UNIVERSITY OF PITTSBURGH SCHOOL OF MEDICINE | SUMMER 2009

PITTMED



CARING FOR KIDS

THE LIFE AND TIMES OF A GREAT CHILDREN'S HOSPITAL

PAVING THE WAY

Thank you for running the announcement [Spring 2009] about the recent death of my mother, Ruth Masters (MD '35). I thought you might enjoy seeing this photograph and knowing a little bit more about her. She was one of very few women who became doctors in those days. In 1933 there were only 650 members of the Medical Women's National Association. By 1941, the number of women physicians in the country had climbed to a mere 7,500 compared to almost 200,000 male doctors. My mother graduated during this time. She had no resentment about her treatment, she just said that by working *twice* as hard as everyone else, she found that she was not looked down upon as a woman. In her 1935 Pitt medical school class of more than 60 students, there was only one other woman.



Ruth (Snyder) Masters c. 1934

My sister Dr. Carol Rumack, who followed in Mother's footsteps, wrote this about her: "Ruth Masters, MD, was born at home September 28, 1913, and raised and educated in Pittsburgh. Dr. Ruth won a scholarship to the University of Pittsburgh, which she entered at age 16 after winning a mathematics competition. She entered medical school at 18 years of age and graduated at 21. (Her mother marched in the women's suffrage movement.) She married a classmate, the late Dr. Raymond Masters, in 1936, during their internship at the University of Pittsburgh. They opened an office in his father's home on November 1, 1936, and practiced there for 64 years. She practiced family medicine and delivered more than 3,200 babies, including 200 home deliveries. She says she always prayed during a delivery that "God would bless me to give me the strength and talent to do it." She arranged adoptions of babies from mothers who did not want to choose abortion. Dr. Ruth was elected the first woman president of the medical staff at University of Pittsburgh Medical Center (UPMC) at McKeesport Hospital, serving from 1979 to 1980. She retired from active practice in 2001 at the age of 88 and remained a member of the hospital's ethics committee."

The other Dr. Masters—Raymond E. Masters, my father—was a physician who pioneered atomic safety methods. Both of my parents had wonderful and productive lives.

Sara Masters
Pittsburgh, Pennsylvania

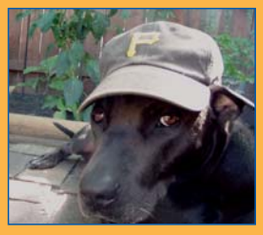
POSTER DOG

Some people (probably not many Pittsburghers this year) watch the Super Bowl for the commercials; apparently some of our readers appreciate Pitt Med*'s ads, as well. In his note below, Scott Kennedy refers to the front and back cover ads in our Fall 2008 issue, including one for Pitt's Winter Academy—featuring Shirley, a black dog in a Pirates hat—and one for planned giving opportunities—featuring former nurse/flight attendant, current sports-car aficionado Mildred Danch.*

Your magazine [Fall 2008] is truly outstanding, from the black lab up front to the flight attendant sans red Corvette on the back.

In truth, I tore off the cover to cut out the lab shot before perusing the rest. So, if possible, I would appreciate a replacement copy to put on our office coffee table. Please?

F. Scott Kennedy, PhD
Assistant Dean of Admissions
LSU Health Sciences Center
Shreveport, La.



Shirley

The pup's companion, associate editor Joe Miksch, responds:

I'm pleased that you're charmed by the photo of my dog, Shirley. I feel compelled though (for reasons I can't fathom) to point out that the lovely little miss is primarily of pit bull and shar-pei extraction, though doubtless many other breeds (including lab, possibly) lurk in her checkered family background.

FLU: READ MORE ABOUT IT

- **Edwin Kiester's 2003 story for this magazine on the Influenza of 1918: http://pittmed.health.pitt.edu/Jan_2003/DrowingBlood.pdf**
- **Chuck Staresinic's story on the evolution of flu: http://pittmed.health.pitt.edu/Winter_2006/evolutionofflu.pdf**
- **UPMC's Center for Biosecurity's updates and original articles: www.upmc-biosecurity.org/**

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:

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

RECENT MAGAZINE HONORS

Carnegie Science Center Journalism Award
(J. Miksch)

CASE District II Accolades
Gold, Periodical Staff Writing

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

CASE District II Accolades
Silver, Covers (Summer 2008)

IABC Golden Triangle Award of Honor
Magazines

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

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

CASE Circle of Excellence
Gold, Covers (Winter 2007/8)

CASE Circle of Excellence
Bronze, Special Interest Magazines

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

PITTMED

UNIVERSITY OF PITTSBURGH SCHOOL OF MEDICINE MAGAZINE, SUMMER 2009 (MAY/JUNE/JULY)

VOL. 11, ISSUE 2



DEPARTMENTS

OF NOTE 3
Emergency medicine abroad.
Making sense of medical records in Malawi.
Separation without anxiety.

CLOSER 7
Practice makes perfect in the move to the new Children's Hospital.

INVESTIGATIONS 8
Preparing for the fallout.
Function at the neuromuscular junction.

ATTENDING 32
Alumnus Jim Withers on taking medicine to the streets.



MATCH RESULTS 35
The Class of 2009 marches onward.

ALUMNI NEWS 36
Probing preeclampsia.
Is there a (Pitt) doctor in the (White) House?

LAST CALL 40
Hands and minds and hearts.





19

FEATURES

For the Good of the Child 12

In 1951, Esther Bubley came to Children's Hospital with a slew of cameras. The scenes of caring she documented never made it to the pages of *Life* magazine as intended, but they are now the foundation of a documentary by filmmaker Ken Love and his wife, pediatrician Barbara McNulty (MD '75).

PHOTO-ESSAY BY ESTHER BUBLEY AND BARBARA MCNULTY

Welcome to the Dark Side 19

Cured meats, beets, and a bit of olive oil could be on the menu for cardio-protection. Could nitrates and nitrites be the secret to the Mediterranean diet? Pitt docs defend the honor of maligned molecules and look to new therapies.

BY CHUCK STARESINIC

The Heart of the Matter 24

Cecilia Lo–founding chair of Pitt's new Department of Developmental Biology–is on an exhaustive search for the mutations behind congenital heart defects.

BY SHARON TREGASKIS

In the Shadow of a Stroke 28

Jun Chen and Peter Vosler may have found a way to limit the damage caused by stroke by leading cells back from the brink of death.

BY JOE MIKSCH

CONTRIBUTORS

Portraits by painter/illustrator FRANK HARRIS regularly grace the pages of *Pitt Med*'s Alumni News section (see p. 37). Harris describes these illustrations as having a "loose, painterly style" consistent from one issue to the next. Rather than being realistic, he paints in bright colors and "breaks the lines a bit." For a feature article in this issue ["Welcome to the Dark Side"], he worked mainly in collage. Harris' clients include *Harvard Magazine* and *Vanity Fair*, for which he produced caricatures of the presidential candidates. He is currently illustrating the program for Major League Baseball's 2009 All-Star Game.

Senior Editor CHUCK STARESINIC ["Welcome to the Dark Side" and other stories] is a six-year veteran of *Pitt Med*. His work has netted him several individual writing awards, including the top prize from the Association of American Medical Colleges for his profile of transplant great Thomas E. Starzl. In this issue, Chuck takes us on a tour behind the mysteries of the healthful Mediterranean diet. His own wellness regimen includes a lot of running these days. This spring, Chuck finished first in his age group in Pitt's Student Leaders in International Medicine and Kenya Pediatric HIV Project 10K race. Last year, he and his wife, Danielle, tried to have their third child, but instead had their third and fourth in rapid succession: twins Juliet and Edward.

COVER

Pediatrician Arthur Coddington has some company while he makes a phone call at Children's Hospital of Pittsburgh in 1951. (Cover: Esther Bubley. © 2007 Children's Hospital of Pittsburgh of UPMC.)

PITTMED

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
Eric Donato, Meaghan Dorff

OBITUARIES CONTRIBUTOR
Macy Levine, MD '43

CIRCULATION MANAGER
Crystal Kubic

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

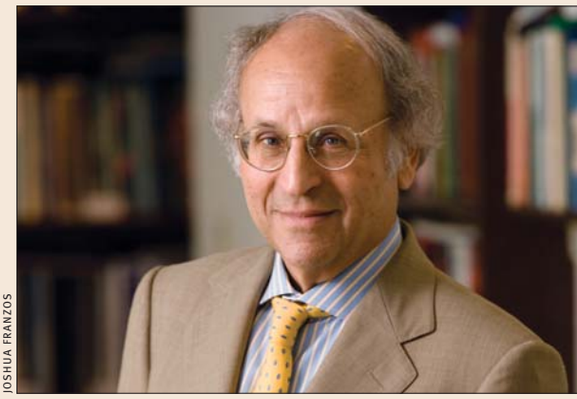
EDITORIAL ADVISORS
Paula Davis, MA
Susan Dunmire, MD '85, Res '88
Jonathon Erlen, PhD
Joan Harvey, MD
John Horn, PhD
Steven Kanter, MD
Joan Lakoski, PhD
Margaret Larkins-Pettigrew, MD '94, Res '98
David Lewis, MD
Margaret C. McDonald, PhD
Ross Musgrave, MD '43
David Perlmutter, MD
Kevin Proctor, Class of '11
Gabriel Silverman, Class of '11
Peter Strick, PhD
Bennett Van Houten, PhD
Gerard Vockley, MD, PhD
Simon Watkins, PhD
Marshall Webster, MD, Res '70
Julius Youngner, ScD

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

University of Pittsburgh

Pitt Med is published by the Office of the Dean and Senior Vice Chancellor for the Health Sciences in cooperation with the alumni and public affairs offices. It is produced quarterly for alumni, students, staff, faculty, and friends of the School of Medicine. PR 6706

The University of Pittsburgh is an affirmative action, equal opportunity institution. © 2009, University of Pittsburgh


JOSHUA FRANZOS

The Simple Life is not a simple life.
—Mason Cooley

Two critical components of health care reform are more complex than perhaps first imagined.

I'm glad to see the Obama Administration is tilting health care reform toward prevention. We know that much of the burden of the cost of care relates to potentially avoidable, chronic diseases—obesity and type 2 diabetes, COPD, lung cancer, cirrhosis, and the like. And we suspect that many illnesses outside the realm of those so closely linked to lifestyle choices are also avoidable. If under health care reform we are going to extend access widely, then we not only have to keep the cost of health care under control, we need to reduce it. So preventing illness becomes critical.

How do you do that? If you're going to prevent illness, it helps to be able to predict it. That's where genomics comes into play. Just a few years ago, we thought that once we mapped the human genome, we'd be well on our way to understanding the origin of most conditions that afflict us. The next step would be targeted therapies. I'm simplifying what the thinking was here, of course. Yet, the reality of decoding disease turns out to be much more complicated. As it turns out, the results of genome-wide association studies are disappointing. With the exception of diseases like sickle cell anemia that are caused by a mutation in a single gene, common chronic diseases are very complex genetically. Obesity and most cancers seem to involve many genes, each with a small effect. Many other common conditions, including schizophrenia and autism, may as well. Beyond that, diseases may involve single nucleotide polymorphisms (small genetic variations at the nucleotide level, nicknamed "snips") in ways that are very difficult to understand. And some of what we were calling "junk DNA," now known to encode untranslated microRNAs, turns out to have a critical role in suppressing messenger RNA. Contemporary genomics offers a window to learning about the wonders of the bodies we inhabit, yet the field isn't necessarily a quick ticket to new therapies.

And what the administration deems a $20 billion problem is equally intricate—the digitizing of medical records. There's no standard in the United States for medical records. So those electronic records we do have aren't interoperable in this country, never mind with our European or other counterparts. Such a system could be enormously valuable. Yet as we sort this out, we should be mindful that being wired doesn't intrinsically mean better care. As Pamela Hartzband and Jerome Groopman cautioned in *The New England Journal of Medicine*, we don't want each record to become a mystifying and unintelligible data dump of lab results (as they are in some systems). Nor do we want to create a cut-and-paste approach to care in which physicians copy the diagnoses of others rather than take time to think independently about the patient when writing a history. And wouldn't it be nice if physicians were able to spend more time interacting with the patient during an exam, and less time with a computer screen?

As educators, we need to put forward a holistic approach to care that does not substitute electronics for the doctor-patient relationship. And we will need to train physicians regarding prediction and prevention as we prepare them for the next chapter—personalized medicine—once we do make sense of our genomes in all of their complexity.

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



Devoted to noteworthy happenings

at the medical school

NEW LEADER AT STARZL INSTITUTE

Abhinav Humar has come to the University of Pittsburgh to take on the clinical directorship of the Thomas E. Starzl Transplantation Institute. The former director of the Liver and Living Donor Programs at the University of Minnesota Medical Center also serves as chief of the Division of Transplantation in the Department of Surgery.

The surgeon said he was attracted to the job by the Starzl Institute's stellar reputation, a reputation he plans to burnish. "If you ask people around the world about transplant, Pittsburgh would be at the top of the list," Humar says. "I appreciate that reputation and the opportunity to improve it."

Humar made his own reputation as an expert in abdominal transplantation but plans to be hands-on in advancing all the institute's programs. "We're going to reach out to the community and make sure that people know we are the place for transplant care from step A to step Z," Humar says. *—Joe Miksch*

FOOTNOTE

Acharya Yashovijaysuri, a guru of Jainism and spiritual leader to millions, only travels by foot so that he may avoid harming even insects. But desperate times call for desperate measures, and he was going blind. The guru flew to Pittsburgh from India after doctors in Mumbai found a golf ball-size tumor pressing on his optic nerve. They deemed it too risky to operate through the cranium. His followers convinced him that minimally invasive brain surgery through the nose—a procedure developed at Pitt—was an option. Days after surgery, the guru began to regain his vision.



COURTESY CHILDREN'S HOSPITAL OF PITTSBURGH OF UPMC

Congrats! It's a Bouncing Baby Hospital

On March 4, David Perlmutter moved into his digs in the recently completed John G. Rangos Research Center building, part of the new Children's Hospital of Pittsburgh of UPMC. Two months later, patients arrived next door at the new nine-story, 296-room hospital building on a 10-acre, $625 million campus (the former site of St. Francis Hospital in Lawrenceville).

Perlmutter, the chief physician and scientific director at Children's and the Vira I. Heinz Professor and chair of pediatrics in the University of Pittsburgh School of Medicine, described the view from his perch: "It's beautiful. I'm looking at the hospital and the river and the North Shore and the neighborhood of Lawrenceville. It's just spectacular."

Almost as spectacular as the hospital itself. Perlmutter says that more than 90 percent of patient rooms are private and that they are considerably larger than those in the Oakland facility. "The design of the rooms is ideal for families, and we believe that has everything to do with how children handle illness," he says.

The hospital boasts a 100 percent paper-free record system, has many more intensive care beds, and it concentrates particular kinds of care on specific floors. (Cancer patients are on the ninth and cardiac patients on the third, for example.) The research facility follows the open-lab model used in Pitt's Biomedical Science Tower 3 and offers investigators a great deal more space. "This will enable us to continue to recruit great pediatric scientists," he says. *—JM*



CAMI MESA

A&Q

Marc-David Munk: Emergency Medicine Abroad

Marc-David Munk (Res '06, Fel '07), shown above, worked as a paramedic, earned a master's degree in public health, and, subsequently, an MD. He was the first graduate of the University of Pittsburgh's fellowship in international emergency medicine. After graduation, he worked as the EMS medical director for UPMC's emergency medicine development project in Qatar and trained EMS workers in the Caribbean and Africa. Today, he is the fellowship program's assistant director and clinical assistant professor of emergency medicine in the School of Medicine. After returning from a stint with the Flying Doctors service out of Nairobi, Munk spoke about the challenges of updating emergency care outside the United States.

On the birth of Pitt's international emergency medicine fellowship

We had no difficulty getting buy-in, initial financial support, and departmental approval—despite the fact that international emergency medicine was new and unproven. I think that the Department of Emergency Medicine has always been willing to take chances, to try new things, and this was certainly true in our case. Our chairman, Dr. Paul Paris, is himself an innovator and unorthodox thinker, and he has set the tone for the entire department. I don't think that anyone is afraid to speak up, to try new things, or to take risks. This is really what is behind Pittsburgh's reputation as one of the world's leading centers for academic emergency medicine.

On the nature of international emergency medicine

Road traffic accidents and trauma are becoming the leading cause of death in [developing nations], and we're seeing that patients are getting older because we've managed to deal with things like malaria and diarrhea in many parts of the world. Patients are now coming in with heart attacks and diabetic emergencies and those kinds of things. If you're looking to make a dent in mortality, you have to start focusing on things like ambulance systems which can deal with time-critical disease.

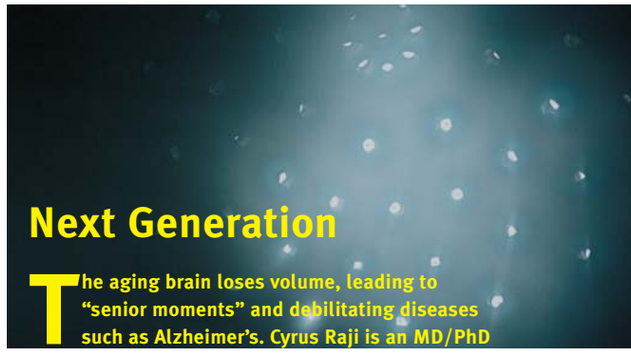
On the future of the fellowship

There's a huge amount of interest. People are always looking for options and opportunities to go abroad and study, which I think is valuable. It's very important for folks to spend some time seeing how medicine is truly practiced in the vast majority of the world.

His question for the world

I'd like to talk to the heads of funding agencies to really impress upon them the urgency of this changing epidemiology and ask, "Are you willing to support our research and our clinical efforts?"

—Interview by Joe Miksch



Next Generation

The aging brain loses volume, leading to "senior moments" and debilitating diseases such as Alzheimer's. Cyrus Raji is an MD/PhD student in pathology at the University of Pittsburgh working with James Becker, a PhD professor of psychiatry, and Oscar Lopez, an MD professor of neurology. Raji studies whether vascular diseases, diabetes, and high blood pressure lead to brain atrophy. He won a prize for best neuroscience paper by a medical student from the American Academy of Neurology. That paper used brain imaging from MRIs to explore the link between heart and brain health. Raji plans to devote his career to studying the aging brain. "I think dementia robs us of the fundamental aspect of who we are," he says.

Traumatic brain injury is a leading cause of death in children, and neurosurgeons have tried to improve the odds for injured children by maintaining oxygen to the brain. Veronica Ortiz, a second-year medical student, received a Dean's Summer Research Program grant to investigate how different brain temperatures affect oxygen in that organ. The study, which she presented at the annual congress of the Society of Critical Care Medicine, found that changes in brain temperature cause small variations in brain oxygen levels, but they are not likely to be clinically relevant. Ortiz plans to keep studying traumatic brain injury to help injured children. Her advisers include Michael Bell, an MD assistant professor of critical care medicine and associate director of pediatric neurointensive care in Pitt's Safar Center for Resuscitation Research, and Patrick Kochanek, MD professor of critical care medicine and director of the Safar Center.

A child who grows up in poverty may experience the chaos of violence and drugs in her neighborhood, strained family bonds, and poor nutrition. Those childhood stressors have been linked to depression and other changes in health later in life. Jeffrey Horenstein, a third-year MD/PhD student at Pitt, studied MRIs of adult brains to write his dissertation on the link between socioeconomic status and mental and physical health. Horenstein, who received a National Research Service Award from the National Institute of Environmental Health Sciences, plans to apply his lab research to suicide and alcohol prevention with the Indian Health Service. Horenstein's adviser is Sheldon Cohen, Carnegie Mellon University's Robert E. Doherty Professor of Psychology, who has adjunct appointments at Pitt.

—Christina Rouvalis

Learning to Educate

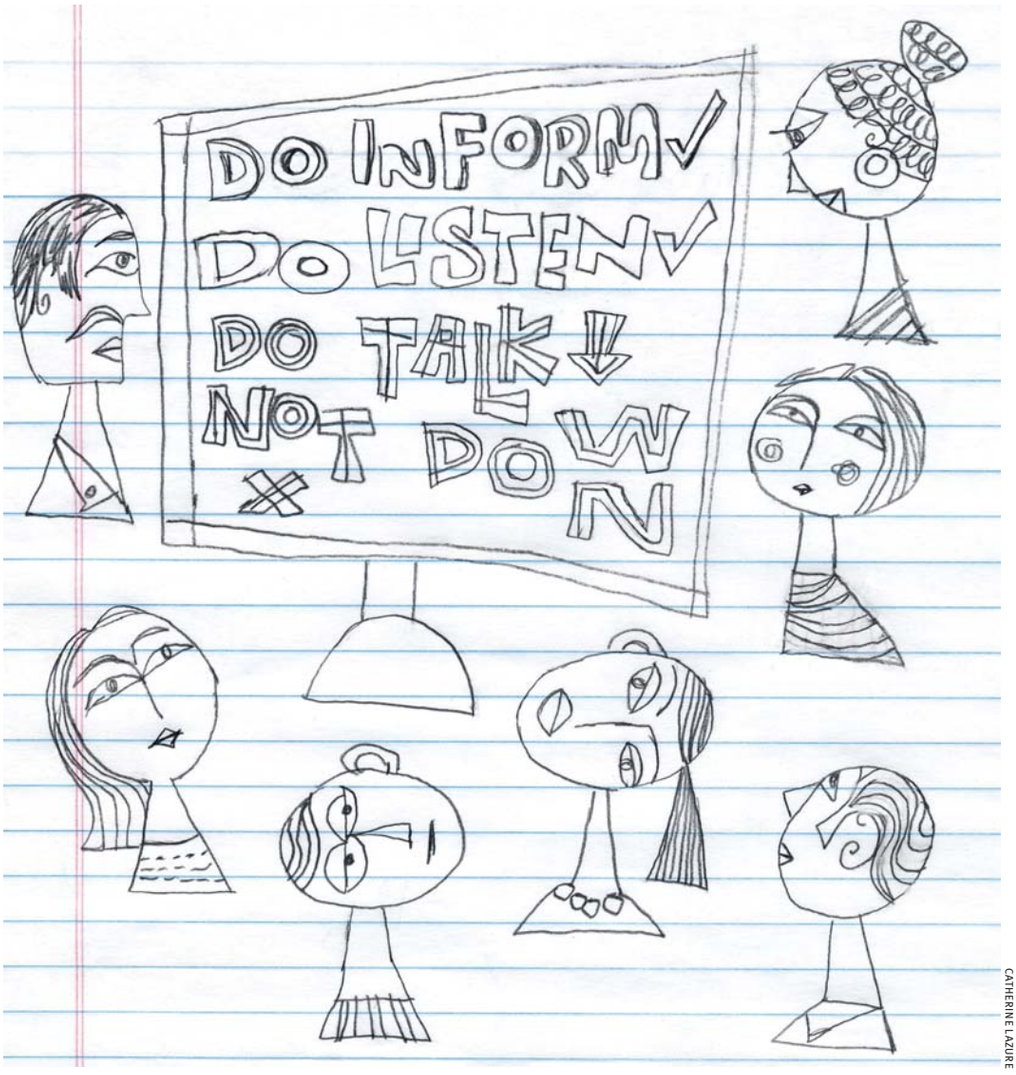
The latest crop of residents sat watching the video. It showed a peer delivering a presentation regarding a patient. The content was fine, medically speaking, but some of the terms the young doc employed could be considered pejorative and judgmental.

"We use this video to show the types of scenarios commonly seen in medical education," says Jamie Johnston, MD professor of medicine in the renal-electrolyte division in the School of Medicine. A postvideo conversation reinforced ideas of professionalism and communication skills in the entering residents of 2008.

The video is one project of Pitt's Academy of Master Educators, which was formed in 2006 and recently announced its new class of 18 faculty members. The academy not only recognizes teaching excellence, Johnston says, it concentrates the teaching experience of faculty members and shares dos and don'ts with the medical school at large through programs like faculty development seminars, mentoring programs, and the new resident orientation mentioned above.

"When I network with my colleagues at other institutions, they're very jealous of what we have," Johnston says.

The newest members of the academy can be found at www.ame.pitt.edu/. *—JM*



CATHERINE LAZURE

FINE FELLOWS

The American Association for the Advancement of Science has asked its members to recognize standouts among their own since 1874. This year, the organization bestowed the honor of fellow status on three professors from the University of Pittsburgh School of Medicine.

The AAAS lauded **Bernie Devlin**, a PhD associate professor of psychiatry and human genetics at Pitt, for his work modeling and analyzing statistical data. His methods for analyzing genetic data have advanced such disparate fields as DNA forensics, genetics of IQ, genetic epidemiology, and cancer biology.

The organization also honored **Herbert Needleman**, an MD professor of psychiatry and pediatrics, and **George Michalopoulos**, an MD/PhD, the Maud L. Menten Professor, and chair of the Department of Pathology.

Michalopoulos is known for his work in liver regeneration. In 1989, his lab identified hepatocyte growth factor, which stimulates liver cell proliferation. (Two other labs independently came across the protein at the same time.)

Needleman's studies, starting in the 1970s, showed that lead exposure in children results in brain damage, made evident by lower IQs and an increase in behavioral problems. His work eventually convinced officials at federal agencies to ban lead from paint and gasoline and lower the blood-lead standard for children. *—Eric Donato*

HONORING TRANSLATORS

Four University of Pittsburgh School of Medicine faculty members now augment the ranks of two groups dedicated to honoring scientists who convert basic science into clinical practice.

Michael Fine, MD professor of medicine and director of the VA Center for Health Equity Research and Promotion, and **Mark Gladwin**, MD and chief of the Division of Pulmonary, Allergy, and Critical Care Medicine and director of the Hemostasis and Vascular Biology Research Institute (see story p. 19), are among the newest members of the Association of American Physicians. Each was nominated by his peers to join the 1,000-member organization. Only 60 physicians are invited to join annually. With the addition of Fine and Gladwin, Pitt boasts 17 AAP members.

David Hackam and **Satdarshan Monga** were recognized by the American Society for Clinical Investigation, which honors standout physician-scientists who are 45 or younger. Hackam is an MD/PhD with appointments in surgery, as well as cell biology and physiology. Monga is an MD associate professor of pathology and medicine. *—JM*



COURTESY CHILDREN'S HOSPITAL OF PITTSBURGH OF UPMC

TWINS BECOME TWO

Catherine Nickson was told she couldn't get pregnant again, but then a doctor told her she was. Then he told her she was carrying twins. Then he told her the twins were conjoined. "I thought it was a joke, that someone was playing a trick on me," says Nickson.

Nickson and the twins—Dagian and Danielle Lee—came to Children's Hospital of Pittsburgh of UPMC from their Cleveland home with the hope that doctors here could separate the girls. It would be the first such surgery performed in Pittsburgh. Dagian and Danielle were joined from the sternum to the groin, shared a colon, and had individual, but connected, livers.

On Dec. 13, two days before Dagian and Danielle turned 2, a team of 50 doctors and nurses led by Joseph Losee, MD associate professor of surgery and pediatrics in the School of Medicine and chief of the Division of Pediatric Plastic Surgery at Children's, began a 24-hour operation to separate them. The operation took place after the girls had undergone scores of earlier procedures in preparation. (The girls are shown above—pre-op, with tissue-expanding balloons beneath their skin. Dagian is on the left; Danielle is on the right.)

Two months later, the twins, looking hale and hearty in their Terrible Towel-draped hospital beds, had begun a long period of rehabilitation. And they were looking forward to going home. Nickson said: "We're going to have a big party." *—JM*

Finding Malawi

Canadian-born Gerry Douglas didn't even know where Malawi was back in 1996 when he was assigned to the country as a member of Voluntary Services Overseas (VSO), a UK-based international volunteer organization like the Peace Corps.

Today, Douglas is so devoted to this Southern African nation that he owns a home in Malawi so he can run Baobab Health Partnership, a nonprofit medical informatics organization.

Malawian medical records are in a state of disarray, which is something Douglas first noticed as a VSO volunteer. Paper records were often incomplete or nonexistent or inaccurate. If a new patient had been treated for high blood pressure, diabetes, or HIV, a doctor often wouldn't know it. "It's a total mess," he says.

Douglas, a 46-year-old PhD student in the University of Pittsburgh's Department of Biomedical Informatics, is changing that. A desktop touch-screen workstation appliance he developed lets overworked doctors input medical records. Doctors have used the system to issue identifiers to more than 800,000 patients, and 18,000 received HIV care facilitated by BART, the Baobab Antiretroviral Therapy system.

For his efforts, Douglas received a Technology, Entertainment, Design (TED) fellowship. Douglas is one of 40 innovators selected from a pool of international fellowship applicants. He presented his work on Baobab Health to the fellows group during the TED Conference in Long Beach, Calif., in February.

Michael Becich, chair of biomedical informatics at Pitt, noted in a press release that "TED fellowships are given to the super-brilliant and rising talents across multiple scientific and creative disciplines."

With his wife and Baobab cofounder, Thuy Bui, whom Douglas met in Africa, Douglas is committed to working in Malawi for another 20 years. The couple—Bui is an MD and medical director of Pitt's Program for Health Care to Underserved Populations—brings their 7-year-old son, Ben, to Africa in the summer.

Baobab employs 25 Malawian software developers, technicians, and other support staff. Douglas himself has not yet drawn a paycheck, but he hopes to receive a salary eventually from the organization, which is funded through the Centers for Disease Control and Prevention and other granting organizations. *—CR*



MOVING FOR DUMMIES

On a chilly Saturday in February, the brand-new Children's Hospital of Pittsburgh of UPMC campus in Lawrenceville receives its very first patients, closed-lipped kids who handle their ailments in stride. (To protect their privacy, they've been assigned numbers.) Seventeen has a low white-blood-cell count. Twenty-five has a bacterial infection. Forty has a broken arm—and, for some reason, looks suspiciously like … a Cabbage Patch Kid?

They're not real patients, dummy. They're CPR mannequins (and at least one doll)—stand-ins for the children during a dress rehearsal for the hospital's big moving day on May 2.

"I've been planning this for two years," says RN Jennifer Iagnemma, the patient coordinator for the move. "It's exciting seeing our group come together to do this."

Her group includes Children's staff and volunteers, plus EMTs from throughout the Pittsburgh area—about 200 people, all told. For four hours, they work in teams—one nurse and one or two EMTs per ambulance—to carefully move 23 mannequins from patient floors on the Oakland campus to the new hospital three miles away.

Not every trip goes without a hitch. "There are a few dead spots for radio communication," says David LaCovey, EMS coordinator. "But that's the idea behind the drill—to identify things like that."

Wheeling the gurney out of 17's room, EMT Terry Salay nods with the assurance of someone who does nothing but transport patients year round. "[Patients] do throw curveballs at you," he says, looking at Dummy No. 17. "But if there is one, we're ready."

—Elaine Vitone

—Photo by John Altdorfer

Explorations and revelations taking place in the medical school



CORBIS/ DRAWING OF TWO FIGURES AND INCENDIARY BOMBS BY LEONARDO DA VINCI

Five hundred years ago, Leonardo da Vinci drew this sketch of incendiary bombs. In case someone else is sketching a bomb today, in particular a dirty bomb or other radioactive weapon, a team at Pitt is developing experimental protective therapy.

NIGHTMARE MITIGATION

DIRTY BOMBS AND DAY-AFTER DRUGS

BY JOE MIKSCH

It's as alarming as it is plausible to Joel Greenberger: He believes that at some point in the next decade or so, someone will detonate a fission bomb, a dirty bomb (in which radioactive material is dispersed by conventional explosives), or release radioactive material into the wind.

"When I go around to meetings, I carry around a briefcase with a 25-pound barbell plate in it," Greenberger says. Twenty-five pounds of fissionable material is all that's needed to build a Hiroshima-type bomb. "I put it in the back of the room, and I have someone open it. Then I explain that, essentially, if it went off in this building, it would be enough to wipe out Oakland, and there would be a good million people who'd experience some degree of fallout."

Obviously, some people would be beyond help in such a grim scenario, but Greenberger is looking for a way to reduce or eliminate the deleterious effects of fallout for those who'd survive. With others, he's testing new therapies that seem to offer protection from radiation exposure.

Greenberger, an MD who is chair and professor of radiation oncology in the University of Pittsburgh School of Medicine, has about $13 million in federal grant money set aside for the job.

In 2005, the National Institute of Allergy and Infectious Diseases bestowed $10 million, with which Pitt established a Center for Medical Countermeasures Against Radiation. Greenberger, the grant's principal investigator, was charged with developing and testing small molecules that can be used to mitigate the effects of ionizing radiation.

The Biomedical Advanced Research and Development Authority of the U.S. Department of Health and Human Services awarded a second grant of $2.7 million in 2008. This grant can be renewed for up to three years and $9.8 million.

That money is intended to help Greenberger and colleagues develop and deliver drugs that combat radiation exposure. His collaborators include Valerian Kagan, a PhD and DSc professor in Pitt's Graduate School of Public Health; Peter Wipf, a PhD University Professor in Pitt's Department of Chemistry; and John Lazo of the School of Medicine, a PhD who is the Allegheny Foundation Professor in the Department of Pharmacology and Chemical Biology and codirector with Wipf of Pitt's Drug Discovery Institute.

This journey began, as many things do in science, with a different intention. In 1993, Greenberger was investigating ways to improve cancer care by selectively protecting normal tissue from radiation therapy.

Ionizing radiation harms cells by creating superoxide, which causes DNA damage and leads to cell death. Greenberger found that overexpressing manganese superoxide dismutase (MnSOD), an enzyme that all cells possess, converts superoxide into hydrogen peroxide. Other molecules then come along and turn the hydrogen peroxide into water. Removing superoxide prevents DNA damage.

Wipf, the chemist, has engineered a drug called JP4-039 that functions like MnSOD. Both target the mitochondria—the cell's power plant. When MnSOD is delivered directly to the mitochondria, Greenberger says, it disrupts the chemical signals caused by radiation that lead to DNA damage and cell death.

Greenberger and colleagues are now in the process of testing JP4-039's safety and efficacy. They've begun animal testing. Shortly after the results are in, Greenberger hopes to begin a phase I trial in nonirradiated people to show JP4-039 is safe for humans.

In another avenue of study, a Pitt research team led by Greenberger found in 2004 that resveratrol, an antioxidant in red wine and many plants, also offers effective protection against radiation exposure. Researchers are investigating whether it can be used clinically.

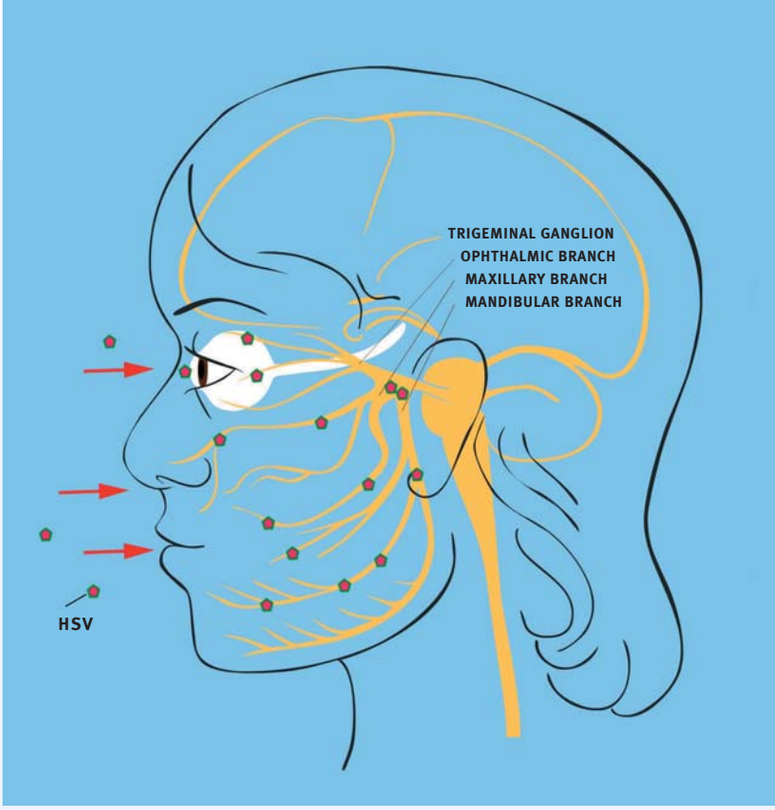
Greenberger says a drug like JP4-039 could be distributed at an earlier point in the testing cycle if the situation requires it. "Let's say we're in the middle of a phase I trial, and we've given the drug, and people aren't getting sick [from it]. A bomb goes off someplace; the FDA could fast-track production of what's in the pipeline."

Work is progressing on delivering JP4-039 through a transdermal patch, similar to how some birth control medications are administered. Safety is especially vital in this case, Greenberger says, because there won't be time to determine who has been exposed to radiation in the wake of a nuclear incident. The drug would be given to everyone who seeks treatment. "A lot of people who come in to emergency rooms 24 or 48 hours after a bomb won't need anything, but they won't know they don't need anything, and they're going to be scared," he says. ■

SLEEPER CELLS

HOW THE BODY KEEPS HERPES AT BAY

BY REID R. FRAZIER



HSV1 hides near the brain and spreads along the facial nerves when awakened.

COURTESY KIRA LATHROP

Herpes is Greek for "crawl" or "creep," referring to the way its lesions spread across the body. Known to science since the Greeks, it's creepy in another way. It hangs around the body in a latent state, often going years without causing any symptoms. At certain times and under certain conditions, the virus reactivates, causing infections and collateral damage the immune system exacts on the body's own tissues. Why the virus reactivates, or remains latent, has been a major source of interest to immunologists and virologists for decades.

The University of Pittsburgh's Robert Hendricks has been fixed on this question for almost 20 years. Hendricks, a PhD, and his team recently found out how the body keeps these virus sleeper cells at bay, through what amounts to an immunological commando raid. Hendricks is the Joseph F. Novak Professor and vice chair for research in ophthalmology; he's also a professor of immunology, as well as microbiology and molecular genetics. His lab studies herpes simplex virus type 1. HSV1, as it's called, is the lesser-known, "above the belt" cousin of HSV2, or genital herpes.

HSV1 typically hides out in the trigeminal ganglion, a bundle of nerves just underneath the brain at the top of the brain stem. These nerves innervate the cornea and parts of the mouth and face, offering a convenient portal through which the virus spreads. The viral DNA migrate into the cellular nuclei of neurons in the ganglion, where the virus goes into a latent state. When reactivated, it travels down the axons from the ganglion to the outer tissues, vexing its host with cold sores or "fever blisters" on the mouth and lesions on the cornea, which can lead to blindness.

Until about 10 years ago, scientists assumed the immune system had nothing to do with keeping the virus in a latent state because the latent virus didn't emit any telltale proteins. But in the 1990s, Hendricks and colleagues at Pitt were among the first to document the immune system's role in keeping the virus dormant. The researchers found a class of lymphocytes called CD8T cells conspicuously clustered around latently infected neurons, like guards around a "high-value" prisoner.

But what is it about these CD8T cells that prevents the virus from reactivating? These cells can work in one of two ways—by scrambling the viral replication sequence or by killing the host cell. This latter function is performed by cytotoxic molecules called lytic granules. The granules are more or less immunological grenades. This is a common way CD8T cells kill viruses. Mice deficient in lytic granules, for instance, are inordinately susceptible to Ebola and HIV infection. The method works relatively well in muscle and skin cells, but neurons are another matter: They don't grow back, at least not as easily.

So the investigators assumed the CD8T cells were scrambling the viral DNA to prevent replication. Jared Knickelbein, an MD/PhD student in the Medical Scientist Training Program and a member of Hendricks' lab, tested this theory. He gave one group of latently infected neuron cultures CD8T cells with faulty lytic granules, the other normal lytic granules. Knickelbein and Hendricks expected the groups to have the same incidence of reactivation. They didn't. Neuronal cells were more likely to reactivate if their T cells were deficient in lytic granules. "Jared went ahead and showed us we were wrong," Hendricks says. They looked closely at the neurons. The lytic granules weren't killing the host cell.

The Hendricks team had found something new—lytic granules that attacked the virus but kept the host cell alive. Kill the soldiers, save the building.

But how?

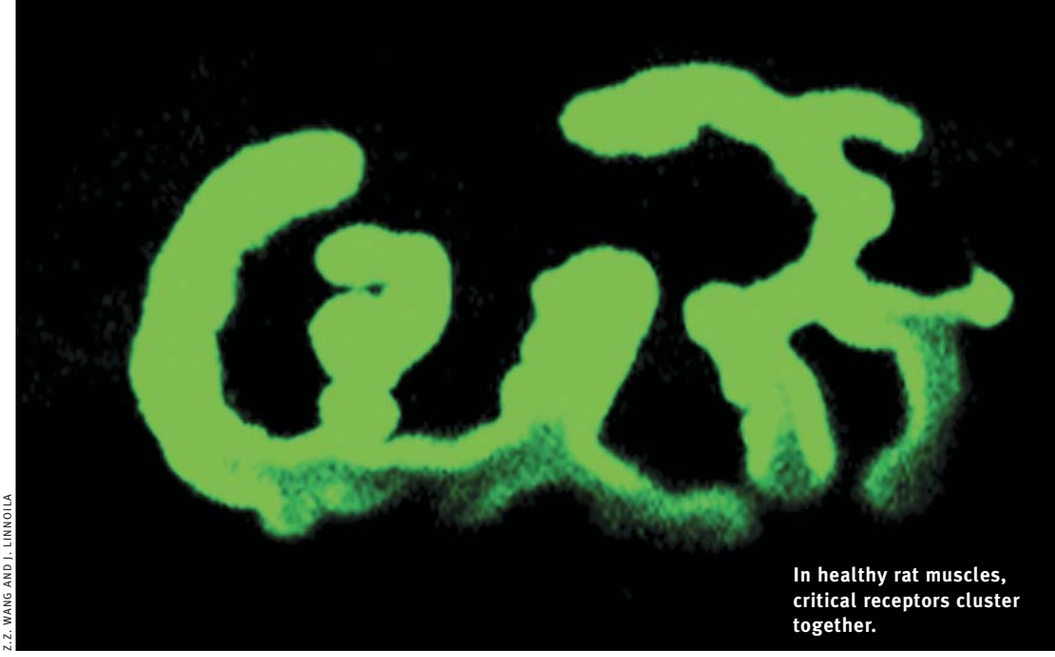
The group focused on a common and potent lytic granule component, granzyme B, which is a protease—an enzyme that cleaves proteins.

"We thought, 'What if this protease was cleaving a viral protein essential for the virus to replicate?'" Knickelbein recalls. With help from bioinformatics software, Knickelbein and Hendricks examined the amino acid sequence of potential target proteins—cleavage sites, in scientific argot—and found one sequence within an important protein in viral replication, ICP4 (infected cellular protein 4). This seemed to solve the puzzle—granzyme B cleaved ICP4 early on in the viral replication process, stopping the process inside the neuron, with minimum damage to the host cell.

This discovery, published in *Science* in 2008, could pave the way toward a herpes vaccine. ■

A CRITICAL PROTEIN IS HOOKING UP NERVES AND MUSCLES ALL DAY

BY ELAINE VITONE



Z.Z. WANG AND J. LINNOILA

In healthy rat muscles, critical receptors cluster together.

NEUROMUSCULAR JUNCTION, HOW'S THAT FUNCTION?

When MD/PhD student Jenny (pronounced Yenny) Linnoila began her PhD studies at the University of Pittsburgh in 2003, her adviser, Zuo-Zhong "Z.Z." Wang, then an associate professor of neurobiology, invited her to investigate one of the great unknowns of the neuromuscular junction—the place where, as the name implies, nerves and muscles meet.

But first he warned her that it wouldn't be a walk in the park. "Do you want to do something that the world hasn't figured out yet?" she recalled him saying. "It's really exciting, but it isn't easy."

After decades of research, neurobiologists learned that as a fetus develops, the motor neuron secretes a protein called agrin, which binds to a receptor on the muscle surface called muscle-specific kinase, or MuSK. If anything keeps agrin and MuSK from getting together—for example, an autoimmune disease that can damage MuSK—the lines of communication between nerve and muscle become disrupted, and the junction cannot function.

Normally, the brain's messages to get moving travel down the spinal cord and through the motor neuron. When a message reaches the neuromuscular junction, the nerve releases onto the muscle a neurotransmitter called acetylcholine. In a healthy muscle, clusters of acetylcholine receptors (AChRs) are already formed along the neuromuscular junction, right where they're needed. Because of this "clustering," the AChRs can work together to relay the message to the muscle, causing it to contract. When these clusters can't form, the junction loses function, and the muscle weakens.

"Say you have a nerve injury," says Linnoila. "When the nerve degenerates, all these receptor clusters spread out with no direction and just go anywhere on the muscle-cell surface."

Wang posed to Linnoila a fundamental question about what puts bodies in motion: What causes clusters to form during development and to hold their ground throughout our lives? MuSK seemed a likely party to it. For one thing, MuSK is a kinase, a class of proteins known to be great communicators. For another, MuSK isn't found anywhere else in the body besides the neuromuscular junction. So what does MuSK talk to?

At Wang's suggestion, Linnoila did a biological assay to hunt for proteins that bind to MuSK; if any proteins did, he reasoned, they were likely to be involved in clustering.

"Lo and behold," says Linnoila. "In particular, one protein called Tid1 bound very strongly to MuSK. Basically, you put those two together, and they're married."

Linnoila believed strongly in the hypothesis and spent the next four years building the case. Studying nerves and muscles in rats from embryo through adulthood, Linnoila found MuSK and Tid1 in wedded bliss. She showed that if you knock out Tid1 in a model of neuromuscular development, clusters never form. And if you knock out Tid1 at a later stage in the life cycle, the clusters fall apart, the AChRs scatter, and the muscle weakens.

Wang accepted a faculty position at the University of Southern California in 2005, so Linnoila moved to Los Angeles to continue her work. (She continued to meet regularly with her Pitt PhD committee.) Wang shepherded her through the exhaustive process of getting a paper on her studies accepted in *Neuron.* It was published in November 2008.

Then, last summer, Wang died in a hiking accident. "It was horrible," says Linnoila.

Like any scientific father and child, they'd grown close. She spoke at Wang's funeral and dedicated the paper to him. She marvels at the skills he demonstrated as a scientist and as a mentor.

Now Linnoila is about to begin her residency in neurology at Harvard University. Once she finishes, the young physician-scientist looks forward to resuming her research, excited by the patient populations that might eventually benefit from it, among them people with myasthenia gravis and muscular dystrophy.

And when she talks about these possibilities, she looks up and smiles.

"It's like Z.Z. said, 'It isn't easy.' But it's worth it." ■











TOP: Through the years, one of the keys to Children's Hospital of Pittsburgh's success has been the attitude that permeates the place—children are not just little adults, they need to be nurtured and loved in the hospital as much they are at home. 2ND ROW, FROM LEFT: In 1951, orthopaedic surgeon William Donaldson (MD '43, Res '50) teaches pediatric residents about treatments for clubfoot. • Parents, volunteers, and "play nurses" all played a part in caring for sick children in the '50s. • Back then, doctors did everything from sharpening needles and drawing and analyzing blood to lifting their patients, as Arthur Coddington does here, with a teenage cancer patient. BOTTOM/LEFT: Medical director Edmund McCluskey at the bedside. OPPOSITE PAGE: Entering the hospital.

THE LIFE AND TIMES OF A GREAT CHILDREN'S HOSPITAL

PHOTOGRAPHY | ESTHER BUBLEY

INTERVIEWS | BARBARA MCNULTY

FOR THE GOOD OF THE CHILD

Pediatrics was a young specialty in 1951. But the University of Pittsburgh–affiliated Children's Hospital of Pittsburgh had a medical director in Edmund McCluskey determined to build a pediatric teaching facility of the highest caliber. He recruited top-notch physicians to help him. It became a memorable time for Pittsburgh pediatrics—when doctors like Albert Ferguson, Paul Gaffney, and Benjamin Spock (down the street at Western Psychiatric Institute and Clinic) were looking after Pittsburgh's children.

Pediatric residents lived at the hospital. The work was hard, but the trainees were met with an infectious culture of caring and dedication, says one now-retired pediatrician.

One day in 1951, a photographer arrived to document the life of the hospital. She was an unassuming woman from Wisconsin with dark hair and bulky cameras dangling from straps around her neck. Her name was Esther Bubley. She was only 30 years old, but she had a wealth of experience. She'd worked for *Ladies' Home Journal* and *Life* magazines. In 1942, she was hired by the Office of War Information, which was a successor of sorts to the renowned Farm Security Administration's photographic unit. Later, she'd traveled the world shooting for Standard Oil.

In Pittsburgh, she was on assignment for the Pittsburgh Photographic Library, an enormous civic documentation project run out of the University of Pittsburgh's Cathedral of Learning. She photographed every sort of event that might happen in a children's hospital—admissions, surgeries, residents trying to catch some sleep, and painful discussions with worried parents. Although Bubley is known as one of the great documentary photographers of the mid-century, the Children's Hospital photographs received scant attention. *Life* had planned to do a piece with Bubley's shots, but cancelled when King George VI died. Instead the magazine covered Queen Elizabeth II's coronation. Bubley's photos were never published. She died in 1998.



Her prints were boxed and stored in no particular order at Children's. They later came to the attention of documentary filmmaker Ken Love and his wife, pediatrician Barbara McNulty (MD '75). *That's Pediatrics*, their film that was inspired by these images, won a 2008 CINE Golden Eagle Award. What follows are photos and interview excerpts from the film. We offer a glimpse of the hospital's rich history as it moves to its new, cutting-edge Lawrenceville home. (*© 2007 Children's Hospital of Pittsburgh of UPMC. Used with permission.*)

—Introduction and captions by Chuck Staresinic



Angelo Runco (MD ’50, Pediatric Resident ’51–’54, Chief Resident ’53–’54, Clinical Professor of Pediatrics): There probably were no more than 15 pediatricians in the whole city of Pittsburgh. We all [the residents] lived at Children’s Hospital, in the residents’ quarters. It was like one big family. The camaraderie was great.

Andrew Gursky (MD ’49, Pediatric Resident ’51–’54): We were few in number, and we also were operating a hospital of approximately 300 inpatient beds.

We not only typed and cross-matched the blood, we also took the blood to the patient and then administered it to the patient. Starting IVs—that used to be a very difficult procedure. It wasn’t unusual for us to try veins anywhere we could find them, be they scalp veins … We would try wrist veins, leg veins.

Pascal Spino (Assistant Chief Resident ’50–’52): Drawing blood—which was so terrible at that time, you had to do that—and we drew it from the jugular vein, believe it or not. The nurse would put the patient over the table and have the baby cry, and this jugular vein would become prominent, and you would draw blood from that.

William Sieber (MD ’41, Res ’50, Pediatric Surgeon ’50–’90, Retired Clinical Professor of Surgery): Appendectomies and hernia operations were commonly done. But by far the greatest number of patients had infections and required drainage of abscesses.

The primary risk in those days was the anesthetic. It was administered primarily by nurses. It consisted primarily of open-drop ether. In most cases, the nurse would monitor the pulse by feeling the pulse. It was, what I would consider, the most dangerous part of the operation.















OPPOSITE PAGE: Two boys learn to give insulin shots to themselves.
CLOCKWISE FROM TOP: Nurse Virginia Anderson feeds an infant. • A bucket of water and some plastic sheeting serves as a humidifier. • A sick boy rests his head on the knee of an adult. • Doctors handled injections and intravenous lines. • They also were known to draw blood from the jugular. • (Two OR photos) Masked nurses administered open-drop ether and monitored pulse by touch during surgery.















Albert Ferguson (Pediatric Orthopaedic Surgeon, Pitt Chair of Orthopaedic Surgery '53–'86): I first came to Children's Hospital in 1950 or 1951, and it was at the invitation of Ed McCluskey, who was one of the greatest physicians that I have ever known. He was really the inspiration for bringing first-class medicine to Pittsburgh.

When Ed McCluskey made rounds, he was teaching from the bedside. The kids loved him, and he was able to evoke in them a feeling that they were being well taken care of.

Runco: One of our outstanding teachers was Dr. Bill Donaldson. He gave us many, many lectures on pediatric orthopaedics, especially dealing with clubfeet.

Sieber: Dr. Gaffney was one of the outstanding pediatricians at Children's Hospital. As a diagnostician he had no peers.

John Troan (Science Editor, *Pittsburgh Press* '45–'57): Paul Gaffney was one of my heroes at Children's Hospital because he saved many blue babies and Rh babies. The blue babies were just children born with a heart defect—a bad valve couldn't pump blood through to the lungs in sufficient quantity to keep them going. I remember one of his patients whose lips looked like he had just eaten huckleberry pie; he turned into a lipstick ad right after [treatment].

Al Ferguson was also one of my heroes at Children's Hospital. He concentrated on straightening out children with curvature of the spine. It would take weeks to do this, but it was marvelous, because the children would be so happy getting ready to walk straight. And he kept visiting them. Each day he would crank the spine, and then as he did so, fill in open spaces with slivers of cartilage and bone about the size of matchsticks to stabilize the spine. And the children, well, they were told they'd be able to go to high school prom, and they did.

OPPOSITE PAGE: Nurses and volunteers greatly influenced the mood of the hospital. TOP: Children and staff gather for a party. 2ND ROW: A girl listens to her doctor, Coddington, on the phone. • McCluskey (hands in pockets) was both a workaholic medical director who inspired fear in some young physicians and a caring pediatrician who inspired devotion in the families for whom he cared. • Paul Gaffney (in dark suit) on rounds with residents. He is remembered by generations of Pittsburgh-trained pediatricians as an influential mentor.

Gursky: This was on a Sunday, and we were in our lunchroom, when we got a call that there was an extremely ill youngster [Patty Clark] in the emergency room, a floor above us. She had severe respiratory distress. She was gasping for air at that point.

Spino: In certain cases of difficult breathing, the infection affects the epiglottis. (The epiglottis is the valve that covers the trachea.) And in Patty's case the epiglottis was so infected that it could not stand upright. And that's often hard to diagnose. And when you see a person like that, they're often turning blue. You have a few minutes only to save their life.







LEFT, TOP AND BOTTOM: Andrew Gursky delivers news to the guardian as 3-year-old Patty Clark requires an emergency tracheotomy in a hallway. RIGHT: Pediatrician Lee Bass plays with a boy he nicknamed "Ike."

Gursky: We were about to perform a tracheotomy, even though we were not surgically trained, when Dr. Silverblatt came in. He said there was no time to obtain anesthesia, or there was no time to play games. Essentially, we held the youngster in the proper position, tilting her neck, head back, so that he had exposure for the tracheotomy. Then immediately Dr. Silverblatt made an incision. Thereafter, she stabilized. She was rather ill throughout the course of that day—being lethargic, being tired, and even not being very alert. But I recall going to the floor on the following day, at which time she was an entirely different youngster. She was sitting up inside her oxygen tent. She was alert. There was a difference in the young lady's behavior and performance.

Clyde Hare, Pittsburgh Photographer: You look at Esther's pictures of the nurses and the children and the parents and you think, *Boy, that's exactly what I'd want to have at a hospital.*

Runco: The length of stay was much longer at Children's Hospital back in the '50s, and the needs of these children who had long stays were many. They needed to be educated, and they needed recreation. We had the people who could do that. They did a wonderful job. We had a great many volunteers at that time—the gray ladies and play nurses. You don't hear much about these people in the history of Children's Hospital, but I thought it was one of the great highlights.

Spino: There was so much love generated by what they did. I think you knew that the main aim in life there was for the child and the good of the child.

Hare: I think the important thing to realize is that Esther was recording that human relationship that makes getting well a successful thing in a hospital. Whether you have high technology or low technology, a lot of it depends on the human relationships between doctors and patient, nurses and patient, parents and patient. It's the human relationships that are liable to make the difference between getting well and not getting well.

Spino: When you see a case like Patty Clark—where you've accomplished so much, where you had a child where the result might have been horrible—and you see a happy, healthy, wholesome child leaving the hospital, you feel very overwhelmed with happiness and satisfaction. And that's pediatrics. ■

Watch *That's Pediatrics* online at www.chp.edu/ThatsPediatrics

THE PHYSICIAN'S TOUCH

The photographs reproduced on these pages were found in an Oakland dumpster. Norman Rabinovitz, director of the medical photography department at Children's Hospital of Pittsburgh until the office was eliminated years ago, saved them from destruction. He shared them with documentary filmmaker (and his former intern) Ken Love, who brought the photos home to see whether a story might emerge.

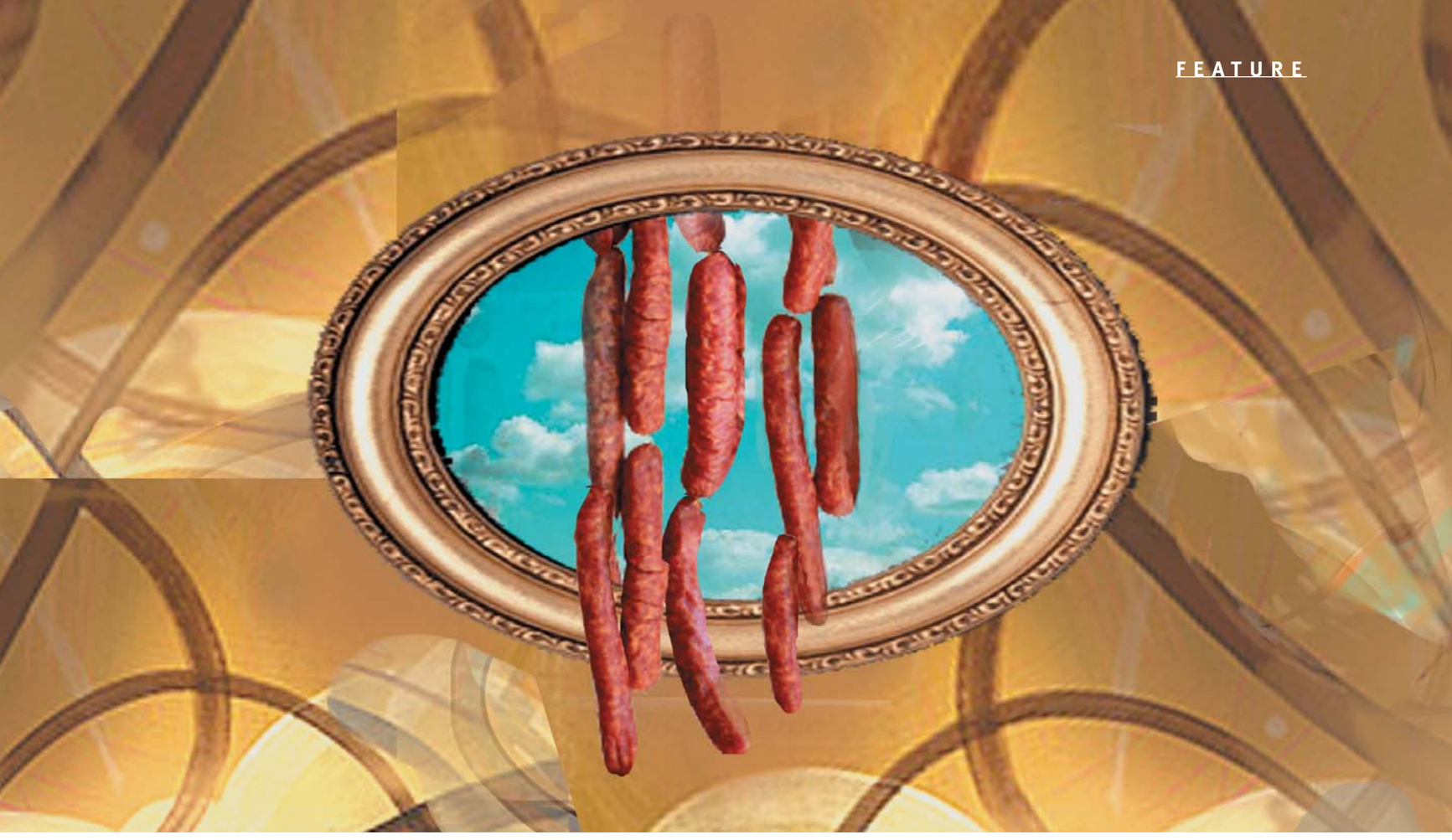
The first thing pediatrician Barbara McNulty (MD '75), Love's wife, did when she looked through the photographs was to search for herself. She would have been just 1 or 2 years old in 1951 and perhaps in a full-body cast. McNulty was born with dislocated hips—shallow hip sockets that did not embrace the rounded tops of her femurs. Nobody noticed until she was already walking. Surgery to repair the damage did not work.

Thumbing through the images, McNulty became enamored with Bubley's project. It reminded her that the most important thing she knows about her own work has always been true: Nothing is more important than the bedside exam. A doctor must listen closely and lay hands on the patient. Even with high-tech tests, there is no replacement for the human touch.

Because of her childhood experience, McNulty and her practice partner James Romberger are particularly sensitive to congenital hip dysplasia today. In fact, a faint clicking clued Romberger in to the condition in this author's newborn daughter (now a well-aligned, and speedy, 3-year-old).

McNulty never did find her childhood self through Bubley's lens, but as a pediatrician, she was able to interpret and order the jumbled photos in a way that Love and film editor Jodi Wu could not.

"Ken and I wanted to give this film to the hospital," says McNulty, the film's director and producer. "We recognized that at this juncture with the new hospital, it's important to look back as you look forward." —*CS*



WELCOME TO THE DARK SIDE

MAYBE WE SHOULD INGEST MORE NITRATES AND NITRITES

BY CHUCK STARESINIC

ILLUSTRATIONS BY FRANK HARRIS

Mark Gladwin is a scientist with something to leverage: a fundamental biological discovery. And that is why he is here in Pittsburgh.

"We think we may have stumbled upon the active ingredient in the Mediterranean diet," he reports in his office on the sixth floor of UPMC Montefiore.

Gladwin says this calmly, without much fanfare, despite the magnitude of such a discovery. He is a youthful guy, with a head of hair just long enough that it might send another scientist to the barber. He wears snazzy shirts. He's outgoing, and some of his colleagues wonder where he gets his energy.

"There are mysterious cardioprotective qualities to the Mediterranean diet," he continues. "And everybody has looked



Mark Gladwin believes maligned molecules are the cardioprotective secret to the Mediterranean diet.

at the vitamin E and the vitamin D and the vitamin C, and none of those things has panned out. But what everybody has ignored is the one molecule that is the richest but that is the bad one."

Gladwin, an MD who came to Pitt in 2008 as a professor of medicine and chief of the Division of Pulmonary, Allergy, and Critical Care Medicine, stumbled upon the power of this "bad molecule" when he was at the National Institutes of Health. He describes the NIH as the sort of place that enabled this discovery. It provided him with a steady level of support without the need to reapply for grants every cycle. By the same token, it offered little hope for leveraging more funding for his lab after a major discovery, such as a key element of the Mediterranean diet—nitrate.

Nitrate has long been seen as belonging to the dark side of biochemistry.

It is considered a pollutant in this country, and the federal government tightly regulates the amount of nitrate in drinking water. Your bottled water is most likely nitrate-free. Municipal water suppliers have become adept at limiting our exposure to nitrate. Over a recent five-year period in Pennsylvania, for example, only a relative handful of communities in the state—with a total population of less than 70,000—had nitrate levels in their drinking water that exceeded the national health-based limits.

The negative press that nitrates receive actually pales in comparison to that of its sibling molecule, nitrite. Both molecules have been indicted because they can lead to the formation of carcinogens called nitrosamines; yet it's unclear if nitrosamines from food or beverages actually lead to cancer in humans.

Our bodies convert dietary nitrate into nitrite. And it's the nitrite that is biologically active and, Gladwin believes, cardioprotective.

Yet, parents are routinely told to avoid giving children hot dogs because of the nitrites they contain.

They are encouraged to lobby school boards to remove nitrite from school lunches. There are petitions one can sign to encourage the FDA to ban nitrite.

Gladwin insists that he isn't advocating therapeutic or even routine hot dog consumption. "But the truth is that if you were about to have a heart attack, and you ate a hot dog," he says with raised eyebrows, "based on all our data, you should have cardioprotection."

Welcome to the Dark Side.

What follows are the instructions for whipping up a potential wonder drug. You don't need much—just a few ingredients that every lab already has lying around or can cheaply and easily get.

Start with an ounce of oil. Nothing exotic, just regular oleic acid. (The olive oil in your kitchen is probably 55–80 percent oleic acid, by the way.) Next, mix in some sodium nitrite, which is common enough around the lab and is really just a type of salt used to cure meat. Stir. That's it. You're done.

That's the *Reader's Digest* version. The recipe is actually more complicated and detailed, but it's nothing a careful and competent chemist can't manage. The instructions ("lipid phenylselenation/nitration protocol") run five pages long. A chemist adds reagents at various stages to encourage particular molecular interactions and to discourage others. He stirs the clear yellowish liquid for several hours with a spinning magnet dropped into the flask. Then he follows up with standard purification measures, such as filtering the mixture through a plug of silica gel. End result: a 99 percent pure solution of a fatty acid with a nitro group (NO_2) added in the middle.

Bruce Freeman, a lanky runner, cyclist, and the UPMC Irwin Fridovich Professor and chair of the Department of Pharmacology and Chemical Biology in the School of Medicine, calls it "one-pot synthesis." His description makes it sound as though it were mixed in the break room while he munched on a sandwich and scanned the latest issue of *Runner's World*, though he later notes that his lab's method for adding a nitro to a lipid in this way is a "tour de force in organic chemistry" that postdoctoral associate Steven Woodcock managed to pull off.

And what does this drug—this nitro-fatty acid—do?

Experiments in Freeman's lab in mice and tissue culture suggest that it might significantly protect your heart from damage before, during, and even after you've had a heart attack. It looks promising for diabetes, too.

Freeman's nitro-fatty acid occurs naturally in low abundance in living tissue, and it appears unlikely to have dramatic, toxic side effects. Quite the opposite: It appears to be safe, stable, and simple to make.

It sounds so simple that one might ask why we shouldn't simply take some nitrite-cured meat—a nice Italian sopressata, for example—and drizzle it with olive oil. Better yet, toss with some cooked beets and serve on a bed of spinach—both rich sources of nitrate, which the body quickly converts to nitrite. Sounds tasty, doesn't it?

Freeman himself may have unintentionally provided us with a name for this dish: One-Pot Synthesis. You are the pot. Forget the flask and the hours of stirring—why not simply slosh it around in your gut?

In 2007, Freeman and Gladwin were featured speakers at a conference at the Karolinska Institute's Nobel Forum in Stockholm. In the place where the Nobel Committee announces the annual Nobel Prize in Physiology or Medicine, these two scientists were part of a program called "Frontiers in Medicine: The Emerging Role of Nitrate and Nitrite in Biology."

How is it that such common, mundane, and purportedly deleterious stuff could turn out to be so biologically important? To understand the research of Freeman and Gladwin, you have to go back to the story of the 1998 Nobel Prize in Physiology or Medicine, which was awarded to three scientists who discovered the role of nitric oxide in basic physiology.

Nitric oxide was mainly known as a pollutant, because it is present in automobile exhaust and cigarette smoke. It's a free radical and was therefore thought to be a dangerous thing to have running loose in the body, where it would initiate uncontrolled reactions with cells and important biological compounds. Nitric oxide—NO, for short—was trouble, so the experts said.

The 1998 Nobel recognized the dramatic new understanding that NO protects the heart, stimulates the brain, kills bacteria, and dilates vessels to draw blood to wherever the body needs it. Most signaling molecules work through specific receptors in the cell membrane. NO, however, proved to be unusually powerful. Because of its small size and the fact that it is soluble in fat, it easily traverses cell membranes to regulate cell activity.

Nitric oxide is so unstable in the body that it is natural to ask what compounds might act as stable sources. That's still an open question, and one that will ultimately have many correct answers. (Nitroglycerin, for example, has been prescribed to alleviate heart conditions for more than 100 years. Now we know the drug works by releasing NO.)

At Pitt, Freeman and Gladwin are on to two big pieces of the NO puzzle, both of which are likely to lead directly to therapy for patients.

In 1990, eight years before the Nobel Committee recognized the importance of NO, Freeman was at the University

of Alabama, Birmingham, where he and others hammered out a landmark paper for the *Proceedings of the National Academy of Sciences* (*PNAS*) describing a confounding observation about nitric oxide. In the lab, NO combined with highly reactive oxygen radicals to generate very toxic byproducts. Clearly, if this were happening in the body, it would be part of an inflammatory event. But that's not what Freeman found. He says:

"When I tried to replicate those test-tube chemistry-based observations in cell or animal models, we observed that nitric oxide, rather than being pro-inflammatory, had anti-inflammatory properties."

At this time, Freeman was about to embark, courtesy of a Fulbright Scholarship, on a monthslong stint in the lab of one of his former trainees in Uruguay. There, while trying to figure out these anomalous anti-inflammatory effects of NO in living tissue, they stumbled upon an unusual fatty acid byproduct. When they looked at a fatty acid that included a long chain of 18 carbons, for example, they discovered a nitrogen compound branching off from one of the carbon bonds—something never seen before.

For nearly 20 years now, these nitro-fatty acids (NO_2FAs) have been a focus in Freeman's lab. On any given day, as many as a dozen people—postdocs, students, and early-career scientists—attack this problem in his lab from multiple angles.

Two postdocs, for example, administer NO_2FA to mice that have elevated blood glucose levels—the same problem that plagues humans with diabetes. This follows an important paper that Freeman and colleagues published in *Nature Structural & Molecular Biology* in 2008, showing that NO_2FA was perhaps a safe and natural alternative to the diabetes drug Avandia. The drug lowers blood glucose levels by activating a receptor on the surface of the cell—the receptor is like a socket that is configured to fit only a molecule with a specific shape. When a molecule binds to the receptor, it initiates a series of anti-inflammatory events. No one knew of a naturally occurring molecule that fit this receptor until Freeman's group showed that NO_2FA does. Avandia's annual global sales total in the billions, but it has lately been associated with elevated risk of bone fracture in women, as well as with heart failure, heart attack, and death.

Freeman says the seminal paper in this area is yet to come. "The real relevance is when we are able to publish the observation that fatty acids have a beneficial, clinically relevant effect in treating sick mice," he says. "That paper is cooking right now, in the peer-review process."

In a small room off Freeman's main lab, the air hums with the activity of two powerful mass spectrometers, machines capable of detecting and identifying molecules in minuscule amounts. Here, researchers learn what other molecules are created along the NO_2FA pathway, what tissues contain them, and how much is found there.

At a table in the main lab, Volker Rudolph, an MD and a visiting research associate in pharmacology and chemical biology, gives a heart-disease/NO_2FA briefing. He says that when someone experiences a blockage in the coronary artery—a myocardial infarction—blood supply to part of the heart muscle is cut off. A cardiologist can then remove the blockage and open the artery with a stent, drugs, or a balloon. As the affected area of the heart muscle is reperfused with blood, the cells there suffer further damage. More than half of the cells that will die as a result of the heart attack will die upon reperfusion. The patient will then live with a damaged heart; the rest of the muscle will have to compensate for this dead muscle tissue—the infarct. The heart may grow larger to compensate, too; and this comes with its own negative health consequences.

In a mouse model of such heart attacks in Freeman's lab, Rudolph injects NO_2FA into mice just before the coronary artery is reopened—sometimes just three minutes before, mimicking the sort of intervention that a cardiologist could someday perform on a human. In his experiments, the mice treated with NO_2FA always have smaller infarcts than the control mice.

In other words, they have cardioprotection. It's as if they had just sidled up to the Dark Side Café and ordered a spinach salad and a round of hot dogs.

Mark Gladwin will never forget the time that he, as a young NIH scientist, presented some of his early work on nitrite at a conference. "Ridiculed" is too strong a word, he says, but it's worth noting that he can't come up with a better one.

In the late 1990s, Gladwin was investigating a mysterious property of nitric oxide gas: You can breathe it, and it will lower blood pressure in the lung. Yet, according to the prevailing wisdom, the gas would not reach the rest of the body because it was unstable in the blood and would be instantaneously destroyed by reactions with hemoglobin.

"We started looking at the possibility that there were some subtle peripheral effects. We called it the 'endocrine effect of inhaled nitric oxide' because it was carried in the blood, distally." They were looking for a blood-borne NO pathway.

Gladwin and colleagues used an inhibitor to block NO production in the arms of healthy volunteers. Then they gave inhaled NO gas and showed that NO was still reaching the arm. Next question: What was the source of NO in the blood?

"So then we started rounding up the suspects," Gladwin says. "What could this species be? And I was looking at all these strange things like nitrosated albumin."

For bookkeeping purposes, Gladwin would always measure nitrite in the blood because it was an oxidation product of NO. Everyone knew that nitrite was an inert waste product that appeared in the blood when you breathed NO gas. So measuring nitrite was a way of demonstrating that your healthy volunteer was, in fact, breathing NO gas exactly as you intended.

"I even had a technician doing the nitrite measurements because they weren't important," Gladwin says. "I spent day and night working on these complicated molecules that were really hard to measure, and my technician was breezing through all the nitrites."

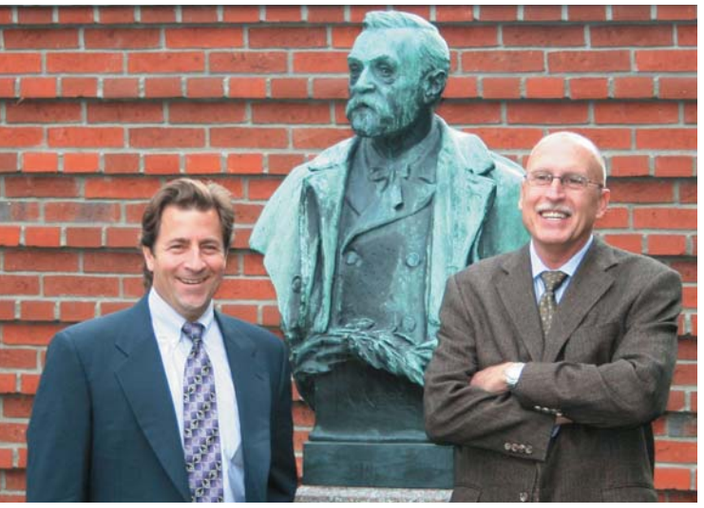
But a telling sign showed up when he looked at the technician's measurements: gradients. There was more nitrite in the artery delivering blood to the arm than there was in the vein leaving the same arm. The nitrite was being consumed.

"So we published a paper in 2000 saying, 'Look, we have this endocrine effect in the arm, and the only species we're seeing is nitrite, and there are gradients suggesting it's being used."

Is it possible, Gladwin asked, that this low concentration of nitrite is a source of NO for dilation of these blood vessels?

This is the question that Gladwin posed to a gathering of other scientists. And he recalls that a very famous scientist, of whom Gladwin was a bit in awe, stood and said, "Mark, very nice work. You're doing really nice work. I just have one question: I use nitrite as a control in my aortic ring experiments. So how could this be active?"

And the room went silent. Gladwin strug-



Mark Gladwin (left) and Bruce Freeman with Alfred Nobel at the Nobel Forum in Stockholm.

gled to come up with an answer on the spot. Maybe it only works at low oxygen, he suggested, whereas your aortic ring experiments probably use 100 percent oxygen. (This turned out to be true, Gladwin says, but at the time, he was just "hand waving" and trying to not look like a fool.)

Gladwin relishes telling this story.

"So then what happened was a paper was published in *PNAS* saying we were completely wrong," he says with glee.

"They claimed to have infused nitrite into three people, and it didn't do anything," Gladwin says. "And that actually set us back a year. … We were going to infuse nitrite into normal volunteers, but when that paper came out," he pauses and throws up his hands. "This was a really good lab that published, too, so we thought they couldn't make a mistake."

The nitrite experiment went to the back burner. A year later, the lab had a surgeon as a research fellow, and he needed a project. He was an MD, so he could do all the blood work, as well as analyze the results.

"We start the experiments, and with the first infusion [of nitrite], the hand turns red, and blood flow goes up 170 percent. It was as if we were infusing a vasodilator drug like nitric oxide." Gladwin and his colleagues repeated this with nine patients, and they called the lab that authored the paper asserting that nitrite was inert in the blood. These were good scientists and friends. Gladwin says: "Even though their paper kind of slammed us, it was good science."

These scientists suggested the nitrite in the IV bag was converting to NO. Perhaps they were actually infusing NO into the patients' arms.

Gladwin's team buffered the nitrite solution and measured the NO in the bag—a negligible amount. They repeated the experiment in nine new people, and they got the same result.

"Whoa!" says Gladwin. "So then we dropped the concentration by two logs—from 200 micromolar in the arm to 2 micromolar. We repeat that, and it dilates 10 of 10 people."

A lot has happened since then, including the 2007 Nobel Forum conference on the emerging role of nitrate and nitrite in biology, where both Gladwin and Freeman spoke. Also, the famous scientist who used nitrite as a control, Gladwin reports, now says that he always knew nitrite was a vasodilator.

Gladwin published in 2005 that low doses of nitrite prevent heart attack.

"It was repeated by people all over the world," he says. Gladwin and Pitt colleagues have proposed a heart attack trial to the National Heart, Lung, and Blood Institute.

What about the idea of nitrates and nitrites being toxins or carcinogens?

One scientist who viewed Gladwin's early papers harshly had been convinced for years that nitrite was harmful. He had a hard time believing Gladwin's results, and data from his own lab showed that nitrite was toxic. But he administered doses hundreds of times higher than Gladwin's. Both Freeman and Gladwin agree that there is at least the potential, with large doses of these compounds, for genotoxicity and DNA damage.

Like all good things, nitrite is only good in the proper amount, says Gladwin, and the same probably holds true for NO_2FA. He cautions that these are reactive nitrogen species that cause powerful reactions. Gladwin thinks the sweet spot for nitrite and nitrited lipids is in very low concentrations.

At Pitt, Gladwin is the first director of the Hemostasis and Vascular Biology Research Institute. In his career, he has made major contributions to understanding the role of lung complications such as pulmonary hypertension in sickle cell patients, and he has advanced the study of nitrite-based therapies for alleviating the vascular complications of sickle cell disease. In 2008, he coauthored a review of the mechanisms of sickle cell disease for *The New England Journal of Medicine* and a review of the nitrate–nitrite–NO pathway for *Nature Reviews: Drug Discovery*.

"What we're doing is thinking of any disease where oxygen is low and nitric oxide might be useful—heart attacks, high blood pressure of the newborn," Gladwin says. "And in all these preclinical models, the nitrite is working. So coming to Pittsburgh is very exciting for me because now I have the opportunity at UPMC to move this discovery into clinical practice. We're limited at the NIH in patient population. Also, one of the ideal targets for nitrite is going to be solid organ transplantation, and Pittsburgh is obviously the center of the universe for that.

"In solid organ [transplants], you essentially take a healthy organ, and you remove it, and you block its blood flow for hours. We think the nitrite—well, we've shown that nitrite—essentially can stabilize organs in the setting of blocking blood flow. We joke that we're turning an organ into a hot dog, but it's a state of suspended animation where that tissue is protected from damage."

Working with the Pittsburgh Life Sciences Greenhouse, Freeman has started up a biotech company to help bring NO_2FA out of the lab, where it has only been tested in animals, and into clinical trials in humans. The potential market is significant.

"There are [University of Pittsburgh] patents covering composition of matter, method claims, and using [NO_2FA] to treat specific disease conditions," confirms Hank Safferstein, CEO of Complexa, the firm he launched with Freeman.

"We're going to focus probably our initial work on metabolic disease, in particular type 2 diabetes. Obviously, this is a big area in terms of unmet medical needs."

Is it also possible that a newfound awareness of these nitric oxide pathways might simply encourage dietary changes that would lead to healthier hearts?

"Look at the Mediterranean diet. It's loaded with prosciuttos and salamis. It's hot, so you have to cure your meat," notes Gladwin, pointing out that such a diet also includes vegetables like beets—rich in nitrates, which the body converts to nitrite. "Also, in the Mediterranean diet, you live on well water—nitrate everywhere. In the U.S., we tightly regulate nitrate in our water. If a well has nitrate, you can't use it. Then the American diet: uncured meat and potatoes, pastas, bread, carbs. Zero nitrate. We have a nitrate-deficient diet. Is it possible that part of the cardiovascular disaster of the Western diet is that we've depleted this essential mineral from our diet?"

To Gladwin, that sounds like a rhetorical question. ■



THE HEART OF THE MATTER

CECILIA LO STALKS THE MOLECULES THAT SHAPE A VITAL ORGAN

BY SHARON TREGASKIS

PHOTOGRAPH BY STEPH HOOTON

In the adult human, healthy function of the respiratory tract relies, among other things, on the rhythmic wave action of hair-like cilia lining the airways. Their coordinated beat, like fields of grain undulating in the wind, clears excess mucus and airborne contaminants from the lungs. In the fallopian tubes, cilia usher mature eggs from the ovaries to the uterus. In the ear, their dance transmits vibrations to auditory nerves that we ultimately register as sound. In the brain cavity, they circulate cerebrospinal fluid and prevent overaccumulations that might compress the skull's precious cargo. Kids in grammar school learn about cilia in tandem with the dangers of smoking: Nicotine temporarily paralyzes our pulmonary street sweepers—and smoker's cough results from their return to work after a few cigarette-free hours.

First described by microscopists more than a century ago, cilia appear in nearly every cell type of the vertebrate organism and in such simple organisms as mollusks and algae. Their ubiquity—even in organ systems where wave action seems irrelevant—once led biologists to dismiss the organelle as a vestige of evolution. That attitude reflects oversight or, perhaps, lack of vision. Previously, scientists could observe the cilia in action only in single-cell organisms, or within the first few hours after the death of more complex creatures. In the past decade, however, scientists armed with advanced imaging equipment and an enhanced view of their microscopic targets—alive and at work—have reconceptualized the cilia as elaborate microsensors, scanning their environment and generating and responding to the molecular signals that convey information from cell to cell, maintain cellular homeostasis, and even pattern the growing embryo.

Research scientist Cecilia Lo, soon to be founding chair of the University of Pittsburgh School of Medicine's new Department of Developmental Biology, has spent the past 30 years investigating the mechanisms of communication between cells in the developing embryo. Her quest: to understand how congenital heart defects emerge during gestation.

Like origami, much of embryonic development depends on the influence of patterning: Fold, turn, divide, repeat, and the neural tube yields a brain and spinal cord, the protean heart splits into quadrants and migrates to the left of the chest, four limb buds differentiate into a pair of arms and a pair of legs.

Most recently, Lo has begun to home in on the role of cilial motion during the first few weeks following conception in the formation of the cardiovascular system.

"You never know where the discoveries will come from that will benefit a patient, whether it's developing diagnostics, medication, or some other therapeutic tool," says Lo, who heads the National Heart, Lung, and Blood Institute's Developmental Biology and Genetics Center in Bethesda, Md., as well as its Laboratory of Developmental Biology. She set out to catalogue all of the genes responsible for congenital heart defects in mice. In the process, her lab revealed a link to a syndrome known as primary ciliary dyskinesia (PCD) that affects the respiratory system in humans. Lo now heads a study at Children's National Medical Center to investigate the relationship between PCD and heart disease, a project she plans to continue at Children's Hospital of Pittsburgh of UPMC when she arrives in Pittsburgh this July.

"When basic science impinges on clinical medicine, it behooves us to really pursue it and bring that science to benefit the clinical population, whether it's diagnostic or therapeutic," she says. "I'm excited that we are at that boundary."

Much like seating assignments at a state dinner, the relative arrangement of organs in the chest and abdomen of a human embryo matters enormously: heart to the left, liver to the right, stomach and spleen to the left, gall bladder to the right.

Occasionally, however, the whole assemblage develops in mirror image, a condition known as *situs inversus totalis*. Providing that the organs are otherwise normally conformed, the condition may go undetected for a lifetime and even supply an elegant plot twist, as in *Dr. No*. In that story, the fictional James Bond lives another day when a would-be assassin misses the spy's right-sided heart by a few vital inches.

Far more worrisome, however, and associated with myriad congenital deformities, is the class of deformities Lo studies known as *situs ambiguous*, or heterotaxy. In heterotaxy, some organs are flipped while others occupy their standard location. Ultimately, the problem boils down to bad plumbing. With the organs themselves out of place, the valves, veins, arteries, and chambers of the heart that normally move oxygenated and deoxygenated blood in discrete circulatory loops develop with quirks and malformations that can be fatal.

Many genes are implicated in heterotaxy, which comes in multiple iterations of varying severity. Even so, the condition is rare—fewer than 2 in 10,000 live births involve cardiac defects associated with left-right asymmetry malformations of any kind, and a diagnosis generally means a fast track to the operating room. Although milder cases often end happily, some infants with heterotaxy weather the open-heart surgery only to spend the rest of their lives tethered to a ventilator. Worse, others undergo multiple operations and still die before their first birthday. Because no one has catalogued all of the genes involved or detailed the specific conformation of organs each mutation yields, pediatric cardiologists have lacked reliable indicators to predict a baby's odds before wielding a scalpel, leaving parents and doctors with little clarity about how to proceed.

"Cecilia has a big vision," says longtime collaborator Linda Leatherbury, a pediatric cardiologist at Children's National Medical Center who oversees imaging of Lo's mice and conducts the study on children with heterotaxy and other congenital heart diseases.

"It's not like she wants to work on one model, one specific defect, for the rest of her career. She wants to find *all* of the genes that cause congenital heart disease."

If Lo succeeds, one day clinicians will be able to test for specific mutations associated with heterotaxy and other complex congenital heart diseases and help parents understand the treatment options for their babies.

In its facility at the National Institutes of Health, Lo's team injects mice with a chemical that causes random genetic mutations, then uses echocardiography to identify fetal mice with heart defects. The team details the genome of every single affected mouse, then compares it with the genome of a healthy mouse to narrow in on anomalies in the mutated genome. In 2007, *The Journal of Clinical Investigation* (*JCI*) published the team's description of a recessive lesion in Dnahc5—an analog to the genetic glitch that in humans causes primary ciliary dyskinesia.

"That was a big surprise, because usually when you think of patients with PCD, it's generally thought that [the] heart is normal," says Lo. "No one really thought of PCD as a disease that could cause structural heart disease. We initially identified this mouse model as a mutant with complex structural heart disease. When we identified the gene, it was a complete surprise."

Stanford University surgical intern Serena Tan was first author of the *JCI* paper. At the time, she was a second-year Duke University medical student with 12 months of funding from the Sarnoff Foundation.

"Dr. Lo was committed to giving me a project," says Tan, whose first project ate up six months and terminated in a dead end. "She gave me the most exciting project going on. She's very hands-on, oriented to detail, and very thorough in her investigation. [In her lab], you can't just be swept away by current trends. My paper, I think, was published partly because no one has made such a detailed study on the phenomenon."

People with PCD have compromised cilial function in their respiratory tracts. In time, mucus and bacteria accumulate in the lung, leading to recurrent infection and compromised pulmonary function. Often the damage is so profound that by the time they reach early adulthood, lung transplantation is the only viable treatment. Clinicians already knew that some kids with PCD have *situs inversus totalis*.

Based on the *JCI* findings, Lo hypothesized that infants with heterotaxy whose open-heart surgery leaves them ventilator dependent have undiagnosed PCD—"respiratory complications in such patients are unfortunately attributed to the heart disease," she says.

The genetic link also validated Lo's hypothesis: She suggested that at the earliest stages of embryonic development, ciliary-wave action programs the pattern and formation of the cardiovascular system. When the cilia don't work properly, the organs form out of place. Effectively, PCD is a secondary outcome of the same genetic anomaly.

In a swank, wood-paneled conference room on the seventh floor of the flagship National Institutes of Health facility that houses her laboratory, Lo gathers with her research team for their weekly journal club meeting. On this late winter morning, a junior associate presents a pair of 2008 *Science* papers investigating the role of three proteins implicated in embryonic development and in ciliary action. Lo sits quietly, a can of diet cola on the table in front of her, flipping between pages of the papers and intent on the slides of data projected on the screen at the front of the room. Finally, as the colleague describes the authors' conclusions, Lo breaks in. "The point is to show specificity," Lo says, glancing again at the manuscript in her hands and back to the screen, "but they haven't done the control. I'd like to see a parallel where they didn't get the result with the original sequence."

The critique sparks a minidebate between the dozen grad students, research techs, and fellows in the room about how the authors could have done better. The study examines the response of the proteins to antibodies, and part of the problem, says Lo, is that the best antibody to serve as a control in this case isn't widely available—its creator has closely guarded distribution. Soon the session is over, but Lo has made her point: Claims by scientists aren't the same as scientific proof from a well-designed experiment, and collaboration can mean the difference between a so-so study and one with the power to convince.

"I send Cecilia a paper to read, and she'll say, 'You haven't proved this,' or 'You haven't done that.' Likewise, she'll take criticism," says Vanderbilt University Medical Center chief of pediatric cardiology Scott Baldwin, who investigates vascular formation in mammalian embryos and worked with Lo when both were on the University of Pennsylvania faculty in the '90s. "She'll often send her work to say, 'What do you think of this? Are we missing something?' It goes both ways."

As the group disperses to go off to their labs and computers, Lo stops to ask staff scientist Biswanath Chatterjee about the status of a litter of mutated mice in the team's animal facility, a 15-minute walk across the NIH campus.

Chatterjee has known Lo since he spent four years as a postdoctoral fellow in her lab at Penn in the late '80s.

"Science is in her blood," says Chatterjee, noting that he'll often receive a series of e-mails from Lo as she reviews literature from home, long after her family has gone to bed. "Sometimes the e-mails just keep coming—1 o'clock, even 2 o'clock at night, and the next at 5 o'clock in the morning. She really enjoys this thing."

Lo's enthusiasm drives the lab forward, says Chatterjee, and she balances rigorous expectations with acknowledgment that not everyone can maintain her pace. She also makes a point, he says, of cultivating and protecting the junior scientists in her group. Late last year, a researcher called Lo after a postdoc presented the group's preliminary identification, using massive-parallel DNA sequencing, of a heterotaxy-inducing mutation of the gene Megf8. The other scientist was also working on Megf8, he said, and if Lo's group would hold their findings for a year, the two groups could collaborate and then publish simultaneously. Lo called a meeting of the 18 scientists working with her and the postdoc and presented the opportunity. Everyone had a chance to voice an opinion, says Chatterjee, a member of the team. "She protected everyone who was working on this project."

There were too many questions about the value of the collaboration for her group, says Lo, and the team opted to stay the course. Their findings appeared in the March 3, 2009 issue of the *Proceedings of the National Academy of Sciences*.

"The human element is really important," she says. "It's not just my career, and it's not just the science. People's lives and careers are at stake. It's my job to do the best



J. ROSENTHAL, ET AL. BIRTH DEFECTS RESEARCH (PART C) 72:213-223 (2004)

Lo and her colleagues can't afford to capture only a fraction of the information needed for heart-defect research, which is what they get with 2-D images. Using a technique known as EFIC, they've created digital, 3-D atlases of both human and mouse embryonic development that allow researchers to view samples from any vantage point, including cross-sections of the heart. The fetal mice above were each imaged at a different stage of maturity and are shown from different angles.

I can for the people in my lab."

Beyond performing their wide-ranging genetic analyses, Lo and her team have also refined and automated the technology to generate a pair of three-dimensional online atlases of human and mouse embryonic development based on a technique known as episcopic fluorescence image capture (EFIC), now a cornerstone of Lo's documentation of complex structural heart defects. Using EFIC, the group creates 3-D, digitized renderings that can be viewed in any plane.

EFIC provides an elegant work-around to a basic problem in conventional histology, in which thin slices of paraffin-embedded samples go under the microscope. Of course, the heart functions and develops in three dimensions; when sectioned into thin slices, critical information gets obscured or destroyed. And though each slice retains its integrity in two dimensions, stretching and compression caused by the slicing itself makes a 3-D reassembled composite impossible. Structural anomalies aren't replicated across specimens, and Lo's team can't afford to capture only a fraction of the information needed from each heart. Using EFIC, they image the block face that remains, instead of the slice they've removed.

Premed student Rajeev Samtani joined Lo's team in 2007 as a freshman in biological engineering at George Washington University, in D.C. Lo's use of EFIC captured Samtani's imagination, and today the 20-year-old has developed some expertise in the technique.

"Dr. Lo is the best mentor I've ever had," says the Maryland native. "It may take twice as long to do a gross necropsy with me, but Dr. Lo stops every second to make sure I know what she's doing—what she's imaging. Some mentors just give you a protocol to follow, but not Dr. Lo. She's always teaching. And if I run into a problem, she has 30 different solutions to try."

This spring, Samtani assisted a cardiology fellow developing a digital video of human cardiac development. "Viewers, other scientific researchers and clinicians, can go through the entire embryo," he explains. "But it may be hard to orient." The challenge is easy to get around in still images. A simple compass icon does the trick. Samtani suggested that incorporating a comparable strategy into the video would enhance its value. "Dr. Lo said, 'Go for it,' and now we're trying to label everything, and we've got some new software. If I have an idea and voice my opinion, everyone in the lab, especially Dr. Lo, is so open."

More recently, a late-night e-mail exchange with Lo about the possibility of combining EFIC with confocal microscopy (which allows scientists to create a sharper image by illuminating one point of a specimen at a time) had Samtani's adrenaline running high. He barely slept. "I was so excited to get to work," he says.

For Lo, the give-and-take of study design and execution is precisely what makes science a rewarding pursuit. "If you can't discuss what you have," she says, "you're missing a big part of the fun of doing science.

"I feel like you can go a lot further in your work, faster, by sharing resources, information, working with others. To me, being generous with your colleagues is a good thing. Ultimately, it's a win-win."

At Pitt, junior developmental biologists populate multiple departments throughout the health sciences. Lo's job will be to provide direction, says Arthur S. Levine, dean of the School of Medicine and senior vice chancellor for the health sciences.

"What's been needed in my view has been a senior developmental biologist of wide repute and recognition to bring together and coalesce the theme, crystallizing what we already have," says Levine. "Adding Cecilia to the mix will accelerate our momentum—give it shape and form and visibility."

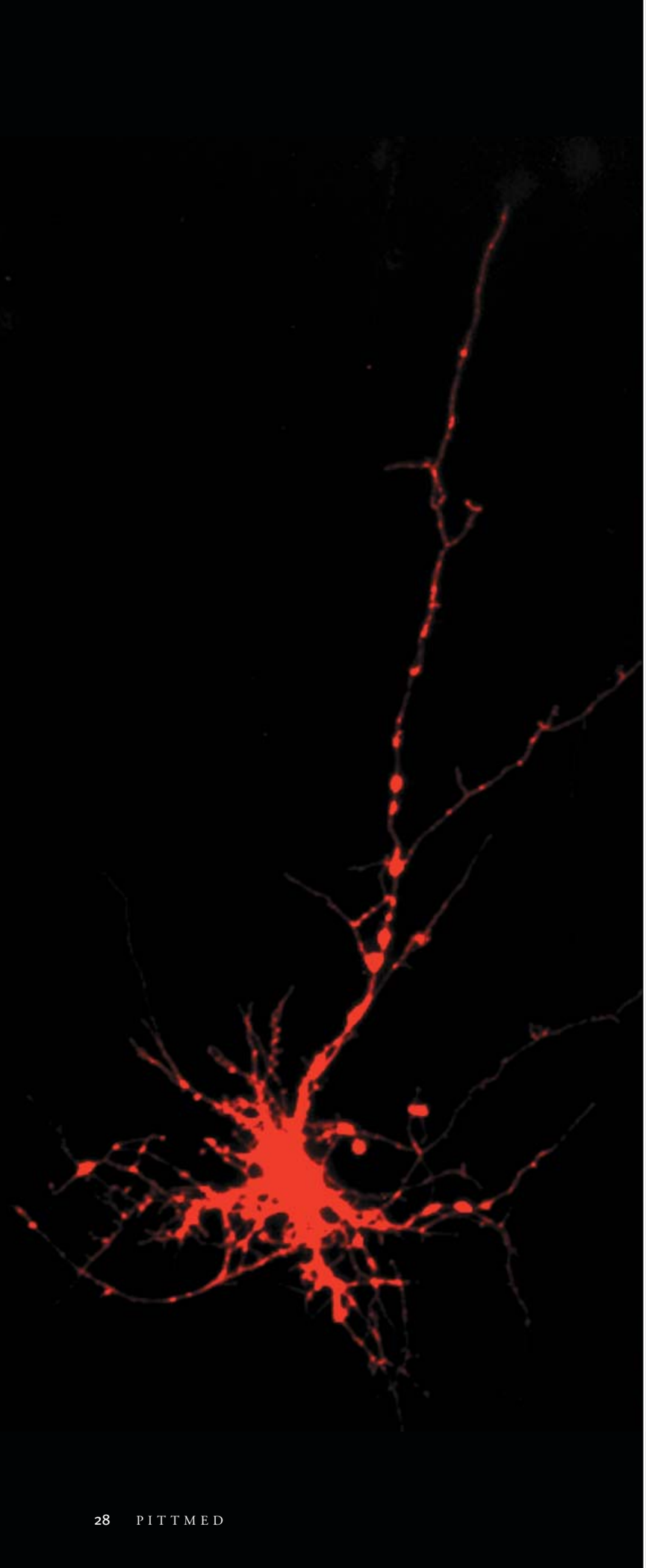
At Pitt, Lo will have a joint appointment in pediatrics, and the proximity of her lab in the John G. Rangos Research Center to the children's hospital (next door instead of a 25-minute drive away, as in Bethesda) will promote the synergy she craves. She has already begun exploring partnerships with Pitt pediatricians who treat congenital cardiovascular and renal disease.

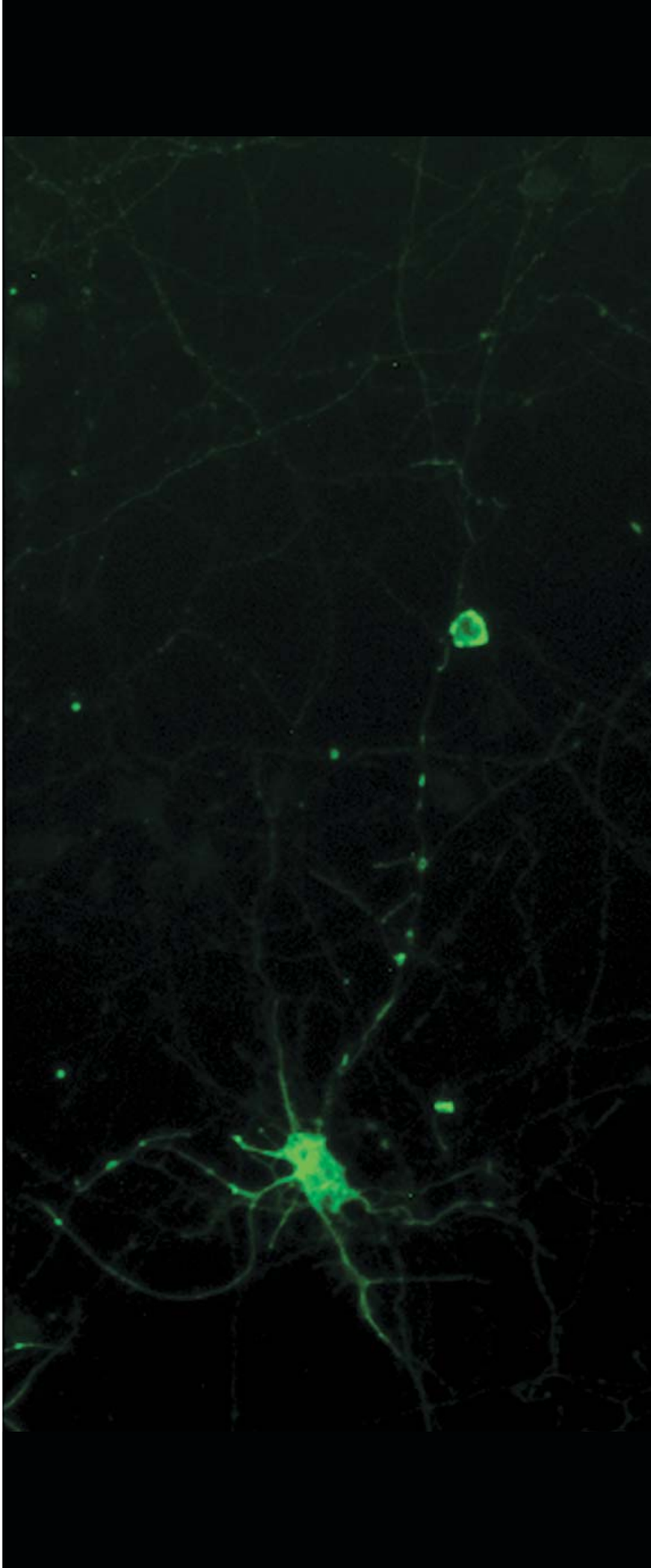
"This offers a whole new area of research to what we've traditionally studied," says Steven Webber, medical director of pediatric heart and heart-lung transplantation and an associate professor of pediatrics whose work with heterotaxic infants makes him particularly interested in Lo's arrival.

"From an intellectual standpoint on our end, clearly [Lo's appointment] broadens the scope of what we do."

Lo's first recruitment effort, to bring a stem cell biologist into the fold, got a boost this winter when President Barack Obama rescinded the Bush Administration's funding restrictions on embryonic stem cell research.

"I hope that in building the department we can take an approach where you have basic scientists pursuing very fundamental issues related to how development is regulated and a translational component with investigators trying to relate those findings to disease processes in children," she says. "I really feel like the time is right to integrate the two. I don't think you can do one or the other alone." ■





A MENTOR AND STUDENT TRY TO KEEP DYING CELLS ALIVE | BY JOE MIKSCH

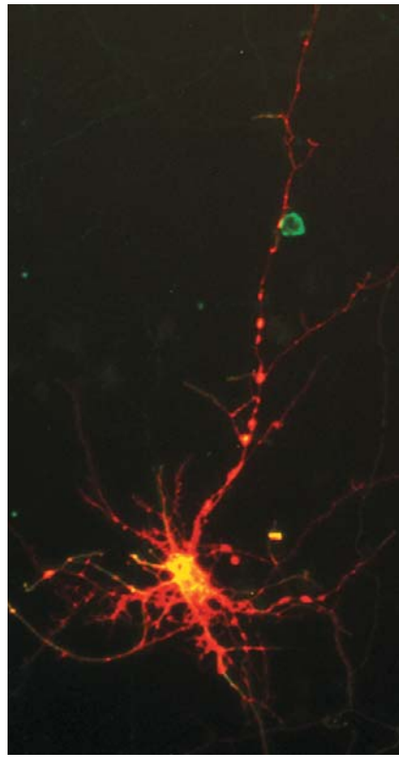
IN THE SHADOW OF A STROKE

About five years ago, 59-year-old Randy Zotter was having some trouble with his knee. So much so, that he arranged to have an X-ray taken at UPMC Passavant in Pittsburgh's North Hills. No big deal, he thought, just a small diversion ahead of his plans to take his wife, Leslie, out that night for their 25th wedding anniversary.

The X-ray completed, Zotter got into his car. "My left hand goes like this," he says, flopping it off a table. "It wouldn't move. Immediately, I went into a state of denial." He started the car and drove off. His left arm still wouldn't move, and recalling that his father had a stroke when he was 39 prompted Zotter to turn around and head back to Passavant.

He parked about 100 yards from the emergency room—"I didn't want to block the entrance," he says, laughing—and hobbled to the door. "I told a woman out there smoking that I was having a stroke. She ran away," Zotter recalls.

Once inside, he was taken in for a CT scan. Doctors confirmed Zotter's self-diagnosis. A cerebral artery had collapsed, they told him. For the next two weeks, Zotter rested in the hospital. For months afterward, he went through round after round of physical and occupational therapy.



Neural cells not immediately killed by a stroke can suffer from a deadly inability to synthesize proteins. Jun Chen and Peter Vosler have found that a protein called eIF4G, vital to synthesis, is torn apart by calpain, a protease, in the wake of a stroke. By inhibiting calpain, the two think they may have found a way to save such cells and perhaps have acquired the tools for an exciting new therapy. (The first image, in red, is a neural cell stained to show the expression of eIF4G. The second, in green, is a normal neuron. The third, at right, is an overlay of the two images.)

COURTESY P. VOSLER

However, Zotter says, his doctors told him there was nothing to be done to save the brain cells injured by the stroke.

Jun Chen and Peter Vosler, of the University of Pittsburgh School of Medicine, are trying to build a brighter future for patients like Zotter who make it to the hospital within a few hours of experiencing a stroke. They have found a way to halt neuronal cell death caused by lack of blood flow, or ischemia.

Chen is an MD professor of neurology and pharmacology and chemical biology. He holds an endowed chair and directs the Cerebrovascular Research Center at Pitt. Vosler is an MD/PhD student who recently completed his PhD work in neuroscience and begins his third year of medical school in the fall.

Stroke is the third-leading cause of death in the United States and the second worldwide. About 80 percent of those cases are considered ischemic—brought on by a lack of blood flow. When a stroke strikes, the halted blood flow decidedly and immediately kills cells at its epicenter. The damage eventually spreads to the penumbra, the area surrounding the dead cells.

According to Chen and Vosler, stopping the death of neuronal cells in the penumbra of a stroke can curtail the long-term physical and emotional damage caused by this serious insult to the brain. These cells don't die immediately in a stroke's wake. But when they do die, the area of the brain affected is greatly expanded, leading to more problems for a stroke survivor.

Zotter regained use of his arm—only after months of physical therapy. He recalls trying to refine his motor skills by attempting to screw a nut onto a bolt. The frustration, he says, was overwhelming. "But I told myself, 'Yes I can, and yes I will.'"

Though he suffers no speech impediment, Zotter says that he has to concentrate much more when speaking. And he's more emotional now: "I tear up during 'chick flicks.' I never did that before," he says.

Although Zotter has recovered well overall—thanks, he thinks, to the fact that he was very close to a hospital when he suffered his stroke—few treatment options were available to him when he entered the emergency room.

One of the most exciting advances in stroke therapy in recent history came in the early 1990s, when doctors began using a clot-buster called tissue plasminogen activator, or tPA. If delivered within three hours of a stroke, tPA breaks up the clot that limits blood flow in the brain. After that window closes, tPA isn't effective and increases the risk of brain bleeding.

"Only about five percent of the 800,000 stroke patients a year in the U.S. can get tPA and benefit from it," says Vosler.

That's because of the small time window and a host of other factors excluding patients from tPA therapy.

The therapy wasn't an option for Zotter, for instance, who didn't have a blood clot but did suffer from what's known as an ischemic infarction.

Chen and Vosler anticipate they've hit upon a molecular mechanism that, if translatable into a drug, could limit the damage done in such cases. Their work is predicated on a discovery European researchers Paul Kleihues and Konstantin-Alexander Hossmann made in the early 1970s. Using animal models of stroke, Kleihues and Hossmann determined that the brain uniformly shuts down protein synthesis in all ischemia-affected areas. Hossmann later found that brain regions that recovered protein synthesis lived, whereas regions where protein synthesis inhibition persisted died.

His doctors told him there was nothing to be done to save the brain cells injured by the stroke.

Chen and Vosler posit that the neuronal cells in the penumbra of a stroke might be salvageable if the disruption of protein synthesis can be remedied.

"[Neuronal cells affected by ischemia] lose over 90 percent of their capacity to synthesize proteins, and if protein synthesis is inefficient and persists, the neuron will die," says Chen. That situation is not remedied by tPA or any other current stroke therapy, including cerebral angioplasty and surgery.

"The question is," adds Chen, "'What causes the persistent protein synthesis deficiency?' That question has been pestering the field for years."

He adds: "We believe that if we are able to identify the molecular mechanism underlying persistent protein synthesis deficiency, we may be able to develop a new therapeutic strategy to prevent cell death after stroke."

Perhaps, Chen says, they've completed the first step and are now on their way to achieving the second.

The effort started with Vosler looking for a PhD project and mentor. In Chen's Starzl Biomedical Science Tower office, the pair recount the history of their nascent partnership.

"When Peter came to my lab, and we sat down to discuss what he wanted to do, I said, 'Peter, we have a major mystery in the [stroke] field, and it's a big challenge,'" Chen recalls. 'Do you want to take it on?' He said, 'Yes.'"

"I was a young, naïve student," Vosler adds, before both he and Chen dissolve into laughter. Chen leans back and lets his student tell the story.

Regaining a bit of composure, Vosler says seriously, "I thought that this work might be risky, but I was sure I was going to learn under Dr. Chen no matter what I did."

The reason for Chen and Vosler's laughing fit is that researchers have been poking around the question of how to rescue stroke-damaged cells for decades. And though Chen discovered that protein synthesis disruption is probably responsible for the death of neuronal cells present in the penumbra of a stroke, getting into the nitty-gritty of protein synthesis could be considered a bit much for a "young, naïve student."

Vosler's charge? First, create a credible model of protein synthesis in the lab. The process of studying the causes and effects of stroke is complicated enough that the additional vagaries introduced by studying it in vivo are excessive and confounding. So Vosler took the petri dish path.

Vosler took primary cortical neurons from rats, cultured them, and was able to mimic ischemic conditions in culture dishes. He also succeeded in reproducing persistent protein synthesis inhibition. "What he did was establish a model system to replicate the condition seen in vivo," Chen says proudly. "Now we can study the mechanism in a very tightly controlled situation."

Chen adds that he's also impressed with Vosler's feat because though the steps by which cells make proteins are understood, there is less familiarity with how the whole business gets started. Thanks to advances in molecular biology, neuroscientists now know that there are 36—read: a whole lot of—proteins involved with initiating protein synthesis. "That's before you get any translation, any elongation, or any amino acids being added," Vosler says.

Earlier in vivo studies indicated that during ischemia there is a decrease in the presence of a scaffolding protein called eukaryotic growth factor 4G (eIF4G), which is responsible for transporting messenger RNA (mRNA)—protein-making instructions—to a cell's ribosome. Ribosomes are cells' protein factories, the seat of protein synthesis. If there's a problem with eIF4g, mRNA messages cannot get to the ribosome, dooming protein synthesis. With that, the cell dies.

Enter calpain. Calpain is a protease that cleaves, or breaks down, eIF4G. As Vosler explains, calpain depends upon calcium in order to be active. In the wake of ischemia, calcium rushes into neurons and stirs up a calpain storm, with the calpain cutting up eIF4G and blocking normal mRNA activity. Chen and Vosler thought, if calpain-mediated eIF4G cleavage and the resultant inhibition of synthesis are a direct consequence of ischemia, perhaps inhibiting calpain could restore the process.

Experiments conducted by Vosler inspire confidence that this hypothesis is correct. Vosler tried to calm down calpain by introducing a load of its inhibitor, calpastatin. Doing so, he found, stopped eIF4G cleavage, restored protein synthesis, and increased the viability of his cultivated rat neurons. And by maintaining the proper level of eIF4G, Vosler was able to sustain these gains.

Don DeGracia, a PhD associate professor of physiology in Wayne State University School of Medicine in Detroit, calls Chen and Vosler's work "impressive." DeGracia is an author of a 1994 paper that implicated calpain as an enemy of eIF4G.

"What Pete and Jun have done is prove beyond a shadow of a doubt that calpain degrades eIF4G," DeGracia says. "There were some possible scientific doubts with our original methods. Pete and Jun have used foolproof methods to prove it."

Also, DeGracia adds, "They've shown that by preventing calpain from degrading eIF4G, they not only recover the cell's ability to make protein, the cells don't die, either."

The process leading to these discoveries wasn't particularly simple, Vosler says.

The eIF4G protein, at 220 kilo daltons (that's equivalent to the mass of 220,000 hydrogen atoms), is pretty huge as these things go. The size, Vosler says, makes it difficult to synthesize its DNA—a process that becomes harder to do without errors the longer a sequence is. Neuronal cells, he adds, are notoriously difficult to transfect—to introduce DNA into a cell.

Volser says he tried a new reagent that was supposed to ease the transfection process. "It was touted to work in primary neurons," he says. But it didn't. Eventually he settled on using a lentiviral vector, a kind of "neutered" virus that can't reproduce but can carry and insert cargo into cells. Vosler feared the size of the cargo might gum up the works. (Lentiviruses can typically carry a 10 kilobase load; Vosler had 12 kilobases of stuff he wanted to put into them.)

"At this size, we expected that either there would be no expression of eIF4G or there would be very little," he says. "Much to our surprise, the virus was able to transfect primary neurons with approximately 75 to 90 percent efficiency."

So with the technical issues solved and after collecting and interpreting their data, Chen and Vosler felt confident that they had established a direct relationship between ischemia, eIF4G, calpain, and the untimely end of protein synthesis in neuronal cells. This, Chen says, is a very big deal: "This is the first time it has been shown that protein synthesis inhibition and cell death are directly related."

With publication of the work pending—Chen hopes the results will see print in the *Proceedings of the National Academy of Sciences* this spring—Vosler has been on a bit of a speaking tour, presenting the findings at the American Heart Association's Fellows Research Day and at a conference at Cold Spring Harbor Laboratory on Long Island, N.Y.

"That I was able to get a platform presentation [at Cold Spring Harbor] in front of all these big-time protein synthesis researchers was great," Vosler says. "Postdocs through senior scientists said it was very interesting work. And the fact that it's related to disease directly and has the potential to really help means a lot."

"Their work is one thread in a tapestry that is being woven by many labs right now recognizing how important it is that brain cells recover their ability to make their own proteins," Wayne State's DeGracia says. "It's the overall picture coming out of this tapestry that will offer a new way to understand stroke and may help us to prevent neurons from dying."

And that's what will mean the most to Chen and Vosler—translating lab-generated knowledge into a clinical application.

"We can develop a way to deliver the [calpain] inhibitor to the brain, and that's the way to attack it," Chen says.

They envision attaching the inhibitor to a segment of HIV protein that can pass the blood-brain barrier. The process uses an 11-amino acid sequence of HIV that does not contain the pathogenic domain of the virus. Earlier this decade, Chen was the first to provide neuroprotecion in an animal model of stroke using a protein connected to this HIV amino acid sequence.

A nanoparticle might also serve as a delivery vehicle for the therapy. Nanoparticles are tiny, inert bubbles that, like the HIV protein segment, can cross the blood-brain barrier. They're particularly attractive for drug delivery because they can be directed toward specific neuronal receptors. Kind of like a GPS system for stroke therapy.

The Randy Zotters of the world, Chen and Vosler hope, will someday be able to receive an injection in the wake of a stroke that will halt and reverse the slow cell death caused by ischemia-related protein synthesis cessation.

The researchers are far from monitoring safety trials, yet they are hopeful that they can avoid the risks related to conventional tPA therapy, such as brain bleeding. Chen imagines a prospective new therapy coming out of their studies that—unlike with tPA and other treatments—wouldn't just restore blood flow to the brain, it would redeem neural cells in the penumbra of a stroke, limiting damage and making a patient's recovery easier.

Time will still be a factor in the treatment, however. "The median time of arrival [to a hospital after a stroke] is six hours," Vosler says. At this point, Vosler and Chen are unable to pinpoint a required time frame for any therapy arising from their work.

Vosler is unsure whether he'll be travelling along with Chen through the intensive lab work and lengthy clinical trials necessary to bring a calpain inhibitor–based therapy to stroke patients. Come fall, he'll resume the pursuit of his MD and, after that, the future is unwritten.

"I want to figure out how I can do clinical and lab work at the same time," Vosler says. "I really enjoy research, but I haven't decided on a field. Surgery is enticing but would limit the amount of time I could have in the lab. I really haven't figured out what I want to do."

In a way, Chen says, it doesn't matter much what discipline Vosler ultimately chooses to pursue.

"The purpose of the MD/PhD program is to train scholars, to train physician-scientists," Chen says. "Regardless of the area he goes into, he is going to be outstanding. What he's doing is very rare, to be honest with you." ■



DEREK WAHILA

Every winter, Operation Safety Net holds a vigil for the homeless who died on the street that year. The organization's founder, alumnus Jim Withers, is shown far right.

CASTING A SAFETY NET

HOW PITTSBURGH'S STREET DOC GOT STARTED

INTERVIEW BY TERRY GROSS

On November 17, 2008, National Public Radio featured University of Pittsburgh School of Medicine alumnus Jim Withers (MD '84) on Fresh Air with Terry Gross*, produced in Philadelphia by WHYY and distributed by NPR. Withers' Operation Safety Net started as an outreach program under the auspices of UPMC Mercy; it's now a nonprofit organization. What follows are excerpts of the interview. (© 2008, WHYY, printed with permission.)*

TERRY GROSS: My guest, Dr. Jim Withers, has practiced medicine in dark alleys and under bridges as he's traveled the streets treating the homeless. In 1992, he founded Operation Safety Net to treat homeless people in Pittsburgh. It's one of the nation's first full-time street-medicine programs and has inspired similar programs in other cities. Last month, Dr. Withers established the Street Medicine Institute, a nonprofit dedicated to helping communities throughout the world develop street-medicine programs. Withers is a doctor of internal medicine.

Dr. Withers, welcome to *Fresh Air*. Being among the first people to set up a street medicine program, what are some of the obstacles you faced in getting something like that off the ground? Or maybe, like, the rules are established now, but they weren't when you started?

JIM WITHERS: There really wasn't anyone to ask, in terms of guidance, even if this was a very good idea. Early on, I think I didn't tell the hospital for the first nine months what I was doing because I wasn't sure how they would accept it. Then I finally confessed that I was doing this work, and I would like some sort of support. At that time, they were able to give us a small grant, which allowed me to hire some of the homeless guys, formerly homeless guys, as outreach workers, and then get a secretary to sort of organize it all. The record-keeping is a challenge—people that gave you different names on different days. Acquiring supplies—we used to sort of steal things from a hospital early on, and then that worked itself out a little better later on.

GROSS: So, during those first few months, when you were dressing like a homeless person, was that helpful?

WITHERS: I think so. But it was amusing, because after I got established on the streets, they called me Doc Jim. And from one bridge to the next they would sort of refer me to someone else that needed help. And then one day a guy said, "Doc, why do you dress so poorly?" And I realized maybe I should dress up a little bit. So then I just got more practical in my outfit.

GROSS: So what do you wear now?

WITHERS: Just dark clothes, cargo pants, and I have a backpack, which has gotten much bigger; it has a lot of medical supplies and things in it.

GROSS: What do you keep in your backpack?

WITHERS: Well, the street really has to teach you how to do this sort of thing. And that's really the underlying philosophy, which I think is why within the medical field this is very timely. We need to learn to let our patients and those populations that are in need teach us. So as time went by, I saw people who—they had prescriptions that were melting in the rain that some emergency room had given them. They were coughing and ill, but they couldn't afford [medicine], and they weren't going to tell anyone. So, I realized that I needed to start taking some medicines out to the street. The police were kind of skeptical at first about me, so I worked on that relationship as well. And also, there was, in the very beginning, a certain individual on the street that I think would have taken advantage of me if I had anything that was of any great street value. So I began filling little Ziploc bags with medicines that could be very useful—antibiotics, pain medicines that weren't addicting, bandage material.

GROSS: You said initially the police were skeptical of you. What were they skeptical of?

WITHERS: Well, they didn't really believe I was a physician. I certainly wasn't dressed like one at that time. And it was at night. We were going into places that—actually we were probably trespassing in a few instances. So, they would stop and ask. And I particularly remember, a guy came up to me, and he handed me a handful of heroin and needles and things and just said, "Doc, I want to get off drugs." I looked down the street; there was a policeman watching us. And so, there really wasn't any precedent for them. But I got to know some of the police pretty quickly. I actually went to the station and talked to them and acknowledged

the hard work that they were doing and made partnerships with them. So that worked out pretty well.

GROSS: So what happened? Did you take the heroin?

WITHERS: I gave it back. I said, "You're going to have to get rid of this yourself."

GROSS: What are the typical problems you've seen on the street—medical problems—since you started doing this work?

WITHERS: Well, we live in a part of the country that's cold, and so we do see people who suffer from frostbite, the loss of toes, and trench foot. There's a lot of trauma. People are injured a great deal on the streets just by living out there, but also people are victimized by nonhomeless people, actually more often and [more] seriously than by other homeless people. But for the vast majority of people, it's medical conditions that we all suffer from but just go untreated due to the living circumstances.

GROSS: Many homeless people are mentally ill and are suffering with delusions and hallucinations. How do you treat someone in that condition? You don't have their medical records; there's no family members to tell you about pre-existing conditions; they're not going to be able to accurately communicate their symptoms or their, you know, long-term medical problems. So what do you do to get oriented to their problems and to communicate to them what they need to do?

WITHERS: Oftentimes you ask them, "What medicines have you been on?" And they'll mention some psychiatric medicines, so you know that's probably part of the history. But you have to be very indirect, because it's very threatening to people to go right to mental health issues.

So I found that even if a person is quite paranoid, delusional, and afraid, they still have a rich emotional life, and they do understand that you care about them, that you're consistent, that you're respectful. These are things that send powerful messages.

GROSS: Did you worry about protecting your own safety when you're on the street?

WITHERS: Well, when I started, basically it was just me and a formerly homeless person. I was quite concerned about my safety. We've been at this for over 16 years, and no one has ever been assaulted or hurt by any homeless person. But the first year was probably a little bit more up for grabs. I had three people point guns at me. I had someone threaten to cut my throat. It really became obvious to me after time that we had become part of the street culture and vice versa, and, if anything, we were well respected and cared for in the street.

GROSS: So when people held guns to you, were they other homeless people, or not?

WITHERS: Well, one was a fellow that we came up on the wrong way, and there's a lot of street etiquette and ways of doing things. (You really need someone who knows the street. And I would say anyone who is going to do this needs their own ambassadors to the street—formerly homeless are great types of folks to do that.) And that person we just surprised.

One guy, I also surprised, he knew me well, but he pulled a shotgun out, and another former homeless guy was able to redirect that—it didn't go off. One was a policeman who pointed the gun at us, and that frightened me more than anything because I knew their aim was good, and I didn't move a muscle. So those are the kinds of things. You just have to be careful how you approach people in remote campsites and things like that.

GROSS: You said, "You have to be careful not to do it the wrong way." What's an example of the "wrong way" that got you into trouble?

WITHERS: There was a guy who was nodding [off], and for whatever reason, he was against a wall, and we came at him in a sort of a horseshoe pattern. So he was surrounded. You know, there are a lot of predators out there that take advantage of the homeless. I guess that would be the way that they would assault someone.

GROSS: Is it difficult to work with people over an extended period of time? Do the homeless people that you see stay in one place? Can you find them after their first treatment?

WITHERS: It is a little challenging. I work with a lot of other cities throughout the United States to help them start programs or to improve the programs that they're doing in street medicine, and one of them had an interesting term. Instead of calling it "case management," he called it "chase management." There's a lot of effort that's put into keeping tabs on people and knowing where they are. Our electronic medical records allow you to put a name in and find out who's likely to know where that person is. We work with the morgue. We work with the libraries. And then the street has its own sort of network of knowing where people are and what's going on with them.

GROSS: Dr. Withers, I understand you started a wall in memory of homeless people whom you've worked with who have died. Would you describe the wall?

WITHERS: Years ago, I was in a *People Magazine* article, and Sidney Sheldon sent some money. It was very kind of him, and I thought, "I know what this money should go for." There were people dying on the streets, and no one was remembering them. So I used the money to buy 10 plaques, and I was going to drill them into the sidewalk or wherever that person had slept. Slowly they would accumulate, and they would make a—almost a political—statement about how many people are dying.

There were people dying on the streets, and no one was remembering them.

Well, it turns out that that's illegal. So we negotiated with the city, and we found a compromise of a wall. Every street person that we can account for [since 1989] has a plaque on that wall, and it's become one of the focal points for a sense of community. The homeless anticipate their friends' names appearing there when they've died. Family members come, and it's a place of healing and of acknowledging also the reality of what's going on. Each year, as in other cities, we have a homeless memorial service on December 21st. It's a candlelight service, and it has great meaning for all of us.

GROSS: Sounds like those plaques are part obituary, part tombstone.

WITHERS: That's right.

GROSS: Well, I want to thank you very much for talking with us.

WITHERS: Thanks for raising awareness. ■

MATCH RESULTS
CLASS OF 2009



KAPELEWSKI / CIDDE

Patience paid off as the Class of 2009 learned of their residency matches; there were many happy and relieved faces in the crowd.

ANESTHESIOLOGY
Busch, Ryan
University Hospitals Case Medical Center/ Case Western Reserve University, Ohio
Gauvin, Jean
Johns Hopkins Hospital, Md.
Lai, Yvonne
Massachusetts General Hospital/Harvard University
Lao, Veronica
University of Virginia Hospital
Olutunmbi, Yetunde
University of Pennsylvania Health System
Peperzak, Katherin
University of Pittsburgh Medical Center
Rohrbaugh, Max
University of Pittsburgh Medical Center
Shah, Pranav
University of Pittsburgh Medical Center
Telford, Charlotte
University of Pennsylvania Health System
Tsai, Annie
UCLA Medical Center, Calif.

DERMATOLOGY
Brown, Patrick
San Antonio Uniformed Services Health Education Center, Texas
Hawryluk, Elena
Massachusetts General Hospital/Harvard University
Pillemer, Brendan
University of Pittsburgh Medical Center
Volker, Kirk
University of Maryland Medical Center

EMERGENCY MEDICINE
Baca, Justin
Brigham & Women's Hospital/ Harvard University, Mass.
Barr, Scott
University of Virginia Health System
Brooks, Deborah
University of Pittsburgh Medical Center
Frank, Virginia
University of Pennsylvania Health System
Henning, Daniel
Beth Israel Deaconess Medical Center/ Harvard University, Mass.
Hilton, Michael
University of Pittsburgh Medical Center
Jones, David
University of Pittsburgh Medical Center
Lee, Dahmi
University of Michigan Hospitals and Health Centers
McGarry, Patrick
Los Angeles County + USC Medical Center
Negron, Deylin
University Hospital/UMDNJ–New Jersey Medical School
Novack, Jared
University of Chicago Medical Center, Ill.
Nuttall, Kevin
Beth Israel Deaconess Medical Center/ Harvard University, Mass.
Raducha-Grace, Laura
University of Pittsburgh Medical Center
Schenfeld, Eric
Carolinas Medical Center/University of North Carolina at Chapel Hill
Stockwell, Carrie
University of Pittsburgh Medical Center
Stoler, Genevieve
University of Pittsburgh Medical Center
Van Epps, J. Scott
University of Michigan Hospitals and Health Centers
Worrall, Christine
Hennepin County Medical Center/University of Minn.

FAMILY MEDICINE
Cortes De Jorge, Vanessa
Greater Lawrence Family Health Center/ University of Massachusetts
D'Agata, Caitlin
University of Wisconsin School of Medicine & Public Health
Davis, Cordula
Carolinas Medical Center/University of North Carolina at Chapel Hill
Ejiasa, Otuodita
Oregon Health & Science University Hospital
Gibbs, Lawrence
Belleville Family Medicine/Scott AFB/St. Louis University, Belleville, Ill.
Itano, Scott
Swedish Medical Center/University of Washington
Luan, Chih-Chen
Lancaster General Hospital/Temple University, Pa.
Swanier, Brandi
Memorial Hospital of Rhode Island/Brown University
Thomas, Stephanie
University of Colorado School of Medicine
Turner, Andres
UCSF Medical Center, Calif.

INTERNAL MEDICINE
Atri, Prashant
Washington University Medical Center, Mo.
Bryk, Jodie
University of Pittsburgh Medical Center
Cai, Xiao
University of California Davis Health System
Caprio, Timothy
McGaw Medical Center/Northwestern University, Ill.
Ceyrolles, William
University of Pittsburgh Medical Center
Fridman, Yaron
University of Michigan Hospitals and Health Centers
Iyer, Sunil
University of Pittsburgh Medical Center
Kearney, Kathleen
University of Washington Affiliate Hospitals
Larochelle, Marc
Johns Hopkins Bayview Medical Center, Md.
Mak, Yinchong
UCSF Medical Center, Calif.
Marsh, Tara
Duke University Medical Center, N.C.
Martin, Elizabeth
University of Wisconsin Hospital and Clinics
Ojeifo, Oluseyi
Massachusetts General Hospital/Harvard University
Oman, Hilary
University of Michigan Hospitals and Health Centers
Proverbs-Singh, Tracy
Mount Sinai School of Medicine, N.Y.
Saghafi, Ramin
Emory University, Ga.
Salerno, Amy
Emory University, Ga.
Shah, Megha
New York University Lagone Medical Center
Shirsalkar, Advayanand
Loyola University Medical Center, Ill.
Song, Christopher
New York University Lagone Medical Center
Thomas, Holly
UCLA Medical Center, Calif.
Wong, Susan
University of Washington Affiliate Hospitals
Zemke, Anna
University of Pittsburgh Medical Center

INTERNAL MEDICINE—PEDIATRICS
Snapinn, Elizabeth
University of Pittsburgh Medical Center
Sturgeon, Tiffany
University at Buffalo School of Medicine and Biomedical Sciences, N.Y.

INTERNAL MEDICINE—PRELIMINARY
Greytak, Ryan
Allegheny General Hospital/Drexel University, Pa.
Kumar, Vikas
University of Pittsburgh Medical Center
Raphael, Anna
Montefiore Medical Center/ Albert Einstein College of Medicine, N.Y.

INTERNAL MEDICINE—WOMEN'S HEALTH
Soni, Amy
University of Pittsburgh Medical Center

MAXILLOFACIAL SURGERY
Bilodeau, Elizabeth
University of Pittsburgh Medical Center
Pavlick, Matthew
University of Pittsburgh Medical Center

NEUROLOGICAL SURGERY
Srinivas, Ravi
University of Pittsburgh Medical Center
Williamson, Richard
St. Joseph's Hospital & Medical Center/ University of Arizona

NEUROLOGY
Bledsoe, Ian
Stanford Hospital and Clinics, Calif.
Linnoila, Jenny
Massachusetts General Hospital/Harvard University
Magge, Rajiv
Massachusetts General Hospital/Harvard University
Van Laar, Amber
University of Pittsburgh Medical Center
Zhang, Fan
McGaw Medical Center/Northwestern University, Ill.

OBSTETRICS/GYNECOLOGY
Foley, Carolyn
University of Minnesota
Makaroun, Sami
Yale—New Haven Hospital, Conn.
McSorley, Meghan
University of Washington Affiliate Hospitals
Nieto, Maria
University of Massachusetts
Parrott, Meredith
University of Pittsburgh Medical Center
Pfaendler, Krista
University Hospital/Univ. of Cincinnati, Ohio
Ramgopal, Sheila
University of Pittsburgh Medical Center
Salati, Jennifer
University of Pittsburgh Medical Center
Semel, Mara
Strong Memorial Hospital/ University of Rochester, N.Y.

OPHTHALMOLOGY
Gushchin, Anna
University of Pittsburgh Medical Center
Kaufman, Matthew
University of Pittsburgh Medical Center
Piluek, Wachirapon
Stanford Hospital and Clinics, Calif.

ORTHOPAEDIC SURGERY
Dahl, Jason
Strong Memorial Hospital/ University of Rochester, N.Y.
Graham, Kraig
University of Pittsburgh Medical Center
Kowalchuk, Deborah
University of Massachusetts
McClure, Philip
Rhode Island Hospital/Brown University
Spina, Nicholas
University of Pittsburgh Medical Center
Wang, William
Long Island Jewish Medical Center/ Albert Einstein College of Medicine, N.Y.
Wright, Adam
University of Pittsburgh Medical Center

OTOLARYNGOLOGY
Chaffin, Phillip
University of Minnesota
Kundaria, Summit
University of Pittsburgh Medical Center
Toney, Lauren
University of Washington Affiliate Hospitals
Ward, Bryan
Johns Hopkins Hospital, Md.

PATHOLOGY
Nguyen, Lananh
University of Pittsburgh Medical Center

PEDIATRICS
Batsuli, Glaivy
Emory University, Ga.
Chan, Steven
Children's Hospital of Pittsburgh of UPMC
Chang, Angela
UCLA Medical Center, Calif.
Dickman, Katherine
Children's Hospital Boston/Harvard University, Mass.
Ewan, Lindsay
Cincinnati Children's Hospital Medical Center/ University of Cincinnati, Ohio
Goldberg, Brittany
Children's Hospital of Wisconsin/ Medical College of Wisconsin
Pires Ervoes, John
McGaw Medical Center/Northwestern University, Ill.
Shinozawa, Yohko
University of Texas Medical School at Houston

PLASTIC SURGERY
Irwin, Chetan
UCSF Medical Center, Calif.
Michelotti, Brett
Milton S. Hershey Medical Center/ Pennsylvania State University
Naran, Sanjay
University of Pittsburgh Medical Center

PSYCHIATRY
Balsamo, Dalia
Jackson Memorial Hospital/University of Miami, Fla.
Carl, Kevin
University of Pittsburgh Medical Center
Keary, Christopher
Massachusetts General Hospital/Harvard University
Rao, Sukumar
New York–Presbyterian Hospital/Cornell University
Small, Jonathan
New York–Presbyterian Hospital/Cornell University
Striebel, Joan
UCLA Medical Center, Calif.
Woldu, Hiwot
Mount Sinai School of Medicine, N.Y.

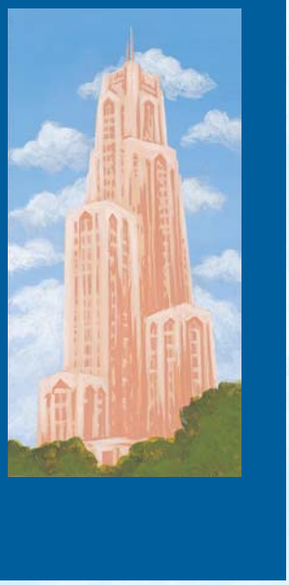
RADIATION ONCOLOGY
Gan, Gregory
University of Colorado

RADIOLOGY—DIAGNOSTIC
Huang, May
North Shore University Hospital/ Albert Einstein College of Medicine, N.Y.
Narla, Vinod
University of Washington Affiliate Hospitals
Paidisetty, Sanjay
Medical College of Wisconsin Affiliated Hospitals
Price, Melissa
UCLA Medical Center, Calif.
Tung, Ka-Wah
University of Pittsburgh Medical Center
Wang, David
University of Pittsburgh Medical Center

SURGERY—GENERAL
Alston, Jane
McGaw Medical Center/Northwestern University, Ill.
Caporaso, Jenna
Louisiana State University
Carter, Sarah
Guthrie/Robert Packer Hospital/Drexel University, Pa.
Castleberry, Anthony
Duke University Medical Center, N.C.
Kilic, Arman
Johns Hopkins Hospital, Md.

SURGERY—PRELIMINARY
Chen, Jennifer
Allegheny General Hospital/Drexel University, Pa.
Gilbert, Mark
University of Colorado

UROLOGY
Ambani, Sapan
University of Michigan Hospitals and Health Centers
Bieniek, Jared
Geisinger Medical Center/Temple University, Pa.
Dudley, Anne
University of Pittsburgh Medical Center
Kaffenberger, Samuel
Vanderbilt University Medical Center, Tenn.



CLASS NOTES

'60s

The past year looks like a major chapter in the storybook ride of **Bert O'Malley** (MD '63). He received the National Medal of Science from President George W. Bush in September 2008. O'Malley, the chair of molecular and cellular biology in Baylor College of Medicine in Houston, is known as one of the leading experts in understanding how hormones turn genes on and off, particularly in breast cancer. In April 2009, as this issue went to press, O'Malley returned to Pitt's campus as commencement speaker for 6,000-some new graduates and their families and to receive an honorary Doctor of Science degree.

"Just as no two human beings are the same, no two cancers are the same," says **Mark Orringer** (MD '67), coauthor of a 2008 paper in *Nature* that genetically characterized 188 individual lung tumors. The researchers identified 26 genes that were mutated at high frequencies in these tumors and, therefore, were likely involved in the genesis of the cancer. The findings shed light on how cancer develops and may lead to new targets for treatment or prevention.

Orringer is a professor and head of the section of thoracic surgery at the University of Michigan. In 2001, he served as president of the Society of Thoracic Surgeons. He says that he takes great pride in balancing professional and family obligations.

"I have five grandkids, and whenever one of the dogs gets hold of their little fluffy toys and rips them apart, they always run them to me to sew them up. That's my job, to save them."

Catherine DeAngelis (MD '69), editor of the *Journal of the American Medical Association*, received the 2009 Catcher in the Rye Humanitarian Award from the American Academy of Child and Adolescent Psychiatry (AACAP) for her leadership on discussions of conflicts of interest in medicine. DeAngelis is credited with enforcing one of the most rigorous disclosure policies of any academic publication. She also consulted on AACAP's new *Guidelines on Conflict of Interest for Child and Adolescent Psychiatrists*.

DeAngelis, a pediatrician and Pitt trustee, said in response to the recognition, "I truly believe that we, as individuals and as countries, display who we really are by the way we treat our children."

'70s

Jan Ehrenworth (MD '73) has been known to set a few fires to make his points. Really. Ehrenworth gives talks at scientific meetings and elsewhere on fires in the operating room—covering safety points, including prevention and what to do when something starts burning. He notes that anesthesiologists and surgeons frequently bring together all the requirements for a blaze in the OR: fuel, oxygen, and an ignition source.

A professor of anesthesiology in the Yale University School of Medicine, Ehrenworth combines clinical work and resident training in the operating room.

One patient ended three years of self-imposed isolation to see **Lester Gottesman** (MD '78). The woman had a sigmoid enterocele, a hernia of the sigmoid into the rectum, and every other doctor she'd seen had told her there was nothing wrong with her. "They told her she was crazy. The symptoms are pretty subtle, but they often occur in young women who are in the prime of their physiological and social lives," Gottesman says. Painful constipation had kept her housebound, but after surgery everything changed.

"She got her life back," Gottesman says. "I think she got married soon afterward."

Gottesman, an associate professor of clinical surgery at Columbia University College of Physicians and Surgeons, also serves as chief of colorectal surgery at St. Luke's–Roosevelt Hospital. He's working on several studies exploring HPV susceptibility in an HIV-positive individual.

'80s

An otherwise normal, healthy boy, age 12, goes with his parents to see the pediatrician because of unexplained redness and swelling around his ankle. An

SHARON MAYNARD

PROBING PREECLAMPSIA

In about 5 percent of pregnancies, preeclampsia causes the mother's body to falter as if poisoned. Her kidneys strain. Her blood pressure rises dangerously high. In severe cases, preeclampsia can cause seizures, organ failure, and even death.

It's long been clear that the source of this toxicity is the placenta, explains nephrologist Sharon Maynard (MD '97, Res '00). The syndrome goes away quickly after delivery of the baby and the placenta. "And when you look at [a preeclamptic] placenta, it's extremely abnormal," she says. "There's evidence of damage from a lack of adequate blood supply."

To date, the only treatment for severe preeclampsia is delivery—a devastating ultimatum in the uncommon case where the fetus is very premature. (Preeclampsia is more common toward the end of pregnancy.)

In 2001, Maynard began a research fellowship in nephrology at Beth Israel Deaconess Medical Center with Ananth Karumanchi. There, she compared gene expression in the placentas of women who had preeclampsia to those who didn't. One stark difference between the two types of samples emerged early on: A protein called sFlt1, which stunts the growth of new blood vessels, is much more abundant in the placentas of preeclamptic women. Maynard then tested the effects of sFlt1 on

FRANK HARRIS



Bradley (right) during the Steelers 2009 championship season.

echocardiogram rules out rheumatic fever but reveals a shocker: a half-inch hole between the upper chambers of the boy's heart. **Mark Hoyer** (Pediatric Cardiology Fellow '85), the director of interventional cardiology at Riley Hospital for Children in Indianapolis, has performed hundreds of minimally invasive catheter-based heart repairs of defects like this, in which open heart surgery might otherwise be indicated. He has published case studies and descriptions of new techniques. In the case of the 12-year-old boy, Hoyer made a 1.5-inch incision—a partial sternotomy—and threaded a catheter into the boy's heart to place a patch over the hole.

Pittsburgh Steelers wide receiver Hines Ward suffered a knee injury in a playoff game two weeks before the Super Bowl this year. In an attempt to speed his recovery, **James Bradley** (Orthopaedics Resident '87), a Pittsburgh Steelers orthopaedic surgeon and clinical professor of orthopaedics at the University of Pittsburgh, performed a new procedure making the rounds in sports medicine—autologous conditioned plasma injection. Bradley drew blood from an arm, concentrated the platelets via centrifuge, and injected the platelet-rich plasma into the injured knee. Although the procedure requires more study, doctors speculate that the treatment concentrates and accelerates the healing process. Ward wasn't 100 percent healed for the Super Bowl, but he did recover enough to play. And, of course, the Steelers managed to bring home their NFL-record sixth Lombardi Trophy.

As a resident in Pittsburgh, **David Servan-Schreiber** (Psychiatry Resident '87) had NIH funding to pursue some MRI research he'd begun as a part of his graduate work in neuroscience. When a volunteer failed to show one day, Servan-Schreiber slid into the tight confines of the MRI, which proceeded to clank and hum as his colleagues took anatomical images of his brain. Suddenly, everything stopped, and his friends said with concern, "We can't do the experiment. There's something in your brain."

That was the day he learned about his brain tumor, as described in his book, *Anti-Cancer: A New Way of Life*, which was published in his native France in 2007 and in this country in 2008.

Today, Servan-Schreiber is cancer-free. He divides his time between the University of Pittsburgh, where he is a clinical professor of psychiatry, and Lyon, France, where he is on the medical faculty at the University of Lyon.

'90s

"It was scary," says **Sheri Mancini** (MD '96), "We had to be immunized for smallpox and anthrax." And her company had to carry injectors with them in case they were hit with nerve gas, she adds.

Mancini was deployed to Iraq as part of a field trauma surgical company in 2003. She served six months in the country as part of her four-year obligation to the navy, which paid her medical school tuition. There she treated American soldiers and Iraqis alike as the marines she accompanied pushed further into the country and ultimately into Baghdad.

Mancini also served on the aircraft carrier *U.S.S. Theodore Roosevelt* from 2001 to 2002 as a surgeon in support of American soldiers in Afghanistan. She returns to Pittsburgh in June to take a teaching position with the general surgery staff at Allegheny General Hospital.

When **Michael Scheel** (MD '98) was entering medical school, the health professional military scholarship seemed like a safe, prudent option. That's not how he would describe his experience today.

Scheel completed an orthopaedics residency then served four years of active military duty, including one tour in Iraq. He was the only orthopaedist for a base of 40,000 troops, so he saw a lot of recreational injuries. But he also saw "about six months of shockingly graphic" battlefield injuries, including gunshot wounds, blast injuries, lost limbs, and damaged-beyond-repair limbs. Unable to offer the definitive treatment, Scheel would clean, wash, and stabilize, then ship the soldier out to a larger facility.

Now in private practice not far from Pittsburgh, Scheel, who had one child before being deployed to Iraq and one after, says, "It's hard to get me rattled at this point. I take a deep breath, and I say, 'It could be a whole lot worse.'"





Alumni in surgery tents in Iraq: Mancini (left) in 2003. Scheel (above) in 2004.



Maynard's findings may one day help women with preeclampsia.

pregnant rats and found that they developed the classic symptoms of preeclampsia.

The reason for the extra sFlt1 is still unclear, but this new insight could eventually lead to better diagnosis, management, and treatment if the protein could be measured, monitored for upticks, and blocked. The initial study, which was published in *The Journal of Clinical Investigation* in 2003, led to several subsequent papers and created a buzz in nephrology and obstetrics circles.

In 2005, Maynard won a three-year Charles E. Culpeper Scholarship in Medical Science to continue this work. She is now an assistant professor in the Division of Renal Disease and Hypertension at George Washington University. In one project, funded by the Washington, D.C., chapter of the National Kidney Foundation, she's hoping to discover the threshold range of sFlt1 levels that separates women whose preeclampsia can be managed with blood-pressure medication and bed rest from women whose health will deteriorate more quickly. Maynard will present her latest findings at the World Congress of Nephrology in Milan in May. *—Elaine Vitone*

'00s

"When patients ask me why it is they have colon cancer, I think that most often they are not looking for an explanation of the molecular oncogenesis of the colonocyte," says **Daniel Hall** (Surgery Resident '07), who is an Episcopal priest, a staff surgeon in the Veterans Affairs Pittsburgh Healthcare System, and a researcher for its Center for Health Equity Research and Promotion. "They are asking questions of meaning and value ... 'Why me? Why do bad things happen to good people?'"

In 2006, Hall did an analysis of data, published in the *Journal of the American Board of Family Medicine*, which showed that people who attend religious services on a weekly basis live 1.8 to 3.1 years longer than those who do not.

He suggests that, over time, religious communities may foster longer life by lowering levels of stress and anxiety.

— Eric Donato, Meaghan Dorff, Chuck Staresinic

THE WAY WE ARE
CLASS OF '90

Robert Neumar (MD '90), associate professor of emergency medicine in the University of Pennsylvania School of Medicine and associate director of Penn's Center for Resuscitation Science, has since 1997 directed a lab aimed at revealing the mechanisms of brain injury caused by acute brain trauma.

"I think there's tremendous potential for reducing brain damage after acute injury, whether that's cardiac arrest, stroke, or trauma," he said.

His lab focuses on identifying molecular events that occur naturally in the brain after injury is sustained—events which eventually lead to neuronal death. A greater understanding of these events, he says, may yield ways to decrease damage caused by acute brain injury.

Judith Badner (Human Genetics PhD '88, MD '90) says it's her job to help unravel the biological mystery of what's behind conditions like schizophrenia, bipolar disorder, and autism. An associate professor of psychiatry at the University of Chicago, Badner does clinical work and statistical genetics research focused on discovering genes that contribute to psychiatric disorders—a challenging task considering studies that show a large number of genes, each with its own small effects, contribute to psychiatric illness.


Neumar

The research she conducts, she says, may in time lead to better understanding of the genetic underpinnings of psychiatric disorders and, she hopes, new treatments for those suffering from them.


Mandel

Keith Mandel (MD '90), vice president of medical affairs for the physician-hospital organization at Cincinnati Children's Hospital Medical Center, is a physician-executive focusing on "the science behind improving care," as he puts it.

Mandel is leading an initiative to improve outcomes for 12,000 children with asthma across 40 primary care practices in Greater Cincinnati. As part of the initiative, parents and physicians complete an in-depth survey during the patient visit. Acquiring this real-time information, Mandel says, engenders a more robust interaction between physician, parent, and patient and a better understanding of how all parties can manage the disease. Children in the program miss fewer school days and experience a marked improvement in symptoms. *–ED*

WILLIAM I. COHEN
FEB. 13, 1946–FEB. 6, 2009

In July 1990, William Cohen (Res '78, Fel '80) became the director of what was then the new Down Syndrome Center at Children's Hospital of Pittsburgh. The developmental-behavioral pediatrician, a professor of both pediatrics and psychiatry at the University of Pittsburgh, once recalled some nervousness on starting the position. At that point, he had seen only a handful of patients with Down syndrome. By the time he died unexpectedly in February, thousands of children with Down syndrome had come to see "Dr. Bill," and the National Down Syndrome Society described him as a "national leader in the Down syndrome movement" and a "dear friend." He coauthored the seminal guidelines for care for children and adolescents with the condition and helped found the Down Syndrome Medical Interest Group.


Cohen

Cohen died Feb. 6 of a heart attack in Miami Beach while pursuing one of his passions—inline skating. On July 4 this year, he and his partner, Donald Arnheim, were planning to exchange vows at a commitment ceremony.

Colleagues describe Cohen as a great listener, teacher, patient advocate, and a man who gave hugs easily. A charter member of Pitt's Academy of Master Educators, he was known for his teaching interests in family counseling, hypnotherapy, adapting families to chronic conditions, and doctor/patient communication. He taught med students how to interview patients.

"He gave so much of himself. He really loved our families and our kids," says Sheila Cannon, program coordinator for the center and one of its founding parents.

She recalls that Cohen enjoyed entertaining children by talking like the gravelly voiced *Sesame Street* character Grover. Cohen was buried with his stethoscope and a Grover doll that he wore with it. *—Erica Lloyd*

ALEXANDER MINNO
APRIL 27, 1921–JAN. 21, 2009

Alexander Minno's Pittsburgh roots ran deep. Minno (MD '47) was the son of a steelworker and a Slovakian immigrant. After receiving his undergraduate degree from the University of Pittsburgh in 1943, he enlisted in the navy and returned to Pitt for medical school while a reservist.


Minno

At the Mayo Clinic in Minnesota, Minno trained in rheumatology under Pitt grad Philip Hench (MD '20), who was instrumental in the discovery of cortisone and its ability to relieve pain and inflammation. Hench won the Nobel Prize in 1950. In 1953, Minno left Minnesota to create the rheumatology department at Lahey Clinic in Boston, where he met and married Frances Fraher. When job offers came in from as far away as San Francisco, says Frances, Pittsburgh won out because of its proximity to friends and family.

Minno practiced rheumatology in Pittsburgh and was a Pitt clinical associate professor until his retirement in the late 1990s. The Minnos were active and generous supporters of the medical school, hosting reunion dinners and encouraging Minno's classmates to donate to the School of Medicine. Minno served for several years on the board of Pitt's Medical Alumni Association. *—CS*

IN MEMORIAM

'40s

GEORGE J. JACOBS
MD '46
MARCH 12, 2009

'50s

JOHN H. SCOTT
MD '54
MARCH 9, 2009

JOHN BRANDON
MD '56
APRIL 4, 2009

'60s

MARCIA MEARS STAVRIDES
MD '61
JAN. 20, 2009

ALAN RENTON
MD '65
JAN. 14, 2009

'70s

VINCENT MACHAJ
MD '76
JAN. 14, 2009

FACULTY
NANCY NIELAND-FISHER
MARCH 28, 2009

J. NADINE GRACIA IN SERVICE, IN THE WHITE HOUSE

BY ELAINE VITONE



COURTESY J.N. GRACIA

The White House Fellows program offers exceptional young men and women experience working at the highest levels of government. Gracia's year includes literacy work in Washington, D.C.

The truck could only take them so far. When the trail steepened, they climbed on foot, bringing vaccines to families in the remote countryside. They announced their arrival with a bullhorn.

"It was a life-altering experience," says J. Nadine Gracia (MD '02, Res '05) of her 1996 medical mission to Haiti.

"It showed me just how difficult living conditions can be—not just in the lack of access to medical care, but also to opportunity."

Gracia, who grew up in Novato, Calif., in a Haitian family, still carries the lessons of that trip as she serves in the most prestigious leadership and public service program in the United States, the White House Fellows program. She is one of two MDs in the current 14-fellow class, which began the yearlong program in September 2008. As part of her assignment in the Department of Health and Human Services, Gracia works on an interagency effort to improve health care delivery systems in the Outer Pacific Islands.

She has met with Presidents George W. Bush and Barack Obama, as well as with members of their respective cabinets. There have been more than a few "pinch me" moments.

"The first one was when I met President Bush for the first time," she says. "Here I was, a daughter of immigrants, sitting in the Oval Office. At one point, I had to pause and ask myself if this was real. My family has worked so hard to get me to this point."

Gracia's parents were both educators in Haiti. Her mother was a math teacher, and her father was a school principal. "They fostered this yearning for learning in me. And they also helped me to embrace diversity," she says.

In 2000, Gracia had the opportunity to bring both passions to the fore when she became Pitt's first med student to serve as the president of SNMA, the Student National Medical Association. During her term, she spearheaded partnerships with more than 15 national organizations and oversaw the development of policy statements on gun violence, organ donation, and diversity in education.

Following her position as chief pediatrics resident at Children's Hospital of Pittsburgh of UPMC, Gracia completed a two-year research fellowship at Children's Hospital of Philadelphia. She examined community-level risk factors for violence, studying the built physical environment and its association with aggravated assault.

Gracia says her mentors in Pittsburgh were instrumental to her success, working with her to design an academic program that would accommodate her travel-heavy schedule throughout her SNMA presidential term—especially Paula Davis, assistant vice chancellor in the Office of Health Sciences Diversity; Joan Harvey, associate dean for student affairs; and Arthur S. Levine, senior vice chancellor for the health sciences and dean of the School of Medicine. Steven Kanter, the school's vice dean, told Gracia about the White House Fellows program when she started med school and continues to mentor her today. Gracia met Henri Ford—a fellow Haitian and then a Pitt professor and chief of pediatric surgery—in her first year of med school.

"We bonded immediately," says Gracia. "He's been like an uncle to me."

Davis, who interviewed Gracia for admission to Pitt and was a reference for her security clearance, saw something exceptional in Gracia from the start.

"Nadine is a gatherer of people," Davis says. "She has a unique ability to bring disparate views together at the table and move them along."

It is, perhaps, a quality of every great public servant, from the hills of Northern Haiti to Capitol Hill. ■

MEDICAL ALUMNI ASSOCIATION OFFICERS

PATRICIA CANFIELD (MD '89)
President

GRAHAM JOHNSTONE (MD '70)
President-elect

MARGARET LARKINS-PETTIGREW (MD '94)
Secretary

PETER FERSON (MD '73)
Treasurer

ROBERT E. LEE (MD '56)
Historian

SUSAN DUNMIRE (MD '85)
Executive Director

ADAM GORDON (MD '95)
BRIAN KLATT (MD '97)
JOHN KOKALES (MD '73)
JAN MADISON (MD '85)
DONALD MRVOS (MD '55)
CHARISSA B. PACELLA (MD '98)
BRETT PERRICELLI (MD '02)
VAISHALI DIXIT SCHUCHERT (MD '94)
DAVID STEED (MD '73)
Members at Large

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



HEART IN HAND

In making a documentary film about Children's Hospital of Pittsburgh in 1951 (see p. 12), pediatrician Barbara McNulty (MD '75) was moved by the images of her professional forebears laying caring, attentive hands on patients. And she was reminded of a child's drawing she received more than a decade ago.

The artist was 4 years old when she accompanied her mother and 2-week-old sister on a visit to the pediatrician. McNulty had noticed that the baby's femoral pulses were absent. Through her stethoscope, she heard the galloping rhythm that indicated serious cardiac trouble. The mother rushed the baby to the hospital on McNulty's urging. The next morning, the baby had surgery to repair a congenital coarctation (constriction) of the aorta.

The big sister said that her drawing showed McNulty checking her blood pressure, adding, "I know you can't really see my heart, but I thought it should be in the picture." The mother said that she and her daughter had talked about things that doctors do to help people, and that the drawing had helped the girl with the emotions she'd been holding in since her baby sister's emergency surgery.

COURTESY B. MCNULTY

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. You can also visit the Web site at www.maa.pitt.edu.

DEPARTMENT OF SURGERY RESEARCH DAY
MAY 13
7 a.m. – 1:30 p.m.
SIMMONS LECTURE
8 a.m.
David Geller, MD, Speaker
William Pitt Union, Ballroom and Assembly Room
For information:
www.surgery.upmc.edu

MEDICAL ALUMNI WEEKEND
MAY 15–18
Reunion Classes:

1949	1954
1959	1964
1969	1974
1979	1984
1989	1994
1999	

SENIOR CLASS LUNCHEON
MAY 15
11 a.m.
Alumni Hall, Connolly Ballroom

ESTATE PLANNING FOR THE CONFLICTED PHILANTHROPIST
MAY 15
1:30 p.m.
Holiday Inn Pittsburgh University Center
For information:
Norma Wilson
412-647-4726
wnorma@pmhsf.org

ALUMNI WEEKEND OPENING RECEPTION
MAY 15
5:30 p.m.
Scaife Hall

CLASS OF 1949 & 1954 REUNION DINNERS
MAY 15
7 p.m.
Scaife Hall

CLASS OF 1959 REUNION DINNER
MAY 15
7:30 p.m.
Concordia Club

ALUMNI CHAMPAGNE BREAKFAST
MAY 16
9 a.m.
Herberman Conference Center

REUNION GALA
MAY 16
7 p.m.
Carnegie Science Center

SCOPE AND SCALPEL'S SCUTDOC MILLIONERRS
MAY 14
7 p.m.
MAY 16 & 17
3 p.m.
Antonian Theatre, Carlow University
For information:
www.scopeandscalpel.org

CLASS OF 2009 COMMENCEMENT
MAY 18
10 a.m.
Carnegie Music Hall

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

MUSGRAVE LECTURESHIP
OCTOBER 30
5:30 p.m.
Magee-Womens Hospital Auditorium
Fu-Chan Wei, MD, FACS, Speaker

HOMECOMING WEEKEND
OCTOBER 22–25
Pitt v. South Florida
Saturday, Oct. 24
For information:
www.alumni.pitt.edu

AAMC PITT RECEPTION
NOVEMBER 8
5:30 p.m.
AAMC Annual Meeting
Boston
For information:
Office of the Vice Dean
412-648-9000
vicedeanstaff@medschool.pitt.edu

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

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

CHANGE SERVICE REQUESTED

NONPROFIT ORG.
U.S. POSTAGE
PAID
PITTSBURGH, PA
PERMIT NO. 1715

COME TOGETHER!



HIPPOCRATEAN

These aspiring physicians of the School of Medicine's Class of 1955 had no idea how much future Pitt med students would pay for a hamburger, not to mention textbooks and tuition. Nevertheless, the class has banded together with the goal of leaving a special legacy under the MD '55 banner.

To contribute to the Class of '55 Scholarship Fund, or to discuss a legacy scholarship for another graduating class, please contact:

Clare Flanagan
Forbes Tower, Suite 8084
3600 Forbes Ave.
Pittsburgh, PA 15213
412-647-0515
fclare@pmhsf.org