's hand-assisted. The incision is just a little bit longer—nothing like the big cuts for open surgery."

He double-clicks on another patient's file. "And look, here's a bigger-than-softball-size tumor. Let me speed this up," he says, skimming through hours of careful cutting and tumor taming. "Here it comes. It's huge. We can do this. We can take out half a liver laparoscopically. It's like delivering a baby."

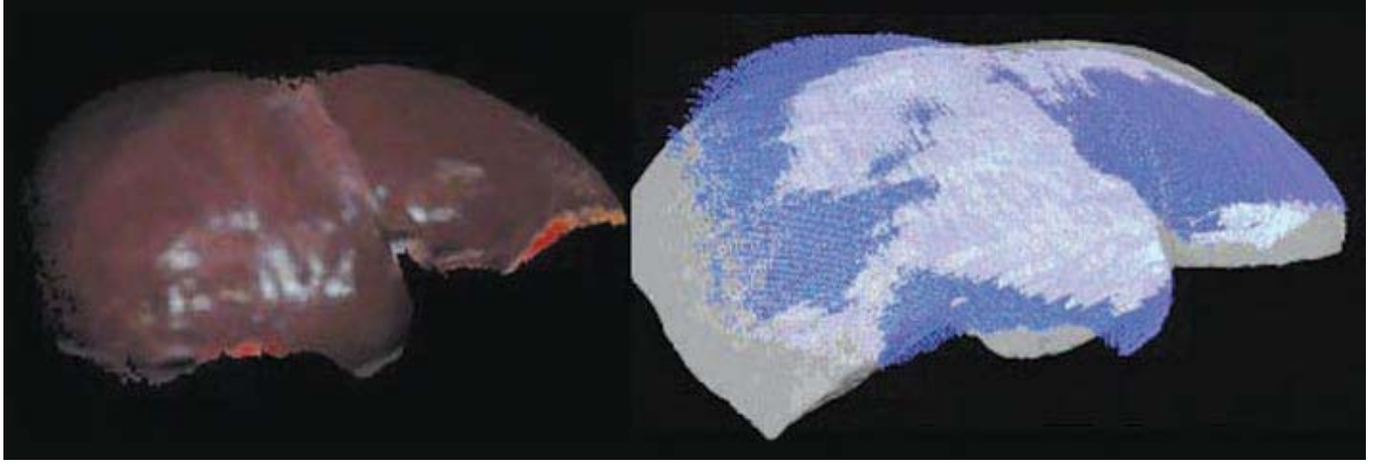
It's 7 p.m. on the Friday before a three-day weekend, but Geller is not eyeing his watch. He wouldn't miss a chance to share his message: Things are changing fast in terms of how surgeons can approach the liver. Because of this, he has been able to offer hope to many patients with liver cancer.

Liver cancer is more common than most people may realize. The most prevalent type of liver cancer doesn't originate in the liver, but spreads from the colon. Some 150,000 new cases of colorectal cancer are reported each year, making it among the four most common cancers. Of these patients, 60 percent will eventually develop liver cancer.

Cancer that does originate from the liver, known as primary liver cancer or hepatocellular carcinoma (HCC), is one of the few cancers that's killing more people each year. With the rise of hepatitis C, HCC cases have doubled in this country in the last two decades, bringing the annual death toll to 16,000. Nationally, only 10–20 percent of HCC cases are considered operable; the other patients usually die within three to six months.

"Historically many patients have been told that liver cancer is a death sentence, that there's nothing more to do but go home and die," Geller says. "But we're able offer some form of treatment to about 95 percent of patients that we see."

The Liver Cancer Center began in 2001 as an extension of the liver-tumor service of the Thomas E. Starzl Transplantation Institute. Its doctors saw 500 patients in the first year. Since then, that number has quadrupled, and the center has quickly become one of the top



Pitt's new prototype image-guided system provides three-dimensional renderings to aid surgeons in distinguishing among the liver's healthy tissue, tumor masses, and major blood vessels. On the left is a 3-D map of the liver, generated from an intraoperative laser scanner. On the right, a blue "point cloud" of the liver surface generated from the laser scanner is mapped on a surface created from a pre-op CT scan to allow for real-time GPS tracking of the tumor position. The Liver Cancer Center will begin using this system in a clinical trial of image-guided hepatic surgery in early 2008.

two authoritative centers on laparoscopic liver surgery nationwide. Until his recent retirement, it was codirected by Brian Carr, professor of medicine and surgery, who is known for his work with targeted chemotherapy. In December 2006, Geller and a colleague at Northwestern University coauthored a paper on laparoscopic surgery for *Hepatology* at the editor's invitation.

The Liver Cancer Center treats patients with surgical, systemic, and regional therapies, as well as novel approaches that are available through clinical trials. For about 25 percent of their patients, the center can offer a cure. Many patients in the other 75 percent are adding months—even years—to their lives.

Colon cancer that has spread to the liver was once a devastating diagnosis; it's now gradually becoming more of a chronic disease, says Gellar. Eighty-two-year-old Lawrence Cohen is living proof. Cohen was first diagnosed with colorectal cancer in 2001. After that first surgery, his doctor told Cohen's family that he only had about six months left.

"I fooled 'em all," Cohen says. "In March it'll be seven years."

Geller has performed open liver surgery on Cohen three times (two-thirds of the doctor's surgeries are not laparoscopic), removing sections of Cohen's liver each time. Although the side effects of chemo and radiation therapy have been trying, it has all been worthwhile for Cohen.

"I've been fortunate," he says. "I have two daughters and two granddaughters here in the city that I'm very, very close with. It's a reason for living.

"Between all these [operations and therapies], I do everything. I'm driving again. I was a road salesman, so it comes naturally to me. I'm president of the men's club at our synagogue. I've signed up for a stained-glass class and a clay-mold class.

"There are a lot of things I still would like to do," says Cohen, "and as long as I feel good and have the energy, I'm going to do them."

The Liver Cancer Center's regional liver-cancer treatment program is run by Clark Gamblin, assistant professor of surgery. His group can poison tumors with localized chemotherapy, cauterize them, choke their blood supply off with radioactive microspheres, or any combination thereof. These methods can stave off recurrence, serve as a lifeboat during that treacherous last stint before a transplant, and fend off inoperable tumors.

Within the next several months Gamblin will launch a new gene-therapy trial of 30 patients in the first-ever use of vaccinia—the virus that was used to eradicate smallpox—to treat HCC. It's one of several studies that the Liver Cancer Center staff have been hard at work on since the center was established.

Within the past several years, the center's J. Wallis Marsh, professor of surgery, has published several articles on a genotyping pilot study he conducted on 183 post-op liver-transplant patients. His team compared mutation rates in a panel of nine microsatellites—parts of the chromosome that serve as markers for certain genes—in the patients throughout a five-year period. They wanted to learn a better way of determining risk of HCC recurrence after transplant. They believe the panel predicts recurrence in 90 percent of patients.

The Liver Cancer Center is using this genotyping strategy to identify patients who need extra monitoring and treatment. It's still too early to say how effectively the strategy is working, but Marsh is optimistic. He believes the microsatellite panel could improve the United Network for Organ Sharing (UNOS) criteria.

Under the current guidelines, an HCC patient must have either one tumor less than 5 centimeters or no more than 3 tumors, none of which is greater than 3 centimeters. Otherwise, the risk of recurrence is considered too high for a transplant.

"We think this is too restrictive," Marsh says, adding that it leaves many low-recurrence-risk patients out.

To strengthen the case, UPMC is planning a new, longer-term study that will include genotyping in the pre-op phase.

For Geller and his colleagues, it's a victory each time the center is mentioned in a story about novel cancer research, like the prototype device they're testing, designed to use targeted radio waves to kill cancer cells noninvasively (it was featured on CBS's *The Early Show* in August); or the *Pittsburgh Post-Gazette* article on Geller's recent gene-therapy trial on patients with colorectal cancer that has spread to the liver (results are due out in 2008); or the phase II trial the center conducted on Nexavar, the first-ever chemotherapy pill, which made ink in the *Wall Street Journal* in June.

"Every time one of these stories runs," he says, "we get half a dozen people calling and saying, 'Can you treat my spouse?' 'Can you treat me?' 'Can you treat my dog?'"

Because of Pitt's growing reputation as one of the top liver-cancer centers in the country, Pathfinder Therapeutics, a Nashville-based medical-device company, selected the Liver Cancer Center to conduct a trial with a prototype image-guided system this October. It's a kind of GPS for surgeons, a way to more accurately navigate the liver, the tumor masses inside it, and the major blood vessels within and around it. The trial is funded by a National Institutes of Health Small Business Innovation Research grant.

That first phone call from Pathfinder

cofounder Will Chapman, who contacted Geller to ask whether he wanted his center to work with the prototype, made this gadget guy very happy. "I'm like, 'Wait, wait, wait. You're telling me you've got the money already, you've got the coolest toy in the world, and all I have to do is say yes and find the patients?'" says Geller.

There was no textbook on laparoscopic liver surgery when Geller started developing his techniques in 2001. He had to learn to see the anatomy from the inside out, to use both hands equally, and to accomplish his work through the tiniest of incisions. He started with a much less intimidating organ—the gallbladder—then worked his way up to liver resections, first with benign lesions, then tumors. As better instruments became available, he tested them on pigs.

As with any surgery, laparoscopic liver procedures still come with risk. Ninety-seven percent of Geller's surgeries are bloodless, but for the other 3 percent, there are tense moments.

In fact, in another patient's surgery just hours after Geller quelled the 3.8-liter monster in Ricci's abdomen, a small, benign liver cyst proved potentially dangerous. It had wrapped around the patient's adrenal gland, and Geller's effort to cut it loose inadvertently went a hair too far. A line of blood trickled out and pooled inside the patient, darkening the monitor overhead.

Geller quickly located and stopped the bleeding, a relief to more than one adrenal gland in the room.

"You learn how to get out of trouble from having been there hundreds of times with open surgery," he says. "You need those kinds of high-blood-loss cases to understand the anatomy."

Geller says it was his background in both liver surgery and minimally invasive surgery that enabled him to take the step toward laparoscopic liver work. For others with similar qualifications, Geller is sharing his rare, hard-won expertise. In September 2003, he taught the first workshop on laparoscopic liver surgery in the United States. Since then, he has taught five more here in Pittsburgh and elsewhere. Every one has been booked solid.

José Cunha-Melo, a senior surgeon specializing in liver and pancreatic cancer surgery and a professor of surgery at Federal University of Minas Gerais in Belo Horizonte, Brazil, has attended two of Geller's workshops—one in 2004 focusing on the liver and another on both the liver and pancreas in 2006.

"Laparoscopic liver surgery is quite revolutionary," Cunha-Melo says. "There were doctors at the workshops from all over."

During a workshop Geller held three years ago, patient Louise Hawk agreed to have her surgery—a laparoscopic left lobectomy for a golf-ball-size HCC tumor—filmed live and shared with a group of attendees in the adjacent building. She remains cancer-free today, has never needed chemo or radiation, and is still working full-time at age 76.

"I haven't had any trouble since the operation. And it's a beautiful, smooth scar—as beautiful as a scar can be," she says. "I feel great, but I'm ready to retire again. Who knows if [retirement] will stick."

Marshall Webster (Res '70), president and chief executive officer of the University of Pittsburgh Physicians and a professor of surgery, is a mentor of Geller's and has known him since he was an intern. He calls Geller "an excellent clinician, teacher, and researcher—a true triple threat."

"And not only is he doing minimally invasive liver resections—an incredible advance over even five years ago—but in addition to Presby, he's also doing this at a community hospital, which is not the norm," says Webster, referring to UPMC Passavant in the North Hills of Pittsburgh. Geller began doing surgeries there in 2005 to help patients whose insurance wouldn't cover them on the Oakland campus.

"Most people would've thought laparoscopic liver surgery is kind of crazy," Webster adds with a laugh, "but it's the young people that reinvent the world."

Two weeks after the surgery that freed her from her basketball-size cyst, Agnes Ricci is recovering well. No more pains that sharpen when she stands or sits upright. No more hiding in zipped-up slack suits and snipped waistbands. No more leaning off-kilter and struggling with her balance. No more walker.

"For years I just lived with the notion that this was the way it was going to be," she says. "I consider myself very fortunate."

Soon, her Band-Aid-size cuts will heal completely, and she'll go out shopping for new clothes. This will be the first time in months that she'll leave the house for something other than a doctor's appointment. Just the thought of exercise and fresh air has a healing power all its own.

Here comes the sun. ■

David Geller also directs Pitt's Liver and Pancreas Institute. In our next issue, we'll see how his colleagues are changing the understanding and treatment of pancreatic disease, including cancer of the pancreas.

HALO EFFECT?

In this age of minimally invasive surgery, when even liver lobectomies are going the way of tiny instruments and big plasma screens, we can't help but wonder: Is mastering video games the first step toward a surgical career?

The University of Pittsburgh's David Geller, codirector of the Liver Cancer Center and head of the center's minimally invasive hepato-pancreato-biliary surgery fellowship, says that was definitely the assumption when he was a Pitt resident back in the early days of laparoscopic surgery. He recalls that in 1991, senior surgeons said they would stick to traditional techniques and leave the minimally invasive controls to the Nintendo-playing, ambidextrous young bucks.

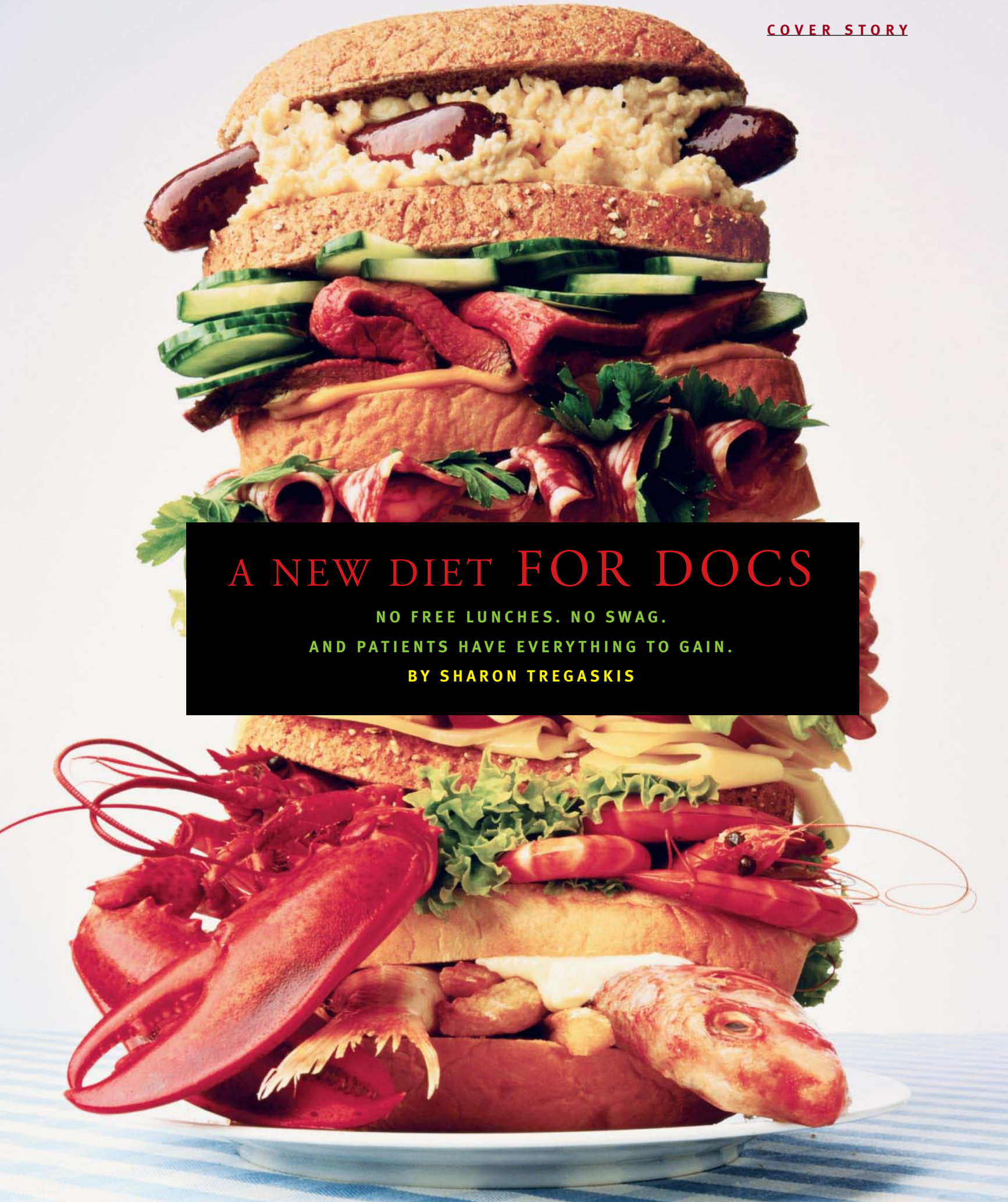
"But a year later everyone was doing laparoscopic gallbladder surgery, or they were giving up those patients," he says.

The Xboxing-surgeon stereotype may have some truth to it. Recent studies in the *Archives of Surgery* and elsewhere suggest a possible link between gaming ability and minimally invasive surgery performance. But for Geller, it only went as far as a bit of Atari and Pac-Man "a million years ago."

In evaluating fellowship candidates, Geller looks for strong backgrounds in either liver surgery, minimally invasive techniques, or both. "Surgery is so specialized now that it's not uncommon for a fellow to consider doing two fellowships in a row," he says.

And a young laparoscopic-liver surgeon's most important trait?

"Enthusiasm for learning," Geller says, adding that the tools of the trade are constantly evolving. Without a willingness to continue evaluating new technologies, it's Game Over. —*EV*



A NEW DIET FOR DOCS

NO FREE LUNCHES. NO SWAG. AND PATIENTS HAVE EVERYTHING TO GAIN.

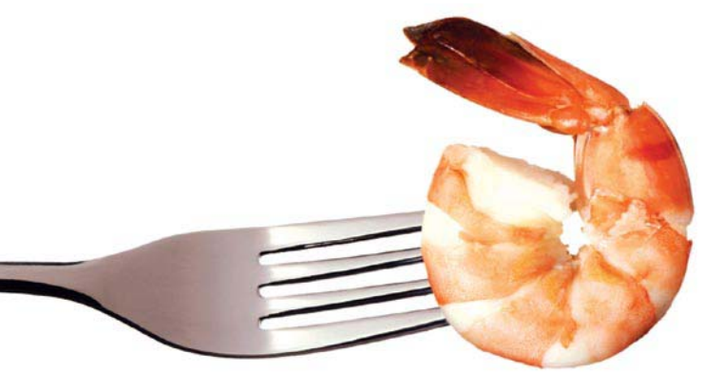
BY SHARON TREGASKIS

When Arthur S. Levine finished medical school, pharmaceutical companies gave the future Pitt dean of medicine two graduation presents: his first physician's bag and his first stethoscope. Pharmacist Randy Juhl, who would go on to serve 16 years as dean of Pitt's School of Pharmacy before his promotion to vice chancellor for research conduct and compliance for the University, has a shelf of mortar-and-pestle sets presented by industry reps to successive graduating classes. And as a pediatric resident in Denver in the '70s, Jerry Vockley recalls the downhill ski weekends in Vail hosted by infant-formula companies. (Vockley and friends organized their own low-budget, self-funded cross-country trips in response. He won't soon forget the tongue-in-check pronouncement of a fellow resident that he could never recommend breast-feeding to a new mother. "La Leche League has never given me anything," the young man declared of the nonprofit breast-feeding advocacy group, by way of explaining his shocking declaration.)

Since the mid-'40s, when pharmaceutical companies began professionalizing their sales enterprise and tracking the prescribing habits of doctors, they have been attempting to get in physicians' good graces.

Doctors are now bombarded with a range of inducements—from free lunches to complimentary samples and generously funded continuing medical education programs—offered by companies selling not only drugs, but medical devices and services to health care providers.

What's the harm now and then in accepting a free slice of pizza or a super-powerful refrigerator magnet with a company logo? Does it really influence the prescription a doctor writes? Docs are likely to say, "No." But the companies that provide these goodies must think otherwise, or they wouldn't spend truckloads of cash each year attempting to build relationships with physicians through these and other tactics.



Today, concern over such practices has reached a fever pitch, with both houses of Congress considering legislation to impose reporting requirements on industry, and physicians and medical students joining groups like No Free Lunch and PharmFree (which eschew handouts from industry and the potential conflict of interest such gifts might create). Building on the trend, academic medical centers nationwide have begun imposing policies to bring transparency and remove any hint of tarnish from what could be an enormously positive association for patients, physicians, and industry.

At Pitt and elsewhere, clinicians have signaled that they do not want to appear insensitive to the high cost of health care by accepting expensive and unnecessary blandishments.

This spring, Pitt will institute a new policy on industry relationships designed to protect the integrity of health care providers throughout the system. The code, which takes effect on February 18, covers all faculty, staff, and students of the University of Pittsburgh schools of the health sciences and the health care professionals and staff employed or contracted at all domestic locations of the University of Pittsburgh Medical Center. The comprehensive document (online at www.coi.pitt.edu, click on "Industry Relationships") prohibits gifts and free lunches, imposes narrow limits on faculty consulting arrangements, disallows participation in speakers' bureaus and ghostwriting, and bars sales reps from all patient areas. The policy, which applies equally on- and off-site, also defines acceptable use of industry funds for continuing education and scholarships. Says Arthur S. Levine, senior vice chancellor for the health sciences and dean of the School of Medicine: "It was my feeling, and that of my colleagues, that we needed to have a very precise, declarative policy."

David Rothman, coauthor of the 2006 *Journal of the American Medical Association* (*JAMA*) article, "Health Industry Practices That Create Conflicts of Interest: A Policy Proposal for Academic Medical Centers," pronounces the new regulations exemplary.

"Pitt's policies are outstanding," says Rothman, the associate director of the $6 million Prescription Project, a two-year, Pew Charitable Trusts–funded effort to overhaul the relationship between doctors and industry, with a particular emphasis on replacing marketing hype with medical evidence to inform physician prescribing habits.

"I'm not just gilding the lily here," says Rothman. "Pitt wants its place clean, and it's got it." And perhaps best of all, he says, though many schools crafting such policies have dedicated minimal thought to follow-up, Pitt has declared clear, unambiguous enforcement mechanisms.

"Development of the policy is the easy part," says Barbara Barnes, Pitt associate dean for continuing medical education in the School of Medicine. Barnes cochaired the committee that drafted the policy with Randy Juhl. "It demands tremendous commitment to implement and create culture change."

Barnes is optimistic because of the policy's strong backing from administrative leaders, including Levine, UPMC President and CEO Jeffrey Romoff, and Marshall Webster, president and CEO of the University of Pittsburgh Physicians and professor of surgery.

"We're part of a national groundswell of concern about these issues," says Webster, who coauthored with Levine the charge to the Industry Relationships Advisory Committee urging its members to take Rothman's *JAMA* article as a starting point.

"We're not operating out there in a vacuum," adds Webster. "Many of our faculty have had concerns and responded appropriately even before a policy was developed."

In 2006, the pharmaceutical industry, which employs some 90,000 sales reps, generated sales of $272 billion and spent more than $25 billion marketing to physicians—including $18 billion in free samples. Former pharmaceutical rep and Lunch and Earn founder Amy Kristjanson, whose online business coordinates take-out meals to physicians' offices paid for by drug companies, estimates the national market for docs dining with reps at close to $1 billion.

Last July, Oregon Representative Peter DeFazio introduced H.R. 3023 to require pharmaceutical and medical device concerns to disclose certain gifts made to physicians. In August, U.S. Senator from Iowa Chuck Grassley introduced the Physician Payment Sunshine Act, which proposes a national registry of payments from industry to physicians who bill Medicare or Medicaid. It covers consulting, lectures, and seminar attendance. The bill, cosponsored by U.S. senators from Massachusetts, Minnesota, Missouri, New York, and Wisconsin, was referred to the Senate Finance Committee. State-level bans on gifts already exist in Maine, Minnesota, and Vermont, and several academic medical centers—including those of Boston University, the University of Pennsylvania, Stanford University, the University of Wisconsin, and Yale University—have instituted policies of their own, which is as it should be, says the Prescription Project's Rothman.

"Medicine itself should take responsibility for getting its house in order and keeping its house in order," he says.

"There are two kinds of businesses," says Juhl. "*Caveat emptor*, let the buyer beware—you go to buy a car, you better do your homework." Health care falls into another category, he says: "*Caveat venditor*, let the seller beware. Our obligation is at all times and in all places to act on behalf of our patients. We should be doing what's best for our patients, not [prescribing something] because some nicely dressed young lady or young gentleman just bought me lunch."

It's a question of motives not lost on patients. Juhl himself sees a physician who tends to run late. "It gives me an opportunity to watch," he says. Often, shortly before lunchtime, a delivery person arrives with boxes of food, followed a few minutes later by a young rep. The receptionist promptly buzzes in each of them.

"When the salespeople who are bringing lunch get to go in before a patient, it doesn't look good," says Juhl. "It's not difficult for patients to figure out that the sales call will further delay their appointment with the physician, and to add insult to injury, they and the other patients huddled in the waiting room are further 'rewarded' by being the ultimate source for the payment of the lunch being shared by the physicians and the salesperson.

"That's an experience a lot of people have, and physicians may not think of it when they're behind the door."

The prospect of eroding trust motivates Gabriel Silverman, an MD/PhD student in Pitt's joint program with Carnegie Mellon University. As a member of the committee that drafted Pitt's industry policy, he drew both on his research—investigating the role of conflicts of interest in physician interpretation of clinical trial data—and his participation in the American Medical Student Association's (AMSA) PharmFree effort.

"Gabe brought a unique perspective," says Barnes. "It's a wonderful demonstration of the richness of an academic environment. We increasingly have a role reversal between physicians and students where we experience them stretching and challenging our thinking."

For AMSA, Silverman helped design a toolkit with materials to make it easier for an interested student to approach his or her dean to request the formation of a committee to craft an industry policy. In December, he was appointed the AMSA PharmFree coordinator for Pitt's region, an extension of his work to craft a scorecard that grades the policies in place at each of the nation's academic medical centers.

"This is our profession," says Silverman. "If we want to advocate for improved quality of care, patient welfare, this is an issue we should be concerned about. Second, this has an impact on the way our profession is perceived. I certainly wouldn't want my patients to doubt my objectivity, or have it interfere with my relationship with my patients."

Pitt just learned that it has won AMSA's 2008 Paul R. Wright Excellence in Medical Education Award in recognition of the school's commitment to professionalism in education, especially its initiatives to reduce pharmaceutical marketing influence.

A few details remain to be resolved about the new policy, including the question of how to handle free samples. A subcommittee is considering the possibility of having the samples



received by a central UPMC location, then delivered to appropriate physicians' offices through an existing internal delivery system.

"We received a lot of feedback from our physicians about the importance of samples, and we recognized they're used in a variety of ways," says Barnes, who notes that Pitt's policy covers close to 400 outpatient sites in both rural and urban settings.

Pitt physicians pointed out that samples help them supply patients with just-in-time medication, allow them to test whether a patient experiences side effects before paying for a full supply, and provide patients with affordable access to pharmaceuticals—a boost, physicians believe, for elderly patients trapped in the Medicare Part-D doughnut hole. Says Barnes: "We wanted to be absolutely sure that whatever we designed for the sample policy was not going to compromise patient care."

In the end, says Juhl, a desire to bolster patient care and confidence in physicians undergirded every decision the committee made. Perhaps, he says, Pitt's policy could engender a new way for industry and health care providers to work together to develop the best treatments—and the best information about those options—for all patients.

"If I were to wave a magic wand," Juhl says, "[I'd make it so the] pharmaceutical industry finds a new way to communicate with practitioners, institutions, and health plans that's much more data driven than relationship driven. We'd like that information to be published in the literature and have it at our fingertips when we need it. The pharmaceutical industry should be rewarded for good drugs and good data on the drugs—not on the basis of who delivers the freshest bagels." ■

THINKING OUT LOUD

THE DEAN CONTEMPLATES TCHOTCHKES AND THE ROLE OF INDUSTRY AT PITT

INTERVIEW | SHARON TREGASKIS

Pitt Med talked in depth with Arthur S. Levine, dean of the University of Pittsburgh School of Medicine and senior vice chancellor for the health sciences, about the issues behind a new industry relationship policy at Pitt. (Related story begins on p. 17.) Here are excerpts from that discussion.

PM: How do you think of the relationship between Pitt and the biomedical industries?
Levine: The challenge for us is equipoise—maintaining a vibrant relationship with industry, but at the same time one that isn't in any way harmful to the public trust, to the public health, or, for that matter, to industry itself.

PM: What made this issue resonate with you?
Levine: I don't think there was a single experience. It's something I've always been aware of. When I was a medical student, I received a medical bag from one company and a stethoscope from another. There isn't anything new about this. What's changed is the magnitude—the money involved, the scale and the scope of this kind of marketing to physicians, and to patients, for that matter.

PM: What brought the issue to the fore at Pitt?
Levine: The 2006 Brennan/Rothman paper in *JAMA* was extremely important—it was our wake-up call. There are a lot of institutions buying into this. It's not only Pitt and Penn, but also Michigan, Hopkins, Yale, and Stanford. We've captured an emerging societal, cultural, political, and financial context of which this is one element.

PM: How does this effort fit with your overall concerns about the crisis in American health care?
Levine: The cost of health care is our greatest domestic crisis. If it hadn't been for the war in Iraq, it would have been the driving domestic issue in the previous presidential election. And it certainly is becoming a driving issue in the current presidential campaign. But if all we address is health insurance, we'll just make the bill for health care even more outrageous than it already is without solving any of the underlying problems.

PM: What underlying problems?
Levine: For one, in the pharmaceutical industry, it's hard to come up with a paradigm-shifting drug. You have to spend a fortune on research, hope that you'll get lucky enough to discover and develop a truly unique drug—the first new antibiotic, the first really important antihypertensive, the first drug that is helpful in schizophrenia. Pharmaceutical companies know that happens rarely. To make themselves fiscally viable and satisfy their shareholders, they have to make knockoffs of somebody else's drug. That's how the industry works. Their knockoff might be a tiny bit better—maybe you can take it two times a day instead of three times, or maybe with food as opposed to without food. But basically, the fundamental drug is the parent drug. To elbow their way into the marketplace, if the me-too drug is only a little bit different, it means you have to spend a fortune on advertising. That's what this marketing stuff—being at the doctor's office and giving them the free pizza and trips to Bermuda—is all about.

PM: What's the alternative?
Levine: If you're a company that makes a unique drug, you don't have to do any advertising or marketing. The drug sells itself. Now that's a little bit of hyperbole, but things that are unique sell themselves—you don't have to do a lot of advertising, whether it's drugs, automobiles, or dresses. When penicillin first came along, no pharmaceutical company had to run full-page ads in the newspaper. It was saving countless lives and everyone knew it, and there wasn't a competitor.

PM: This is a strong, comprehensive policy. Why take such a detailed approach?
Levine: You have to decide between evolution and revolution. If you're changing the culture in a very major way, you have to take a major position. We already had policies that had not been effective in addressing the issue. They touched on the issue.

PM: What philosophy informed your attitude toward instituting this policy?
Levine: I'm a researcher and an experimentalist. I felt that this was a worthwhile experiment to undertake. I can't know the effect of this policy on research funding or access to free sample medications for impoverished patients. My hope and my intuition are that no bad things will happen. But they could. We'll have to see.

PM: What are the implications of policies like Pitt's for industry?
Levine: I think [our policy] will be helpful to the pharmaceutical industry. They have been tainted by this notion that they can buy their way into the marketplace with gifts. .... That's not healthy for them.

And perhaps if they aren't spending so much on marketing, and put that money into research instead, they'll be more likely to hit the jackpot with paradigm-shifting drugs.

PM: Why was it necessary to form a subcommittee to address pharmaceutical samples?
Levine: That's a logistical issue. It's technical, fiscal. We've done a lot of work on how we're actually going to get drug samples to the offices of doctors who use them and who need them. There's no problem with free drug samples provided that they're centrally managed and triaged in such a way that one particular drug isn't aggressively marketed by a detail man visiting the doc's office to the exclusion of other drugs that might be better, safer, or cheaper.

ROB KELLY

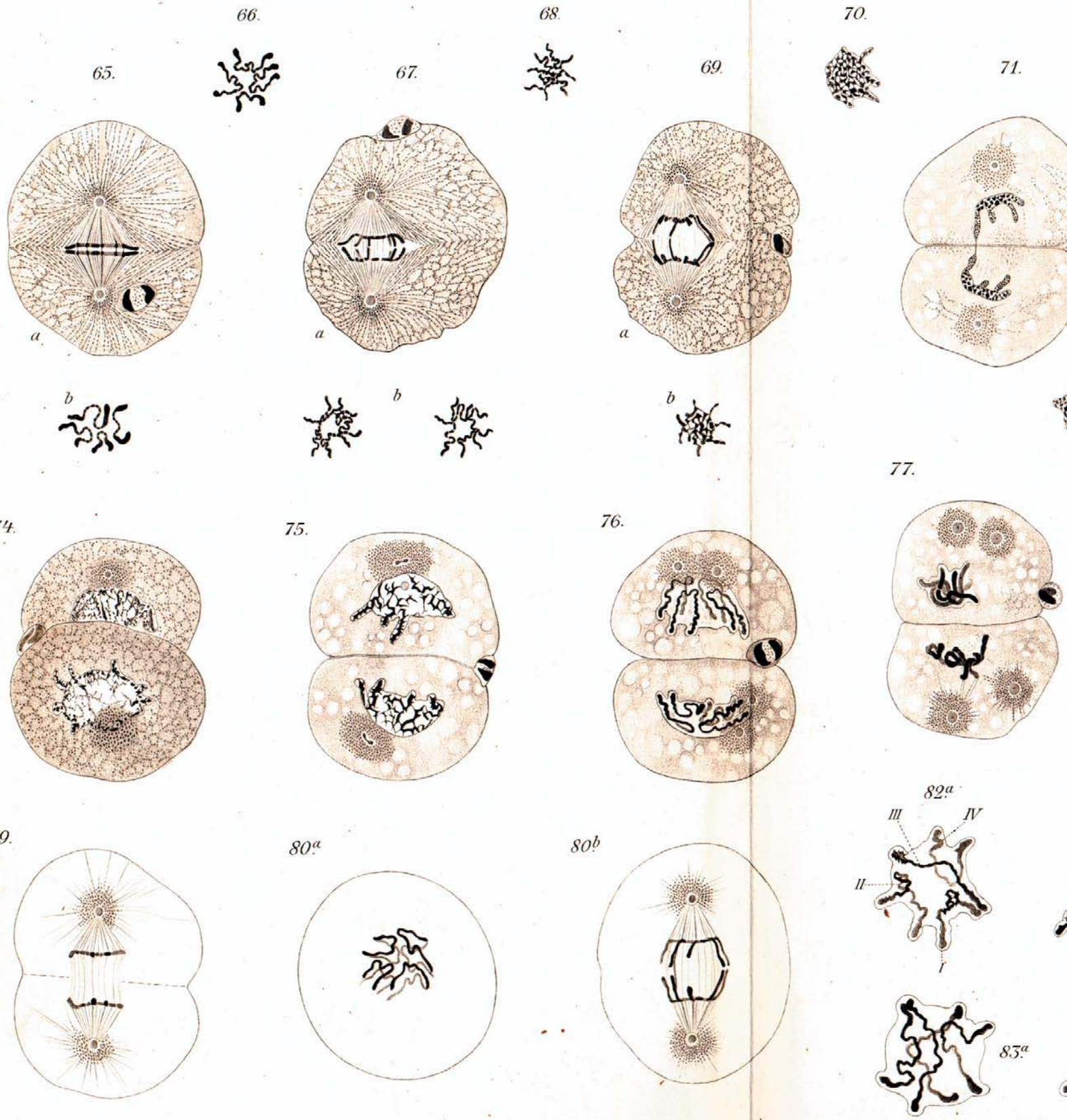


PM: In 2005, when the University of Michigan instituted a policy banning free lunches, they estimated the value of such meals at $2.5 million annually.
Levine: That's a lot of Domino's Pizza.

PM: Did anyone calculate comparable numbers at Pitt?
Levine: No. This is a huge institution. We have almost 50,000 people working for UPMC. I've got 2,000 medical school faculty, thousands of students. We'd have to ask every one of them whether they had a free tuna-fish sandwich today.

PM: Why did ghostwriting warrant a dedicated section in the policy?
Levine: I don't think that any physician should sign his or her name to an article in the medical literature that he or she cannot fully back, up to and including real authorship. Unless you struggle over the paper yourself, examine the raw data, vouchsafe for the data and its interpretation, there is no way to ensure accountability or credibility of the data or its interpretation.

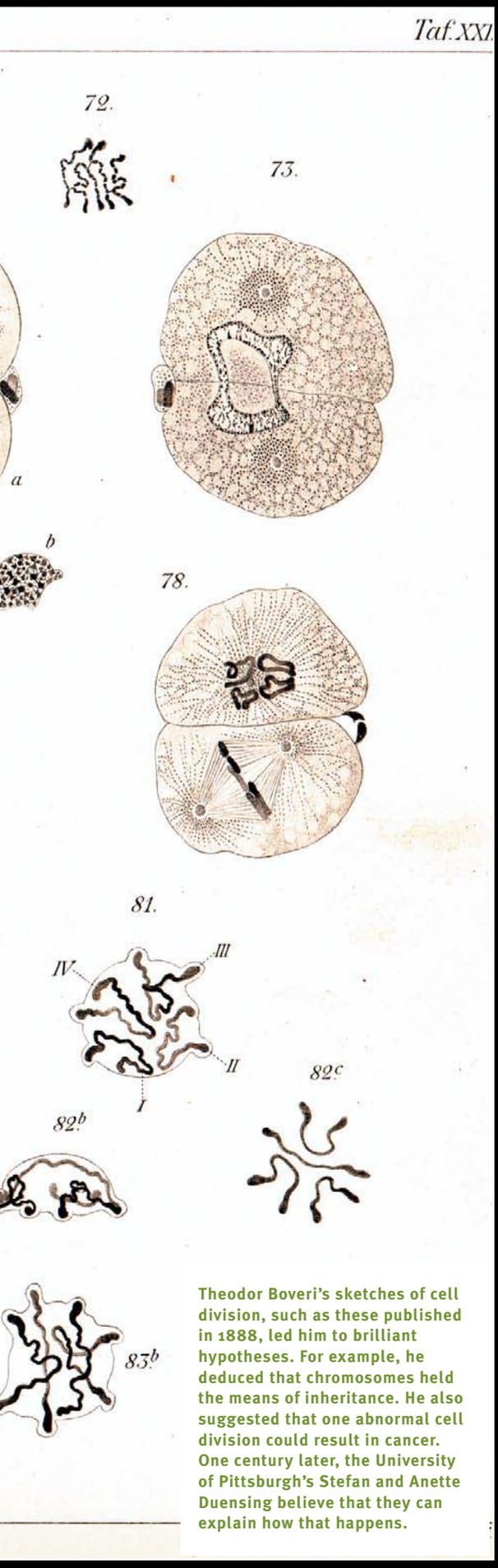
PM: Do you fear that this policy could provoke retaliation in the form of lower research funding from industry?
Levine: Academia and industry rely on each other. Pharmaceutical companies will continue to turn to universities to help answer their research questions. As I noted earlier, if companies can free up money they are spending on marketing and put it toward research, that will present more opportunities to make really important discoveries that lead to life-saving and life-enhancing drugs. ■



Boveri del.

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DRAWINGS FROM THE COLLECTIONS OF THE ERNST MAYR LIBRARY, MUSEUM OF COMPARATIVE ZOOLOGY, HARVARD UNIVERSITY. BOVERI, T., ZELLEN-STUDIEN (VERLAG VON GUSTAV FISCHER, 1888).



Theodor Boveri's sketches of cell division, such as these published in 1888, led him to brilliant hypotheses. For example, he deduced that chromosomes held the means of inheritance. He also suggested that one abnormal cell division could result in cancer. One century later, the University of Pittsburgh's Stefan and Anette Duensing believe that they can explain how that happens.

DON'T SEND FLOWERS

DRAWINGS | THEODOR BOVERI

PHOTOGRAPHY | ANETTE & STEFAN DUENSING

TEXT | CHUCK STARESINIC

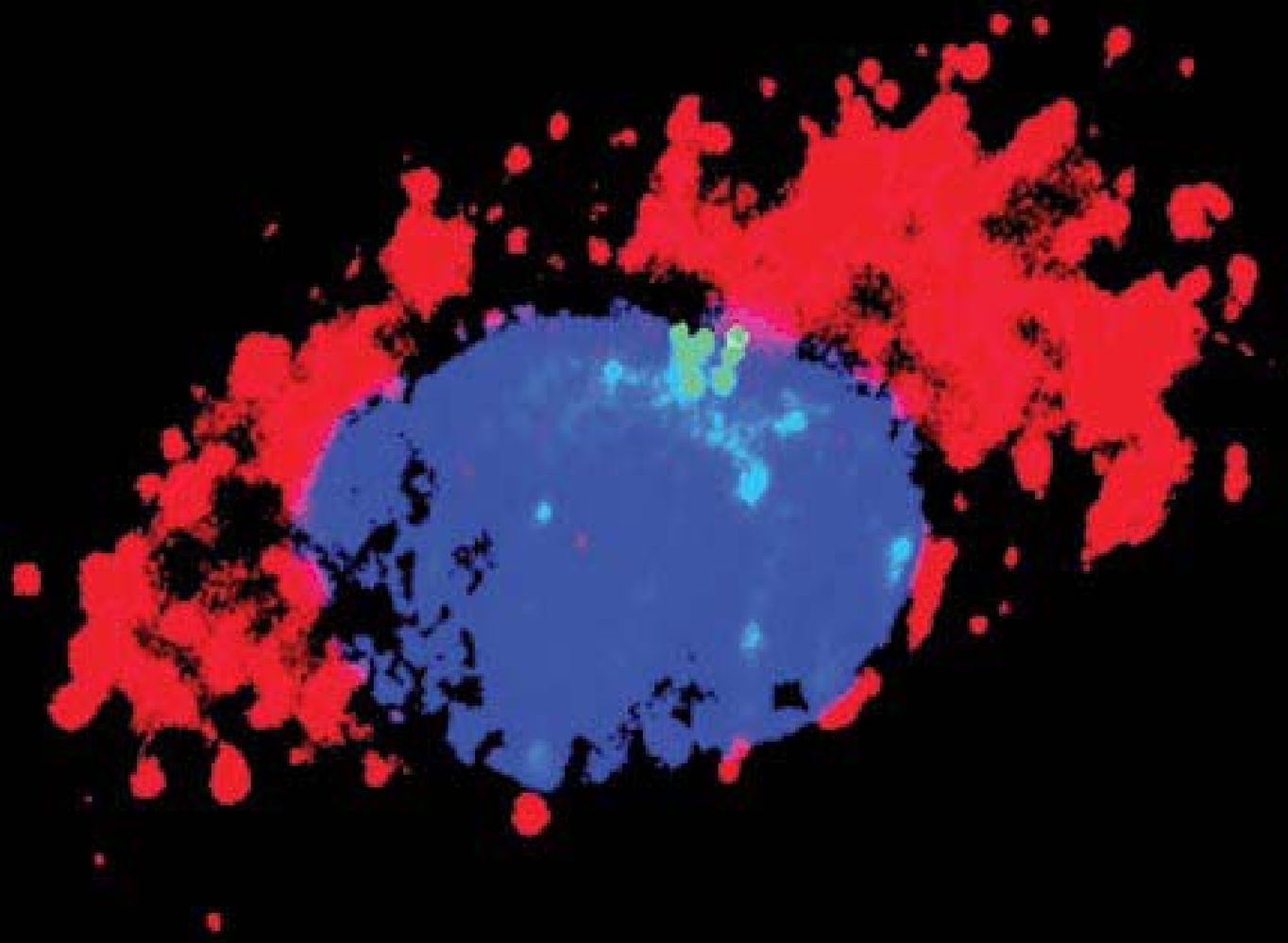
BIRTH OF A TUMOR

Beginning in the 1880s, a German scientist named Theodor Boveri probed some of the great mysteries of cell biology—the origin of cancer, for example—using just a microscope and a sketch pad.

Growing up in a distinguished family, Boveri excelled in painting and drawing. He was thought to be suited for a career in architecture or engineering. Instead, he became an academic physician. His colleagues at the University of Würzburg often photographed their microscope slides, but Boveri insisted that drawing led to more precise analysis. And drawing was a delight, he said. As he sketched, he theorized—rather brilliantly, as it turns out—about what he was observing.

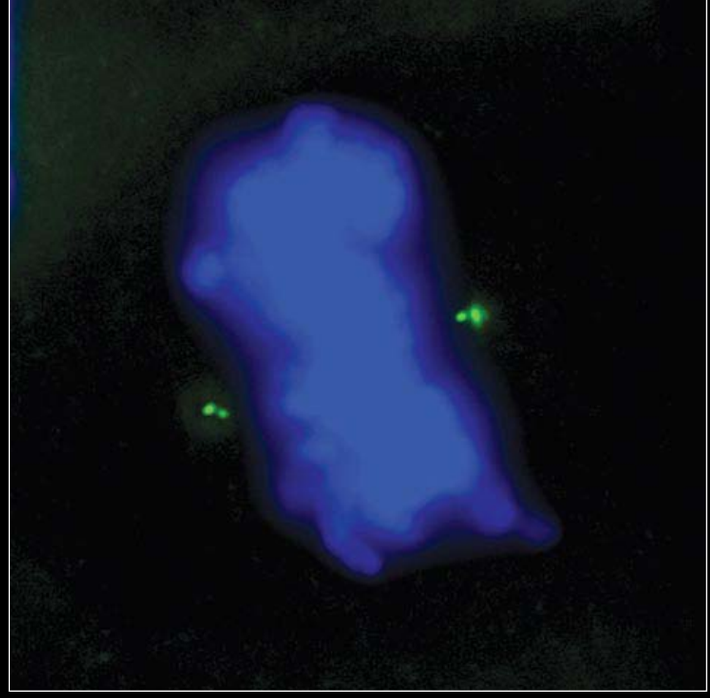
"Of course, the language is different," says the University of Pittsburgh's Stefan Duensing as he pages through a Boveri text from 1914. "But in this book, he predicts that there are oncogenes. He predicts that there are tumor suppressor genes."

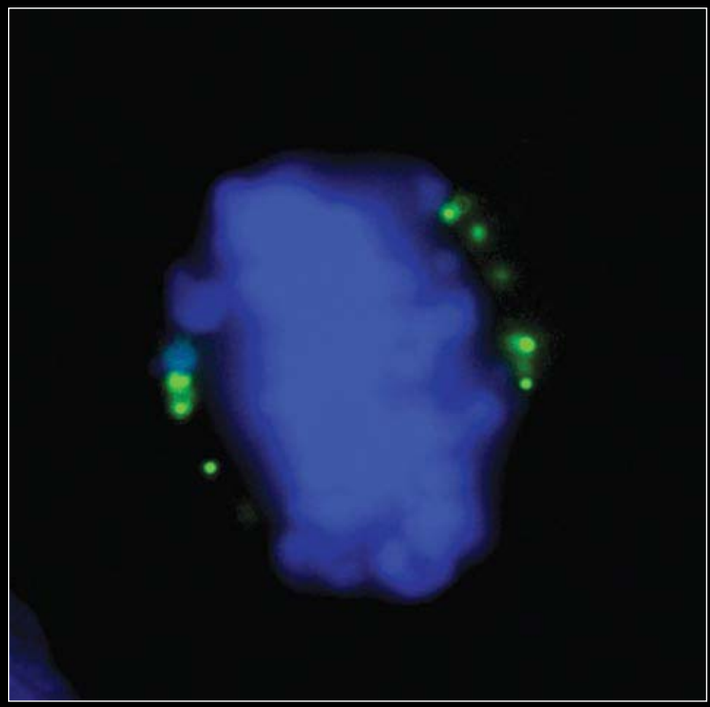
A century after his work, modern molecular biologists have verified much of what Boveri proposed. Duensing, an assistant professor of microbiology and molecular genetics, is resurrecting what was, until recently, thought to be one of the artist-MD's sketchier hypotheses.

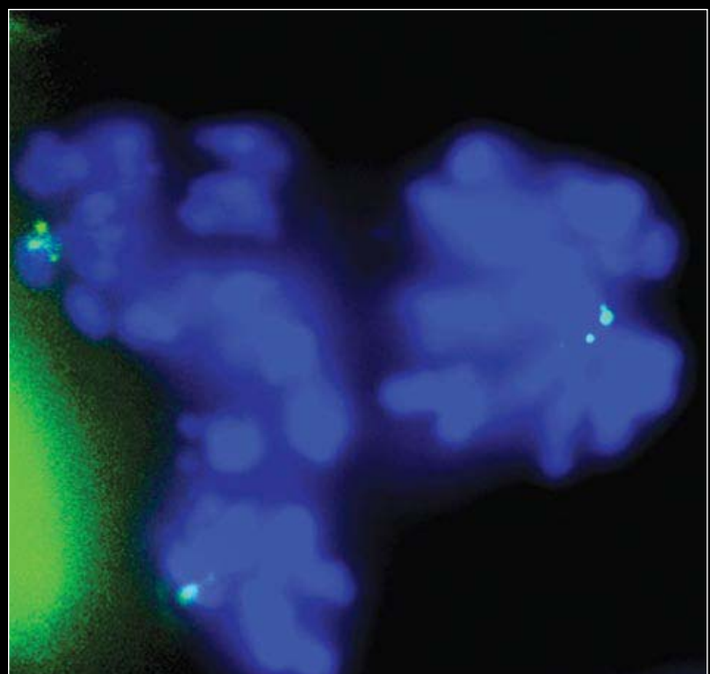


THIS PAGE: With this image, which appeared on the cover of the *Journal of Virology* in November 2003, Stefan Duensing showed that cells expressing a human papilloma virus (HPV) oncoprotein for just 48 hours produced an abnormal number of centrioles. The nucleus is stained blue, mitochondria are red, and centrioles are green.

OPPOSITE PAGE: A normal cell entering mitosis (top image) shows the centrioles (green) at opposite ends of the nucleus. In normal cell division, these centrioles will pull the duplicating chromosomes (blue) into two identical sets. Cells expressing just two viral oncoproteins from HPV-16 produce multiple abnormal centrioles (middle image). The resulting tug of war can divide the chromosomes unevenly (bottom image), perhaps creating extra and abnormal daughter cells. Boveri believed that a single such mishap could lead to cancer. The Duensings believe that is exactly what happens with cancers caused by HPV.







Nodding toward the Boveri text, Duensing notes, "He predicts that a tumor arises from a single abnormal cell, which we think is true because most tumors are clonal."

Duensing's molecular virology lab at the University of Pittsburgh Cancer Institute has uncovered mechanisms that can cause a single cell to divide abnormally and beget an abnormal daughter cell, which, if it keeps reproducing itself through cell division (mitosis), can become a tumor.

At Würzburg, Boveri sketched duplicating chromosomes. He deduced that they carried the means of inheritance, which we now know as DNA. He observed a structure he called the centrosome. In normal cell division, the centrosome duplicates in perfect synchrony with DNA. The two centrosomes then move to opposite ends of the nucleus, where they produce long spindly microtubules that pull the chromosomes into two identical sets in preparation for the cell to cleave.

In cancer, however, three centrosomes might engage in a tug of war over the chromosomes, which can lead to three daughter cells instead of two, says Duensing. And that's dangerous. The daughter cells end up with chromosomal imbalances of the sort that Boveri predicted. An abnormal cell may have an extra copy of a gene that promotes rampant growth, or it may completely lack a critical tumor suppressor gene. In either case, the cell is considered genomically unstable. Duensing believes just one single instance of centrosome overduplication can lead to cancer.

Duensing collaborates and shares a lab with his wife, Anette Duensing, a Pitt assistant professor of pathology. (Her primary interest is a rare gastrointestinal cancer.) Both received MDs in their native Germany and happened upon the work of their countryman Boveri during research fellowships at Harvard University.

To explore Boveri's single-cell hypothesis, the Duensings carefully observed the initiation of cancer, trying to see the moment when mitosis became abnormal. Because of its simplicity, they chose as their research model a cancer caused by HPV—human papilloma virus. A strain of virus called HPV-16 has two genes (oncogenes) that, once inserted into the host cell's genome, are enough to cause cancer. (Breast or lung cancers, by comparison, can have more than 200 such mutations.) The Duensings wanted to know whether these oncogenes could cause the abnormal number of centrosomes seen in HPV cancers. In fact, both did, and one caused it rapidly, within 24 to 48 hours. Those findings were published in 2000 in *Proceedings of the National Academy of Sciences.*

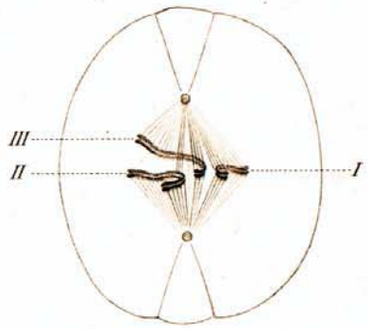
"This was the first report that an oncogene relevant to human cancer could stimulate centrosome overduplication," says Duensing.

In a series of experiments, the Duensings showed that extra centrosomes appeared before the cell became genomically unstable. One problem with this story: Scientists who studied the centrosome said there was no way to produce that many centrosomes in a day or two. Textbooks reported that centrosomes doubled once per cell division cycle, which lasts about 24 hours. There was no way to get five, six, or seven centrosomes—like what the Duensings observed—that quickly.

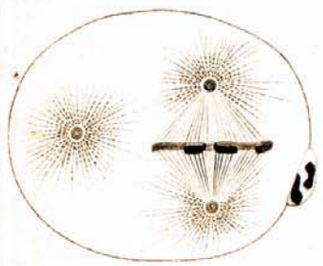
The obvious solution? Rewrite the textbooks. That's what's

OPPOSITE PAGE: COURTESY JOURNAL OF VIROLOGY, NOVEMBER 2003, VOL. 77, NO 22, © 2003, AMERICAN SOCIETY FOR MICROBIOLOGY. THIS PAGE AND P. 27: ADAPTED BY PERMISSION FROM MACMILLAN PUBLISHERS LTD: ONCOGENE, 26, 6280-6288 "CENTRIOLE OVERDUPLICATION THROUGH THE CONCURRENT FORMATION OF MULTIPLE DAUGHTER CENTRIOLES AT SINGLE MATERNAL TEMPLATES," © 2007.

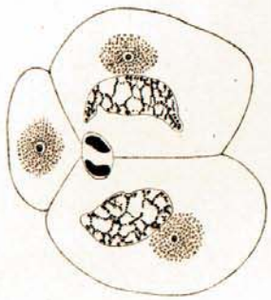
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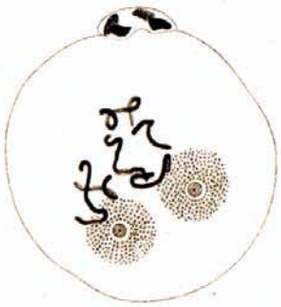
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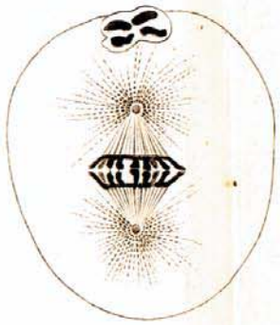
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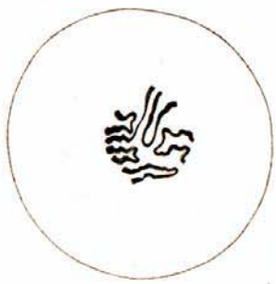
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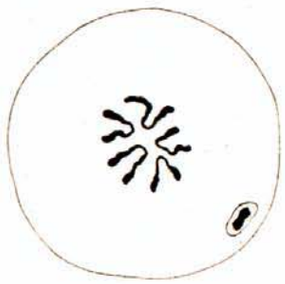
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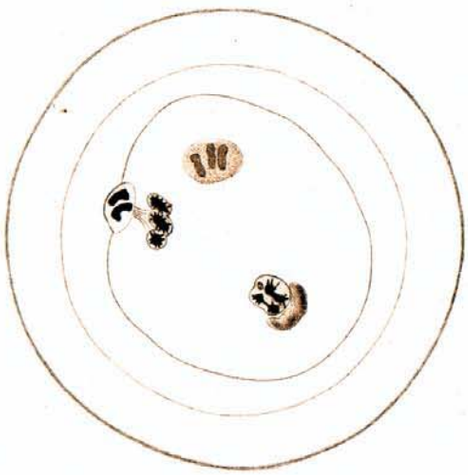
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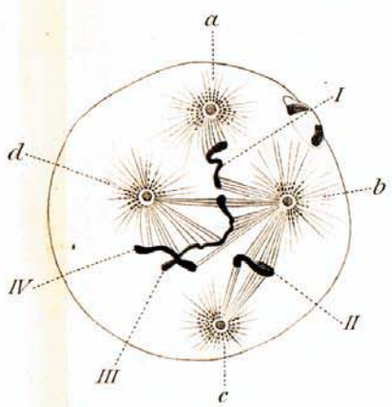
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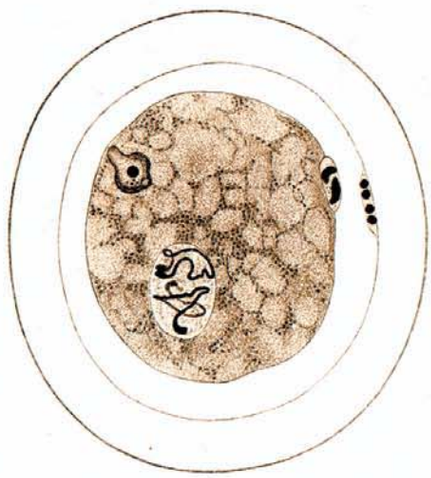
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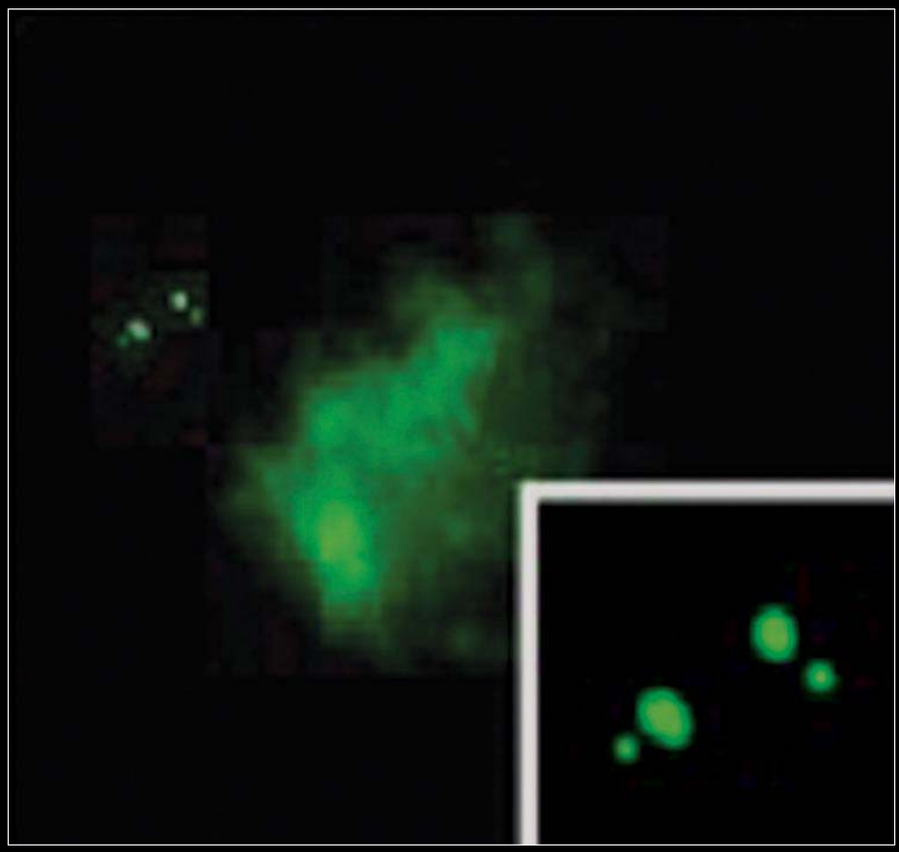


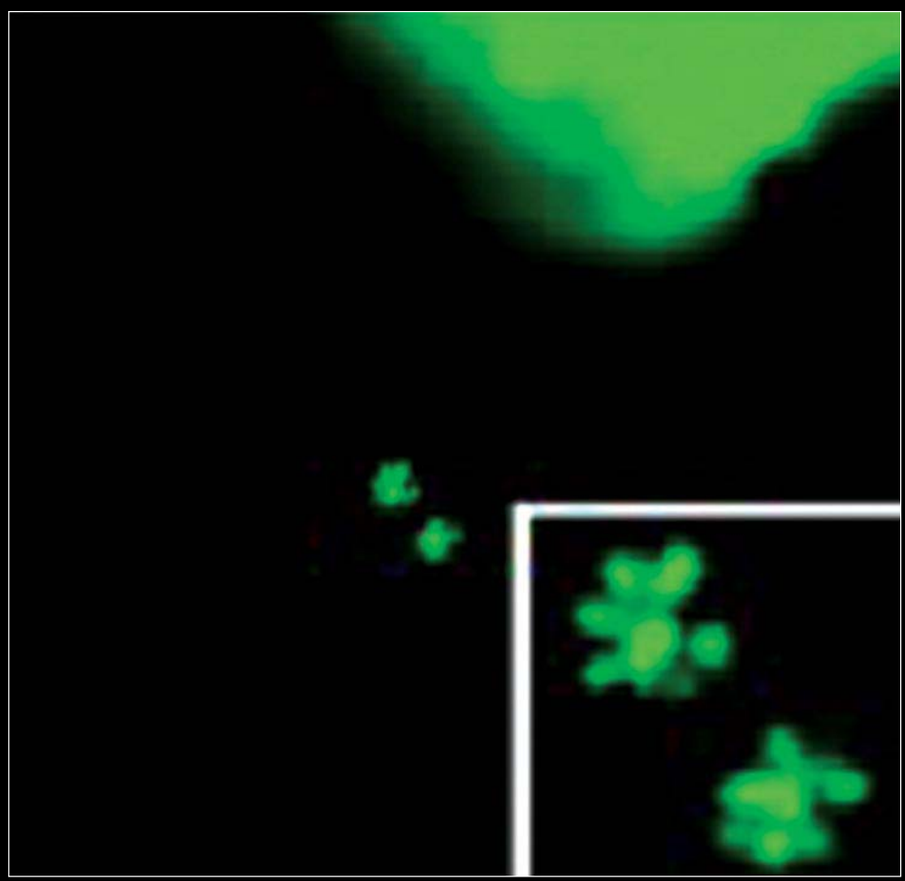
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been happening since Stefan Duensing made the biggest discovery of his young career in the summer of 2005. He describes it as a typical scientific experiment—one that required him to go nearly cross-eyed looking at hundreds of slides.

While examining extraordinarily thin slices from cells that had been treated with a drug so they would divide abnormally, he hoped to stumble upon a centrosome perfectly sliced to reveal a tiny structure within called a centriole. (A normal centrosome has two centrioles; they move apart and duplicate at the start of centrosome duplication.)

"It was one of these long, hot, and humid August Pittsburgh Saturdays," says Duensing. "I was about to go home, and I said, 'One more slide. Let's do it.' I looked under the electron microscope, and there it was—this flower under the electron microscope."

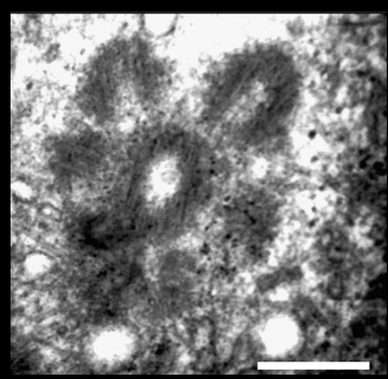
The "flower" was a centriole that was doing more than just doubling as the textbook said it should. Multiple, smaller daughter centrioles surrounded it like petals on a daisy.

Here was the evidence the Duensings had hoped for. Now the couple had convincingly shown that an abnormal number of centrioles could occur in just one cell division cycle. The centriole flower—a term the Duensings have introduced into the scientific vernacular—would help explain how cell division gone awry initiates cancer.

Boveri presumably came to his hypothesis about abnormal mitosis leading to cancer as he gazed through a microscope in Würzburg and meticulously refined sketches of centrosomes pulling chromosomes into abnormal bunches. One century later in Pittsburgh, Duensing snapped a picture.

"It was just the best day I ever had," he says. "I took a ton of pictures. I went home, showed it to Anette, and said, 'Here we go. The paper is done.'" ■

OPPOSITE PAGE: Boveri drew pictures of cells undergoing abnormal mitosis, including some that had too many centrosomes. In the image marked with a numeral 93, four centrosomes tug at the chromosomes, potentially leading to abnormal cells and even cancer.
LEFT AND BELOW: On a muggy Saturday in Pittsburgh, Duensing looked through an electron microscope and snapped a grainy black and white photo of what he termed "a centriole flower." The center of the "flower" is a structure within the centrosome called a centriole (also shown in green), which produces one daughter in normal mitosis. Duensing had found something unheard of: a centriole producing multiple daughter centrioles that surround it like daisy petals. This could be the first step in the overduplication of centrosomes.





TAKE-OUT MEDICINE

HOW TO STIR UP HEALTH CARE IN ONE EASY READ

BY CHUCK STARESINIC

ILLUSTRATIONS BY DAVID POHL

Here's a story with the potential to raise the blood pressure of a physician.

Geoff Larrson is the father of two girls, ages 2 and 4. They live in Pittsburgh. When both girls woke up feverish and generally miserable back in November, their father didn't think there was much mystery as to what was bothering them. Different playmates up and down their street had strep throat. Five children at the local day-care center had been diagnosed with it, and Larrson's girls were probably sheltering their own little colonies of *Streptococcus* bacteria. If so, all they needed was a course of antibiotics, and they'd soon be right as rain.

But Larrson never took his girls to see their doctor. The family has health insurance and a good relationship with the girls' pediatrician, but he didn't want to wait until the office was open to schedule an appointment for another day.

Instead, he drove 10 minutes to a strip mall with one of those ubiquitous national chain stores with a pharmacy. There, at an in-store clinic, a nurse-practitioner swabbed the back of the girls' throats. No appointment necessary. The clinic accepted their medical insurance with a small copay, as their pediatrician would. They waited a few minutes for the results of a rapid strep test, which came back positive, and their prescriptions were filled at the pharmacy in the same store.

Around the country, the number of these "retail clinics," as they are called, is increasing rapidly. One national chain opened 10 clinics in the Pittsburgh area in 2007 and was on pace to start 100 nationwide by the end of that same year. The company's executives recently reported their plan to have 500 clinics in 2008.

Retail clinics offer treatment for a limited menu of ailments, including urinary tract infections, ear infections, sinusitis, pink eye, and early Lyme disease. They also offer vaccinations, including those for influenza, hepatitis B, and human papilloma virus. Under Pennsylvania law, a physician need not be on the premises for these visits and for certain prescriptions.

The trend concerns some physicians. A pediatrician in a small group practice near Pittsburgh, for example, worries that clinics like this will weaken the relationship between doctor and patient and lower the standards for health care. As a doctor in private practice, she also worries about how the trend will affect her bottom line.

Terence Starz, chair of the Allegheny County Medical Society, addresses retail clinics in a November 2007 column in the *Pittsburgh Post-Gazette* with the headline "Quick health care is not the same as primary care." He writes, "In a setting where a physician is not present to examine patients, there is a risk of an inaccurate diagnosis or of missing a serious medical condition. Seemingly 'simple' cases often aren't simple."

Hal Rosenbluth, the chair of Take Care Health Systems, countered a week later in the *Post-Gazette* that Americans are not adequately served by the health care system in this country. Retail clinics were created to fill a critical need for accessible, high-quality, and affordable health care, he says.

"Patients are not our patients or your patients," he writes. "They have options and their own rights."

How do we begin to answer the questions raised here? Enter the policy wonk.

Ateev Mehrotra is a physician who isn't afraid of shaking things up. He's not an advocate of change for the sake of change. He's just extremely curious about fundamental issues of cost, quality, and access in our health care system. Give him a tough question—about retail clinics, for example—and his response is to ask more questions. How can we learn more about the phenomenon? How can we get some data? Intuition is the enemy of data here. Data have the power to remove at least some of the emotion and assumptions from the discussion.

Mehrotra, a Pitt assistant professor of medicine, occupies an academic office in the School of Medicine's Center for Research on Health Care. A photo of his two preschool-age children is posted outside his office just above the nameplate. There would be nothing to make Mehrotra stand out from other young dads at the playground, except his resume makes it seem that he might have arrived in Pittsburgh in 2006 rather breathless. This was his first job since completing a decade or so of medical training that began at the University of California, San Francisco (MD) and ended at Harvard University (fellowship in general internal medicine). In between, there was a master's degree in public health at UC Berkeley, an internal medicine and pediatrics residency at Massachusetts General Hospital and Boston Children's Hospital, and a master's degree in epidemiology from Harvard.

Mehrotra is a chimera of sorts. He practices medicine and analyzes health policy for RAND, the independent policy think tank with a reputation for dispassionate analysis, rigor, and excellence.

The phrase "health policy research" might sound drier than month-old pound cake, but Mehrotra explores nuts-and-bolts questions that are of interest to almost anyone. He asks what keeps your doctor from giving you an appointment within 48 hours of your call. He explores alternative ways of paying your doctor and ways your doctor might provide better care. In September 2007, he authored a study in the *Archives of Internal Medicine* that dared to address the question of whether the annual physical exam was good or bad for your health. (The answers to such questions can be surprising and, to say the least, counterintuitive.)

If Mehrotra's research bio were turned into a late-night comedy bit, it could be titled, "Top 10 Ways to Shake up Your Doctor's World."

(Number one: Tell him you're skipping your annual physical for health reasons.)

RAND has a storied history that began in the 1950s, when the federal government realized that the Cold War called for defense policy analysis from outside Pentagon circles. RAND recruited some of the brightest economists, statisticians, and analysts to the cause. In the 1970s, RAND (born of the phrase "research and development") made the strategic decision to expand into other arenas. While defense work remains a RAND mainstay, health policy research has become another pillar of the think tank's expertise.

About 10 years ago, RAND started casting about for a new city in which to expand. It was based in two of the most expensive real estate markets in the country—Santa Monica, Calif., and Washington, D.C. These were good locations, except when it came to recruiting talented young staffers who were starting families and purchasing first homes. They looked at several cities, and Pittsburgh won out.

"The main driving force behind the selection of Pittsburgh was to offer an alternative to staff that was lower cost of living and higher quality of life," says RAND senior health policy analyst Donna Farley. The new RAND building on Fifth Avenue was built to house 200 employees, and she says they are approaching that number ahead of schedule. Some RAND statisticians have relocated to Pittsburgh solely for quality of life, despite the fact that their main collaborators are in California or Washington, D.C. (Lucky for them, data travel well.)

Shortly after RAND's arrival in Pittsburgh, the organization's representatives met with Arthur S. Levine, dean of Pitt's School of Medicine and senior vice chancellor for the health sciences, about collaborations with Pitt. This was quickly followed by a financial commitment from the School of Medicine and RAND to formalize the arrangement as RUPHI (RAND–University of Pittsburgh Health Institute), which is pronounced the same as the Indian unit of currency. The institute is jointly headed by Farley, of RAND, and Wishwa Kapoor, Pitt professor of medicine and chief of the Division of General Internal Medicine.

Kapoor says that one of the surprising things for RAND was the strength of health policy research already under way at Pitt.

"There were 60 investigators studying health policy and $50 million dollars in funded studies. There were studies going on in the community, which RAND was very interested in, plus studies in hospitals and clinics."

Nevertheless, Pittsburgh was not considered a go-to location for health policy research. That has changed in less than 10 years.

Mehrotra was a fellow at Harvard University, which has a med school department devoted to policy research, when he interviewed with RAND in Santa Monica and separately with the University of Pittsburgh. In 2006, he became the first joint hire under RUPHI. (At least two others have followed. In addition, dozens of collaborations have sprung up between existing Pitt and RAND researchers.)

Like a lot of Pitt researchers, Mehrotra splits his time between different locations on Pitt's urban campus. At his RAND office, he is an MD surrounded by PhD economists, sociologists, policy analysts, and even lawyers. He calls it a very enriching environment when paired with the School of Medicine and the clinic. For weeks at a time, Mehrotra will go on clinical service as a hospitalist, which he says keeps his policy work grounded in the real world of patients, doctors, and hospitals.

If Mehrotra's research bio were turned into a late-night comedy bit, it could be titled, "Top 10 Ways to Shake up Your Doctor's World." (Number one: Tell him you're skipping your annual physical.)

While still at Harvard, Mehrotra's work as a primary care physician caused him to rethink the annual exam.

"I was spending a lot of time doing physical exams for patients," he says. "I was encouraging them all to come on an annual basis. Yet I knew the literature on the physical exam was limited. There were no guidelines out there to tell me how often, or what they should entail. I just did what I learned in residency."

Something else that contributed to his doubts was that he would occasionally get telephone calls from friends and relatives, saying, "I got this blood work at my annual exam, and a few things came back abnormal. What should I do?"

"In the back of my head," says Mehrotra, "I'm thinking, 'You shouldn't have had that blood work.'"

He goes on to explain, "I was trained in the era of evidence-based medicine and taught that ordering annual blood work [a complete blood count and electrolyte panel] was more likely to result in a false positive than detect true disease." Doctors trained in another era, however, may believe they are not doing their jobs if they don't order these tests.

"Yet there's no guidelines to support it," says Mehrotra. "No evidence. … No consensus on who should get a physical exam and what the content should be."

In 1979, Mehrotra points out, a Canadian task force charged with studying the annual exam stated their conclusion as plainly and forcefully as they could in the *Canadian Medical Association Journal*: "We recommend that the annual checkup, as practiced almost ritualistically for several decades in North America, be abandoned."

More than 25 years later, Mehrotra's study, done with colleagues at Harvard, turned up some striking numbers: Physical exams are the number one reason adults see their doctors. Doctors perform such exams 63 million times a year, adding up to $7.8 billion in revenues.

An intuitive response is to say that an annual exam could hardly be bad. It strengthens the relationship between doctor and patient that could become vital when health fails. That may be true, says Mehrotra, but rates of preventative care are much too low in this country. And unnecessary tests, by definition, lead to more problems than they solve. They do this at significant costs.

Unscientific polls indicate a level of support among doctors and patients for continuing the annual exam. Advocates say that allows the doctor to keep the patient current on preventative care measures like mammograms and smoking cessation counseling. Others say that there's no reason preventative care can't be delivered during the periodic office visits scheduled for acute problems.

"We did some back-of-the-envelope calculations," Mehrotra says. "And we found that there's no way an individual physician could provide an annual exam for all [his] patients," without spending half of all the available time doing them.

Reporters covering the story came to Mehrotra with various versions of the question, "Why do you have yourself up on a wire, doc?" His answer comes from another of his research interests: patient access to doctors.



No appointment necessary at many retail clinics popping up around the country.

In Massachusetts, he worked with a number of practices that experimented with open access scheduling, meaning that a patient could get an appointment within a day or two of calling. The goal was to open the schedule for patients who were ill and needed to be seen right away. Problem was, the schedule filled up with annual physical exams anyway. Around the same time, Mehrotra talked to doctors from a large practice in Minnesota who had decided to stop encouraging annual exams. It sounds like a bad business model, but it worked. The doctors were more available to their ill patients, and it didn't hurt the bottom line. The schedule filled up. Preventative care wasn't compromised.

The question of access brings us back to the topic of retail clinics. Mehrotra is in the middle of a major study to find out who goes to these clinics and why. His team is interviewing patients to find out why they choose the clinic over a primary care doctor. His goal is simply to get the facts about this emerging way of delivering care. How many clinic visits are supplanting visits to physicians? What is the economic impact? Are the clinics delivering care to the uninsured and others who might not get it otherwise? Do the clinics have something to teach us about the delivery of preventative care such as vaccinations? Is the quality of care higher or lower than that provided in a doctor's office?

Speaking of paradigm shifts, Mehrotra has a career development award from the National Institutes of Health to look at "consumer-directed health care." The idea behind this reform? People who pay a small amount for health insurance but pay out of pocket for their care become more discerning consumers. This model requires that patients know their options, including the costs of different procedures and tests, the pros and cons of different treatment options, exact fees that specific doctors charge, and a given doctor's track record in treating patients.

Mehrotra also studies the pay-for-performance model, in which hospitals get rated on quality metrics and rewarded accordingly.

"But the devil is in the details," says Mehrotra. "How can you create reliable and valid metrics upon which to judge a provider?"

Over the past year, he and colleagues have been helping Medicare explore pay-for-performance options through a contract with RAND.

"Congress told [Medicare] that they wanted to create a pay-for-performance program," Mehrotra says. A plan went to Congress a couple of months ago. "If approved, it's probably one of the largest pay-for-performance programs in the world, with billions of dollars involved in terms of incentive payments."

"These are really important questions," says Kapoor.

"Pay for performance is huge. Studies from England show it to be very successful in primary care, but there were huge incentives." The incentives proposed in this country include more modest reimbursements for meeting guidelines for care of certain conditions.

"It's not clear whether that's going to work, or if it's going to be a waste of money," says Kapoor. "I think Ateev is going to be one of the national leaders in this area, because he's going to look at this as pay for performance evolves in this country."

In the world of retail clinics, Mehrotra's research won't be completed for some time, but he is finding the emerging story fascinating.

In interviews with people who patronized retail clinics, for example, it seems that many had already visited a clinic in another part of the country. They chose the same chain pharmacy's clinic when they were traveling, or after moving to another location, for the same reason that people patronize Starbucks for coffee or Curves for a workout as they travel—because they know what they are getting.

Some physicians may be uncomfortable with retail clinics for the opposite reason: They are not certain what these patients are getting.

Whatever the future is for retail clinics, payment reforms, and other mass experiments in care, it leaves plenty of work for health policy researchers like Mehrotra. ■

A family's name and details were changed in this story to protect privacy.



In Mozambique, there are 33,500 people for every doctor. In the United States, that ratio is 390 to 1.

TWINS

A PITT PARTNERSHIP HELPS TRAIN MOZAMBIQUE'S NEWEST DOCTORS

BY CASSANDRA ZINCHINI

When Aurelio Gomes graduated from Eduardo Mondlane University in Mozambique in 1980, the government sent the new MD to Catandica Health Center in Manica, a rural province of mountains and shining green vegetation. Anthropologists have often called East Africa the birthplace of humankind, and Manica province even has rock paintings on its cave walls. Manica was a place of beginnings for Gomes, too: the site of his first job as a doctor. That was an exciting time for Gomes—but also depressing.

It is difficult to imagine Gomes down. He has an easy sense of humor and laughs often. But for the first six months at the center, Gomes could not sleep.

He was terrified of making a mistake, and even simple diagnoses presented challenges. Not only did he grapple with cases of pneumonia and wonder whether antibiotics were working, but Gomes also had to contend with the civil war raging nearby. The rebel group, Renamo, conducted ambushes at night. Many wounded ended up at the rural clinic. Land mines exploded. Men missing legs would arrive in the wee hours of the morning, along with men and women with bullet wounds. The Catandica center had no surgical facilities, and Gomes would wait anxiously for the military convoy to arrive the next day so he could send patients to an OR.

Mozambique's medical education system didn't include hands-on training in the form of residencies. And because of the lack of doctors and resources typical of most Sub-Saharan African countries, the rookie doc had no mentors or even colleagues at the center.

Today the situation is even worse for young doctors in need of practical training. AIDS is claiming the lives of physicians and nurses. One of the teachers at the medical school at the Catholic University of Mozambique (UCM) in Beira, where Gomes holds an appointment as the director of the medical research center, died from AIDS a few months ago.

Mozambique, a country of 19 million, has about one doctor for every 33,500 people. In the United States, that ratio is 390 to 1. Until recently, Mozambique had only one medical school.

The Catholic Church had been part of the peace process that ended the civil war that lasted for almost two decades in Mozambique. During negotiations in 1992, the church promised Renamo it would open a university if the rebels would end hostilities. In 1994, UCM started a school of economics in Beira, a coastal city in the central province. In 2000, it opened the medical school.

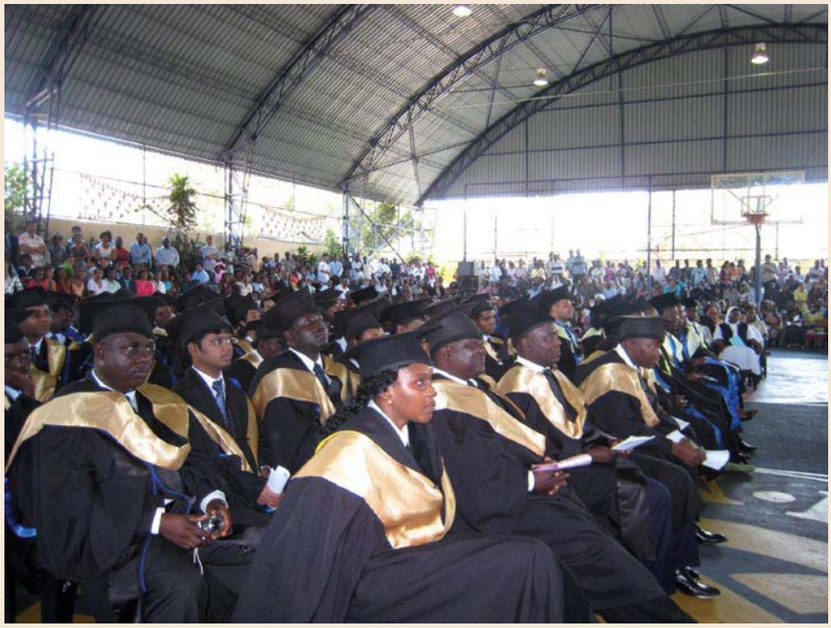
Before the partnership, UCM health care workers went to didactic lectures but had no hands-on training.

Gomes connected UCM and the University of Pittsburgh in a partnership through the American International Health Alliance, which addresses public health challenges around the world. He now holds his primary appointment at Pitt as research assistant professor in the Division of Infectious Diseases; Gomes acts as a bridge between Mozambique and Pittsburgh, splitting his time between the United States and his home country.

The doctor first approached the infectious diseases team at the University of Pittsburgh in 2002 when applying for a grant from the National Institutes of Health called the Comprehensive International Program for Research on AIDS (CIPRA). To qualify for the CIPRA grant, which would fund research development for UCM, Gomes needed the collaboration of a U.S. institution. A colleague from West Virginia University pointed him toward Pitt. Mozambique already met the other criteria: It had a low gross national product (in 1999, the country's GNP broke down to U.S. $230 per capita, making it one of the poorest countries in the world) and a serious HIV/AIDS problem, yet few existing programs.

The team at Pitt was interested in hearing about UCM's new medical program and further attracted to Mozambique when it visited to do an initial needs assessment. Although Margaret Palumbo, former administrator of Pitt's HIV/AIDS program, and Deborah McMahon, associate professor of medicine at Pitt and now medical director of the Pitt/UCM partnership, enjoyed the beauty of the country—the blue skies; the wild, green land; the quality of the light that made everything seem brighter—they were appalled by the health conditions. In the central province of Sofala, about 25 percent of the general population was infected with HIV. The one hospital often had no electricity or water. Palumbo and McMahon saw doctors who were frustrated and a hospital so overcrowded

PHOTOS COURTESY C. ZINCHINI





PHOTOS COURTESY C. ZINCHINI

On Aug. 25, 2007, the first med student class of the Catholic University of Mozambique graduated. ABOVE: John Mellors, the University of Pittsburgh's chief of infectious diseases, handed each graduate a doctor's bag with instruments that he'd brought from Pittsburgh.

(sometimes three people shared one bed), that people were lying in the halls.

The CIPRA grant focused on enhancing UCM's research capacity, but Mozambique's need for patient care and trained doctors was immense.

"I thought, 'We need to get care here.' [The visit] reaffirmed our feeling that we needed to be involved in any way we could," Palumbo says.

So they could improve care and spur research, Pitt and UCM designed a twinning partnership. The partnership aims to increase personnel to provide HIV services and palliative care through the development of an HIV training center on the grounds of UCM's medical school. It also focuses on fostering UCM faculty development and building the school's research capacity. Through the partnership, Pitt med students will be able to learn about tropical diseases and global health issues at Beira.

Before UCM and Pitt faculty started working together, Beira's health care workers went to didactic lectures but had no hands-on training. At the new Beira training center, however, they will help care for 1,000 patients, under the watchful eyes of mentors. Students benefit, too.

"My best training comes from the time I spend working at the clinic," says one of Gomes' students.

Part of the inspiration for the training center came from a clinic in Mangunde that Gomes established. It was the first rural HIV clinic in Mozambique.

The four-hour drive from Beira to the Mangunde clinic in central Mozambique is mostly on orange dirt roads marked with potholes that can swallow a tire. There are few cars. Most people walk on the side of the road. It is not uncommon to see men transporting live goats on bicycles.

Far from any organized town and 25 kilometers off the main road, the Mangunde clinic is a handsome, white-washed building with a red cross on the front.

When patients check in, a staff member enters their information into the electronic health records system powered by a generator. (There are no power lines in the area.) The clinic staff members know patient names, which ethnic groups they come from, whether there are issues in the family, when patients miss appointments. The clinic also provides food supplements to pregnant women and any patient who looks malnourished. The staff treats everything from crocodile bites to HIV.

Peter Veldkamp, assistant professor of medicine in the Division of Infectious Diseases at Pitt and educational director of the UCM/Pitt partnership, has visited the Mangunde clinic a number of times and is impressed. In many ways, care is comparable to the UPMC HIV clinic in Pittsburgh, he says.

"Professional satisfaction is essential for staff," says Gomes, who received a master's degree in public health at the University of Hawaii.

"They need electricity, supplies, and a working lab. They need a professional environment."

He's trying to combat Mozambique's "brain drain."

"I came back to Mozambique because I wanted to do something good for my country," Gomes says. He remembers particular cases, like the 3-year-old boy who was brought in with severe convulsions from cerebral malaria. (Many poor children suffer from malaria because their parents can't afford bed nets.) Days after treatment, this boy ran down the hall to Gomes. His arms were outstretched, and he was giggling.

Gomes hopes his students will have many rewarding experiences like his—and he hopes they'll have them in Mozambique.

UCM's jubilant first med school class graduated this past August.

"For me, the practice of medicine is the best way to help others," says Filipe Vicente, now in his fourth year at UCM.

Vicente is the oldest of five children. His father and mother split up when he was young, and his mother had no income. She then sold fish, cakes, and drinks and worked on farms so that she could pay school fees for Vicente and his siblings. Vicente wondered how he could help his mother, but jobs are few and far between in the countryside.

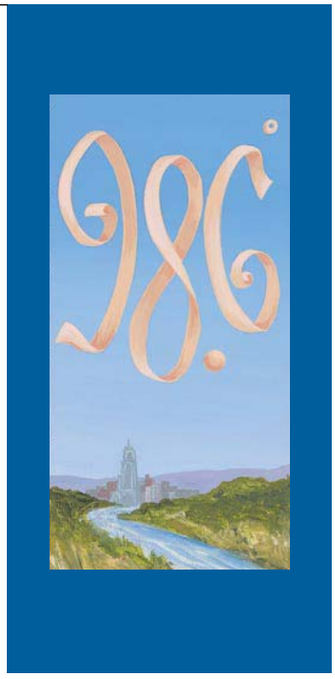
Then Vicente's uncle took him in as well as one of his younger brothers. Vicente's aunt, a nurse, suggested he could go to medical school, and his uncle agreed to pay his fees, the equivalent of U.S. $1,500 a year. When his uncle died, Vicente was no longer able to afford the tuition. Had it not been for a scholarship awarded to him, paid for by Pitt's infectious diseases faculty's holiday contributions, Vicente would have had to drop out.

His story is not an unusual one among UCM med students.

In a few years, Vicente will probably make his way on bumpy roads to an assigned area like Gomes did 20-some years ago.

But first, Vicente will train with experienced doctors. ■

People and programs that keep the school healthy and vibrant





COURTESY CHILDREN'S HOSPITAL OF PITTSBURGH OF UPMC

The new Children's, ready for patients in early 2009.

RAISING CHILDREN'S

GOING UP

BY CHUCK STARESINIC

It's not often that a hospital for kids gets built from scratch. But we have a chance to do it right here in Pittsburgh. With that in mind, foundations and corporate citizens have been pitching in to help make the new Children's Hospital of Pittsburgh of UPMC something special.

As recently as 2002, UPMC and Children's had planned to build a new 500,000-square-foot hospital on the somewhat cramped Oakland campus. That notion changed dramatically with the purchase of the former St. Francis Hospital complex a few miles away in Lawrenceville. The site covers 10 acres, with several existing buildings to link to the new hospital.

The $625 million campus will have 900,000 square feet of facilities, including a 9-story hospital. Nearly all of the 296 beds will be in private rooms that are 50 percent larger than those in the current Children's Hospital.

The Children's Hospital of Pittsburgh Foundation reports $66.2 million so far raised for the new hospital. This includes $10 million from the Henry L. Hillman Foundation for a transplantation institute and $2 million from the Richard P. Simmons Family Foundation.

The Eden Hall Foundation gave $3 million in 2007 for a family resource center that planners describe as the hospital's "town hall." It will link the hospital chapel, libraries, 24-hour playroom, young adult resource center, lounges, and patient representatives offices. The center also will have a business room for moms and dads to check in on work obligations and classrooms for family programs. The Elsa M. and Alma E. Mueller Family Resource Center is named for the daughters of Pittsburgh philanthropist Sebastian Mueller, whose fortune endowed the foundation. His daughters died of diphtheria as children in the 1800s.

Corporations also have signed on. Children's will name its four-story atrium for Eat 'n Park, and the outdoor garden on the sixth floor will bear the name of Howard Hanna.

A NEW MELLON INSTITUTE

Nobody in the University of Pittsburgh Department of Pediatrics denies the importance of federal research dollars. On the contrary, you'll be reminded that Pitt's pediatric research program is in the top 10 nationally. Still the chair of pediatrics might suggest that relying solely on the National Institutes of Health these days carries a risk.

"Declining availability of NIH funding creates uncertainty that leads to conventional types of science," noted David Perlmutter, the chief physician and scientific director at Children's Hospital of Pittsburgh of UPMC and Pitt's Vira I. Heinz Professor and chair of pediatrics. He said this in October as the Richard King Mellon Foundation announced a gift of $23 million to create a pediatric research institute at the new Children's.

The institute will seek to overcome research inertia by recruiting a cadre of innovative physician scientists early in their careers. At Pitt, they will receive continuous funding to pursue their most exciting ideas, many of which would not be able to garner NIH support in their early stages. The institute will apply this high-risk, high-reward approach to critical areas of pediatric medicine, with the aim of creating "transformational advances," according to Perlmutter. "The most important discoveries are made when brilliant investigators have the resources and flexibility to follow their instincts," he says.

The institute will be housed in Children's new 10-story, John G. Rangos Sr. Research Center adjacent to the new hospital. ■

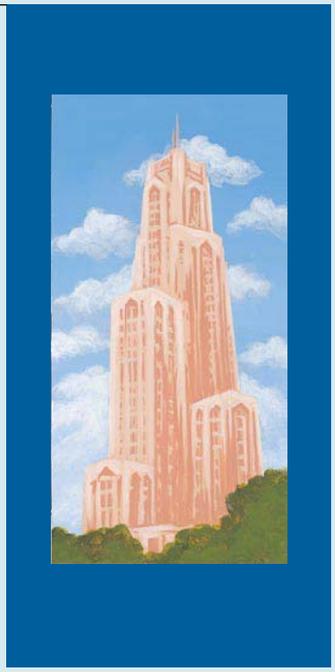
FOR INFORMATION ON GIVING TO CHILDREN'S:
412-586-6335, jessica.urbanik@chp.edu

BOOSTER SHOTS

Medical students and alumni worked the telephones to raise scholarship funds with the University of Pittsburgh's Medical Alumni Association in November. One caller reached **Perry Engstrom** (MD '47) out in Wahpeton, N.D., who promptly pledged $40,000 to the Class of '47 Legacy Scholarship Fund. He couldn't talk long because, at age 83, he had to get up early the next day to perform surgery. Engstrom is a general surgeon in Wheaton, Minn., a prairie town that has a tough time attracting new docs. Shortly after that call, Engstrom pledged another $10,000. The phonathon brought in around $115,000 in pledges.

The University of Pittsburgh School of Medicine recently received a commitment of $325,000 from the **Respironics Foundation** to fund a new fellowship program in sleep medicine. With the influx, Pitt's Divison of Pulmonary, Allergy and Critical Care Medicine will offer a one-year clinical training experience, the Gerald E. McGinnis Fellowship in Sleep Medicine. The fellowship is named for Pitt graduate Gerald E. McGinnis, the founder and chair of Respironics. *–CS*

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



CLASS NOTES

'60s

In the 1960s, ultrasound was a newfangled idea that many thought would never be useful in medicine. **George Leopold** (MD '62, Radiology Resident '68) was a resident when the chief of radiology made him lug the heavy machine around the hospital and see what he could make of it. Leopold was hooked. He went home and read all the available literature, which at that time was so scant that it could be covered in an evening. Leopold became a promoter of ultrasound technology, convincing hesitant radiologists that it was a valuable tool. He established the first ultrasound lab on the West Coast, at the University of California, San Diego. He focused his research on using ultrasound to detect everything from breast cancer to diseases of the biliary tract and published more than 100 articles.

"Every day was something new. We were constantly learning," says Leopold, who retired as UCSD's chair of radiology in 2001. "Every day was a different piece of anatomy or a different pathology that had never been seen in any way before. It was a very small nucleus of people who were interested in ultrasound, and the camaraderie, the zeal that people had in pursuing this, was really fantastic."



The Leopolds

After **Emerson Farley** (MD '64) retired from his internal medicine practice in 2002, he began to volunteer at Kijabe Hospital, which is one hour north of Nairobi, Kenya. He spent one month each year at Kijabe for three years. Farley says five to seven patients a week would die on his watch, most of them from HIV/AIDS complications.

He tells the story of one young man who woke up without the use of his legs. With very little diagnostic equipment, all they could determine was that his paralysis was caused by a form of transverse myelitis. Farley treated the boy with the highest dose of steroids he'd ever used.

"In five days he walked out of the hospital," says Farley. "If there was any patient who epitomized why I went over there, it was this kid. All you did was the best you could to help people."

Recently, Farley worked with Hope for Humanity to build a high school in southern Sudan, which should open its doors in April 2008.

'70s

Thirty years ago, **George Fatula** says he was known as the "no charge doctor" because he never turned a child away. For Fatula (MD '71), the chief of pediatrics at DuBois Medical Group in Central Pennsylvania, this policy still holds. Years ago, Fatula took care of a dangerously underweight premature baby who survived and recently sent Fatula an invitation to her wedding. Former patients have become pediatricians and traveled distances just to do their pediatric rotations under him. In 2006, he was named Pediatrician of the Year by the Pennsylvania Chapter of the American Academy of Pediatrics.

VONDA WRIGHT

RESPECTS HER ELDERS

At the 2001 Senior Olympic Games in Baton Rouge, La., Vonda Wright (Res '05) was inspired by the sight of athletes older than 40, 50, 60, and even 70 years of age running those magic 4-minute miles—the ones high school track stars often lay claim to. That experience, as part of a group of researchers from Pitt's Department of Orthopaedic Surgery, helped to turn her interest in sports medicine toward what she says is a neglected population.

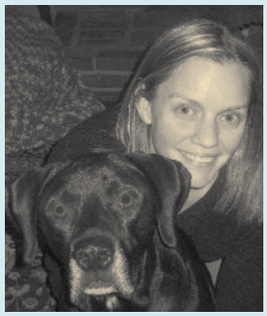
"We have virtually ignored the most active athletes over 40," says the 41-year-old assistant professor of orthopaedic surgery in the University of Pittsburgh School of Medicine. But they enjoy a quality of life that often eludes their more sedentary counterparts, she says, and could teach us a lot about remaining active and aging well.

Wright is director of a program called Performance and Research Initiative for Masters Athletes (PRIMA), which is designed for aging marathon runners, long-distance cyclists, and triathletes. She teaches injury prevention, sets up training programs, and treats sports-related injuries.

In 2005, she coordinated research for the Summer National Senior Games in Pittsburgh. She has found that even the most fit cannot overcome the effects of

'80s

In 1997, as pediatric neurosurgeon **Mark Dias** (Neurological Surgery Resident '89) sat feeding his sobbing newborn son in the middle of the night, he was surprised to find that he was able to feel some empathy for people who lose control and shake their babies.



Barwell

"I started to understand the frustration of being up at night with a baby who is crying and won't go to sleep, and you have to get up early in the morning to go to work. You're tired, and you want to go back to bed," he says. "I didn't lose it, but I understood how they could."

Dias, professor and vice chair of clinical neurosurgery at Pennsylvania State University, now heads a Shaken Baby Syndrome prevention program that covers parts of New York and Pennsylvania. The program runs a campaign to inform new parents and the community of the prevalence and the dangers of shaken baby syndrome. Since the program's inception in 1998, the number of incidents detected or reported has decreased by more than 50 percent. Dias says similar programs are being introduced worldwide based on the model.

'00s

Psychiatrist **Michelle Barwell** (MD '97, Psychiatry Resident '01) once had a patient who threatened suicide because he would never have the things he wanted in life. "It's easy to put in your own judgments or needs when you hear people say things like that," says Barwell. "But I asked him, 'What is it that you want in life?' And what he wanted was his own apartment and a bus pass every month. It was a graphic reminder that you shouldn't ever assume what someone means."

Barwell is a community psychiatrist at UPMC. She works with Health Care for the Homeless and is on the board of CONTACT Pittsburgh, a 24-hour crisis hotline. *Pittsburgh Magazine* named her one of the city's top young community leaders for 2007. She says that she has always rooted for the underdog. "[My patients] struggle. They struggle to find people who care."

On her computer, epidemiologist **Ume Abbas** (Biomedical Informatics/Infectious Diseases Fellow '03) can unleash a virus and watch it spread. Then she introduces a vaccine or a prevention tool; she can study disease transmission based on a vaccine's efficacy as well as its psychological effect on people.

Abbas, an assistant professor in the Division of Infectious Diseases at the University of Pittsburgh, uses computer models to simulate the spread of HIV. Currently she is studying the effects of antiretroviral drugs, which, though they are not a vaccine or a cure, can prevent transmission in some instances.

Abbas notes her models can describe, prescribe, or predict. "I think infectious disease modeling is a powerful research tool which needs to be developed more," she says.

Omar Bhutta (MD '05) was named chief pediatric resident of the University of Washington's Children's Hospital and Regional Medical Center in Seattle.

It was his three-month rotation at Children's Hospital of Pittsburgh of UPMC as a third-year med student that put him on the pediatrics path. "I remembered the day I had to go back to the land of adult medicine and feeling so sad," he says.

After his year as chief resident, Bhutta plans to pursue a pediatric critical care fellowship, then to continue working in an academic setting where he can teach fellows, residents, and med students.

—Sarah Evans, Joe Miksch, & Chuck Staresinic



Wright, a Panthers physician, shown last fall expecting a touchdown and, eventually, a baby.

aging after 75, when physical decline accelerates.

"We have a finite number of years," she says.

Wright finished the 2003 Chicago Marathon with her then-67-year-old father. The athletes she works with have inspired her to push further, she says.

"In my 39th year, I quit jogging around. I asked, 'Why are you doing this? What are you running for?'" she says about her own workout regimen. So she ran hills and pushed herself, knocking two minutes off her 10-kilometer pace.

Her current research involves gender and age differences in healing: "It's like *Men Are From Mars, Women Are From Venus* on a cellular level," she says, laughing. "We know from [Pitt professor] Johnny Huard's lab that female cells heal muscle better, and male cells heal bone better. What kind of cells heal tendons better?" And how much does age matter, she wonders. "Can I take my cells at age 40, or do I have to borrow them from a 20-year-old?" *— Kathleen Phalen Tomaselli*

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M-200K Scaife Hall
University of Pittsburgh
Pittsburgh, PA 15261
tel 412-648-9090; fax 412-648-9500
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THE WAY WE ARE
CLASS OF '72

Henry Higman, the former University of Pittsburgh chair of neurology, reportedly used to interview patients in front of his class, arrive at a diagnosis using deductive logic, then attempt to confirm his diagnosis after the patient's surgery.

"He was probably the best neurologist I have ever known," says **Jacob Sage** (MD '72), professor of neurology at Robert Wood Johnson University Hospital and director of its Movement Disorders and Parkinson's Disease Center. Sage was a medical student during what he calls "the first years of really good Parkinson's treatment."


Sage

"Henry Higman made it feel like an exciting field to be in," he says.


Goorin

Sage researches motor function fluctuations in Parkinson's disease. After about five years on the medication levodopa, 50 percent of patients begin to have fluctuating responses and abnormal involuntary movements. He and his team are researching the cause behind these fluctuations.


Coull

Like many in his class, **Allen Goorin** (MD '72) is in a reflective mood these days. He's playing around with writing a memoir, mainly about what he's learned from 35 years with cancer patients. But there's probably room in there for a bit about his father, too—a Russian immigrant, who, when dying of cancer, told 16-year-old Goorin that he wanted him to be a doctor. Goorin only recently stopped seeing pediatric cancer patients at Dana-Farber Cancer Institute in Boston.


Shulman

An associate clinical professor of pediatrics at Harvard University, Goorin has built a career caring for children with osteosarcomas—solid tumors of the bone. Clinical trials to treat a rare cancer require the cooperation of multiple institutions to get anything published, so he estimates his name is on two-thirds of the osteosarcoma papers published in the past few decades. More importantly, the patient survival rate has gone from 40 percent to 70 percent during that time.


Laufman

Goorin recalls one osteosarcoma patient whom he proposed treating with an experimental therapy that had been successful in a different cancer. She was out of options, and this therapy helped her get another five years, he says, during which she married. That therapy—high-dose ifosfamide combined with etoposide—is now the subject of an international osteosarcoma clinical trial.


McClure

As professor and head of the Department of Neurology at the University of Arizona, **Bruce Coull** (MD '72) often reflects on the decades-long trajectory of Pitt's School of Medicine. He and several classmates contacted for this article invoked the names of revered Pitt professors of the past—Ken Rogers and Jack Myers, for example—whom they hold second to none. And since those days, Coull says, the entire school has catapulted to the upper tier of American medical education. (He recalls reflecting on Pitt's rise years ago in the office of a classmate who was subsequently moved to display his Pitt degree more prominently alongside his training credentials from a certain ivy-covered institution.) In addition to running a department at Arizona, Coull conducts research on stroke prevention. He is co-editing a book on clinical trial design in clinical neuroscience.

Thomas Johnson (MD '72) calls training with Myers, the former chair of Pitt's Department of Medicine, "one of the brightest spots of my Pitt medical experience. He was able to explain very complicated subjects in a clear manner. If you could remember what Jack Myers said, you were not going to get into trouble."

Johnson focuses on both family medicine and critical care in Oakland, Md., and says he loves working with patients he has known for so long they are like family. He plays the recorder and performs Renaissance and Baroque music, races sailboats, and cycles on a tandem bike with his wife in such places as Tuscany and Ireland.

Among **Ivan Shulman's** (MD '72) proudest accomplishments is that he has been able to take a break from practicing medicine when music called. An oboist and conductor, Shulman has been the music director of the Los Angeles Doctors Symphony Orchestra since 1990. He earned his master's degree in music and has just begun teaching in the field at California State University at Long Beach.

Hematologist/oncologist **Leslie Laufman** (MD '72, Internal Medicine Resident '75) is clinical assistant professor of internal medicine at Ohio State University and, in private practice, president of Hematology Oncology Consultants in Columbus. She designs and runs clinical trials for new chemotherapy and drug treatments for colon, lung, ovarian, and breast cancers. She serves as an editor for several oncology journals and is the editor of the National Cancer Institute's website on cancer screening and prevention. In the late 1990s, she was a member of the National Institutes of Health Consensus Panel on screening mammography, which was charged with evaluating the data to determine screening recommendations for women in their 40s.

Greg McClure (MD '72) is medical director of South Jersey Physicians Associates, an occupational and environmental medical practice that provides medical and legal expert testimony. Despite having appeared before the Supreme Court of New Jersey, McClure says that "there's no testimony in court that has ever been as stressful as presenting a case to Jack Myers."

—Chuck Staresinic and Sarah Evans

IN MEMORIAM

'30s

WILLIAM LINHART JR.
MD '38
DEC. 12, 2007

BERNARD SILVERBLATT
MD '38
NOV. 23, 2007

'40s

BETTY BRADLEY
MD '41
DEC. 23, 2007

SIDNEY KAUFMAN
MD '41
AUG. 6, 2007

FRANK SCHWARTZ
MD '43B
DEC. 7, 2007

ROBERT GATES
MD '45
DEC. 3, 2007

JOHN BYERS
MD '48
NOV. 8, 2007

'50s

THOMAS CUDDEBACK JR.
MD '50
NOV. 28, 2007

CARLO DE ANTONIO
RES '50
MAY 23, 2007

ARTHUR VARGA
MD '52
OCT. 29, 2007

WILLIAM CUNNINGHAM
MD '57
NOV. 30, 2007

'60s

CHARLES HINKES
MD '67
SEPT. 29, 2007

'70s

DAVID REED
MD '76
OCT. 15, 2007

'80s

CHESTER BERES
MD '82
OCT. 29, 2007

LORI WEST ONE COLD VALENTINE'S DAY

BY SARAH EVANS



FRANK HARRIS

West at the site of her future digs at the University of Alberta.

Lori West (Fel '94) knew the rules: Transplanting a heart from a donor with a different blood type means certain death for the recipient. At the same time, she knew that being on the waiting list for a heart was fraught with peril.

West, a pediatric cardiologist, was in charge of cardiac transplantation at Toronto's Hospital for Sick Children, where the mortality rate for infants awaiting a new heart was more than 50 percent. For babies, there just weren't enough compatible hearts to go around.

After seeing many heartbroken families, West began to question transplant dogma, which said that transplants from donors outside of certain blood-type matches led to extreme rejection because of antibodies primed to attack foreign blood types. It had long been known that newborns don't have these antibodies yet, but it seemed no one had ever challenged this bit of dogma.

"You'd think someone must have looked at this already," says West. "Nobody had ever reexamined transplantation in an age-appropriate way."

Her idea was simple: No antibodies should mean no blood-type rejection. If she was right, there might be fewer desperately ill babies dying on the wait list.

The chance to test this theory came when West sat down with an expectant couple. The woman was carrying a fetus with a defective heart. After birth, the boy would have only months to live without a transplant. The chance of finding a compatible heart in time was so slim, West remembers, that talking about it "was like offering them a lifesaver and then grabbing it away."

On a cold Valentine's Day in 1996, West watched as surgeons transplanted what, by convention, should have been an incompatible heart. The boy was 25 days old. The tiny heart didn't turn blue or falter. It started pumping and a palpable relief went through the room—a feeling that increased exponentially as days and weeks went by with no sign of blood-type rejection. The boy is now 12 years old and thriving, though he is expected to require drugs to suppress his immune system for the rest of his life to combat other types of rejection.

After that boy, West oversaw heart transplants for nine more babies—all from donors with other blood types. She compared them to 10 cases of babies transplanted with conventionally matched hearts for a 2001 paper in the *New England Journal of Medicine*, showing that her procedure was as safe as conventional transplants. She and her coauthors reported that the procedure reduced the mortality rate for infants on the hospital's waiting list from 58 percent to 7 percent. Currently, there are more than 100 children worldwide who have been transplanted with hearts from donors with different blood types. Most of those children are in Canada and the United Kingdom. West says that there have been no significant blood-type rejection problems to date.

The procedure led to another discovery: Patients who receive organs of a different blood type will lack antibodies of either type. A baby boy with type O blood, but who received a type B heart, has both O and B antigens. In theory, he could accept a donor organ later in life from either type.

"If we can continue to explore how these babies become tolerant—what the molecules are, how they turn on, how they turn off—then we may be able to develop a strategy that would be sensible to try in adults," says West.

West is now the director of heart transplantation research at the University of Alberta in Edmonton and a professor of pediatrics with appointments in surgery and immunology. She says that she found significant inspiration in Pittsburgh in the work of transplant surgeon and Pitt Distinguished Service Professor Thomas Starzl.

"It takes people like that," she adds, "to build a culture that not only accepts transplantation, but sees the potential for a better future for many people and is willing to push it forward." ■



OVER FATE AND FOE VICTORIOUS

When the School of Medicine's *a cappella* group, PalPITTations, was invited to sing the national anthem at the Association of American Medical Colleges annual meeting in November, the group also put together something special for an alumni gathering at the same meeting. The lyricists reworked Pitt's alma mater so it would be more to their liking. Some choice lines:

Dear old Pittsburgh, Alma Mater, God preserve thee evermore

All our academic rivals may believe that they're the best
Please allow us to convince you why Pittsburgh can beat the rest
Once we hit the clinics it's a given that we shall excel
We can diagnose it all because we talked about it in a PBL

We're proud of our WISER center, home to artificial lives
We use mannequins to practice putting in our central lines
There we don't see real patients, but we're pretty sure we know
How to treat a heart attack if it happens in a robot like C-3PO

ILLUSTRATION | FRANK HARRIS

CALENDAR

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.

WINTER ACADEMY
FEBRUARY 22
Ritz-Carlton
Naples, Fla.
For information:
Pat Carver, 412-647-5307
cpat@pitt.edu
www.winteracademy.pitt.edu

FISHER LECTURE
FEBRUARY 27
3:30 p.m.
Lecture Room 6, Scaife Hall
James Holland, MD, Speaker
For information:
www.surgery.upmc.edu

BAHNSON LECTURE
MARCH 5
8 a.m.
Lecture Room 5, Scaife Hall
Bruce Lytle, MD, Speaker
For information:
www.surgery.upmc.edu

WINTER ACADEMY WEST
MARCH 15
Arizona Biltmore Resort & Spa
Phoenix, Ariz.
For information:
Pat Carver, 412-647-5307
cpat@pitt.edu
www.winteracademy.pitt.edu

STARZL LECTURE
APRIL 2
4 p.m.
Lecture Room 6, Scaife Hall
Herman Waldmann, PhD, Speaker
For information:
www.surgery.upmc.edu

HEALTH SCIENCES ALUMNI RECEPTIONS
APRIL 10: Lancaster, Pa.
APRIL: Philadelphia, Pa.
MAY: Cleveland, Ohio
For information:
Pat Carver, 412-647-5307
cpat@pitt.edu

PITT MED GOLF OUTING
MAY 3
Quicksilver Golf Club
Midway, Pa.
For information:
komanduri.paavani@medstudent.pitt.edu

MEDICAL ALUMNI WEEKEND 2008
MAY 16-18
Reunion Classes:
1943 1948
1953 1958
1963 1968
1973 1978
1983 1988
1993 1998
2003

SENIOR CLASS LUNCHEON
MAY 16
11 a.m.
Soldiers & Sailors Memorial Hall

ALUMNI WEEKEND OPENING RECEPTION
MAY 16
5:30 p.m.
Pittsburgh Athletic Association

REUNION DINNERS
MAY 16
7 p.m.
Pittsburgh Athletic Association
Classes Dining:
1943 1948
1953 1958
1968 1983

CME LECTURE
MAY 17
8:30 a.m.
"Update on Resuscitation 2008"
Peter M. Winter Institute for Simulation Education and Research

ALUMNI BRUNCH & MEDICAL SCHOOL TOUR
MAY 17
10:30 a.m.
Scaife Hall

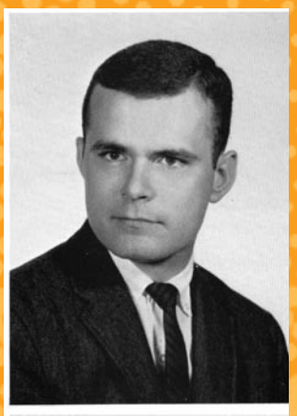
REUNION GALA
MAY 17
6 p.m.
LeMont Restaurant

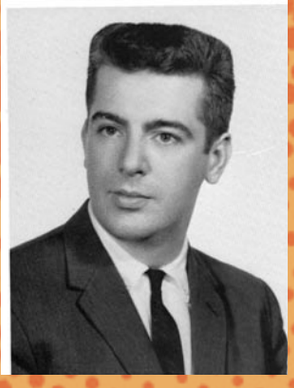
SCOPE AND SCALPEL'S "THE FULL MONTEFIORE"
MAY 17
7 p.m.
MAY 18
4 p.m.
Hillman Center for Performing Arts
Shady Side Academy
For information:
www.scopeandscalpel.org

CLASS OF 2008 COMMENCEMENT
MAY 19
10 a.m.
Carnegie Music Hall

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



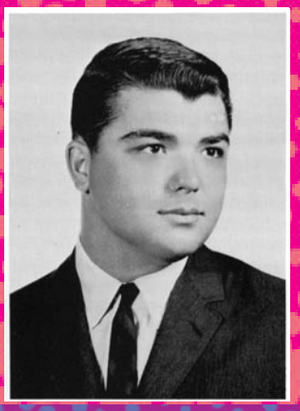




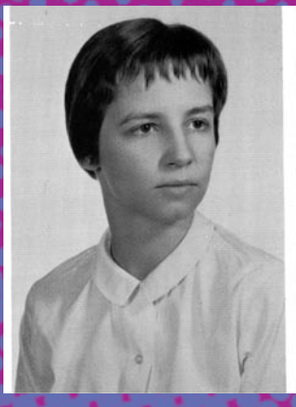


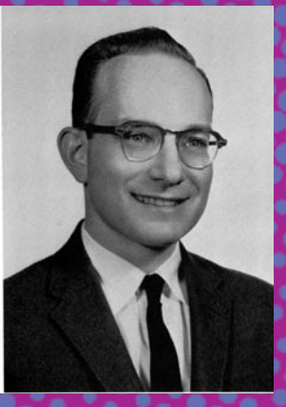












GUESS WHO?

Time to warm up for Medical Alumni Weekend 2008. Dust off your copy of the *Hippocratean*—as we did here with the 1963 edition—and reminisce. Extra credit for anyone who can tell us a good med school story about these or any other members of the Class of '63. Send your stories to medmag@pitt.edu, or *Pitt Med*, 400 Craig Hall, Pittsburgh, PA 15260.

Medical Alumni Weekend
May 16–18, 2008
For a list of classes having reunions this spring, turn to the other side of this page.

FOR MORE INFORMATION: 1-877-MED-ALUM
medalum@medschool.pitt.edu
www.medschool.pitt.edu/alumni

PHOTOGRAPHY: HIPPOCRATEAN, 1963

UNIVERSITY OF PITTSBURGH
SCHOOL OF MEDICINE
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