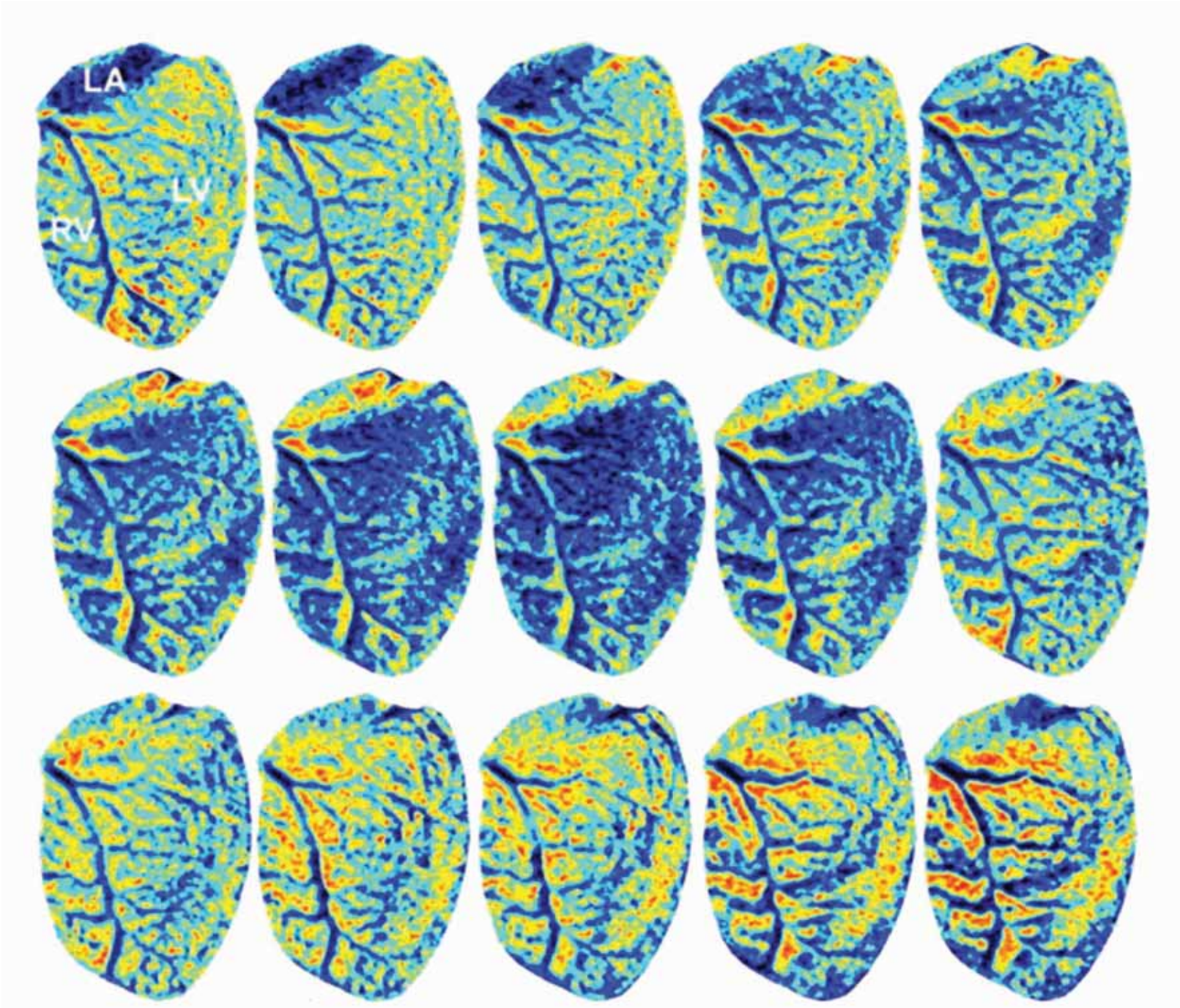
UNIVERSITY OF PITTSBURGH SCHOOL OF MEDICINE | SPRING 2007

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UNIVERSITY OF PITTSBURGH SCHOOL OF MEDICINE MAGAZINE, SPRING 2007 (FEB/MAR/APR)

VOL. 9, ISSUE 1



DEPARTMENTS

OF NOTE 3
HIV pathway discovered.
The Class of '09 has big plans.
Deadly medicine.

CLOSER 7
Drop and give her eight—
then Melanie Grubisha will give you
a new appreciation of biomechanics.

INVESTIGATIONS 8
A machine for regrowing skin.
Genes that protect against Crohn's.

ATTENDING 32
Students shaped by war.

98.6 DEGREES 35
A dying cancer researcher made sure
the work she cared about continues.

ALUMNI NEWS 36
Many Pittsburghers with scoliosis remember
how William Donaldson Jr. changed their lives.
Todd Wolynn on mother's milk.

LAST CALL 40
Last wishes.







12

FEATURES

The Beginner's Mind 12
How team mentoring and $4.5 million a year are changing clinical research at Pitt.
BY JOE MIKSCH
FOLLOW-UP BY MEGHAN HOLOHAN

Learning What Their Hands Already Know 18
A study in trauma and recovery.
BY REID R. FRAZIER

Peculiar Material 23
Scientists have linked 24 disorders, starting with Alzheimer's, to unruly mobs of proteins. Now David Perlmutter and Jeffrey Brodsky think they're on to how to keep such proteins from causing so much trouble.
BY JIM SWYERS

To Live and Dye 28
When exactly does someone become vulnerable to an arrhythmia? To find out, Guy Salama studies how hearts are wired.
COVER STORY BY CHUCK STARESINIC

CONTRIBUTORS

REID R. FRAZIER ["Learning What Their Hands Already Know" and "A Most Unwelcome Visitor"] is a freelance writer and radio producer living in Wilkinsburg. Before becoming a journalist, Frazier was a door-to-door pie salesman in Southern France, a night-shift doughnut finisher in Pittsburgh, and a wedding photographer's assistant in New York City. He was a reporter for the *North Jersey Herald & News* and the *Pittsburgh Tribune-Review*. Frazier considers himself a Pittsburgh native though he has lived in New York, New England, Bolivia, and spent parts of his childhood in Panama. He came to *Pitt Med* after meeting senior editor Chuck Staresinic at a "bug party" in Penn Hills, where insects were discussed and their virtues celebrated.

When ROB KELLY ["Learning What Their Hands Already Know"] was a boy, he didn't play outside like other children—he stayed indoors to draw comic book characters. Now Kelly is a full-time illustrator out of Cherry Hill, N.J., who, for personal enjoyment, designs movie posters of classics like *The Mask of Fu Manchu* and of the filmstrips running in his head, including his noir tale *Cat O' Nine Lives*. Just like when he was a boy, Kelly prefers creating art "in lieu of going outside, like normal people." Kelly categorizes his work as "stylized photo-realism," and his primary clientele includes magazines, newspapers, and ad agencies. Kelly sketches either in pencil or in pixels and lists his pet peeve as "not hitting the 'save' button before the cat jumps on the keyboard."

COVER

Guy Salama inspects heart wiring in the kind of detail that few others can. His work may one day tell cardiologists exactly when an arrhythmia is likely to occur. (Heart images courtesy Tallini, YN, et al. National Academy of Sciences, USA. © 2006. Full credit p. 29)

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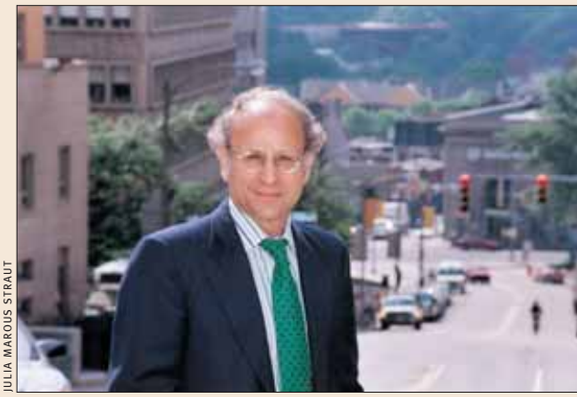
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JULIA MAROUS STRAUT

You can never solve a problem on the level on which it was created.
—Albert Einstein

When I was in medical school, my classmates and I often volunteered to work after classes and clerkships in the larger urban community. We helped to care for patients who might have easily slipped through one of the many gaps in our healthcare system (and those gaps have only grown since my days as a student). But when I look at the medical students around me today, it's clear that something different is afoot. As a matter of course, medical students at the University of Pittsburgh provide care for underserved populations, as my classmates and I did. But their personal commitment to public service is truly impressive and sometimes heroic. The Class of '09 has committed to raising $90,000 by graduation to support a network of five free clinics in the Pittsburgh area. Another group of students was so moved by their experiences working with HIV-infected patients in Kenya that they founded the Kenyan Pediatric HIV Project to raise money to provide care and support for infected children and their families. Other students have stepped forward to care for the homeless; to be paired as a "novice physician and friend" with a pediatric cancer patient or a pregnant teen; or to cook meals at a men's shelter. That's the short list of student outreach activities. There's a level of humanism in our student body that greatly inspires us as mentors; and it bodes well for our students' future careers as physicians and medical scientists.

I credit the admissions committee—not blind chance—for creating this student body. It is a given that a person accepted to this medical school will be exceptionally bright and accomplished. But there are two things that I ask of the admissions committee over and over: Find those students who are creative and who are leaders. Why? One needs to be creative to be a successful scientist or to be among the best of diagnosticians, and we need leaders to address the extremely complicated problems that we face in the economics and delivery of medical care.

Our student body includes poets, composers, choreographers, entrepreneurs, and activists engaged in their communities. When these creative and driven men and women arrive on campus, it is our responsibility to further develop the fertile substrate we've recruited. To that end, we've designed research opportunities and minielective courses that expose our students to topics like the unfolding of evolution, physicians as authors, and the perceptions of artists—topics that place human health and illness in an appropriately larger context of history, society, and culture. In fact, this is precisely why our medical school is in a university. But beyond this campus, we are collaborating now with world-class institutions like the Carnegie Museums of Natural History and Art, so that our students' time here ignites their imaginations and expands their deepest sense of their potential as creative physicians and humanists.

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



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

HIV Pathway Discovered

University of Pittsburgh researchers have discovered a previously unknown mechanism by which HIV spreads through the body.

Charles Rinaldo and Giovanna Rappocciolo unexpectedly came upon the mechanism when researching how the immune system responds to the herpesvirus that can cause Kaposi's sarcoma, a common cancer in AIDS patients.

Following a hunch, they learned that a B-cell surface molecule unlocks T cells and allows HIV entry. (B cells and T cells both can be thought of as surveillance patrols for the immune system.) T-cell infection subsided significantly when the scientists curtailed expression of the surface molecule in HIV-carrying B cells.

Rinaldo is a PhD professor and chair of the Department of Infectious Diseases and Microbiology in Pitt's Graduate School of Public Health; he has a joint appointment as professor of pathology in the School of Medicine. Rappocciolo is a PhD research assistant professor of infectious diseases and microbiology in GSPH.

This pathway is not the only manner in which HIV spreads, but Rinaldo imagines that therapies that disrupt it could help fight HIV. *—Joe Miksch*



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HIV budding from the surface of a host T-lymphocyte white blood cell

FLASHBACK

Ninety years ago, as the country prepared to enter World War I, 22 members of the School of Medicine faculty became the officer class of an army hospital unit. Thanks to $75,000 in individual donations and support from the Pittsburgh chapter of the American Red Cross, they were particularly well-equipped. However, the unit's sergeant major was not impressed. To a superior officer, he remarked, "Sir, I'm afraid we can't ever make soldiers out of them there college boys."

MAGEE RESEARCHER LEADS INTERNATIONAL HIV EFFORT

Each year, 4 million people are infected by HIV. To try to curtail the disease here and abroad, the National Institutes of Health has restructured its clinical networks for HIV prevention and treatment. Magee-Womens Research Institute is one of six institutions that's been selected to lead the way. The NIH expects to spend $285 million in the first year of the new leadership effort.

Sharon Hillier, a PhD professor of obstetrics, gynecology, and reproductive sciences and of molecular genetics and biochemistry, is the principal investigator for the Pittsburgh group. She will run an international research program looking into ways to stop transmission of the disease. Hillier and colleagues are evaluating HIV microbicides, which are applied topically and give women greater control over their health than condoms, whose use is usually a man's prerogative.

"In many parts of the world, a woman's single biggest risk factor for the acquisition of HIV is being married," Hillier says. "Currently, women have no way to protect themselves except condoms." *—JM*



CAMI MESA

A&Q

Personhood in a Brave New World

As scientists are able to shape how humans develop, Gerald Nora (above) wonders what it means—what it means in the big picture, that is. Putting things in the light of philosophy and history, he says, helps "keep the wonder, it keeps the lab from being routine." Not that anything about his lab work sounds routine—Nora, as an MD/PhD student in the University of Pittsburgh/Carnegie Mellon University Medical Scientist Training Program, studies telomeres, those DNA extremities that may hold clues to aging and cancer. He is in the third year of his PhD work and has finished his psychiatry rotation.

We talked with Nora about why he was drawn to pursue an MA in bioethics as well. He spoke to us about issues of personhood and identity in the rapidly changing arena of genetics and biology.

Shaping identity

Our identities are tied up in our physical being: *I'm deaf. I'm depressed*. When science can change these features, we need to ask, "What am I changing with this treatment? How tightly bound are our personal identities with our genes?"

You alter a gene in an embryo after in-vitro fertilization, and then implant it. What sort of change did you [make] to its identity? If that child later on gets angry about whatever the alteration was [and says], "I didn't want to be blond or tall. Why did you do this to me, Mom and Dad?" can that child actually sue? Was this a wrong? There have been some cases called wrongful birth cases in both the U.S. and France [where during] a prenatal diagnosis, the doctors didn't catch something, and the patients had a child that was handicapped in some way. They said, "Well look, if we'd known about this [birth defect] we would have aborted the child." They sued on the child's behalf, saying that child should have never been born. He would have been better off dead. I think it's going to get even more complicated as time goes on and as our capabilities expand.

How science will create new ethical dilemmas

What's the line between curing a disease and augmenting a person? .... Is it ethical for the doctor to give [human growth hormone] even if there's nothing really wrong with the kid?

His question for the world

How do we develop a moral reasoning, and a moral vocabulary, to adapt to these situations? Not only do we have to come up with an answer, but a reasonably logical one, because if we use bad reasoning, it can haunt us. ***—Interview by Reid R. Frazier***

Faculty Snapshots

In the quarter-century plus that Margaretha Casselbrant has been at the University of Pittsburgh, she has pursued the causes and effects of otitis media, middle ear inflammation common in children. **The disease can affect hearing, speech, and balance. Casselbrant, an MD/PhD professor of otolaryngology, was recently appointed one of 18 members of the National Deafness and Other Communications Disorders Advisory Council. The council assesses grant applications and provides recommendations regarding the conduct and support of research related to hearing, speech, and balance for the National Institute on Deafness and Other Communication Disorders.**

In her own lab, Casselbrant is seeking a genetic link for otitis media.



Casselbrant

In 1980, at Children's Hospital of Pittsburgh, David Brent was responsible for determining which young people who'd attempted suicide needed psychiatric hospitalization. He was shocked at his inability to find much in the way of empirical guidelines. **Brent, now a University of Pittsburgh professor of psychiatry, went on to make suicide-risk assessment and treatment in youth the focus of his career.**



Brent

Brent, an MD, is the holder of the University of Pittsburgh's endowed chair in suicide studies, academic chief of the Division of Child and Adolescent Psychiatry at the Western Psychiatric Institute and Clinic, and cofounder and director of the state-funded Services for Teens At Risk (STAR) Center. And now he has been awarded the Ruane Prize by the National Alliance for Research on Schizophrenia and Depression. The prize honors outstanding work pertaining to childhood mental illness. Brent is a leader in assessing the risk of teen suicide as it relates to mood disorder, substance abuse, impulsive aggression, parental suicide, and access to guns.



Billiar

Timothy Billiar, Pitt's George V. Foster Professor of Surgery and chair of the Department of Surgery, was recently elected to the Institute of Medicine. **The election puts the surgeon in the illustrious company of his mentor, Pitt's Richard Simmons, Distinguished Service Professor of Surgery, and his nominators, Thomas Starzl, also a Distinguished Service Professor of Surgery, and Nobel laureate Ferid Murad, of the University of Texas Health Science Center at Houston, all of whom are in the institute.**

Billiar is an accomplished trauma surgeon and researcher. In the latter capacity, he has deepened understanding of the role nitric oxide plays in the body's response to septic shock. ***—JM***

Can You Spare $90K?

On a fine July day, Brett Michelotti (Class of '09) was in the kitchen at the Station Square amphitheater toiling over some ribs. A worker walking the floor near the buffet dining area—not far from the stage where country music performers Big & Rich were holding forth—noticed a lack of that barbecued delight. So, Michelotti loaded up the hotbox with a substantial ration of ribs, jumped onto a four-wheeler, and traversed 100-party-goer-packed meters—avoiding Major League Baseball Commissioner Bud Selig and former Pittsburgh Pirate Bobby Bonilla—to avert a meat emergency.

Michelotti and about 30 of his classmates were caterers for the thousands of guests at the Major League Baseball All-Star Game Gala. When he enrolled in med school, Michelotti probably didn't imagine ever being concerned with how much protein Bobby Bonilla had access to on a given night, but he had good reason for taking on that role last summer. The student workers donated at least half of the earnings from their 10-hour shifts to a campaign they're calling "90K from 2009."

The $90,000 the class plans to raise by its commencement will support the Program for Health Care to Underserved Populations, which operates five free Pittsburgh-area clinics.

Thus far, the students have also raised money selling T-shirts, staffing concession booths at Steelers games, and soliciting friends and family. We hear they'll be hosting a wine tasting next. *—JM*

TO DONATE: www.giveto.pitt.edu
Specify, "University of Pittsburgh—90K from 2009."



CATHERINE LAZURE

ANESTHETICS AND ALZHEIMER'S LINK

Some elderly patients experience cognitive dysfunction and memory lapses after surgery under a general anesthetic. The University of Pittsburgh's Pravat K. Mandal recently uncovered the molecular mechanism that seems to be responsible.

Mandal's study, published in the Jan. 23 issue of *Biochemistry*, used nuclear magnetic resonance spectroscopy (NMR) to examine the connection between several commonly used anesthetics and amyloid beta-peptide. The peptide is known to accumulate and form plaques in the brains of patients with Alzheimer's disease. Scientists believe such plaques are responsible for the disease.

Mandal is a PhD assistant professor of psychiatry with a secondary appointment in bioengineering. He performed in vitro experiments in which he exposed the peptide to two inhaled anesthetics: halothane, which is no longer used in U.S. hospitals but is common elsewhere, and isoflurane, which is popular in this country. Both anesthetics caused the peptide to clump into plaques. Advanced NMR, Mandal says, allowed his team of researchers to identify, at the atomic level, the specific binding region of the anesthetic to the peptide. "We now know the molecular mechanism ... responsible for the clumping," he says.

In addition, Mandal's lab studied two intravenous anesthetics, propofol and thiopental. Propofol only interacted with the peptide at very high concentrations. Thiopental did not interact at all. Mandal believes that the larger size of the propofol and thiopental molecules handicaps the anesthetics' ability to affect the peptide.

Mandal plans to perform animal experiments and hopes to study the anesthetic/peptide interaction in the human brain eventually. The research, he says, may lead to safer anesthetics and could contribute to the overall understanding of amyloid plaque formation. *—JM*



DEADLY MEDICINE

The contraption shown left is not an ice cube tray, and, yes, it's holding eyeballs. (They're glass.) Such tools used for studies of differences in "races" in Nazi Germany are on display at "Deadly Medicine: Creating the Master Race," at the Andy Warhol Museum until March 18. The exhibition explores how the misuse of medical and other research helped eugenics take hold in Germany. Susan Bachrach, the exhibition's curator at the United States Holocaust Memorial Museum, in D.C., lectured at Scaife Hall in December. On Feb. 20, the School of Medicine with the Memorial Museum will cohost a Pittsburgh summit examining how the study of the Holocaust can inform ethical dilemmas facing health professions today. "Science is never good nor evil, but it can be put to good or evil purposes," notes Arthur S. Levine, dean of the medical school and senior vice chancellor, health sciences.

USHMM

Appointments

Jennifer Condon studies maternal-fetal signaling in the mouse to understand how it initiates labor. Condon, a PhD, joined the University of Pittsburgh School of Medicine faculty in October as an assistant professor in cell biology and physiology. She and her husband, **Jeyasuria Pancharatnam**, who is a PhD and research assistant professor, transferred here from the University of Texas Southwestern Medical Center at Dallas. Their recent work has shown that the fetal lung, when it is ready to breathe, produces a protein that causes fetal cells to migrate into the mother's uterus, signaling it to contract. The researchers hope to find the exact mechanisms of labor induction to prevent preterm labor.



Condon (right) and Pancharatnam

Kenton Zehr, a cardiac surgeon, wants Pitt's academic heart surgery program to become the busiest in the country. Zehr, newly appointed cardiac surgery division chief and professor of surgery at the School of Medicine, is working to expand Pitt's expertise in valve and aneurysm repairs. His own lab explores how to limit invasiveness and speed up procedures in the O.R. Zehr, who came from the Mayo Clinic, believes the U.S. medical community and the world's physicians have much to teach one another. "We are going to be stormed by countries like China and India," he says, because their ideas are so interesting.



Zehr

Michael Becich and his research team have been international leaders in creating a system of patient-consent donations of serum, cells, and tissue, all of which are accompanied by detailed clinical descriptions. When using a breast cancer sample in research, you can imagine that it would help to know the type of cancer, whether the patient lived or died, whether she'd been treated, whether she had any genetic susceptibility to cancer, and other pertinent information. Becich, an MD/PhD, heads the new Department of Biomedical Informatics at Pitt. *—Katie Hammer*



Becich



GLUTEAL MORNING

Sunday morning. Time to sleep in a bit. Time for that extra cup of coffee as you linger over the newspaper. Time to relax. Or for a crash course in physiology and biomechanics with Melanie Grubisha.

Hip-hop blasted from the stereo at the kickboxing class. Second-year med student Grubisha, leading a group of nine, shot her right leg upward at a 45-degree angle. Her charges followed suit.

"Keep your abs tight," the Medical Scientist Training Program participant exhorted.

Grubisha, fit and muscular enough to have recently won three awards at a natural bodybuilding competition, moved more quickly and surely than her students—which makes sense, considering she learned Tae Bo from the master himself, Billy Blanks.

"Get lower," she shouted over the music as the group faced the floor, extended their legs back like pistons, and worked the glutes.

The class held all physical types—from a young woman as fit as Grubisha to folks older and less so. After 20 minutes had elapsed from the hour-long class, all were sweating profusely, and many were winded.

Not Grubisha, who ordered the class to drop and give her eight push-ups. "Go! Make 'em good ones!"

Before beginning her medical education, Grubisha played volleyball at Carlow University, her undergraduate home. That ended when she fractured her back during her sophomore season. Clearly, though, the injury didn't curtail her dedication to fitness. She's often at the gym by 7 a.m. and teaches six fitness classes plus an occasional on campus kickboxing class for med students.

She also studies cell signaling in prostate cancer development and plans to get a PhD in pharmacology.

The class began to cool down with a jog around the room. The lone spectator wandered out to his car, where a thermos of coffee awaited. Time to relax. *—Joe Miksch*

PHOTOGRAPHY | FRANK WALSH



SOWING THE SEEDS

SPRAYING CELLS TO REGROW SKIN

BY JOE MIKSCH

PHOTOGRAPHY BY JIM JUDKIS



Patients with Crohn's disease often suffer from a severe narrowing of the small intestine.

COURTESY M. FEDERLE

PROTECTION FROM CROHN'S

GENETIC FINDING MAY CONTRIBUTE TO NEW THERAPIES

BY ERICA LLOYD

Crohn's disease has long been part of Anna Stein's family story. Her dad, once a high school football player, was diagnosed at 16 and became too ill with the inflammatory bowel disease (IBD) to graduate with his classmates.

"He was in bed for a few years," says Stein.

Her dad went on to get his GED and become an optometrist in Chicago. But he was often hospitalized for Crohn's flare-ups.

The disease makes it difficult to absorb nutrients and is notorious for causing severe cramps and diarrhea and tunneling intestinal ulcers. (To get a sense for how miserable the disease can be, consider this. For a recent experimental therapy, patients desperate for relief volunteered to ingest eggs of parasitic worms.)

"He was in excruciating pain," says Stein of her father. "He was in pain all the time.

"Having a chronic disease in the family is like having another family member," says Stein. Surgeries to remove sections of her father's bowel as well as kidney stone complications severely restricted his diet. He couldn't digest most vegetables. Whole grains, nuts, and, eventually, fats were off limits, too. He'd try to sneak his forbidden favorites—peanut butter and chocolate—when Stein's mother wasn't looking.

Her father died only three years ago at the age of 82 from an unrelated condition.

"People didn't think he'd live that long, marry, or have children," says Stein.

A few months after her father's death, Stein's then-16-year-old son, Robert, was diagnosed with Crohn's.

Crohn's is an inherited disease, and scientists are just beginning to understand the genetics behind it, notes Richard Duerr, University of Pittsburgh associate professor of medicine and human genetics who runs Pitt's IBD genetics program. Duerr was part of a group of researchers in 2001 who unveiled the first gene linked to Crohn's disease.

"That gene has been widely replicated as a Crohn's disease gene. But it, by itself, doesn't anywhere near explain the genetic risk for Crohn's disease," says Duerr.

Now Duerr and his collaborators have evidence that many people afflicted with Crohn's lack a genetic variant that protects against the disease.

The collaborators make up a U.S./Canadian consortium that includes Pitt's IBD program clinical director and associate professor of medicine, Miguel Regueiro, and M. Michael Barmada, a PhD associate professor in Pitt's Department of Human Genetics. The researchers used 300,000 genetic markers to compare the genomes of several hundred Crohn's patients and healthy controls. Duerr says that the scans yielded many "hits" but that the protective variant was notably absent among cases of people with Crohn's. Its absence was a hundred times more significant than the next most common genetic marker difference found between cases and controls. It was also less common in people with ulcerative colitis.

The protective variant appears to block or alter the effects of a proinflammatory mediator known as IL23. (IL stands for interleukin, a protein released by the immune system.) Research shows the IL23 pathway is a likely culprit in Crohn's as well as other disorders thought to be caused by abnormal operations of the immune system, including rheumatoid arthritis, multiple sclerosis, and psoriasis. "The genetic findings made sense," says Duerr.

When Anna Stein, who now lives in Michigan, read about the links between these diseases in a *New York Times* story about the research, she contacted Duerr. Robert has psoriasis as well as Crohn's. "It was amazing to me. I'd always wondered if there was a connection," she says.

Duerr expects several genes will be linked to Crohn's, yet he is excited about the potential for new therapies that mimic the protective work of the IL23 variant. One recent clinical trial, begun before the consortium released its findings, has already shown promise with a therapy targeting IL23 and another pathway (called IL12).

Robert is in his first year of college. Fortunately, his Crohn's disease history has not resembled his grandfather's. After Robert's initial bouts with the disease, he has been in remission. Yet his mother knows the disease can assert itself again: "I have a fear about that. But I'm also so encouraged by all the advances made." ■

Names were changed in this story to protect patient privacy.



CORBIS

CODE PERSONAL

NEW GRAD PROGRAM INTEGRATES MEDICINE AND COMPUTER SCIENCE

BY SHARON TREGASKIS

More than one-third of all electronic health records systems fail. Like Tolstoy's unhappy families, each unhappy in its own way, the narratives of abandoned systems blame myriad factors—weak interface with existing systems, inattentive tech support, inadequate customization, and other such woes.

Chris Bartos has another theory about why the systems implode so frequently: The opposition of MDs to new roles in the healthcare delivery system.

"An electronic health record changes the work flow of doctors, nurses, and medical secretaries," says Bartos, a nurse with 30 years of experience and a master's degree in information science who worked on the implementation of UPMC's electronic order entry system in the late '80s.

"In some cases, there's tremendous resistance on the part of physicians because [it changes] the way they do their work. My premise is that it's based on issues of personal power and control over work domain." To test her hunch, Bartos will examine individual attitudes and then develop recommendations to enhance system implementation.

Bartos is one of 42 students enrolled in the University of Pittsburgh School of Medicine's new graduate program in biomedical informatics. Thirty core faculty from disciplines including dentistry, biostatistics, genetics, and radiology train the students.

Michael Becich calls the field a "Rosetta stone" for converting raw data into knowledge. Becich, a pathologist and MD/PhD, chairs the Department of Biomedical Informatics, which the school launched this fall.

The field has already changed medicine. Clinicians now benefit from software that flags dangerous drug combinations. Robotic assistants help with diagnosis, treatment, and even patient recovery. In the laboratory, researchers model biological functions, screen chemical compounds, and interpret vast quantities of experimental data with help from computers.

"In biomedical informatics," Becich says, "software, hardware, and telecommunications technologies converge to serve all of medicine—research as well as the clinical practice."

As the field matures, says Becich, clinical care and primary research will converge, with technology bridging the gap. Already, scientists have begun transitioning from publishing only their findings to sharing the raw data that undergird further analysis.

Ultimately, access to extensive data sets will allow researchers to ask increasingly sophisticated—and personalized—questions, says Becich, who studies electronic tissue banking, developing strategies for coding information to accompany tissue samples without compromising patient privacy. Imagine if a scientist studying prostate cancer were able to review not only serum samples or frozen tissue but clinical details about the patient from whom each sample was collected, such as his basic demographics, what stage of the disease he presented with, what treatments he received, even his PSA (prostate specific antigen) numbers over time. Such a study could delve much deeper than one restricted to an analysis of samples independent of patient details.

"We're moving into the era of personalized patient care," says Becich. "The integration of information is the only way to customize treatments."

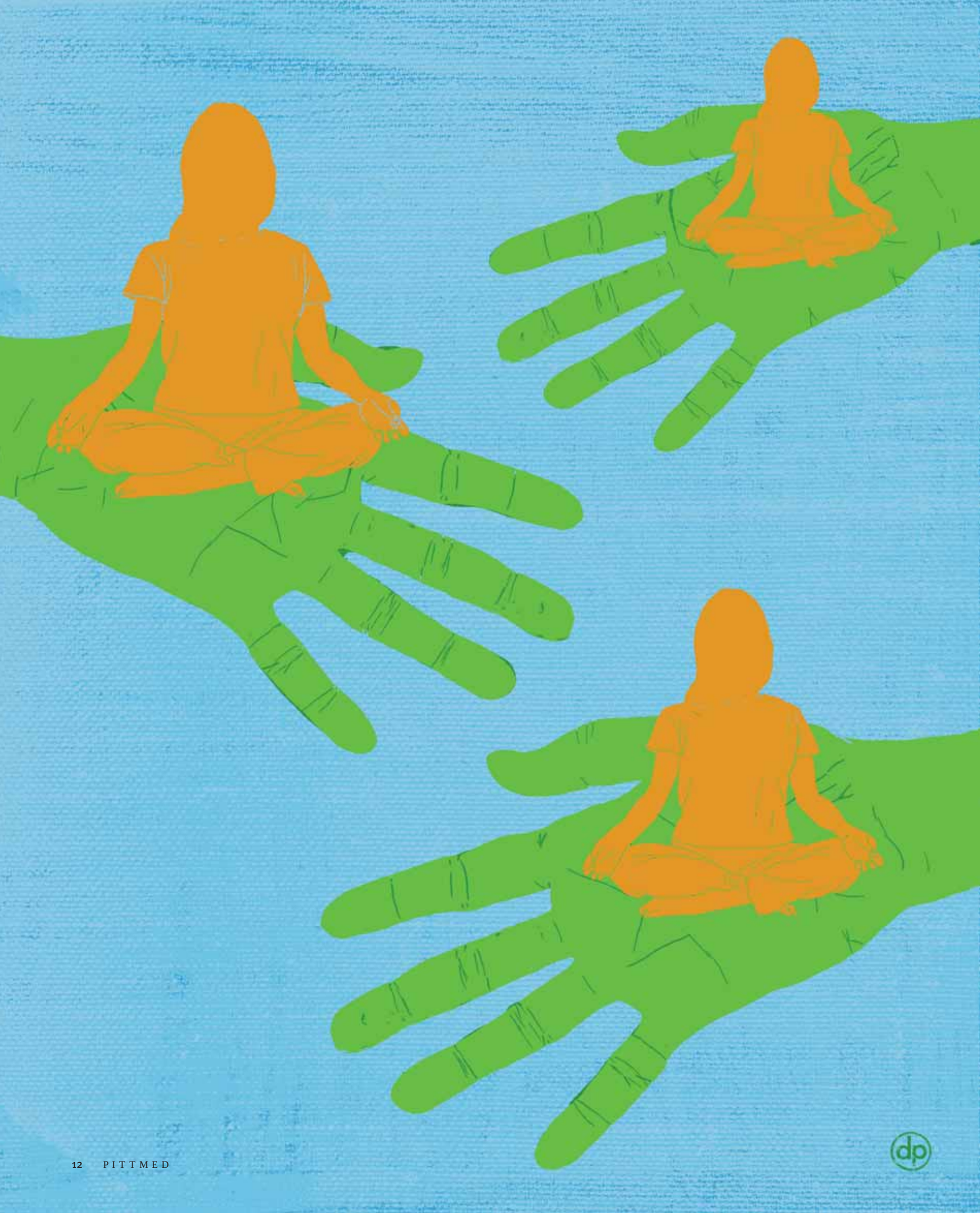
Geriatrician Steven Handler, a PhD student in the program, has another vision for customized care—this one for frail, older adults. He's creating a system to alert physicians of the potential for adverse reactions in nursing home patients by analyzing medication and lab result combinations.

"It's something that's been done before in hospitals, but never before in the nursing home setting, where there are more beds," he says.

Handler's approach tracks outcomes, alerting clinicians when an individual patient may be at risk. "Say kidney function begins worsening while a patient is receiving a drug," says Handler, who is also an MD. "The system sends an alert to the doctor so he can change the dose or cancel the drug."

Pitt's biomedical informatics program—one of only 13 nationwide—is part of a growing emphasis on graduate science training throughout the medical school, where currently one-third of students plan to earn PhDs.

"There are all kinds of discoveries to be made," says John Horn, the school's associate dean of graduate studies and a professor of neurobiology. "Not just those that inspire the imagination, but those that have huge practical importance for improving human health and treating diseases." ■



HOW TEAM MENTORING AND $4.5 MILLION A YEAR ARE CHANGING CLINICAL RESEARCH

BY JOE MIKSCH

THE BEGINNER'S MIND

Pick young doctors with great ideas, pair each with a team of dedicated mentors, and watch them soar. A program that takes this approach to grooming clinical research scholars is part of Pitt's response to what some saw as a failure among the nation's academic medical institutions to turn a sufficient number of their young researchers into established, self-sustaining members of the senior faculty who engage in clinical research.

On a winter day, Debra Weiner and Thomas Rudy stand in the UPMC Pain Medicine Program conference room, casually discussing the impact ratings of various scientific journals, which reflect how many times papers in a given journal are cited. On the whole, they conclude, the ratings have little to do with the quality of science in a particular publication.

With that decided, in comes Natalia Morone, who's experiencing a sort of pain, one familiar to those who inhabit the world of academic medicine: figuring out just what all the data she intends to publish in one of those journals mean.

A bit harried, the curly-haired and bespectacled Morone takes a seat. She, like Weiner and UPMC Pain Medicine Program research director Rudy, is interested in pain, particularly in nonpharmacologic ways in which this bane of humanity can be treated.

ILLUSTRATIONS | DAVID POHL

One tool she's studying as an analgesic is mindfulness meditation, a practice of consciously living in the moment and maintaining focus. Morone has practiced meditation since she was 19 and plans to teach the mindfulness meditation technique to older people with chronic pain as part of a study. By imparting a skill that allows adherents to focus on the here and now, Morone hopes to help study participants ameliorate their suffering. She'll then examine the effect the technique has on the severity of their suffering. Recruiting participants is still a few months off, she says.

Also in the works for Morone is a functional magnetic resonance imaging study looking into what areas of the brain respond to pain. But today's meeting is about yet another project.

Morone is an MD and assistant professor of medicine at the University of Pittsburgh. She's soliciting Weiner's and Rudy's expertise today for a study seeking answers to the question: What common characteristics bind older people who seek alternative therapies for pain?

"This is making me nervous," she says to Weiner and Rudy about preparing to publish her findings. "It shouldn't, but it is. If I seem frantic to you, it's not caffeine."

"What about that meditation you teach?" chides Rudy, whose beard and past-ear-length red hair somehow complement his ready humor.

"I'm doing something you have to be a meditator to understand," Morone replies. She explains that she can be aware of her nervousness and other physical sensations while keeping her mind calm. She sits upright and gently shakes her arms over the table in a good-natured demonstration.

Weiner and Rudy are on hand to help Morone keep her cool—as well as to help her refine her data, plan studies, apply for grants, suggest worthwhile meetings for her to attend, and generally guide this junior faculty member through the early stages of becoming an established clinical researcher. They're her mentors.

Mentorship is nothing new to academic medicine. Really, it's a component of more or less any professional career. The older, more established doctor, lawyer, or businessperson takes the fledgling under her wing.

The difference with what's on the verge of happening here in the austere UPMC Pain Medicine Program conference room is that this mentoring relationship—like nearly 30 others involving junior faculty among all the schools of the health sciences—is organized, team-based, multidisciplinary, and funded by the National Institutes of Health to the tune of $4.5 million a year over the course of five years.

Called the Clinical Research Scholars Program (those in the know pronounce the acronym *crisp*), this approach to career development is a response to what the NIH saw as a failure among academic medical institutions to turn a sufficient number of their young researchers into established, self-sustaining members of the senior faculty engaged in clinical research.

CRSP codirector Doris Rubio, a PhD associate professor of medicine, says the NIH saw that only 40 percent of those receiving its early career development grants went on to earn an R01 grant, the gold standard of funding for advanced investigators. (R01s are typically the first grants received by independent, experienced researchers.) Research careers were stalling, burning out, or simply never taking off. Money was being wasted, and opportunities to advance health care were lost.

To establish a new, more reliable path, the NIH sought help from academic medical institutions. Pitt's School of Medicine and other schools of the health sciences weren't shy about pitching ideas. The NIH liked Pitt's approach, which focused on multidisciplinary research and team mentoring and would become CRSP. Pitt's is one of 12 such programs supported by the NIH.

Wishwa Kapoor is a striking man, with his shiny pate, closely cropped gray beard, and athletic physique. He's calm and self-possessed. His research has set the standard for treatment of syncope and community-acquired pneumonia. He's also known for his work training future leaders in academic medicine, with his role in creating CRSP being the most recent contribution. (His colleagues rave about him: "A natural mentor and a very impressive person," says Rubio.) Kapoor was instrumental in designing CRSP. Today, as the program is about to enter its third year, he remains its director.

"It used to be you could sit in your lab, and you could do something by yourself," says Kapoor, an MD/MPH who, in addition to his leadership of CRSP, is chief of the Division of General Internal Medicine and the Falk Professor of Medicine. "Today, things are so complicated that you need a wider approach."

Kapoor gives the example of a researcher keen to divine genetic links to congestive heart failure. Such a study requires expertise in cardiac disease, genetics, the lab procedures necessary to analyze genes, and statistics.

"One single person doesn't have all that," Kapoor says. "That's why you need multiple people to come together."

At the UPMC Pain Medicine Center, we see Kapoor's hypothetical in practice. Morone, with seven others, is a member of Pitt's inaugural CRSP Class of 2005. Nine more scholars joined in the summer of 2006, and another class will be chosen later this year. (The CRSP staff is digging through 40 applications of about 100 pages each.)

Morone's expertise is in internal medicine and pediatrics. Before arriving at Pitt, she earned her medical degree from Michigan State University; undertook a residency in internal medicine and pediatrics in Phoenix; and practiced general medicine in rural Colorado. Along the way, she became interested in pain research and, with that in mind, earned a Master of Science in Clinical Research degree here in 2005. When the call first went out for CRSP applicants, she leapt.

Pain is multidisciplinary, she thought—with elements of anesthesiology, physical therapy, psychiatry, and samplings of other disciplines—and CRSP is multidisciplinary in nature.

"It was kind of natural for me to apply for it," she says. "I feel I was lucky to be here and receive the [CRSP] award."

CRSP scholars are required to find at least two mentors, which is the short answer to how Morone ended up consulting with Rudy and Weiner in the pain center conference room on a snowy December afternoon.

Rudy is a PhD professor of anesthesiology, psychiatry, and biostatistics and Weiner, an MD, is an associate professor of medicine, psychiatry, and anesthesiology with an interest in acupuncture. This day's mentoring session—they typically take place every two weeks—calls upon Rudy to wear his biostatistician's hat and for Weiner to call upon her knowledge of complementary and alternative medicine (CAM), earned through her experience in acupuncture.

Morone is hoping to divine the factors that make an older person suffering from knee pain more or less likely to use CAM techniques like acupuncture, homeopathy, massage therapy, aromatherapy, naturopathy, or biofeedback. Morone's tools are a questionnaire of her design and patient-related data collected by Weiner and Rudy.



At the conference table, the questions and answers start to fly.

Morone brings up issues like "Should I put the questionnaire itself in an appendix to the forthcoming paper?" (Yes, Weiner says. She and Rudy have been deluged with requests for copies of questionnaires by readers of previously published articles. Save yourself the aggravation and put it in, they tell Morone.)

Morone solicits guidance for larger issues, too, like "What makes a good questionnaire?"

"This last table I'm starting to do is getting at the idea as to what might be some of the barriers to CAM," Morone tells her mentors.

"So this is basically a yes/no question. 'Have you ever heard of this therapy?' I assumed 100 percent would have said 'yes' to acupuncture, but I didn't get that," she continues.

This sparks a conversation about the subtlety of questions and responses.

Weiner talks about the logic:

"It's parsing out the difference between 'Have you heard?' and 'Do you know?' The former implies less familiarity.

"It's the trick of language."

"That's why questionnaires are so hard," Morone says, shaking her head.

Weiner chimes in: "The immediate question after that, though, is, 'How much do you know about this treatment? A lot? Some? A little?' It would become pretty obvious if they'd just heard of it or if they have real familiarity."

"I think [the analysis] would be useful information to put into a table," Rudy says.

"OK, good. I have that [data about degree of familiarity], and I'll add it," Morone agrees.

She's still struggling with an even larger question: What does she have to say in this paper?

In addition to being asked how many types of CAM they practice, Morone's subjects were asked about their degree of spirituality and their "paternalism," or how much they rely on the word of a physician. From Rudy's workup of the data, it looks like those who use two or more types of CAM are highly spiritual (they pray rather than seek conventional medical treatments) and highly paternal. Morone didn't expect this.

"Everything in the CAM literature says a CAM person wants more control," she says. "But we're finding it's not the case."

Rudy flips through seven pages of data, looks up, and says, "The lower the score, the more they believe that way." He realized he has made a typo. "I have to change the signs. They *are* taking more control. They're disagreeing with those statements." Sometimes an act as simple as changing a minus to a plus can make all the difference.

This interpretation is in line with Morone's instinct after all—CAM users do want more control. There's a sense of relief in the room.

Weiner chuckles about the typo. "That totally changes how we interpret it," she says with a laugh.

"I might be able to actually report something in my article," Morone says happily, knowing that her thesis has been borne out.

Which is exactly what Joan Lakoski hopes will happen. After all, she says on another day, the earlier young investigators compile track records of significant publications, the earlier they can move on to assume leadership positions at the University of Pittsburgh.

"I'm convinced that every one of our scholars is on the cutting edge of [his or her] fields," she says. "I hope CRSP will help us retain our own, because these individuals are all going to be national leaders in their respective fields."

Lakoski mentions Hilary Tindle, an MD/MPH assistant professor of medicine. Tindle is in search of smoking-cessation therapies that quell mood, sleep, and cognitive disturbances often related to kicking the habit. Her mentors are experts in cardiology and psychology.

There's also Bruce Lee, an MD/MBA assistant professor of medicine, who is working with faculty in medicine, health policy and management, industrial engineering, computer science, and sociology. Lee creates computer models to better predict the spread of epidemics and optimize how we respond to them. And there are more than a dozen others whose praises Lakoski would be more than happy to sing.

If Lakoski seems passionate about CRSP, particularly the team mentoring aspect, that's because she is. Lakoski, a PhD, is Pitt's CRSP codirector in charge of mentoring. She also serves as associate vice chancellor for academic career development, health sciences; executive director of the Office of Career Development; associate dean for postdoctoral

education; and professor of pharmacology.

Lakoski is a true believer in team mentoring and CRSP. A writer visiting her Scaife Hall office left with enough material on those topics to turn his featherweight briefcase into the reporting equivalent of a bowling bag.

Explaining the rationale behind the team mentoring approach, Lakoski turns to the business world.

"[In academic medicine] the concept has emerged over the past three or four years," she says. "Some of the best approaches and information we rely on are from industry. They've long valued teamwork over autonomy."

Don't get Lakoski wrong. As a tenured professor she truly enjoys her autonomy. But she also knows that "I won't get my R01s funded unless I bring in multiple [technical] approaches. We've all been collaborating with each other for a long time, but [the idea of creating formal multidisciplinary teams] is slowly but steadily becoming the culture of biomedical research.

"You don't do it alone," Lakoski says of academic medicine. "It's a team sport."

"You don't do it alone," Lakoski says of academic medicine. "It's a team sport."

In the world of CRSP, mentors are trained (and compensated), team meetings are regular, the exchange of ideas is candid, expectations are codified in a signed contract between the mentee and her mentors, and all involved are expected to not only look at the short-term goals of a particular project, but to attend to the mentee's career in the long-term. Lakoski and her CRSP colleagues Kapoor and Rubio give formal oversight to make sure both the scholars' and mentors' expectations are met.

The Morone/Rudy/Weiner team has fostered a sense of camaraderie, even friendship. "I went to Dr. Weiner's wedding, and Dr. Rudy played the guitar," Morone says.

"They've guided me on what kind of articles I need to read, which conferences are important to attend, and they've introduced me to other people I can collaborate with," Morone says. "They've helped me with other nuts and bolts—things like reviewing grants and manuscripts." She says she wouldn't be on her way to becoming a clinical researcher without them. "I don't have any doubt about that."

Rudy and Weiner say they don't just give, they gain. "This is a great program because of the interdisciplinary nature," Rudy says. "We challenge each other to think in different ways. And a good student is always teaching you. I believe in the impact of 'the beginner's mind.'"

"The value for the mentor," Weiner adds, "is the same benefit that comes from any teaching role: It helps you solidify what you know and what you don't, what's important and what's not. And I like the nurturing aspect of it. I like seeing that I'm contributing to someone's personal growth and development."

Kapoor sees another benefit for the mentor, one that lies in benevolent self-interest. "Practically, it means that I have faculty, for example in my own division, who I'm developing who can help advance my own area of research. They write papers; I'm on their papers. They write grants; I'm on their grants," he says.

Kapoor, Lakoski, Weiner, and Rudy all recall the impact others had on their own careers. When Kapoor was a young investigator and a recent immigrant from Afghanistan, he had a great deal of support learning how to write well in English.

When Lakoski was about to take her first faculty job, she was "9.999 months pregnant." Her mentor knew she was eager to hit the ground running and also anticipated that being a new mother at a new job would be demanding. He advised her to take it slowly.

"And, you know what, he was right," Lakoski says. "I didn't just show up and, when my brain was all postnatal, send that first grant in. I [sent it] in six, seven months later and got it funded the first time."

Weiner and Rudy say they got a lot of help along the way but see how the more formal nature and multidisciplinary approach of CRSP mentoring might have propelled them further faster.

"I've had a couple of different people [as mentors]," Weiner says. "But I wish the relationships would have been more structured. I wish people would have pushed me more."

"In retrospect," Rudy adds, "in some of my early training I didn't have as much support as [Morone] is getting. I think that support is one of the great things about this."

In addition to team mentoring, scholars can count on support in the form of having NIH pay 75 percent of their salaries for up to five years; pay for tuition, books, travel, and lab expenses; and fund access to statisticians, a data management team, and a grant writer.

"It's tremendous," Rubio says. "With other [early career] grants you do get funding, but you don't really have to do anything except file an annual report. There's nobody higher up checking on you, making sure you've done things, and trying to help you remove obstacles.

"I've told the scholars, 'We'll do whatever we can to make sure you guys are successful.' If they're not successful, our program has failed, and we as an institution are only going to have the leaders we're going to need in the future if these scholars make it."

Morone, thus far, is making it, her colleagues agree. As the mentoring session ends, she, Weiner, and Rudy set up their next meeting, two weeks hence. "I've got lots to think about," Morone says. "I'm going home, and I'll have a draft for you by the end of January. We still need to decide where to publish." She also has to plan for her mindfulness meditation study, her fMRI study, her next foray into the ins and outs of CAM use, and myriad other responsibilities.

"Not only am I happy with the mentoring," says Morone later, "but the program in general. Certainly we've been given the tools to succeed. They can't give us [future] grants, but they have given us the tools."

"In the long run, [teamwork] is going to set us apart," says Lakoski, leaning forward and exuding enthusiasm. "Look at the new medical buildings. … They're all collaborative spaces. Look at the patient who needs a team to help him through a chronic illness. It's all teamwork."

Lakoski believes that Pitt's approach to mentoring and clinical research puts it on the cutting edge of academic medical institutions. "There's some literature on mentoring, but there are very few 'best practices' on team mentoring," she says.

Kapoor says it's Pitt's intention to add to that body of literature by studying the successes and failures of its mentoring programs. By collecting data on publications by CRSP scholars and the grants they earn, by surveying mentees and mentors to find out how to make the relationships pay off, Kapoor expects to "be at the forefront of the science on this."

Lakoski, Kapoor, and Rubio don't just want to contribute to the team mentoring literature, they hope to write the book. ■



GET RESULTS

FROM BENCH TO BEDSIDE, FASTER

BY MEGHAN HOLOHAN

A few years ago, Steven Reis faced a problem. He needed to find 2,000 people to participate in his clinical trial on heart disease. But how?

As associate vice chancellor for clinical research at the University of Pittsburgh, Reis sees patients only weekly, so he couldn't rely on his patient pool. He could put up flyers in the hospitals, announcing his need for participants. But then he'd have to rely on a patient's initiative to join.

Some patients fear that participating in a clinical trial will require them to take dangerous drugs or go to a lot of doctor's appointments. Some patients are unaware of the studies. And physicians who might refer patients can't be expected to remember all 5,600 studies going on at the University of Pittsburgh at any given time.

Across the country, researchers who conduct clinical research often labor to find participants. The search for volunteers can postpone clinical trials. And the longer it takes to complete a study, the longer patients wait to see solutions in the form of approved therapies.

The leadership at the National Institutes of Health noticed that clinical research sluggishly reaped benefits in the form of new treatments. Recruitment issues, like what Reis experienced, are just one barrier along the way. In its "Roadmap for Medical Research," the NIH made the issue of streamlining clinical and translational research a major priority. Last fall, it awarded 12 inaugural grants to institutions that created plans to improve the bench-to-bedside-to-community process. The University of Pittsburgh is one of the first institutions to secure a Clinical and Translational Science Award, which it will use to fund its new Clinical and Translational Science Institute (CTSI). The NIH will award Pitt $83.5 million toward the effort. Fifty-three million dollars of the total comes from existing programs, like those at the University that educate and groom doctors to do clinical research, including the Clinical Research Scholars Program featured on p. 12 of this magazine and the master's degree in clinical research discussed in the p. 18 story.

Reis, the principal investigator on the $83.5 million grant, is one of many Pitt faculty whose work may be supported by the new institute. His own study was spurred by the fact that, overall, Blacks tend to have less coronary artery calcium than Whites. "This is particularly interesting," says Reis, "because less coronary calcium is expected to confer a lower CVD [cardiovascular disease] risk. But, as a group, Blacks have a higher CVD risk than Whites."

He thought that if he could understand the relevant physiological differences, it would translate into better treatments for everyone.

So Reis didn't just want to recruit 2,000 patients, he wanted half to be African American. He approached Lee Hipps, vice president of the Urban League of Pittsburgh. When the cardiologist explained his project, Hipps agreed to help. The two figured out the best way for Reis to recruit patients and to schedule follow-up meetings with them. Reis expects his preliminary study results to come out this winter.

Like Reis, many researchers don't start out with the appropriate community ties for recruiting their participant pools. As part of the CTSI, Hipps, along with the dean of Pitt's nursing school, Jacqueline Dunbar-Jacob, will codirect a program that establishes ties between Pitt researchers and community groups. The program architects also hope that community members will approach University representatives to inform them of health issues that concern their communities.

Pitt's CTSI is putting together another solution to the recruitment problem—a patient registry. When patients are admitted to UPMC hospitals or visit UPMC doctors, they can consent to receive information regarding upcoming studies. Each quarter, Pitt will send mailings to the patients explaining the ongoing studies for which they qualify.

Reis hopes that soon no Pitt scientist will need to post flyers advertising studies. Instead, the patients will come to the researchers. ■

COLOMBIAN SURGEONS ARE SOME OF THE WORLD'S BEST AT SAVING LIVES WITH THE SIMPLEST OF TOOLS: A PLASTIC BAG TO COVER AN OPEN WOUND, A SCALPEL AND LAVAGE TUBE TO CHECK FOR ABDOMINAL BLEEDING. FORGET CT SCANS—PUBLIC HOSPITALS MAY NOT EVEN HAVE MATTRESSES ON THE GURNEYS.



A STUDY IN TRAUMA AND RECOVERY

BY REID R. FRAZIER

LEARNING

WHAT THEIR HANDS ALREADY KNOW

A typical night for an on-call trauma surgeon in Cali, Colombia, looks something like this. The patient in Operating Room 1 has a bullet wound in the heart. There's an abdominal stab victim in Room 2. And in 3, a car crash victim is on a ventilator, barely holding on. The patients will come in ambulances, police cars, taxis. There will be punctured torsos, lacerated blood vessels, and head traumas requiring a series of delicate surgeries. The wounds are mostly from *balas y cuchillos*, bullets and knives. At least one person will die on the table.

Every once in a while, a call will come in telling the doctor to get ready: *A dozen or so soldiers with serious injuries are coming in by chopper.* A few minutes later, the trauma team will hear the *thump-thump* of helicopter blades above. The aircraft carries a load of soldiers who were caught in a firefight with rebels or paramilitaries or were torn up by a car bomb. The victims are too young to die, the surgeon will think.

Welcome to Alberto García's world.

ILLUSTRATIONS | ROB KELLY

García has been a surgeon in Cali, a city of more than 2 million, since 1989. Cali hospitals have among the heaviest trauma loads in the world. Few trauma centers in the United States see more than 3,000 patients a year. UPMC Presbyterian, one of the busiest in this country, with 140 ICU beds, gets about 5,000 patients a year. The public university hospital in Cali, at the Universidad del Valle, with 40 ICU beds, sees about 10,000.

"It's an enormous figure," García says, in emphatic, professorial Spanish.

The reasons for the immense trauma load are diverse. The Colombian civil war, which began in 1948 and reignited in the 1960s, and the rise of the drug trade (often a main source of cash for the war), can account for only part of the story. A heavily armed populace and urban crime all play a part. Some of the country's academics have even established a new type of social science: violentology, the study of violence and its causes.

Whatever the causes for the trauma load, García and other surgeons in Colombia must function on a shoestring budget. The big-ticket diagnostic aids, such as echocardiograms and CT scans, are luxury items, especially in the public hospital where García was head of critical care until early last year. (Private hospital wards are likely to be as well equipped as those in the United States.)

UPMC Presbyterian has more than a dozen state-of-the-art scanners. Cali has one. It is reserved for the most serious injuries.

So most Colombian doctors have figured out how to save lives without advanced equipment. In cases of abdominal bullet wounds, for example, they've found a physical exam once every hour tells them as much as a CT scan would.

In the mid-1990s, García and fellow Cali surgeon Carlos Ordoñez studied hundreds of patients to determine whether X-rays were needed to detect a pelvic fracture, a common injury in a car crash. They found the physical exam worked just as well as the X-ray at diagnosing the injuries. The hospital stopped giving X-rays for most pelvic fractures; X-rays few patients could afford.

A couple of years later, García and Ordoñez's team surveyed all 2,500 trauma deaths in Cali for a one-year period. The researchers handpicked their way through paper files in offices around the city. They found an astounding 34 percent died of preventable causes—usually because someone didn't diagnose a hemorrhage, a perforated bowel, or an infection in time. They are now studying whether an ensuing education campaign for the city's first responders and doctors has lowered the number of preventable deaths in Cali.

García grew up in a small town a few hours from Bogotá, the country's capital city. The son of a school teacher and a dressmaker, he considered following some of his classmates to the United States to build a career.

"It was attractive," he says. "But I felt that, with the things I wanted to do, I would be more useful here. The impact I could have had in the U.S. wouldn't have been as big; so I decided to stay here and fight on."

García and other doctors in Colombia are hungry for more progress. There is very little money in Colombia for the kind of research García would like to do—like studying the efficacy of certain antibiotics on infections. The patient information system is improving, but it's a far cry from what it could be. Information is scattered, basic, and hard to access.

On the days when the ban was enforced, Villaveces found a 14 percent reduction in homicide rates.

In a big-city U.S. hospital, two or three staff members will oversee a trauma database with 400 or so data points per patient. In Cali, the information is collected mostly on paper and stored in files.

Therein lies a problem.

Colombia's hospitals are eye-opening places to learn about trauma surgery. Colombian surgeons are some of the best in the world at saving lives with the simplest of tools: a plastic bag to cover an open wound, a scalpel and lavage tube to check for abdominal bleeding. Forget CT scans—public hospitals may not even have mattresses on the gurneys. Their feats in the O.R. may be Herculean at times, but most of the trauma world isn't learning from Colombian surgeons. Their work isn't, generally, written about in international journals. They simply don't do as much research as their counterparts in more developed countries. There is no time. No money. No training.

Doctors like García and Ordoñez are the exceptions. They believe a stronger research program would make a difference for Cali's trauma patients and perhaps for trauma patients throughout the world.

Juan Carlos Puyana, García's former classmate, shares these sentiments. Puyana and García both received their medical degrees at the Universidad Javeriana in Bogotá, where Puyana was born. Tall and lanky, with a thick head of straight dark hair and a bushy dark mustache flecked with silver, the 47-year-old Puyana is an associate professor of critical care medicine and surgery at the University of Pittsburgh. He has a jaunty manner and thick crow's feet around his eyes; they fold in when he smiles. His eyebrows arch upwards when he gets excited in conversation, like when he's talking about novelist Gabriel García Márquez or Pitt's new Colombian partnership, of which he is the architect. The partnership is sponsored by the Fogarty International Center at the National Institutes of Health.

Puyana and his Pitt colleagues are partnering with professors at the Universidad del Valle, including García and Ordoñez, to build the program. The new five-year initiative, dubbed Trauma and Injury Excellence in Education on Research (TRAINEER) will immerse young Colombian doctors in the American system of research, particularly clinical research.

"One thing is to teach people in Colombia to learn how to do research with what they have," Puyana explains from his office on the 12th floor of UPMC Presbyterian.

Puyana has already been inspired by studies he published recently with García and Ordoñez. And he notes that the first Fogarty-sponsored results are in hand. In September, just six months into the partnership, Ordoñez presented results of a study examining surgical alternatives to ostomies (which are linked to high mortality rates) before the annual meeting of the American Association for the Surgery of Trauma in New Orleans.

"We want impact now," Puyana says, grabbing a sheet of paper from his desk. As he talks, he sketches a flowchart of the program, drawing arrows between boxes surrounding acronyms of various university programs in Pittsburgh and Cali. One of the boxes surrounds *CRTP*, Pitt's Clinical Research Training Program, through which visiting Colombian Fogarty trainees can pursue certificates or master's degrees in clinical research. Another box contains *CISALVA*, the

partner program at the Universidad del Valle and Colombia's national injury prevention center. Arrows zigzag all over the page, and an arrow from CISALVA's box lands on the word *VIOLENCE*.

Puyana talks about CISALVA's director and coinvestigator for the Fogarty, Maria Isabel Gutiérrez, an MD and Johns Hopkins University–trained PhD epidemiologist. Among other things, she has studied how to prevent child abuse in some of Cali's roughest neighborhoods. Her systematic research found public awareness campaigns can curb such violence by 10 percent, reducing the number of people entering the city's strained hospital system.

CISALVA was created by physicians, social scientists, and epidemiologists at the Universidad del Valle in response to escalating levels of violence during the early 1990s. At the time, murder rates were at or near the highest in the world. One of CISALVA's first triumphs was to help the city study the nature of murders in Cali—when, where, how, and why they happened. The researchers found that most occurred on weekends, especially after holidays or paydays. So city authorities stepped up police patrols in crime hotspots and, on weekends, banned concealed firearm possession and late-night alcohol sales. Curiously, the gun bans were enforced during some but not all weekends.

"Methodologically, it was wonderful, because it provided us with all types of days or weekends where there was an intervention," said Andrés Villaveces, the CISALVA study author who is now research assistant professor of epidemiology at the University of North Carolina at Chapel Hill. On the days when the ban was enforced, Villaveces found a 14 percent reduction in homicide rates.

"That translated into hundreds of deaths prevented," says Villaveces.

With these data in hand, Gutiérrez and her colleagues were able to spread the policies to other cities. They started with big cities like Medellín and Bogotá. Gradually, she and her collaborators convinced authorities in smaller cities and towns to enact similar policies. The results are clear. Colombia has cut its murder rate by a third in the past 10 years. Part of the decline, researchers say, is a result of the country's peace process, which has curbed bloodshed in some areas. But CISALVA's campaign also gets credited for contributing to the drop. Bogotá's murder rate is a fraction of what it used to be. Now it's half that of Washington, D.C., and about the same as Phoenix's.



Juan Carlos Puyana, architect of the Colombian partnership, with the Cali hospital in the background

Colleagues describe Gutiérrez as warm, undaunted by problems she might face, and among the most energetic people they know. She says having data helped her convince local officials to go along with CISALVA's recommendations.

"When you show them that these interventions can show results, you have them on your side. You have an ally with them," she says.

Gutiérrez sees Colombia's problems as a series of solvable puzzles. Violence is still the country's number one public health problem. Gutiérrez and colleagues treat it in much the same way scientists might treat other problems. They monitor patterns and employ appropriate tools. In the domestic violence program, her tools were public awareness campaigns developed by major ad agencies. Her team also orchestrated the spread of a targeted message through churches and social service groups. Gutiérrez has worked in some of the country's "red areas," places where left-wing guerillas and right-wing paramilitary groups battle with each other and the army. To her, the young men caught up in the civil war are just "ordinary people, like you and me," people with problems to be solved, she says.

Gutiérrez, like García and Ordoñez, is an exemplar of what the Fogarty program is trying to promote—Colombians who can create homegrown solutions through research.

"To me, it would be awesome if, [in] these five years, we can train 10 people to do what Maria Isabel does, not only in Cali, but in the rest of the country," says Puyana. "If we do that, we'd probably have a greater impact on health care than if we'd developed a new protein. At least in the reality of Colombian health care."

The son of a retired general in the Colombian Army, Puyana traveled widely as a boy, living in the United States and Chile before his family settled in Bogotá again when he was 10. He smiles when asked about growing up in Colombia's capital, recalling a childhood with few worries, before the escalation of the country's civil war. When he graduated from high school, he wanted to go into a field where he could help people, and medicine seemed the best way to do that.

After receiving his medical degree, he did his residency in general surgery at McGill University in Montreal, with the plan of returning to Colombia. At the end of his residency, he told his adviser he needed to go to the United States for trauma surgery training before returning home.

"He told me, 'If you go to the States, you'll never go back to Colombia.' Of course, he was right."

Puyana went off to Yale University and Pitt but stayed close to his classmates in Colombia, largely through his affiliation with the Pan American Trauma Society. Still, he felt some remorse about leaving his home.

"The Colombians were waiting for me. And I kind of stood them up," he says. "When [the Fogarty application] came on my desk, I said, 'This is it.'"

He and Andrew Peitzman, professor of surgery and director of trauma and surgical critical care at Pitt, applied for the Fogarty grant in the summer of 2005. By the spring of 2006, they learned they would receive $150,000 a year for five years. Timothy Billiar, the George V. Foster Professor and chair of the Department of Surgery, is the grant's principal investigator. Puyana and Peitzman oversee the day-to-day operations of the program.

The American-born, -bred, and -trained Peitzman has traveled extensively in Latin America but visited Cali for the first time this fall. He describes that first visit to a Colombian trauma room as "humbling."

"Colombian doctors can operate circles around us," he says. "Taking our trauma experience to them in Colombia is like taking coal to Newcastle."

But he notes that without clinical trials, it will be impossible to prove to a skeptical scientific community that a given Colombian approach might be of benefit elsewhere.

"The best of the best studies are clinical studies that are randomized, blind, in level-1 trauma centers, with big enough patient samples, and good statistics," Peitzman says. "In order for us to change anything that we do, that's the kind of data that people want."

Colombian doctors have loads of experience, Puyana confirms, but their medical school training is usually more vocational and pragmatic than training here. In terms of research, they may not be versed in "the ability to ask the right questions," he says, or in developing the methods to figure out the best way to approach a research problem.

With a cadre of Pitt mentors, Fogarty trainees will have the support and the ability to create a database to track, for example, all the penetrating heart wounds they treat over the course of a year. They will learn how to design a proper clinical trial and apply the right statistical methods to the results. They will know how to write and present research papers.

Once a trainee's studies in Pittsburgh are complete, the program will give the doctors minigrants to help them start their own studies in Colombia.

In addition to training Colombian surgeons here, Pitt docs are offering in-country instruction. In November, 58 general and trauma surgeons from Colombia, Brazil, and elsewhere gathered in Cartagena, Colombia, for TRAINEER's first such seminar, which explored clinical and basic science research methodologies. (Puyana was particularly happy to see people still in their seminar seats at 8 p.m. on a Friday instead of seeking out one of the Caribbean town's many fine restaurants.) Since the seminar, Puyana has been contacted by several young surgeons who want to learn more.

Eventually, TRAINEER organizers would like to offer online instruction in Spanish to reach a broader audience and mentor graduates of the program remotely.

"We may see things they're doing in Colombia that make sense that might be translated here," says Hank Weiss, a Fogarty participant who is director of Pitt's Center for Injury Research and Control and a PhD associate professor of neurological surgery.

The Bogotá Bag is a perfect example.

When surgeons at a Bogotá hospital could not close the swelling abdomen of a severely traumatized patient, they cut open a plastic I.V. bag and sutured it directly to the skin. It saved his life. After hearing about this, star trauma surgeon Kenneth Mattox at Baylor College of Medicine in Houston, developed the Bogotá Bag in clinical trials in the United States. Now the technique is widely used during treatment of abdominal compartment syndrome.

Fogarty participants shake their heads when they report the end of the story:

American doctors now teach Colombians how to use the Bogotá Bag.

Puyana describes his work with Fogarty as the "most important project he has ever done."

"Right now," he says, "I have an NIH grant. I work with the DOD and study combat casualties. That's helping a lot of people. But I didn't stay there [in Colombia] with Alberto and stay up nights caring for people. Being able to bring something back to Colombia at this stage of my life is the most satisfying thing."

He hopes the Fogarty will have a snowball effect, both sparking Colombians' interest in research and sparking worldwide interest in research by Colombians.

The first two trainees are scheduled to arrive this summer, including Andrés Rubiano, a neurosurgeon.

Rubiano says he would like to develop better prehospital care for brain injuries. To do that, he needs to show the Colombian government why it's important, just as Gutiérrez has done so successfully with CISALVA programs. "If you want to change any of the government policies about trauma care, you need to be really prepared and show them good data," says Rubiano, who will enroll in Pitt's Master of Science in Clinical Research program. He'll begin coursework this summer in biostatistics, research design, and computer-based data analysis.

Rubiano's hospital, in the city of Neiva, sees patients from a broad swath of Colombia's rural South, including an area the size of Switzerland with a lot of rebel activity. He treats brain injuries from motorcycle accidents, gunshots, machetes, and an occasional bomb. Relying on treatment protocols developed in the United States, where trauma patients receive care within minutes, is of little use in Neiva, he says. His typical patient arrives two to four hours into an injury.

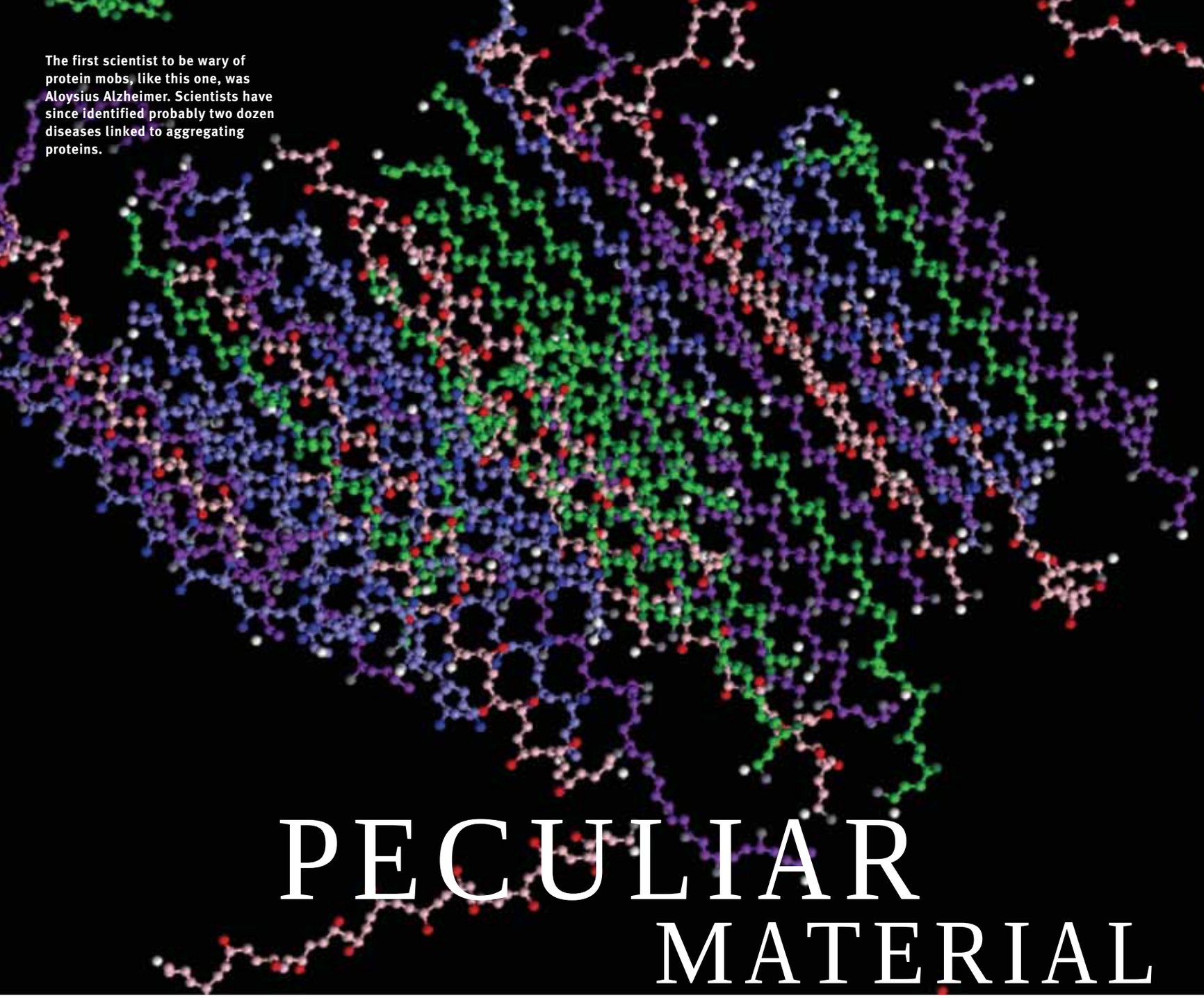
To her, the young men caught up in the civil war are just "ordinary people, like you and me," people with problems to be solved, she says.

"Here in Colombia, clinicians work a lot with research from other countries, but the population here is different, the context is different," says Álvaro Sánchez, a 28-year-old MD pursuing a master's degree in epidemiology in Cali. He'll also arrive this summer as a Fogarty trainee and pursue the master's degree in clinical research at Pitt. His summer course load will look a lot like Rubiano's.

When he returns home, Sánchez would like to design injury-prevention studies appropriate to Colombia. A U.S. study on, say, treating firearm injuries, would have little efficacy in Colombia, where ambulance service is sporadic. As in other parts of the country, most of his patients wait hours, not minutes, before getting medical attention.

"We need more information from our own situation, not from other countries," he says. ■

Jessica Mesman Griffith contributed to this story.



The first scientist to be wary of protein mobs, like this one, was Aloysius Alzheimer. Scientists have since identified probably two dozen diseases linked to aggregating proteins.

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PECULIAR MATERIAL

DISBANDING UNRULY MOBS OF PROTEINS

BY JIM SWYERS

In 1901, a middle-aged man named Karl Deter reluctantly took his wife, Auguste, to the nearby Asylum for the Insane and Epileptic in Frankfurt, Germany. He did so on the advice of his family doctor, after months of witnessing her dramatic and tumultuous descent into a personal hell. The doctor's prescription read:

Auguste D. has been suffering for a long time from weakening of memory, persecution mania, sleeplessness, restlessness. She is unable to perform any physical or mental work. Her condition needs treatment from the local mental institution.

At the asylum, the physician assigned to care for her, Aloysius Alzheimer, found Auguste D., as he would always refer to her, to be in good physical condition. However, as he noted in his report, there was something terribly wrong with her mind:

Her ability to observe is severely disturbed. If one shows objects to her, she names these usually correctly, but immediately thereafter she has forgotten everything. When reading, she drifts from one line to another, reads by spelling or with senseless intonation; when writing, she repeats individual syllables repeatedly, drops others, and bogs down rather quickly. When speaking, she often uses phrases of embarrassment, some paraphasic expressions (creamer instead of cup), sometimes she gets stuck (in speaking). Some questions she obviously does not understand. She does not comprehend anymore the usage of certain objects.

Although Auguste D.'s symptoms fit the diagnosis of senile dementia—a general term used back then to describe the condition of elderly people who were too mentally impaired to care for themselves—because she was only 51 and the onset of her dementia was so rapid, Alzheimer, a psychiatrist and neuropathologist, became convinced that her symptoms were not age related. Rather, he suspected something far more aggressive and destructive was assaulting her brain.

As he watched her progressive decline in the following weeks and months, he became equally convinced that whatever it was, it would do irreversible damage to her brain and eventually claim her life. This conviction was based on his experience in examining the brains of dozens of other patients who had died while living at the asylum.

Alzheimer had honed his forensic skills while working with Franz Nissl, a neurologist who'd joined the asylum faculty shortly after Alzheimer's arrival in 1889. Even before landing in Frankfurt, Nissl was well known for developing a method of staining nerve cells. (The Nissl protocol is still in use today in laboratories throughout the world.)

Alzheimer and Nissl used this stain to look for clues about the potential causes of a number of illnesses, including epilepsy, dementia, and cerebral palsy. They made detailed case studies of a total of 170 asylum patients and postmortem examinations of their brains before Nissl left in 1895 for a position in the clinic of the famed Emil Kraepelin at the University of Heidelberg.

During their time together in Frankfurt, Alzheimer and Nissl became confidants as well as collaborators. Alzheimer frequently wrote to Nissl about Auguste D.

By the time Alzheimer joined Nissl in Kraepelin's clinic in Heidelberg, he had become obsessed with Auguste D.'s case. From Heidelberg, he sent regular messages inquiring about her welfare. As one dispatch to him reported, Auguste D. was in the final throes of the disease:

She is completely stupefied, always lying in bed with legs drawn up. Regularly soiled with urine and faeces: never says anything, mutters to herself, has to be fed.

A year later, when Kraepelin was appointed professor of psychiatry at the Royal Psychiatric Clinic in Munich, Alzheimer went with him while Nissl stayed in Heidelberg, assuming Kraepelin's old position.

When news reached Alzheimer in 1906 that Auguste D. had died at age 55, he wasted little time submitting a request to the asylum in Frankfurt for her brain and medical records. It was granted. Using Nissl's stain, he finally got to see Auguste D.'s killer under the microscope.

He described it in his notes as a dark "peculiar material" deposited inside and around her nerve cells. Although he wasn't quite sure what the material was, he had little doubt it had caused her aggressive dementia. He became even more convinced when he found similar deposits among the brain cells of two other people who'd suffered from early onset dementia.

Medical researchers would eventually show that these peculiar deposits, or "aggregates," that Alzheimer saw in Auguste D.'s brain cells consist of naturally occurring proteins. They would also show that the protein aggregates are toxic to cells, particularly brain and nerve cells. It turns out that protein aggregation is responsible for some of the most destructive neurological diseases known to humankind, including amyotrophic lateral sclerosis, Huntington's disease, and prion diseases like Creutzfeldt-Jakob.

Protein-aggregate diseases occur in other tissues besides nerve cells. In sickle cell disease, protein aggregates damage red blood cells. In type 2 diabetes, they taint the pancreatic cells. (There is a high prevalence of Alzheimer's disease among people with type 2 diabetes, prompting some to believe that the two conditions are closely related.)

To date, scientists have found at least two dozen protein-aggregate disorders, each with its own distinct course and symptoms. Although it has been more than a century since Alzheimer first discovered one, which now bears his name, only recently has medical science understood enough about what makes proteins aggregate to begin developing strategies for fighting back. Progress at the University of Pittsburgh in understanding the cell's normal protein quality-control apparatus is giving scientists new insights into why this process fails in protein aggregate diseases and how it might be bolstered to prevent bandit proteins from causing problems in the first place.

As he watched her progressive decline in the following weeks and months, he became equally convinced that whatever it was, it would do irreversible damage to her brain and eventually claim her life.

Fran Welek had a baby boy in the mid-1980s in Columbia, Mo. She and her husband, John, named him Sean. At six weeks of age, Sean's skin turned yellow, and his liver swelled. Doctors at the hospital, where Fran Welek also worked as a registered nurse, diagnosed Sean with hepatitis but were unable to determine its cause. They couldn't find any bacteria or viruses known to cause hepatitis in the newborn's bloodstream.

So the doctors took a biopsy of the infant's liver and sent it off for testing. A few weeks later, the diagnosis came back. Sean had a genetic condition called alpha-1-antitrypsin (A1AT) deficiency, which is sometimes fatal. A1AT is an enzyme inhibitor made in the liver and released

JIM JUDKIS



David Perlmutter (left) and Jeffrey Brodsky are working on ways to stop proteins from aggregating, a process that causes many disabling diseases.

into the blood, where it finds its way to the lungs and protects them from inflammation caused by infection and inhaled irritants such as tobacco smoke. A1AT deficiency was first discovered in adults with an aggressive form of emphysema. It was later found that some people with the deficiency end up with abnormal protein aggregates, typically called globules, in the liver—resulting in inflammation and swelling, as Sean experienced. It is the most common genetic cause of liver disease in children. About a quarter of patients with liver problems require a transplant to survive.

Welek and her husband were in "total shock" about the diagnosis. Not only had they never heard of the disease, neither had Sean's doctors in Columbia. Although his hepatitis would eventually subside, Sean would still be a very sick little boy, often requiring hospitalizations to control his symptoms, which included bruising, frequent nosebleeds, and swelling in his feet and legs. Because their doctors knew so little about the disease or how to manage it, the Weleks felt completely alone and were fearful for their son's life.

When Sean turned 3, the Weleks got a break. Sean's aunt was a resident at St. Louis Children's Hospital; there, she came across a patient who had the same diagnosis as her nephew. When she asked who the patient's doctor was, she was introduced to David Perlmutter, who turned out to be one of the leading experts on the disease.

Perlmutter—now chair of the Department of Pediatrics in the University of Pittsburgh School of Medicine, physician-in-chief at Children's Hospital of Pittsburgh, and scientific director of the Rangos Research Center—had begun caring for children with A1AT deficiency a few years earlier, while completing his own training at Children's Hospital Boston. When it came time to choose a project for his research fellowship, Perlmutter decided to explore A1AT deficiency. He was involved in another project at the time that involved the ability of cells to secrete proteins. He believed, somewhat erroneously, that the globules seen in A1AT-deficient liver cell biopsies were the result of a defective protein secretion mechanism.

Perlmutter began traveling all over New England collecting samples from children diagnosed with the deficiency. When he followed his mentor to Washington University School of Medicine in St. Louis, he continued that research. Before long, doctors from all over the Midwest were referring their A1AT-deficient patients to him.

Meeting Perlmutter not only gave the Weleks peace of mind, it also gave Sean a relatively normal life. "His doctors in Columbia said we needed to be very careful with him," says Welek, "and set limits for what he could do and couldn't do. But Dr. Perlmutter told us just to let him be a kid and have fun, and he would help us manage whatever happened. It was extremely comforting to find someone who could explain what was happening to Sean and give us the most up-to-date information on how to manage his condition."

The Weleks began taking Sean to see Perlmutter every six months and sometimes more often when he had flare-ups or complications.

Once, when Sean developed a bad infection, the Weleks rushed him to St. Louis. It looked as though Sean might not pull through. The whole family, including aunts and uncles, gathered to stand vigil. After a long night, Perlmutter emerged from Sean's room and assured everyone that the boy was going to be okay.

In 1995, when Sean was 10, his liver failed and he required a transplant. Perlmutter was there to help the Weleks through the ordeal. The transplant was successful, and Sean, who is now a scout for an NFL team, has had very few complications and no hospitalizations since.

Of course, a liver transplant is a life-altering procedure that often requires long-term use of antirejection drugs, which can lead to other serious health problems. For some 20 years now, Perlmutter has been looking for a way to stop A1AT deficiency before it can destroy patients' livers.

Early on, he says, he began to wonder why only about 10 percent of children with the deficiency get liver disease.

"The more children I saw with the deficiency, the more I wondered why the other 90 percent of children with this deficiency don't develop liver disease," he says.

Despite Alzheimer's remarkable finding, for more than 50 years after his untimely death in 1915 his discoveries were largely overlooked by psychiatry. All eyes were turning instead toward the theories and writings of Kraepelin's contemporary and rival, Sigmund Freud.

Unlike Kraepelin, Freud believed that most psychiatric diseases were caused by emotional trauma or repressed sexual desires and not by organic disease. Whereas Kraepelin sought evidence to support or refute his theories, Freud held up his theories as infallible and had little tolerance for those who questioned them. He even had dissidents expelled from their posts.

As Freud's doctrines began to dominate psychiatry, Alzheimer's reports and others that proposed a biological cause of psychiatric illness would become cold cases for decades. It wasn't until the 1970s, some 30 years after Freud's death, that the tide began to shift toward Kraepelin's model of psychiatric disease and Alzheimer's writings were rediscovered.

We now know the plaques that Alzheimer first observed in the spaces between Auguste D.'s brain cells consist mostly of beta amyloid, a fragment of a protein called amyloid precursor protein that occurs naturally in nerve cells. (Many now refer to aggregate diseases as amyloid diseases.) The tangles found inside the brain cells of Alzheimer's disease (AD) patients turned out to consist mostly of a protein called tau. In normal cells, tau is part of a structure called a microtubule, which helps support the cell's architecture and also transports molecules back and forth. In AD cells, however, tau is twisted out of shape, which badly contorts the microtubule, causing the cell to become sick or die. Tau is the most commonly found protein in neurodegenerative diseases.

We also know now that most protein aggregate diseases involve misshapen proteins, which appear, at least in some cases, to be caused by genetic mutations in the protein. Scientists believe that the more "destabilizing" the mutation, the more likely protein will gather together into an unruly mob.

Such destabilizing mutations do not always alter the structure or function of the protein immediately. Rather, they may predispose it to adopt an inappropriate structure and muck things up later on. This is why the symptoms of many of these conditions do not show up until adulthood or, as in Auguste D.'s case, middle age.

In some protein aggregate diseases, it is not a genetic mutation but the excess production of a protein that leads to its aggregation. In others, rogue proteins called prions set off the clumping phenomenon.

Regardless of the biological instigator, treatment strategies for protein aggregate diseases have met with little success.

In 1996, Perlmutter reported the discovery of an apparatus in cells that might be harnessed for degrading the globules that caused so much trouble for Sean and his other young patients. In a genetically engineered human fibroblast cell, he found that a well-known degradative enzyme called the proteasome played a role in the disposal of the mutant A1AT protein.

This was a surprise. The mutant A1AT protein accumulates in a membrane-bound compartment of the cell called the endoplasmic reticulum (ER). There, everyone supposed, it would stay put or the ER's own system would dispose of it as required. The proteasome resides in the cytoplasm, the fluid part of the cell that surrounds the ER, the nucleus, and other membrane-bound subcellular compartments. Perlmutter's results implied that the mutant A1AT was somehow transported out of the ER and into the cytoplasm.

At almost the same time, Jeffrey Brodsky, now the Avinoff Professor of Biological Sciences at Pitt, reported that the proteasome played a key role in disposal of the mutant A1AT protein in yeast cells. By manipulating genes in yeast, Brodsky made a powerful case for the proteasomal pathway.

Evidence was mounting: Others were also finding misshapen ER proteins could be degraded in the cytoplasm. Yet when Perlmutter first tried to report his findings, he encountered a great deal of skepticism. His observations ran counter to the then-prevailing notion that an ER protein would be taken care of by the ER exclusively.

"No one remembers now how heretical that finding was back then. But, it was a bear getting that paper published because no one wanted to touch it," he says.

Brodsky's team had a similar experience. He reports that he and his coauthors were so nervous about their finding that they omitted it from the initial draft of the paper. They only put it back in response to one reviewer's questions.

"The overwhelming, prevailing belief at the time was that the mechanism for getting rid of [such] unwanted or defective proteins resides entirely in the endoplasmic reticulum. However, our data showed that misshaped proteins were somehow getting out of the endoplasmic reticulum and being degraded in the cytoplasm of the cell. It was both exciting and scary at the same time," Brodsky says.

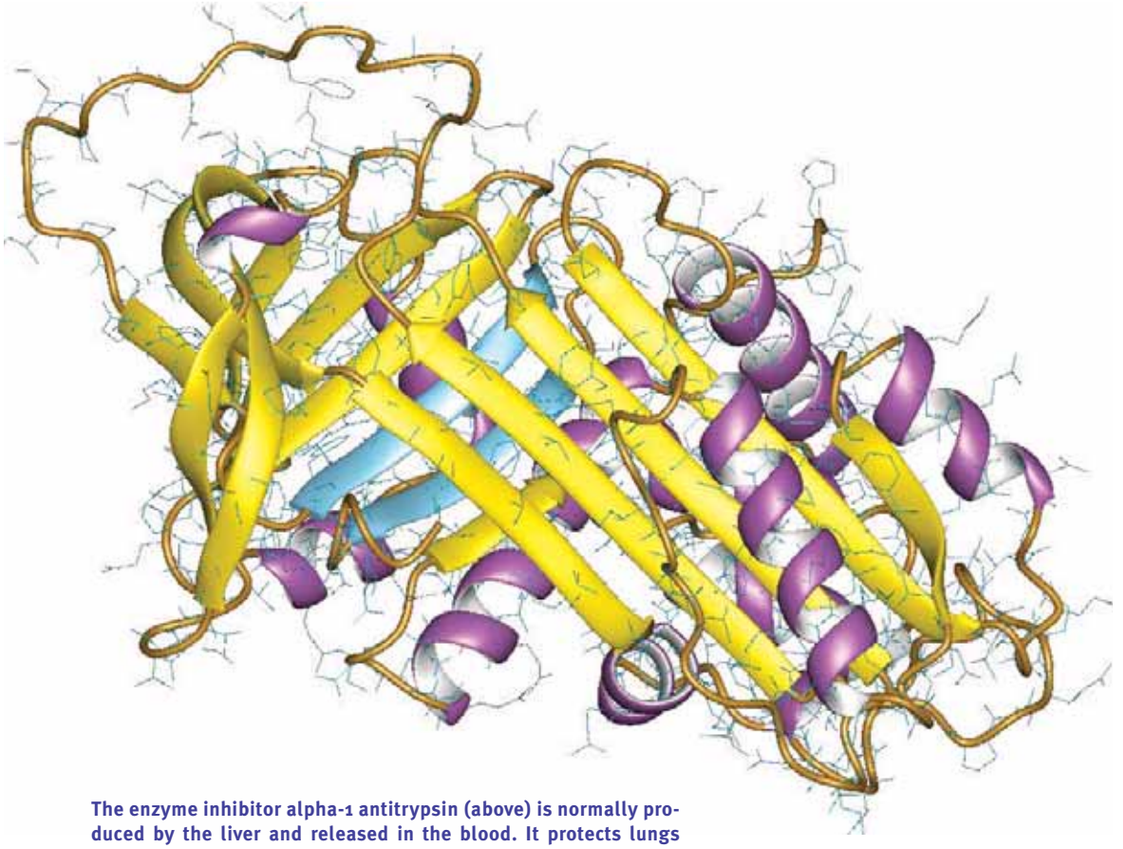
"It was heretical at the time. Now it's dogma," says Perlmutter.

Just as Alzheimer, Nissl, and Kraepelin helped launch a new field of research, Perlmutter and Brodsky were contributing to a new area of investigation into how mutant proteins were degraded in the cytoplasm of the cell by the proteasome.

In 1998, Perlmutter and Brodsky finally got the chance to meet and compare notes when Brodsky visited Perlmutter's lab in St. Louis as part of a grant review team. Although they initially viewed each other as potential rivals, they soon recognized they could complement each other. Perlmutter had the experience treating people that Brodsky knew would be critical in someday bringing his laboratory findings to the clinic. Brodsky had the in-depth understanding of cell and molecular biology that Perlmutter needed to fully comprehend the mechanisms for degrading proteins in the cell. Perlmutter works with mammalian cell systems and models. Brodsky works with yeast. The synergy was palpable to each.

A year later, they met again at a scientific meeting. At a tavern, Perlmutter told Brodsky he was considering coming to Pitt. Brodsky encouraged him, and they began a

"No one remembers how heretical that finding was back then. But, it was a bear getting that paper published because no one wanted to touch it."



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The enzyme inhibitor alpha-1 antitrypsin (above) is normally produced by the liver and released in the blood. It protects lungs from inflammation caused by irritants like tobacco smoke. When it's missing in the body, the result can be emphysema. In some patients who lack the inhibitor, usually children, proteins aggregate in the liver and cause severe damage.

collaboration, and friendship, that continues to this day.

But first, another surprise was in store. Just before Perlmutter joined the Pitt faculty in 2000, his lab implicated a little-known process called autophagy in the cytoplasm's disposal system for mutant proteins.

Before this, most cell biologists believed autophagy was active only under stressful conditions, such as when cells are starving. The word means "self eating" and refers to the process cells use to consume and recycle structures in the cell when deprived of nutrients. Perlmutter was among the first to demonstrate that it might be active under normal conditions.

By 2006, both Perlmutter's and Brodsky's labs independently showed—through entirely different approaches—that autophagy degraded A1AT. At low levels, the defective protein was degraded by the proteasomal pathway. However, when they turned up the production of the defective protein to a very high level, it was degraded by autophagy.

They also demonstrated, says Perlmutter, "that cells lacking a normal autophagic response are susceptible to greater aggregation when they are exposed to too much of the mutated protein."

Autophagy seems to be the preferred pathway for cells to degrade misfolded and other defective proteins that tend to form into aggregates. Perlmutter now believes subtle defects in autophagic response could be among the processes that cause liver damage in 10 percent of patients with A1AT deficiency. He and Brodsky are searching for compounds that might restore this response in A1AT deficiency and other protein aggregate diseases.

To find such agents, they've enlisted the staff at the Molecular Libraries Screening Center at Pitt. This high-throughput center allows them to test thousands of compounds at once.

Perlmutter has also enlisted the help of a worm. Or more precisely, with Gary Silverman, Pitt professor of pediatrics, and Stephen Pak, a research assistant professor of pediatrics in the Silverman lab, he is developing a worm model of A1AT deficiency that develops protein aggregates. They are testing promising compounds to see if any degrade the aggregates without hurting the worms.

Although preliminary, Perlmutter says the results are promising. A man who chooses his words carefully, the 54-year-old Perlmutter is barely able to contain his enthusiasm when talking about the potential impact of his current work with Brodsky and Silverman—not only for A1AT deficiency: "We're cautiously optimistic about our chances of finding some interesting compounds that will have application to a number of protein aggregate diseases," he says.

Stimulating autophagy to chew up bad proteins in worms is one thing; doing it in people is something entirely different. For starters, worms don't have a blood-brain barrier, a membrane that controls the passage of substances from the blood into the central nervous system in humans. Countless researchers have been stymied in their efforts to develop treatments for diseases of the brain because the blood-brain barrier prevents entry to many large molecules.

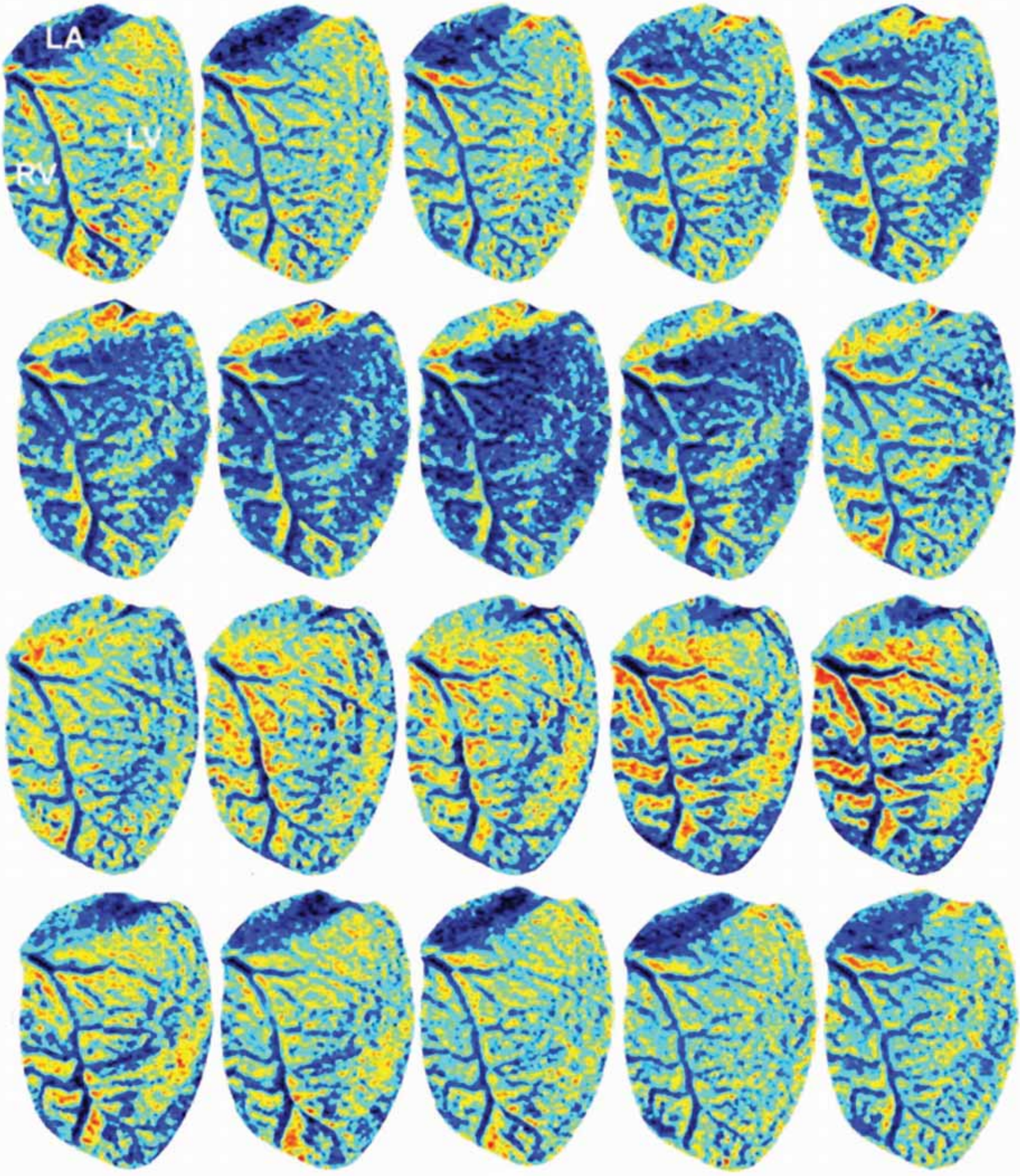
Autophagy itself could present a problem. When autophagic activity is especially high, it induces cell death. So attempts to boost it could be risky.

These problems are surmountable, Brodsky and Perlmutter believe. They are screening for molecules that are small enough to pass through the blood-brain barrier. In addition, Brodsky notes, you can stimulate autophagy without going overboard:

"We have evidence that autophagy can be turned up slightly without causing cellular damage. Ultimately, however, the most effective approach to reversing or preventing protein aggregation in cells may involve treating these diseases much the way AIDS is treated today. A multipronged approach that combines therapies and fine-tunes them to the particular condition may be optimal."

Speaking with Brodsky and Perlmutter, it's easy to think that effective therapies are around the corner. It seems, at least, that if scientists keep collaborating this productively, we won't need to wait another century to find worthwhile approaches to treating protein aggregate diseases. The Brodsky/Perlmutter and Alzheimer/Nissl teams have, in a sense, mimicked the rogue proteins making up that "peculiar material"—they've shown that by banding together, they are a force to be reckoned with.

"I've always found that science works better when people combine their collective talents," says Perlmutter. ■


LA
LV
RV

A PEEK AT HOW AN ARRHYTHMIA IS WIRED

BY CHUCK STARESINIC

TO LIVE AND DYE

It's easy to picture the human heart as a pump. Children readily grasp this concept when introduced to it in school. Most will never forget this basic fact of anatomy and physiology, though they might never learn what the liver does.

But the purpose and mechanics of this pump were not always so obvious. Galen theorized in the second century that venous blood originated in the liver and arterial blood in the heart. He suggested that blood flowed from those organs to all of the body's parts, where it was consumed. This view prevailed until the early 1600s, around the time when an English physician named William Harvey met a man who, as a child, fell from his horse and wounded his chest. Though he recovered, the wound never closed properly. Harvey inquired about the old injury, and the man promptly removed a plate affixed to his chest, revealing what Harvey described as "a vast hole." The physician reached in. He later wrote that he "perceived a certain fleshy part sticking out, which was driven in and out by a reciprocal motion, whereupon I gently handled it in my hand."

Harvey had been told it was the young man's lung that could be observed moving within his chest. The doctor was skeptical, however, so he placed one hand on the man's wrist to measure his pulse as he

Few scientists really understand the electrical system that keeps our hearts ticking reliably. But Guy Salama probes why fatal arrhythmias happen by mapping voltage changes in the heart. LEFT: This series shows a single cardiac cycle of a beating mouse heart. A genetically coded protein reveals changing concentrations of positively charged calcium ions. (Red shows the highest concentrations; dark blue the lowest.) Mapping calcium ions is a way of tracking the changing polarity of heart cells that occurs with each beat.

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reached inside his chest with the other. He noted the synchrony. He carefully watched the man inhale and exhale and measured his breaths against the pulsing of the flesh he held in his hand. He concluded that he was holding the man's heart through a thin layer of skin that had grown within the wound.

Harvey is often remembered as the discoverer of blood circulation. (The Syrian physician Ibn Al Nafis described the circulatory system 400 years earlier, but his text was not rediscovered until the 20th century.) Humanity has now had several hundred years to get used to the rather mechanistic but accurate notion of the heart as a hollow, blood-filled pump in a circular plumbing system.

The electrophysiology of the heart is a different story. The notion of the heart as an electrical organ is newer and less intuitive. It also suggests that your heart has some affinity with your toaster, and that's not really the case.

In 1856, two German researchers dissecting a frog accidentally let the sciatic nerve fall across the frog's heart, which was beating. The result was similar to what you might get if your electrician inadvertently crossed two live wires—say, for the porch light and the doorbell. Ring the doorbell and the porch light turns on. In this case, the frog's leg muscles contracted with each beat of the heart, demonstrating that a pulsing signal controlled the beating of the heart and that nerves conducted such signals.

We've learned since that power surges and other disruptions of the electrical signals in the heart can mean trouble. Yet few understand this vital electrical system in real detail.

Guy Salama, who was born in Egypt and moved to France when he was 12, came to the field of biophysics with a chip on his shoulder. This was in the 1970s at the University of Pennsylvania, where he was working on a PhD in physics. "I was a solid-state physicist working on superconductivity," he says, as a way of explaining why he was so cocksure that physics was real science and anything involving living organisms was a bit, well, fluffy.

"It's not even science," Salama says, jokingly, three decades into a productive career as a biophysicist, the past 15 years in the University of Pittsburgh's Department of Cell Biology and Physiology, where he is a professor. "Needless to say, I can't even figure out the other science now."

Salama's onetime mentor in Penn's physics department, Alan Heeger, would go on to win the Nobel Prize in Chemistry. Salama, however, switched mentors and switched fields as a student, bringing a physicist's mindset to the study of the beating heart. Back then, studying the electrophysiology of the human heart was mostly limited to tools like the electrocardiogram or echocardiogram, which record the voltage changes of large regions of heart tissue as they occur with each cycle of muscle contraction and recovery. What if it were possible to record voltage at the cellular level? Could we learn how electrical signals travel through the entire heart—billions of cells that contract in concert billions of times without fail?

And why would it matter? Revealing this basic electrophysiology of the heart will inform scientists about deadly forms of arrhythmia—when that steady heartbeat inexplicably loses its way and never recovers.

Scientists like Salama's second PhD mentor, Britton Chance, were interested in measuring voltage changes in outrageously small spaces, such as across the mitochondrial membrane within a living cell. It was possible in the '70s, says Salama, to take an electrode with a half-micron tip and impale a single neuronal cell. But that was a struggle, and how would one monitor thousands of cells to learn about the electrical activity of the entire heart? Biophysicists began to dream of other means.

"Could one imagine having a molecule that would report voltage without impaling the cell?" Salama asks rhetorically. "That was essentially the gold ring."

Making a molecule that reports voltage—now that's science, and it's enough to make even a physicist's heart beat faster.

Salama started with dyes from the photographic industry that changed colors in different environments. In the lab, Salama photographed their changing fluorescence in the beating heart. In 1976, while Salama was still a graduate student, *Science* published his report on the most promising of these dyes—merocyanine 540. The gold ring.

The electrical signal that causes your heart to beat begins in the upper right chamber with a cluster of pacemaker cells. They produce electricity by rapidly changing their electrical charge from negative to positive and back again. The signal spreads like a wave through the cells of both upper chambers, causing them to contract and relax. The signal reaches the lower chambers after a slight delay, which causes them to contract immediately after the upper chambers do. This is your normal heartbeat.

Your heart cells change their charge, or reverse their polarity, by alternately taking in and expelling charged atoms called ions. Positively charged ions are missing electrons, and negatively charged ions have extra electrons. Heart cells are swimming in potassium ions, sodium ions, calcium ions, and other ions. These atoms surge in and out of your cells with each beat. They enter and exit through pores called ion channels—large proteins that straddle cell membranes like countless little automated security checkpoints on the perimeter of a stadium. Each type of channel permits the passage of only one type of ion. Some channels allow ions to flow across the cell membrane at rates of 10 million per second with error rates of only 1 in 1,000.

This is the cellular traffic that Salama began to spy on with voltage-sensitive dyes in the mid-1970s; it has kept him occupied ever since.

What he has uncovered about the wiring and cell-to-cell conduction system of the heart can fill books. Yet, he says, "Every time I try to elucidate something new and come to an epiphany that I understand how things work, I discover new things that make me realize that I understand so little." So he continues to make better dyes and to devise better ways to use them.

Salama's lab is a small, windowless room in Pitt's Thomas E. Starzl Biomedical Science Tower. During an experiment, researchers switch off the overhead lights. The only illumination comes from a bright green bulb and a nearby computer screen. The intense green glow—from a 100-watt bulb—shines on a transparent plastic box containing clear fluid and a mass of tissue excised from a rabbit. A sort of lid, also transparent, sits askew across the middle of the box, leaving an opening at either end for tubes, catheters, and electrodes. Catheters deliver nutrient-rich fluid to keep the tissue oxygenated and moist. The box holds the rabbit's central nervous system and heart, with the latter pressed firmly against the underside of the lid and beating steadily. It has been infused with the latest version of Salama's voltage-sensitive dye, and it will continue beating for several hours this way.

Two cameras sit permanently mounted above the beating heart, and they are focused on this plane of visible heart tissue pressed against the underside of the transparent lid. The scientists take high-speed photos of the heart.

The changing fluorescence is not visible to the naked eye. However, the optical imaging system designed by Salama, expertly built and improved upon by Pitt's electricians and machinists, cap-

Such a map would be an enormous step forward in learning exactly what goes wrong to create arrhythmias.

tures the images every few milliseconds.

Few places in the world and few people can carry out this sort of work. Most have some connection to Salama.

Pitt has shared the specialized technology and expertise coming out of Salama's lab with other researchers in the field.

"Our machine shop made five or six units," says Salama, and they are in labs throughout the country.

When switched on, the overhead lights reveal electrical components that resemble stereo receivers and amplifiers. These transmit electrical signals through tiny wires clamped to individual nerve bundles that lead to the heart. To start an experiment, a researcher turns the dial and stimulates a nerve. The rabbit's heart rate increases accordingly, just as yours does as you walk up a steep hill or when you became frightened and experience a spike of adrenaline. When the researcher cuts the electrical stimulation, the heart rate slowly returns to baseline. Salama's cameras capture the entire event in the changing concentration of calcium ions—a strong indicator of voltage—and in the overall voltage changes in very precise local environments. The voltage maps and stop-action movies he creates with this information show the electrical signal moving across the heart as a wave.

Using this technology, Salama has demonstrated how a myocardial infarction—a heart attack that results in a mass of dead tissue in the heart—creates a barrier to this wave. When it encounters the barrier, the wave can split into two, potentially setting off an arrhythmia. The heart might survive these extra beats—there's a period between beats when waves seem to die off rather than propagate. Or the irregular rhythm could set off a chain reaction of continuing uncontrolled and uncoordinated beats. This is fibrillation, the sight of which has been described as a heart writhing like a can of worms.

"Guy sort of sits astride two different disciplines," says Michael Kotlikoff, professor and chair of biomedical sciences at Cornell University's College of Veterinary Medicine.

"He's very unusual in that he's a physicist and a biomedical engineer on one side and a biologist on the other … a superb cardiac physiologist and also a superb optical physicist."

Kotlikoff and Salama are collaborating on another novel means of imaging a beating heart in the lab. Kotlikoff's lab genetically engineered a mouse to express a protein that fluoresces in the presence of calcium. With Salama's imaging expertise, the researchers are able to observe the movement of calcium ions in the heart of a living animal—ions that change the polarity of heart cells as they move in an out of the cell.

As the combined work of these friends of Salama advances, cardiologists may one day be able to identify more precisely who is at risk for experiencing a fatal arrhythmia, know why they are at risk today more than they were last week, and take steps to reduce that risk.

Salama also intends to find out the difference between an arrhythmia that your heart can handle and one that is life threatening.

Many heart attacks are mechanical malfunctions of the pump that result from blocked vessels and necrotic tissue. Salama and his colleagues have, through calcium mapping, identified purely electrical malfunctions of the heart that lead to arrhythmias.

These actually happen all the time, and the heart usually has no problem with them.

Yet, sometimes, they become a big problem, perhaps because of genetic mutations in the ion channels. A fraction of the people who take various drugs that affect the behavior of the ion channels can also experience problems. Essentially, these hearts develop a prolonged interval during which the cells become depolarized—that is, they accumulate a positive charge at a time when the cell usually has a negative charge. The heart then acts like an overheated circuit, because it has more electrical juice than it can handle. The cells overload and spawn spontaneous extra beats. Drugs that may contribute to this include methadone and certain antibiotics and antiarrhythmics. But the good news is that Salama's discoveries may point the way to lessening the risk of arrhythmia in people who take such medications or who have a genetic predisposition to these electrical disasters.

Back when Salama was a grad student querying the photographic industry for voltage-sensitive dyes, others were exploring similar questions. One was Alan Waggoner, a young chemist at Yale University. He was part of a group making dyes by cooking, combining, and distilling chemical compounds to fashion custom molecules. Today, he's a molecular craftsman extraordinaire in his own right, known for cooking up dyes that can make the essential and minuscule operations of cells visible to mere mortals. By coincidence, Waggoner and Salama both have been in Pittsburgh for some years now, Waggoner at Carnegie Mellon University's Molecular Biosensor and Imaging Center, which he directs, and Salama at Pitt. For the past four years, it has been possible to find them at opposite ends of a conference table as they collaborate on the next generation of dyes.

Waggoner is the synthesizer—the dyes are cooked and created in his lab. This willowy, laid-back scientist with a white beard might be seen with an unlit, partially chomped cigar lying on a table in front of him. Salama is the implementer—his lab takes the dyes and puts them through their paces in beating hearts. His salt-and-pepper beard is as meticulously trimmed as Waggoner's is shaggy.

In 2006, these two, with colleagues, published a description of seven new dyes—the Pittsburgh Dyes, as they call them—in the *Journal of Membrane Biology*. Salama and Waggoner hope that these dyes will help them achieve a first: 3-D imaging of voltage changes in the heart.

The fluorescence of these dyes is several orders of magnitude greater than those Salama started with long ago. With the right imaging technology—currently being developed and tested in Salama's lab—it should be possible to study voltage changes deep within the heart tissue as well as on its surface.

With this information, says Salama, he would like to construct a 3-D map of the electrophysiology of the heart—a map that would show the electrical and chemical changes that sweep through all layers of the heart with each beat. Such a map would be an enormous step forward in learning exactly what goes wrong to create arrhythmias, Salama believes. He points out that today cardiologists often know when a person is at risk for an arrhythmia.

"What they don't know is why did this person experience a fatal arrhythmia on Wednesday and not Tuesday? What pattern of ion channels must we pay attention to in order to understand the transition between vulnerable and not vulnerable?"

"It's discovery science, too," Waggoner chimes in. "It's like a game. ... Could we make this tool useful? Can we make it useful for studying heart disease? Those are big challenges—that makes it interesting! And there are very high stakes if you're successful." ■



A MOST UNWELCOME VISITOR

STUDENTS SHAPED BY WAR

BY REID R. FRAZIER

PHOTOGRAPHY BY CAMI MESA

One walked hundreds of miles to safety, fleeing men with assault rifles and machetes. Another drove in the middle of the night over roads pocked by mortars, traveling to a city where rockets were falling. Both of their paths led them to Pittsburgh, where they dug in this fall to start their careers in medicine and medical research. Shoghag Panjarian-Balian, an interdisciplinary biomedical PhD student from Beirut, Lebanon, and Jean-Claude Rwigema, a first-year med student from Rwanda, have both learned to live along the hard contours of war. They spoke with *Pitt Med* about growing up amid violence.

When the violence escalated between Hutus and Tutsis in Rwanda in 1994, millions fled for their lives. Among those fleeing were three boys, the sons of a businessman and Hutu politician. The middle son, Jean-Claude Rwigema, was 13 years old. His brothers, Jean-Pierre and Jean-Paul were 16 and 10, respectively. He'd make a great doctor someday, people always told the 13-year-old Rwigema. But in 1994, all that was on his mind was survival."The killing started in the city," says Rwigema, now 26 and in his first year of medical school at Pitt. "So we started walking. We just walked a really long time. My parents were trapped in Kigali. We thought they were dead for three months."

The Hutu militias turned their weapons, including machetes, on the country's minority Tutsis and many Hutus while the international community stood on the sidelines. Bill Clinton has called the United States' failure to act to prevent the genocide in Rwanda his worst foreign policy mistake as president. More than 800,000 died in three months. The Rwigema boys found shelter wherever they could. "We didn't stay in any one place for [long]," he says. Rwigema initially brought a bag of his belongings. Quickly, he learned to travel light. "After a while, I learned to just leave things behind." The boys often traveled with groups of other refugees, Hutus and Tutsis alike. All around them were signs of danger: deserted towns, reports of gunfire, corpses on the roadside. The boys were perhaps too young to understand the danger they were in, Rwigema now says.

After several weeks of walking as many as 20 miles a day, the boys made it to a safe section of the country. When the fighting ended, Rwigema heard over the radio that his father, Pierre-Celestin Rwigema, had been named the country's minister of education. That was the first proof that his father was alive. The boys were elated.

"Sometimes there are moments that you can't explain. When I think of my life, it's a little like this," the med student says, tracing a sine wave in the air with his finger, representing extreme highs and lows.

His parents later described to him how they were among the 1,000 refugees protected by the manager of the Hôtel des Mille Collines, the real-life "Hotel Rwanda" made famous by the 2004 Hollywood release. The hotel's manager, Paul Rusesabagina, had bribed generals and others with liquor and money to keep those in his shelter safe. In 1995, Pierre-Celestin Rwigema was named the country's prime minister in a Tutsi-led unity government. The next year, Jean-Claude Rwigema went to Pretoria, South Africa, for high school. There he lived in an apartment with his younger brother and learned English. Rwigema eventually landed a scholarship at La Roche College in Pittsburgh's North Hills. He later transferred as an undergraduate to Pitt, studying chemical engineering and becoming a student researcher at the Pitt-UPMC McGowan Institute for Regenerative Medicine.



Rwigema

Meanwhile, Rwanda's poisoned political climate forced his family to flee their home country. Pierre-Celestin Rwigema resigned as prime minister in 2000 after the ascendance of a rival politician, Paul Kagame, the country's current president. Jean-Claude Rwigema says his father was threatened and forced to flee. The family was granted political asylum in the United States and has settled in California.

Rwigema says it would be difficult for anyone in his family to go back to Rwanda because they will likely be targets. "I'm attached to my father's history," he says. Yet he still thinks of returning to Rwanda someday, maybe to start a free clinic.

"Everybody used to say I would be a good doctor. In a way, I kind of hated it because they were choosing a profession for me. Later on, I kind of figured out it was my true calling."

He decided on medicine as a career after working as a home health provider in the Pittsburgh area. "One patient in particular, he had [muscular dystrophy]. We would just talk while he did his exercises. I just enjoyed being there. I liked taking care of him." The two talked movies, sports, PlayStation, anything at all. When Rwigema left the job, the patient's mother wrote to tell him he was the best aide her son ever had. "It's almost priceless when you see somebody is grateful for you helping them," he now says. "That's when I realized I belonged to this profession."

The young man with large, searching eyes and a quick smile says he has a heavy burden to carry.

"I feel a responsibility to serve. I feel like I owe my country.

"How many people make it out of Rwanda and get to go to one of the best medical schools in the country?"



Panjarian-Balian

Shoghag Panjarian-Balian and Alec Balian went to Bangkok, Thailand, for their honeymoon last summer, a few days after getting married in their home city of Beirut. Before heading out to sightsee one morning, Panjarian-Balian checked the television news. She was stunned to see that Beirut was under attack. Israel and Hezbollah were trading mortar fire. The city's airport had been bombed. Much of the country was shut down.

Panjarian-Balian was born in Beirut, a few years into Lebanon's 15-year civil war, which broke out in 1975. Back then, she and her neighbors saw fighting between a dizzying array of factions and militias: Syrians, Palestinians, Israelis, Druze, Shiites, Sunnis, and Christians. Beirut, formerly known as the Paris of the Middle East, had become a war zone. Her apartment building was bombed three times. The last time was in 1990, when Panjarian-Balian was 13.

"The bombs came during the day. We came at night and cleaned up. The next day it was bombarded again," she says.

Panjarian-Balian says she didn't pay much attention to which side was responsible for the damage to her home.

"I don't go into the why, the how, the 'What's next?' It was hit. That's it."

Now, war had returned to Beirut, an uninvited guest.

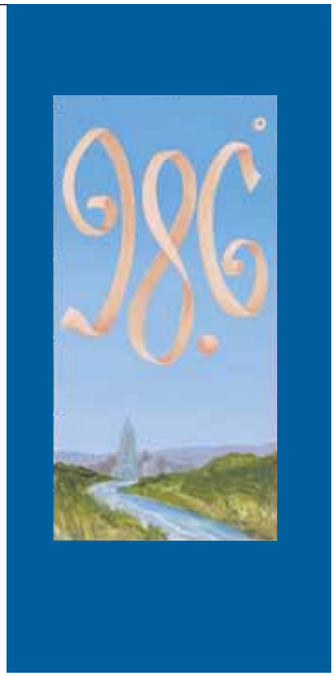
The couple flew back to the Middle East, through Damascus, which is normally a three-hour drive from Beirut. Somehow they found a driver who agreed to take them across the Syria-Lebanon border along a road that had been bombed just days before. Their circuitous route took seven hours. At dawn, they saw that a Lebanese military barracks along the northern coast near Tripoli had been bombed.

"Everyone was leaving the city, leaving the country, and we were the only ones driving towards it," she says. The city she returned to was worse off than she had feared. "We were born in war; we've seen several phases of the war. This time it was different. There was nobody on the roads. Everyone was depressed. Everybody [said], 'This is it—we can't take it anymore.'"

Panjarian-Balian had been planning to come to Pitt for graduate school. After completing a master's degree in physiology at the American University of Beirut, she'd decided to pursue her PhD so she could research cancer and teach. After looking into several programs in the United States, Panjarian-Balian was accepted into the School of Medicine's Interdisciplinary Biomedical Graduate Program. She was supposed to arrive in Pittsburgh in early August, but the war threatened to keep her away. The U.S. embassy in Beirut was busy evacuating thousands of Americans from Lebanon, so she had to go to Damascus to get her visa. There, she was told she might have to wait as long as three months to secure her papers. If Panjarian-Balian didn't make it out by early September, she would have to wait another year to start her studies.

The newlyweds went to the city of Aleppo, a five-hour drive north of Damascus, to stay with a friend while they awaited word on the visa. On Aug. 20, she went to bed but couldn't sleep until 7:30 a.m. Her husband woke her at 9:30. Church bells were ringing. The embassy had called, he said. Her visa was ready. They touched down in Pittsburgh late on a Thursday night. Her first class was Monday morning. ■

People and programs that keep the school healthy and vibrant



CHEMO ON THURSDAYS, WORK ON FRIDAYS

EVEN CANCER CAN'T STOP CANCER RESEARCH

BY KATIE HAMMER

Heidi Browning was both fun and driven. As a girl, she was driven to keep up with her two older brothers. When her aunt presented her with a makeup kit on her 16th birthday, she happily wore its contents as war paint. Later, as a molecular biologist, Browning was driven to contribute to cancer research, even when cancer came for her.

After she earned her PhD at Indiana University in Bloomington, Browning's career took off as though it were powered by rocket fuel. She worked in labs in Zurich, Colorado, and London. She won a postdoctoral fellowship from the World Health Organization's International Agency for Research on Cancer. With 2001 Nobel Prize laureate Paul Nurse, she published in *Nature Cell Biology* on the mechanisms by which cellular proteins transport cargo to specific locations in the cell. She came to Pittsburgh to continue that work as a postdoc in Carnegie Mellon University's Department of Biological Sciences.

It was about that time, in early 2003, that she seemed to lose her pep. While visiting her parents in Florida, Browning and her mother went shopping for dresses in preparation for a friend's wedding in Paris, but it was difficult to find one that fit properly. Sonia Browning thought her daughter's stomach didn't look quite right but didn't say anything. Shortly after she returned to Pittsburgh, Browning went for a checkup, and her physician referred her to an oncologist, who discovered a tumor. The party dress went unused as she traveled to an operating room in Pittsburgh instead of a wedding in Paris. Surgeons removed her ovaries, uterus, and sections of tumor that had spread to her abdominal cavity.

Browning was back at the bench one month after surgery. She had chemotherapy on Thursdays and showed up for work on Fridays. By November of 2003, doctors declared the cancer was in remission, and she moved forward with her work as if she had never slowed down. A couple of months later, Browning came to work as a research associate at the University of Pittsburgh Cancer Institute (UPCI) in the lab of Theresa Whiteside, Pitt professor of pathology and otolaryngology. With Whiteside, Browning was studying exosomes in ovarian cancer. These cellular microvesicles are released from cancerous cells and enter bodily fluids. Whiteside, a PhD, and Browning wanted to uncover the structure and biologic activity of exosomes to understand how they contribute to cancer.

But Browning's cancer returned in March 2004, just a few months after beginning at Pitt. She was 40 years old.

"She probably didn't feel very well for a bit of time, but she was in the lab and working, reading, and talking about her project," Whiteside says.

In April, Browning's neighbor rushed her to the ER when she had difficulty breathing deeply—her chest was filling up with fluid. Her parents came from Florida to be with her. Browning questioned her doctors about when she could get back to the lab.

A few days before her death on June 1, Browning requested that her assets become a gift to help others investigate ovarian cancer when she could not. Her parents established the Heidi L. Browning Endowed Ovarian Cancer Research Scholars Fund of $250,000, which will be used to recruit, train, and provide support for talented investigators to focus on ovarian cancer in UPCI labs. ■



COURTESY BROWNING FAMILY

Browning in 2000

BOOSTER SHOTS

Arnold Palmer played professional golf for more than a half century after he burst onto the scene by winning the U.S. Amateur Championship in 1954. This quiet, charismatic golfer from Latrobe, Pa., is now positioned to make a big mark in the cancer prevention arena. Palmer, who underwent surgery for prostate cancer in 1997 and whose first wife died in 1999 while being treated for ovarian cancer, has created the Arnold Palmer Endowed Chair in Cancer Prevention at UPCI. A gift of $2 million from the Arnold Palmer 2003 Charitable Trust enabled the recruitment of **Emanuela Taioli**, the first to hold the chair. Taioli, a Pitt MD/PhD professor of hematology and oncology and director of UPCI's Division of Cancer Prevention and Population Science, studies environmental and genetic causes of cancer in hopes of developing a model for prevention.

Helen Katz was always a big Pitt booster, supporting programs from the arts to the health sciences. The School of Medicine held a special place in her heart because both her brother, **Robert Blockstein** (MD '56), and her late husband, **Louis Katz** (MD '41), were grads. After Helen Katz died last year, the University learned that she had willed $100,000 to a medical scholarship fund in her husband's name and $150,000 to support diabetes research at Pitt.

—Chuck Staresinic

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



CLASS NOTES

'60s

In the world of clinical trials, the status quo was shaken up a bit a few years ago, when University of Pittsburgh Trustee **Catherine DeAngelis** (MD '69), the editor-in-chief of the *Journal of the American Medical Association*, and others on the International Committee of Medical Journal Editors (ICMJE) jointly decided that they would not publish reports of trials that withheld information from public view and failed to register with a public database. Federal law had long mandated that trials be registered in this way, but the law had never been enforced. DeAngelis and the ICMJE had, in effect, declared themselves the enforcers of this rule by pledging to deny publication to studies that came up short in the disclosure department. A recent *New England Journal of Medicine* editorial pointed out that only 8 percent of the nearly 3,000 pharmaceutical-industry registrations in the clinical trials registry from 2006 were missing outcomes information, compared to 26 percent of the more than 5,000 registrations before 2006.

'80s

Barbara Mittleman spent several years organizing youth programs in European community centers before switching gears and attending medical school. Mittleman (MD '86, Internal Medicine Resident '89, Rheumatology Fellow '91) is the director of the program on public-private partnerships at the National Institutes of Health (NIH), working to leverage the resources and expertise of the NIH in synergy with a wide variety of for-profit and not-for-profit partners. Currently, she is the principal investigator on a large research project looking at health disparities in rheumatic diseases. The study is sponsored by the National Institute of Arthritis and Musculoskeletal and Skin Diseases, and it is based out of a novel community-based research clinic in Washington, D.C., that cares for many underserved and minority patients. She also chairs an international effort to identify and validate biomarkers for systemic lupus erythematosus.

The first patient **Rosalind Ramsey-Goldman** (Rheumatology Fellow '86) cared for during her fellowship was pregnant—her fetus had a slow heartbeat caused by an antibody in the mother's blood. The mother had lupus. Prior to the 1980s, women with lupus were told it was dangerous to get pregnant. This baby had a heart condition, but its full-term delivery and others like it demonstrated that women with lupus could conceive and carry babies with proper monitoring and counseling. Ramsey-Goldman, who also holds an MPH and a PhD from Pitt's Graduate School of Public Health, is now professor of medicine at Northwestern University. For the past 20 years, she has probed the genetics of lupus, hoping that enhanced understanding will lead to a therapy that controls symptoms of the disease with fewer side effects and less toxicity than currently available treatments like chemotherapy.

During his internal medicine rotation as a Pitt med student, **Alan Remaley** (MD/PhD '87) was asked a question about Tangier disease that he didn't know how to answer. He went to the library to read about it, and that was when he learned about the NIH lab where Tangier disease was first described in 1961. The genetic disorder can cause people to have low levels of good cholesterol (HDL), orange tonsils, and an enlarged liver and spleen. Remaley, section chief of the lipoprotein metabolism section at the National Heart, Lung, and Blood Institute, now studies Tangier disease at the same lab he read about in medical school. In 1999, Remaley and others discovered that the genetic defect was in a transporter called ABCA1 that helps rid cells of excess cholesterol. Those with the disease experience cholesterol buildup in the tonsils and other organs. Now Remaley attempts to create synthetic peptides mimicking the proteins of HDL in hopes of using them to remove bad cholesterol or to act as antioxidants.

When most of **Dave Shulkin's** (Internal Medicine Resident '89, Internal Medicine Fellow '90) colleagues were doing their rotations in oncology or cardiology, he was completing his at Blue Cross of Western Pennsylvania. "At that point, physicians really didn't have an administrative track, so having an internal medi-

GEOFFREY ROBB

MICROSURGERY AND HERDING CATS



Robb

Geoffrey Robb was an unlikely candidate for the residency he coveted at Pitt. He had excellent qualifications, including four years as a head and neck surgeon in the U.S. Navy. But the military was the source of his obstacles, too. Each year, only one navy surgeon was permitted to train outside the military. In 1982, Robb was the alternate. He came out on top the following year, but residency positions were filled almost a year earlier than the navy gave him permission to apply.

His target was plastic surgery, and Pitt had one of the top two programs in the country, he says. Plastic surgery was the only way to get training in microsurgery—a delicate specialty that involves transplanting composite tissue (any combination of muscle, skin, bone, and fat) complete with its blood supply. Robb had seen disfiguring cancer as a head and neck surgeon, and microsurgery was the set of skills that would allow him to, for example, reconstruct a cancer patient's jaw.

cine resident come [to Pitt] and want to do something in administrative medicine was a pretty offbeat type of thing," Shulkin says. He believes the support he received from Pitt was instrumental in being able to launch his career. Shulkin, president and chief executive officer of Beth Israel Medical Center in New York City, talks passionately about understanding and implementing ways for hospitals to improve quality and safety. He also focuses on training future leaders—he created a program at Beth Israel specifically for physicians who want to become physician executives.

'90s

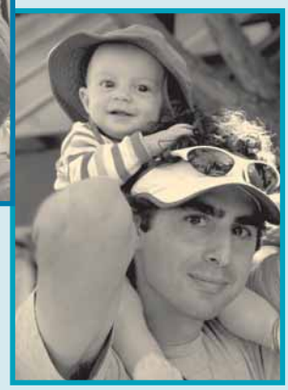
Jamie Calabrese (MD '91), medical director of The Children's Institute of Pittsburgh, codirects a new pediatric cardiac recovery program for children who require heart surgery. She and her colleagues are trying to improve the quality of life for these children and their families through neurodevelopmental assessments before and after surgery. Calabrese hopes this program (the only one like it in the world, she says) will redefine the standard of care for kids with heart disease. Another new venture at The Children's Institute is a treatment program for chronic pain for children with reflex neurovascular dystrophy; these children's muscles appear to be oversensitized, and they have pain out of proportion to their original injuries. The therapy includes overexercising them through five to six hours of physical and occupational therapy per day and supporting that with a therapy program to learn pain control methods. Calabrese was recently nominated to the American Academy of Pediatrics Committee on Hospital Care (which determines standards of care for hospitalized children). She hopes to elevate the profile of rehabilitation in the academy.

Aviva Abosch (MD/PhD '93) implants silicon-coated electrodes deep into the brains of her patients with essential tremor, Parkinson's disease, and dystonia—a rare movement disorder. (You can picture the symptoms of dystonia as trying to bend your arm if your biceps and triceps contract at the same time. Imagine that type of problem throughout the body.) These implanted "deep brain stimulators" cause muscle tremors to abate and movement to return to normal. It is uncertain exactly how the electrical stimulation resets the brain activity, but if the stimulator is turned off, the motor symptoms return. Abosch, assistant professor of neurosurgery and director of epilepsy and functional stereotactic neurosurgery at the University of Minnesota, plans to figure out how to fine-tune the electrical stimulation for a patient's disease—currently the stimulator must be on 24 hours a day. With this technology, she envisions helping patients with severe dystonia by stopping their seizures with surgery. "You can potentially give them independence and allow them to move easily and hold down jobs," she says.

If it aggravated your chronic pain, would you stick with a physical therapy program designed to benefit you in the long-term? In her research, **Akiko Okifuji** (Clinical Psychology Intern '93, Psychiatry Fellow '96) challenges sedentary fibromyalgia patients to do that, with the help of a behavioral preparation program to keep them motivated. Okifuji, associate professor of anesthesiology at the University of Utah, and her team are trying to understand the pathology of chronic pain caused by fibromyalgia and discover a successful treatment. Okifuji sees patients in the university's pain management center.

Bert O'Malley Jr. (Head and Neck Oncology and Cranial Base Surgery Fellow '95) codeveloped transoral robotic surgery (TORS) with Gregory Weinstein at the University of Pennsylvania. The system is made up of a mechanical robot with four arms—one arm has an endoscope to view the site more closely than human vision allows, and the others have instruments that allow the surgeons to operate in tight spaces with "miniature hands." O'Malley, professor and chair in the Department of Otorhinolaryngology at Penn, and vice chair Weinstein have together removed head and neck cancers through the mouth, developing new techniques and procedures as they go. The reduction in surgical time (one to two hours for TORS versus six to 12 for standard open surgery), smaller incisions, fewer complications, and reduced bleeding are encouraging them to push further, developing instrumentation and techniques for skull-base surgeries (behind and above the eyes to the brain). Because these are new techniques not yet FDA-approved or available at other centers, all of these procedures are part of a clinical trial.





ABOVE: **Abosch,** RIGHT: **Sorce with son, Colton**

'00s

One man's kidney was destroyed by a gunshot. That same night another man punctured his bladder in a car accident. Both men ended up in the operating room when **Damian Sorce** (MD '02), a third-year urology resident at the University of Colorado, was on call. These rare urologic traumas were valuable learning experiences for the doctor (and ultimately both patients recovered). Sorce spent two years in general surgery residency at Cornell University. His interest in urology began there. It really took off when he observed urologists performing donor nephrectomies—removing a kidney from a living donor—then assisted the general surgeons as they transplanted the organ to a patient. Urology has allowed Sorce to pursue his dream of becoming a surgeon, he says, while offering a work schedule that enables him to spend lots of time with his young son.

Katie Kwiatkowski (MD '04) chose a residency in internal medicine in large part because of her participation in the Women's Health Area of Concentration as a Pitt med student. Kwiatkowski realized during her outpatient clinic that she gravitated toward the patients with psychological problems and wished she could do more to help them. Today you can find her at Allegheny General Hospital as a third-year psychiatry resident.

—Katie Hammer & Chuck Staresinic

When someone backed out of Pitt's program at the last minute, Robb (Plastic Surgery Resident '85, Microsurgical and Hand Surgery Fellow '86) was accepted. His last-minute entrance has more than panned out. For 10 years, he has been professor and chair of plastic surgery at the University of Texas M.D. Anderson Cancer Center in Houston, which is among the largest plastic surgery groups at any cancer center in the world. All 14 faculty surgeons are experts in microsurgical reconstruction to restore form and function to cancer patients.

In the operating room, Robb specializes in breast, head, and neck reconstruction. He describes his administrative specialty as "herding cats." The latest example of his herding skills: The tissue engineering initiative he and others have long fostered in M.D. Anderson's plastic surgery department has taken on a life of its own, becoming a fully fledged Department of Bioengineering. *—Chuck Staresinic*

THE WAY WE ARE
CLASS OF '82

Carol Krupski (MD '82, Res '85), likes to think that the Class of 1982 was the "most in shape" class of its era. Back when the curriculum had students in the classroom for two straight years before they saw any patients, Krupski encouraged more than half of her classmates to work out at Trees Hall during their 90-minute lunch break. Krupski now specializes in obstetrics and gynecology and is president of the medical staff at Magee-Womens Hospital of UPMC. And though she can't get into Trees Hall since she gave up her student ID, Krupski says that she continues to work out faithfully, including playing squash, which she learned as a med student with classmate **Dante Landucci**.


Krupski

Landucci (MD '82) lives in Greenville, N.C., where he seems to be collecting titles. He currently has four: assistant clinical professor of medicine at East Carolina University, clinical decision support coordinator for information systems (he is creating integrated medical records for all patients at his hospital), medical director of nutrition support (coordinating IV and tube feeding), and medical director of a LTACH program (long-term acute hospital care for people who need more medical attention than a nursing home and a longer stay than a 30-day hospital visit). The latter three positions are all at Pitt County Memorial Hospital. He is collaborating in research investigating long-term survival of patients who require ventilator support for more than 10 days.


Kukin

April Dworetz (MD '82, Res '85, Fel '86) stayed in Pittsburgh for a pediatrics residency and a pulmonary research fellowship at Children's Hospital of Pittsburgh. She finished her training with a National Institutes of Health fellowship in neonatology at Yale University. She is now a neonatologist and assistant professor of pediatrics at Emory University in Atlanta, Ga. She says she loves taking care of babies, because "they don't answer back." Dworetz investigates some of the parent/infant interactions that can help profoundly ill newborns in the NICU improve faster, go home sooner, and be healthier after they've been discharged.

Marrick Kukin (MD '82) directs the congestive heart failure program at St. Luke's Roosevelt in New York City and is a professor of clinical medicine at Columbia University College of Physicians & Surgeons. His current clinical trial evaluates the effects of beta blocker dosages after placement of a pacemaker in heart-failure patients. Beta blockers have been shown to reduce patients' morbidity and mortality. This study evaluates the combined effects of electrical resynchronization therapy and optimal beta-blocker dosing.

His classmate Krupski may be onto something about that fitness thing. Kukin fondly remembers spirited softball matches during his med school years, as well as the cold pints that followed. *—KH*

WILLIAM F. DONALDSON JR.

MAY 12, 1921 – NOV. 22, 2006


Donaldson

William F. Donaldson Jr. (MD '43, Res '50) started many a Saturday by loading a few of his four children into the car and driving to Children's Hospital of Pittsburgh to do rounds. The orthopaedic surgeon was treating children with scoliosis then. He corrected the curvature of their spines, and he often got to know the children and their families well as they spent a few months in casts at the hospital.

His son, William Donaldson III, played with his dad's patients on those rounds and is now a Pitt associate professor of orthopaedic surgery and of neurological surgery.

After the elder Donaldson died in November, cards and letters began to arrive in the mail. By mid-December, his son estimated there were about 60. Each writer seemed to say the same thing: *You don't know me, but I need to tell you how important your father was.* Most talked about how spinal surgery had dramatically changed their lives when they were children.

Donaldson was medical director of Children's Hospital for 13 years. In retirement, he served on Children's Board of Trustees and was an emeritus trustee of the University of Pittsburgh. He was also a Distinguished Clinical Professor in the med school.

—Chuck Staresinic

EVA ANNE "EV" VOGELEY

JAN. 29, 1950—DEC. 27, 2006


Vogeley

Eva Anne Vogeley, who spent 20 years as an emergency room physician at Children's Hospital of Pittsburgh, died in December. A 1975 graduate of the University of Pittsburgh School of Medicine, Vogeley also earned a law degree from Duquesne University (she took classes at night), and a Master of Divinity from the Pittsburgh Theological Seminary.

She was also a musician and photographer. "She was voraciously interested in everything," says Richard Hurst, her photography teacher at the Pittsburgh Center for the Arts, with whom Vogeley traveled the Rust Belt chronicling industrial decay.

Vogeley chaired the Human Rights Committee at Children's, served on two Institutional Review Board committees, and mentored medical students in research and pediatric emergency care, says colleague Willa Dean Lowery (Res '68).

"In whatever she did, she was guided by a supreme sense of justice and fairness and the right of all people to be treated with decency," Lowery says, recalling the tender manner in which Vogeley treated the harried, worried, and, sometimes, grieving parents of her patients.

—Joe Miksch

IN MEMORIAM

'40s

JOHN ROGERS FRIDAY
MD '43A
NOV. 9, 2006

FRANK M. MATEER
MD '44
NOV. 10, 2006

THOMAS MCHENRY III
MD '44
SEPT. 30, 2006

'50s

RICHARD P. SHAPERA
MD '51
OCT. 18, 2006

ROBERT O. SARVER
MD '53
NOV. 27, 2006

MARCIA S. GLOSSER
MD '55
NOV. 2, 2006

JOSEPH J. POLIDORA
MD '55
NOV. 8, 2006

EDWARD H. SLAGLE
MD '58
OCT. 15, 2006

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TODD WOLYNN ON MOTHER'S MILK

BY HATTIE FLETCHER



Wolynn, shown here with a patient, would like to see more pediatricians learn to help new mothers breast-feed.

When a woman is expecting a baby in America, her name somehow ends up on a list. And while she's knitting booties and painting the nursery, free samples of disposable diapers and baby formula start arriving in the mail. There's often more swag waiting in her hospital room after the birth, such as a diaper bag with more free formula samples.

"That's not by accident," points out Todd Wolynn (MD '92). "There are billions of dollars out there, and they're all aimed at getting kids to use formula because it's a huge moneymaker."

Wolynn, a pediatrician, is unusually well-versed in the economics of breast-feeding. He's also familiar with the obstacles facing women who want to breast-feed—the ubiquity of formula, the sexualization of the breast, and the general loss of a culture in which breast-feeding is the unquestioned norm and mothers, aunts, sisters, and neighbors provide support for new moms.

Wolynn's group practice in Pittsburgh's Greenfield neighborhood goes to great lengths to help breast-feeding mothers. Five doctors (soon to be six) in the practice, including Wolynn, are certified lactation consultants. In August 2006, they opened the Breastfeeding Center of Pittsburgh and hired four nonphysician lactation consultants. As of this January, they operate a freestanding office in Squirrel Hill with room enough to hold classes for 20 to 30 people and two lactation consultation rooms.

It's an unusual model for a pediatric practice. Pediatricians are experts in children, not grown women, and breast-feeding generally falls outside their realm of expertise.

Women who encounter trouble breast-feeding may see a lactation consultant, but this often involves a return to the hospital. The visit is rarely covered by insurance. But all babies should visit the pediatrician in the first days out of the hospital—which is also when most lactation issues must be addressed if mothers are going to breast-feed successfully. So, Wolynn says, it's only natural that pediatricians should help with breast-feeding.

Plus, he says, it's not that hard to make a difference. Wolynn estimates that 75 to 90 percent of the issues that bring women from as far away as Ohio and West Virginia to see him and his partners—who include Albert Wolf (MD '97) and Nancy Brent (Res '82)—are related to the latch where the mother's breast meets the infant's mouth. Many breast-feeding difficulties can be resolved with one visit, while others will require follow-up visits. It's an incredibly fulfilling experience, he says: "Women come in with pain, or significantly distraught, and to be able to show them a couple of little, easy things about how to latch better, and how to tell when the baby is on and nursing well … It's a really cool thing to make such a difference on such an important thing without having to order lab work and get a surgeon or something like that."

Wolynn is also working on a master's degree in medical management at Carnegie Mellon University; his pet project is to develop a breast-feeding business model that could be applied nationally.

"I'm not deluding myself thinking that I'm changing the world," he says. "But if I can help create a model where pediatricians, at least from a business standpoint, aren't afraid to get directly involved … then they may feel more comfortable and can be more supportive of breast-feeding." ■

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LAST WISHES

When Chuck Ward was a city firefighter, he was the first one into the burning building and the last one out, says his wife of 30 years, Dotti Ward. Every day of his retirement, he walked four miles, lifted weights, and played the trumpet for at least two hours. If he heard the U.S. Marines Hymn, the corps veteran stood at attention. Then at 74, Ward's lungs began to fail him. He was diagnosed with idiopathic pulmonary fibrosis (IPF). Doctors don't know why the condition causes lungs to scar and thicken, and most patients don't recover.

In typical Chuck-Ward style, he didn't sit idle on hearing the news. Shortly after he was diagnosed, Ward pulled his wife aside and told her he wanted to donate his lungs for research.

"If I could keep one man from going through what we're going through right now, it would be worth it," he said.

Ward, who died on May 19, 2003, was probably the first patient to donate his lungs for IPF research. To be useful, the lung must be studied within hours after death, which requires a "rapid autopsy." His gift inspired 13 other patients in the UPMC Simmons Center for Interstitial Lung Diseases IPF support group, which he attended faithfully, to do the same. Those gifts have given doctors at Pitt an extraordinary opportunity to delve into the genetics behind IPF.

PHOTO COURTESY DOTTI WARD

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.

PHILADELPHIA-AREA ADMISSIONS RECEPTION
FEBRUARY 22
Hyatt Regency Philadelphia
at Penn's Landing
For information:
412-648-9891
admissions@medschool.pitt.edu

BLACK BAG BALL
FEBRUARY 24
Riverwatch
1501 Smallman St.
Pittsburgh

FISHER LECTURE
FEBRUARY 28
3:30 p.m.
Lecture Room 6, Scaife Hall
Robert A. Weinberg, MD, Speaker
For information:
www.surgery.upmc.edu

HEALTH SCIENCES ALUMNI RECEPTIONS
MARCH 20: Raleigh-Durham, N.C.
MAY 2: Erie, Pa.
For information:
Pat Carver
412-647-5307
cpat@pitt.edu

CHICAGO-AREA ADMISSIONS RECEPTION
APRIL 12
Wyndham Chicago
For information:
412-648-9891
admissions@medschool.pitt.edu

STARZL LECTURE
APRIL 21
10 a.m.
Lecture Room 5, Scaife Hall
Christian P. Larsen, MD, PhD, Speaker
For information:
www.surgery.upmc.edu

PITT MED GOLF OUTING
APRIL 28
8:30 a.m.
Quicksilver Golf Club
Midway, Pa.
For information:
kaufman.matthew
@medstudent.pitt.edu
www.pittmedgolfouting.org
412-648-9090

MEDICAL ALUMNI WEEKEND 2007
MAY 18–20
Reunion Classes:

1947	1952
1957	1962
1967	1972
1977	1982
1987	1992
1997	

SENIOR CLASS LUNCHEON
MAY 18

SCHOLARSHIP APPRECIATION TEA
MAY 18

SCOPE AND SCALPEL
MAY 18 & 19
The Antonian Theater
Carlow University
For information:
www.scopeandscalpel.org

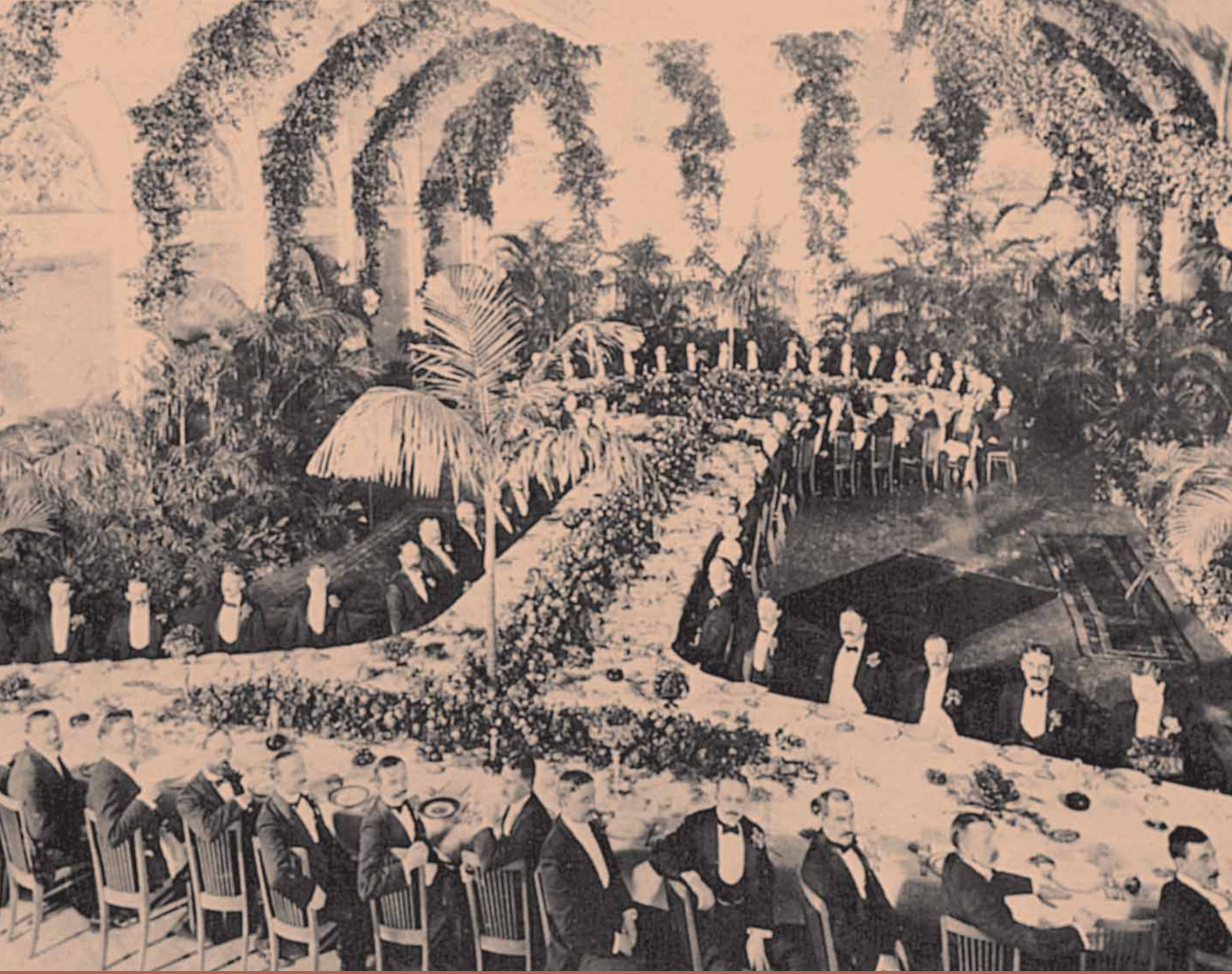
ALUMNI BRUNCH & MED SCHOOL TOUR
MAY 19
10 a.m.
Scaife Hall

REUNION GALA
MAY 19
6 p.m.
Heinz Regional History Center

CLASS OF 2007 COMMENCEMENT
MAY 21
10 a.m.
Carnegie Music Hall

SIMMONS LECTURE
MAY 23
8 a.m.
Room S100A
Starzl Biomedical Science Tower
John C. Alverdy, MD, FACS, Speaker
For information:
www.surgery.upmc.edu

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WHERE'S OUR WAITER?

Don't worry, the good folks who organize your reunions haven't forgotten anything in planning the 2007 Medical Alumni Weekend. Join your mates for the reunion gala, dean's brunch, campus tours, continuing education, and more.

May 18–20, 2007

FOR MORE INFORMATION: 1-877-MED-ALUM, medalum@medschool.pitt.edu
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THE OWL, 1976. PHOTO TAKEN AT A 1901 GATHERING OF CARNEGIE COMPANY OFFICIALS AT THE HOTEL SCHENLEY, WHICH IS NOW THE WILLIAM PITT UNION.

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