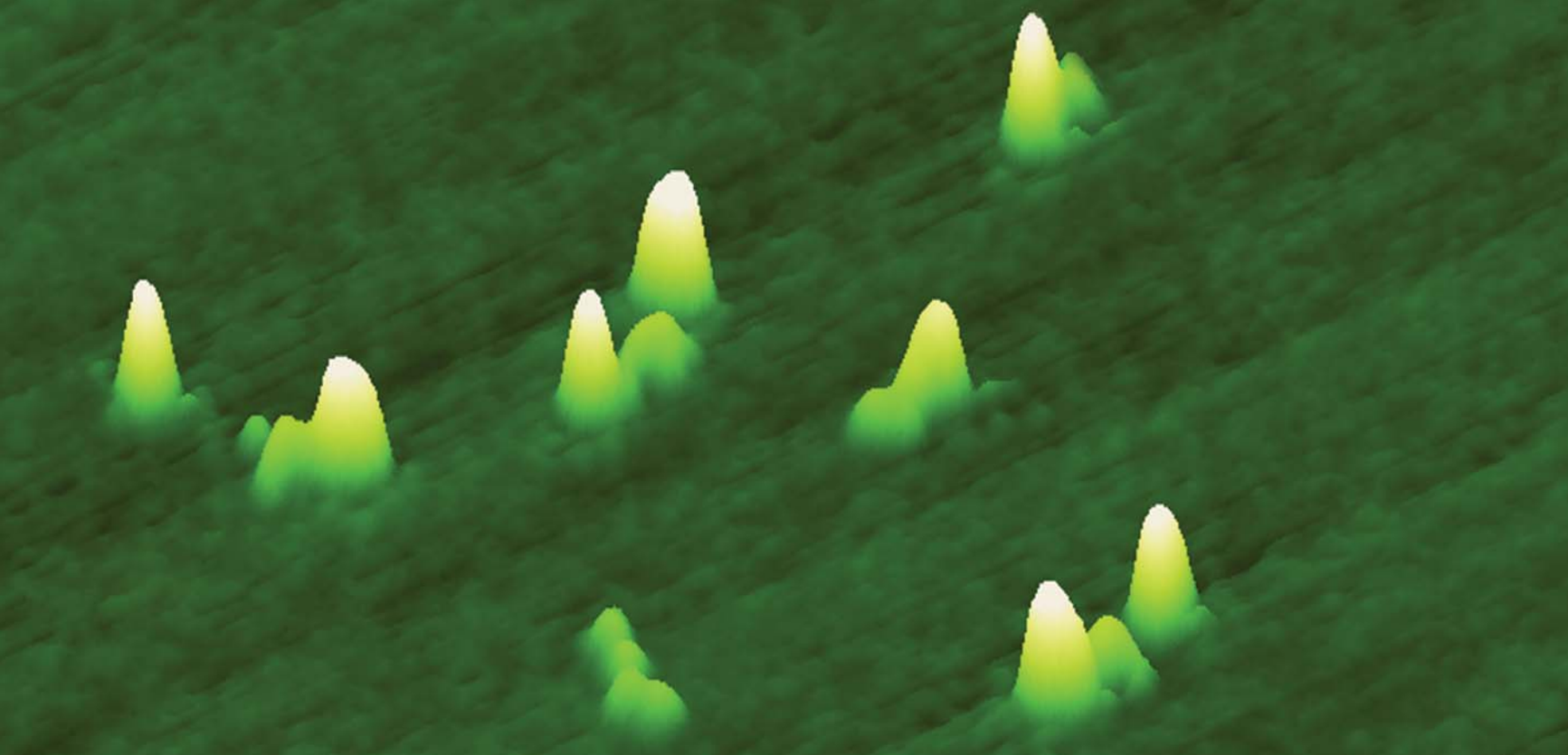
UNIVERSITY OF PITTSBURGH SCHOOL OF MEDICINE | SPRING 2009

PITTMED



IN A SEA OF DNA

WITH BILLIONS OF BASE PAIRS, HOW DO PROTEINS KNOW WHICH TO FIX?

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

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CASE District II Accolades
Gold, Periodical Staff Writing

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

CASE District II Accolades
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IABC Golden Triangle Award of Honor
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(E. Vitone, "What Possessed You?")

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Gold, Covers (Winter 2007/8)

CASE Circle of Excellence
Bronze, Special Interest Magazines

Pittsburgh Black Media Federation
Robert L. Vann Media Award, Photography
Honorable Mention
(C. Mesa)

CORRECTION: In the Winter 2008/09 issue, we listed David Torkelson (MD '83) as having been a member of the Class of '78. Our apologies to his family. (Dr. Torkelson died on Sept. 7, 2008.)



A CHILDREN'S PARTY

This spring, physician alumni and medical staff of Children's Hospital of Pittsburgh of UPMC are invited to catch up with old friends in new digs: Children's new, 10-acre campus in Lawrenceville. Celebrate the homecoming, housewarming-style, with a tour of the facility and presentations by Christopher Gessner, president of Children's and UPMC's Children's Community Pediatrics; Nina Schor, former Children's staff member and current chair of pediatrics at the University of Rochester Medical Center; and other intriguing speakers.

ALUMNI DAY (AND NIGHT)
May 14–15, 2009
Children's Hospital of Pittsburgh of UPMC
and Phipps Conservatory.
For more information or to request an invitation:
Sharon Mastro
412-692-5376
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LEFT: MARGARET MCDONALD, NOW ASSOCIATE VICE CHANCELLOR FOR ACADEMIC AFFAIRS, HEALTH SCIENCES, KNOWS HOW TO CELEBRATE.

PITTMED

UNIVERSITY OF PITTSBURGH SCHOOL OF MEDICINE MAGAZINE, SPRING 2009 (FEB/MAR/APR)

VOL. 11, ISSUE 1



DEPARTMENTS

OF NOTE 3
Those with loved ones in the ICU are at risk for post-traumatic stress.
A semi for science.

CLOSER 7
After a harrowing accident, Meghan Wilson began to think she wouldn't fulfill her dreams.

INVESTIGATIONS 8
Growing big hearts.
Bipolar disorder in children.

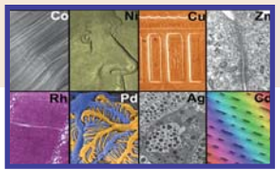
ATTENDING 32
Arguments for and against the existence of God.



98.6 DEGREES 35
New funding to defuse a genetic time bomb.

ALUMNI NEWS 36
Eberlein on what he'd like surgeons to do differently.
Bergman's beard made things hairy at Pitt.

LAST CALL 40
What would Mendeleev do?



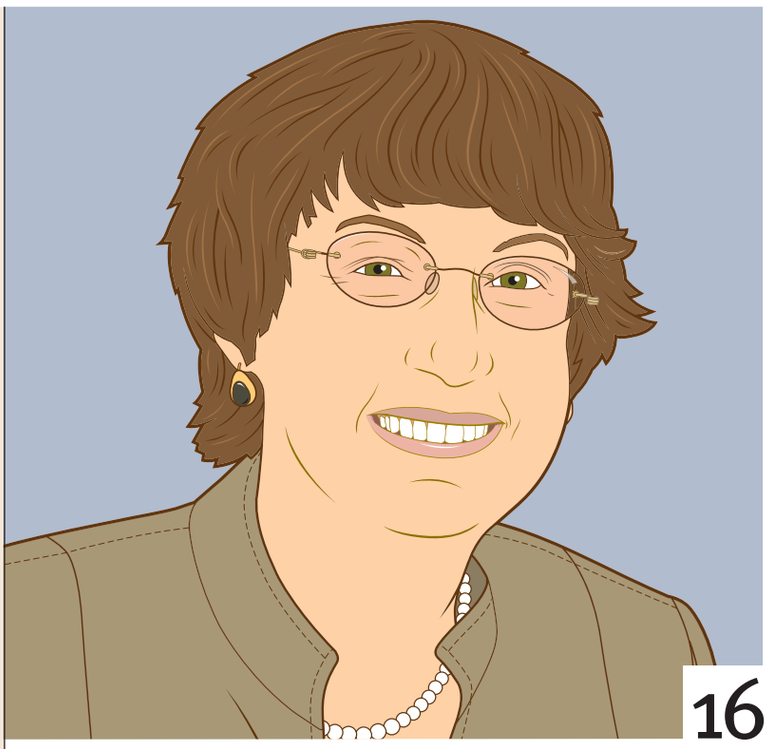
CONTRIBUTORS

Fine art documentary photographer and regular *Pitt Med* contributor CHARLEE BRODSKY ["I Thought I Could Fly"] focuses her lens on social issues and beauty. In this issue, *Pitt Med* excerpts photographs and personal essays from her most recent book, "I Thought I Could Fly … Portraits of Anguish, Compulsion, and Despair," an intimate portrayal of mental illness. The book was published with support from UPMC's Western Psychiatric Institute and Clinic. Brodsky, a professor of photography at Carnegie Mellon University, has also used her lens to capture the transformation of the former steel town Homestead into a retail mecca, working with poets Jane McCafferty and Jim Daniels to tell the story.

Freelance illustrator TIMMY KUCYNDA ["Invisible No More" and "A Choice Choice"], whose previous clients include such science and technology magazines as *Wired* and *MAKE*, enjoys exploring the nuts and bolts of how things work—"with a twist," he says. "I love the aesthetic, and I like helping someone explain or retell their vision. I love when things are made clear and simple, while at the same time being more interesting and alive than they're expected to be." Kucynda lives in San Francisco with his toy fox terrier, Munky, whom he's included in his work whenever possible for the past 12 years.

COVER

A new Pitt researcher has figured out how to watch DNA repair live and in real time. (Cover: Courtesy Bennett Van Houten © 2008.)



16

FEATURES

Invisible No More 12
Ronald Herberman steps down as director of the University of Pittsburgh Cancer Institute this winter, ending an era of remarkable growth.
BY JAMES P. SWYERS

A Choice Choice 16
Renowned breast cancer expert Nancy Davidson will lead the University of Pittsburgh Cancer Institute. Her colleagues and patients at Johns Hopkins want Pittsburgh to know how lucky we are to have her on the team.
BY ELAINE VITONE

How Does It Do That? 20
How does a small team of DNA repair proteins keep billions of base pairs in good working order? You could hypothesize about it, or you could just take a look. That's what Bennett Van Houten did.
COVER STORY BY JOE MIKSCH

I Thought I Could Fly 24
Mental illness in the first person.
PHOTO-ESSAY BY CHARLEE BRODSKY AND ANONYMOUS CONTRIBUTORS

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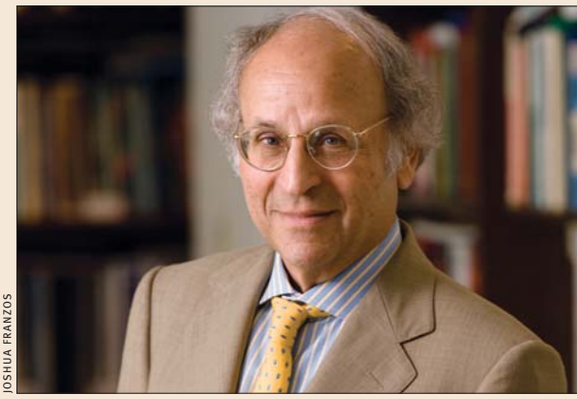
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'Twas brillig, and the slithy toves
Did gyre and gimble in the wabe
— Lewis Carroll,
Through the Looking-Glass


JOSHUA FRANZOS

Recently, I read an article in *Nature* by William Martin and Eugene Koonin that frames a hypothesis about the origin of the nuclei within our cells. The cells that emerged earliest in evolution, e.g., bacterial cells, lacked nuclei, and the question of why nuclei later appeared has long intrigued contemplative and philosophic biologists. The common wisdom has been that the nuclear envelope was "invented" to protect chromosomes from shearing during cell division, but this seems to be a less-than-plausible selective mechanism. Martin and Koonin, in contrast, propose that the origin of the nucleus marked a seminal evolutionary transition, a transition that came about when bacterial DNA invaded cells morphologically similar to our own but sufficiently early in evolution to not yet have nuclei. This invasion had two consequences: Bacterial genes became the ancestors of mitochondria (they now act as "power plants" for cellular metabolism); further, bacterial DNA also invaded the central genome, creating stretches of DNA sequence in that genome ("introns") that, after mutational decay, disrupted the job of our information-laden genes to code for proteins. This information is copied from the DNA into messenger RNA (mRNA), which is exported to the cell sap, where the mRNA is "translated" into proteins. To protect the function of the informative DNA stretches ("exons"), cells developed a mechanism to splice out the introns and join the exons before the mRNA is exported. One problem remained: Splicing is a slow process, but translation is rapid, so the two processes had to be separated. This then, in the Martin-Koonin hypothesis, explains the emergence of nuclei and their surrounding envelopes—which serve to slow mRNA export until the cell is done splicing.

I have warmed to this notion of necessary, time-dependent separation and its underlying evolutionary selective pressure. Why? I worry that we are so bombarded—and so rapidly—by the "unspliced" information that invades our lives through the Internet that we often fail to translate that information in productive ways. The metaphoric "introns" in our brains may even be harmful, yielding, for example, misleading medical advice or political imperatives lacking in true and unbiased substance. Before the Internet, when we queried one another in writing, we didn't expect instantaneous responses. Now, we read the screen and respond in an instant. Information may be absorbed but not metabolized, and if it is parsed at all, the parsing is done often without context and nuance. We're a bit like Lewis Carroll's Alice, bumping up against half-baked ideas or a dose of nonsense at every turn. Imagine if our brains had a semipermeable barrier that would allow information and the response to that information to equilibrate. Regrettably, evolution has not caught up with the Internet!

This is not to say that computers aren't welcome. I could not function professionally (nor retrieve my shirts from the cleaners) without them. Yet we pay a price when our rate of accurate comprehension is challenged. Here again, science not only yields data and hypotheses about the world, it instructs us—even if by metaphor—as to how we might better live our lives.

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



Devoted to noteworthy happenings

at the medical school

ACS Professors Named

Patrick Moore and Yuan Chang are two of three newly named American Cancer Society Research Professors. The collaborators search for newly identified viruses and related human tumors. Each professorship carries with it a five-year, $400,000 grant.

"The research funds are not restricted," says Moore. "This allows us to explore more cutting-edge areas of cancer research that we can't fund through traditional grants."

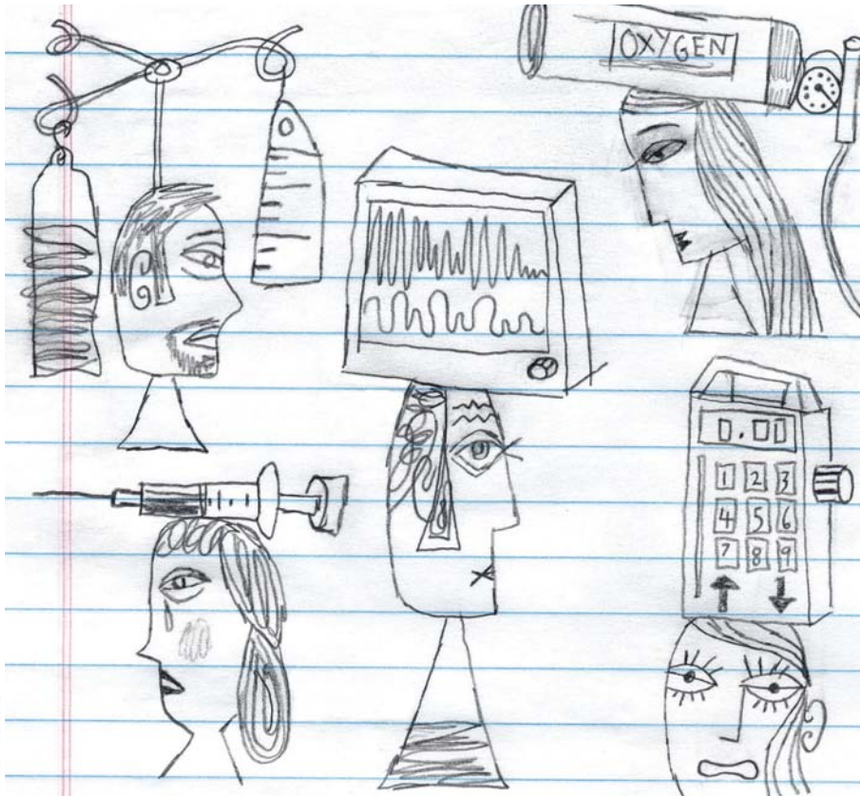
Moore, an MD/MPH, is director of the Molecular Virology Program at the University of Pittsburgh Cancer Institute and professor of microbiology and molecular genetics in the School of Medicine. Chang, an MD, is a Pitt professor of pathology.

Pitt's Jennifer Rubin Grandis (MD '87, Res '93) received an ACS clinical research professorship earlier last year. A professor of otolaryngology and pharmacology, she studies genetic abnormalities associated with head and neck squamous-cell carcinoma. ***—Joe Miksch***

FOOTNOTE

The day before new carpeting was to be installed in Scaife Hall, workers exposed concrete underneath the old flooring. So John Mahoney, associate dean for medical education, posted a sign encouraging students to leave their marks, asking, "Keep it small. Keep it clean." Some penned their names. Others left messages.

J.D. Zipkin (Class of 2012) wrote, "Dear Future Med Students: You may be smarter, younger, and better looking, but by the time you read this, I'll be debt free."



CATHERINE LAZURE

IN THE ICU, FAMILIES SUFFER, TOO

Watching a loved one in the intensive care unit is depressing, draining, and may lead to another troubling consequence down the road—post-traumatic stress disorder.

Researchers at the University of Pittsburgh and the University of California, San Francisco, tracked 50 family members of ICU patients. At a six-month follow-up, 35 percent had post-traumatic stress, and 46 percent of family members of patients who'd died experienced complicated grief, where the pain of losing a loved one becomes debilitating.

It was hard to predict who would work through their grief normally and who would sink into deeper problems that required treatment, says Cindy Bryce, a PhD associate professor of medicine and health policy and management at Pitt.

"Even those who looked fine in the hospital and seemed to be coping might show some signs of problems down the road," Bryce says.

Surprisingly, post-traumatic stress was not more prevalent among family members whose loved ones had died. *—Christina Rouvalis*



CAMI MESA

A&Q

What We Can Learn from the Anthrax Investigations

When biodefense researcher Bruce Ivins—the man federal prosecutors named as the sole culprit of the anthrax attacks of 2001—committed suicide last summer, the answers to many lingering questions surrounding the incidents may have died with him. However, regardless of the uncertainties, there is still much we can learn from the anthrax investigations, says Thomas Inglesby (shown above), chief operating officer of the Center for Biosecurity of UPMC and University of Pittsburgh associate professor of medicine and public health.

On the science of the anthrax investigations

One lesson here is that identifying the source of biological attacks is an extraordinary and complex problem. And it's one of great importance, because our success in identifying the sources of bacteria or viruses used against us can deter others from similar attacks.

Also—because at present there are limits to what we can do in forensics and because we don't yet have a deterrent strategy for bioterrorism like we did in the Cold War with nuclear weapons—another lesson is that we have to be prepared to respond to the consequences of biological weapons used against the U.S. or elsewhere around the world.

On biosecurity policy

We obviously need to make sure we have smart and sensible policies so that we know who is working on these diseases and pathogens. However, what we can't do in the process is make it so onerous and locked down that scientists can no longer work on developing vaccines and medicines we need. It's a complicated balance.

In some places in the security community, there's still a misconception that making or using a biological weapon is beyond the technical reach of all but a very limited few countries or groups. But if it's possible that one scientist working alone was behind this whole series of events that happened in 2001, then that's quite obviously not the case.

His question for us

An increasing number of great societal problems in the 21st century are related to the life sciences: the prospect of an emerging pandemic disease or attacks using biological weapons, climate change and the carbon cycle, Alzheimer's and [caring for] an aging population, and [ethical quandaries of] stem cell science, to name a few. And we have a vast amount of scientific talent in this country. What can we do collectively to take all that we know and apply it more rapidly to solving these problems? *—Interview by Elaine Vitone*

Faculty Snapshots

Paul Rogers says he'd be happy to talk about the national teaching award he recently received, but not at this particular moment. "I have to go teach," he says.

Later, Rogers, one of four recipients of the Association of American Medical Colleges' 2008 Alpha Omega Alpha Robert J. Glaser Distinguished Teacher Award, says, "It's a huge award. … I have to thank the University of Pittsburgh for giving me the time and resources to teach."

Rogers, an MD professor of critical care medicine, teaches acute care medicine to third-year students and a fourth-year elective in critical care.



Rogers

How do we age well? Bret Goodpaster, a PhD associate professor of medicine in endocrinology and metabolism, is trying to answer that question, and his work has earned him the National Institute on Aging's Nathan W. Shock Memorial Lecture Award. Goodpaster focuses on age-related loss of physical function because of excessive weight. He also hopes to identify molecular and biochemical signals that correlate with good health in our later years.



Goodpaster

David Perlmutter was recently elected to the Institute of Medicine. Perlmutter is an MD, the Vira I. Heinz Professor, and chair of the Department of Pediatrics in the School of Medicine. His research delves into the causes of, and treatments for, genetic liver disease in children. He also is largely responsible for expanding the Children's Hospital of Pittsburgh of UPMC's basic and clinical research programs.



Perlmutter

Barry London thinks that there must be a better way to image the heart than 100-year-old electrocardiogram technology. He recently received one of 16 National Institutes of Health Director's Pioneer Awards (worth $2.5 million) that will allow him to investigate this idea.



London

London is the Harry S. Tack Professor of Medicine and chief of the Division of Cardiology at Pitt. He also directs the UPMC Cardiovascular Institute. The MD/PhD plans to investigate the use of tiny magnetic particles coupled with ultrasound, as well as modified adult stem cell implants, to help predict a patient's risk for sudden cardiac arrest. On these studies, he will collaborate with Flordeliza Villanueva, an MD professor of medicine and director of noninvasive cardiac imaging. *—JM*

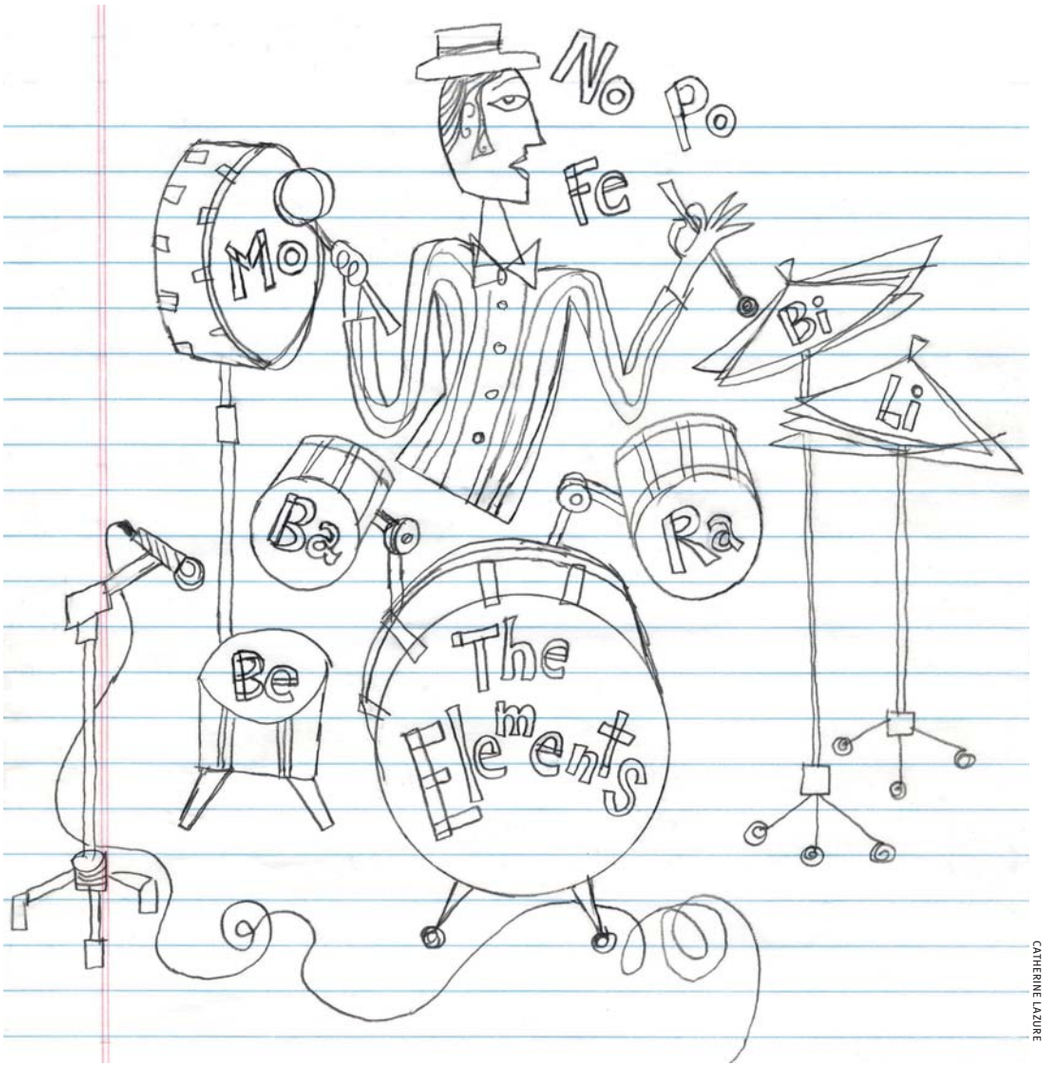
Different Drummers

The level of excitement in the lecture hall was at a rock-and-roll concert pitch. Instead of teens looking for a nod or handshake from their guitar-wielding idols, scientists were jockeying to have a word with Peter Walter before he delivered his talk on the endoplasmic reticulum.

Walter, PhD professor of biochemistry and biophysics at the University of California, San Francisco, was in Pittsburgh this fall to deliver the 87th Mellon Lecture at Science 2008, the University of Pittsburgh's annual celebration of science, medicine, and technology. Looking around the packed room at Alumni Hall, the burly and bearded Walter said, in his German-accented English, "This is a fantastic forum for celebrating science. Scientists have failed miserably in communicating what they do to a broader audience, and this gives us a chance to do so."

Elsewhere in the building, visitors wended their way through a massive poster exhibit, huddled to chat about the state of science funding and the difficulty of nailing down that first R01 grant, and heard other lectures on scores of topics.

After greeting another well-wisher, Walter remarked, "I've been at events like this in Europe, but not here. I think we should institute programs like this in other cities." *—JM*



CATHERINE LAZURE

ONLINE THERAPY FOR BULIMIA

People suffering from bulimia nervosa have long undergone cognitive behavioral therapy to rid themselves of unhealthy thoughts such as, "Only thin people are worthwhile."

Now doctors are hoping this therapy will also work through the Internet.

University of North Carolina at Chapel Hill and University of Pittsburgh researchers are testing chat rooms moderated by cognitive behavioral therapists for women and men suffering from bulimia. The study is led by UNC's Cynthia Bulik, the William R. and Jeanne H. Jordan Distinguished Professor of Eating Disorders.

There are advantages to being behind a computer screen, says Marsha Marcus, Pitt professor of psychiatry and psychology and service chief in the Center for Overcoming Problem Eating of the Western Psychiatric Institute and Clinic of UPMC. For example, a patient might be more open to talking about the pain of binge eating and purging online.

If effective, online cognitive behavioral therapy could reach people in rural areas or those who want convenience. "They don't have to lose half a day, drive 20 miles, park, and then go to an appointment," Marcus (PhD '84) says. *—CR*

FLASHBACK

In 1934 [Children's Hospital] handled more nonpaying patients than any other hospital in Pittsburgh. ... a measles epidemic further burdened the staff. Walter Rome, long associated with Children's as an administrator, recalled that the hospital was so short of funds that its trustees would come in on weekends to run the elevators, help out in the laundry or put a few dollars toward purchase of groceries.

***—Barbara I. Paull,* A Century of Medical Excellence: The History of the University of Pittsburgh School of Medicine**



MARY JANE BENT/ CIDDE

TRUCK-O-SCIENCE

Some tractor-trailers haul consumer goods. At least one was destined for a more erudite purpose, becoming a 70-foot mobile biology lab.

In November, Pitt unveiled a lab-on-wheels funded and operated by the University's Clinical and Translational Science Institute. The tractor-trailer of science will be used in community outreach—including a current Arts and Sciences program in high and middle schools—and in health screenings. *—JM*

Appointments

Neil Resnick, an MD professor of medicine, chief of the Division of Geriatric Medicine, and director of the University of Pittsburgh Institute on Aging, has dedicated his life's work to upending the assumption that certain diseases are a necessary consequence of aging. The University recently named Resnick to the Thomas Detre Chair in Geriatric Medicine. During his term as Pitt's senior vice chancellor for the health sciences, Detre, a psychiatrist, established Pitt's now nationally recognized geriatric medicine division. He felt that a multidisciplinary and comprehensive approach was necessary to treat elderly patients who often suffer from complicated and competing health conditions. "Detre was a giant," Resnick says. "He changed the way people in his field thought about psychiatry." Resnick hopes to call upon Detre's multidisciplinary and pioneering spirit as he continues to shape the field of geriatrics at Pitt.



Resnick

Ira Fox joins the Pitt faculty from the University of Nebraska College of Medicine. Fox will direct the new Center for Innovative Pediatric Regenerative Therapies, a joint program of Pitt's Department of Surgery, the McGowan Institute for Regenerative Medicine, and Children's Hospital of Pittsburgh of UPMC. Fox is an MD and leading transplantation surgeon and stem cell researcher. His first goal is to build a network of investigators to develop new treatments for pediatric liver dysfunction. He hopes that the center's doors will be open to patients in May.



Fox

Even after more than 20 years in the world of science, including a postdoctoral fellowship at the National Institutes of Health and more than 90 peer-reviewed articles, Thomas Smithgall admits that having a paper accepted for publication still delivers a huge rush of excitement. Smithgall, a highly regarded teacher and mentor at Pitt, is known for his work on an enzyme family important in the development of cancer and AIDS. His lab recently identified promising protein-signaling targets for chronic myelogenous leukemia. Smithgall is now chair of the Department of Microbiology and Molecular Genetics. He succeeds prominent gene-therapy and herpes simplex virus investigator Joseph Glorioso, who served as chair at Pitt from 1989 to 2008.



Smithgall

Constance Chu now holds the Dr. Albert Ferguson Endowed Chair in Orthopaedic Surgery in the School of Medicine. (Ferguson, former Pitt chair of orthopaedic surgery, is known for training dozens of the world's leaders in the field.) By using new imaging technologies, Chu has been able to reveal previously undetectable signs of cartilage damage in patients who have torn the anterior cruciate ligament, an injury that dramatically increases risk for osteoarthritis. She has received several major grants from the National Institutes of Health to further her research on tissue engineering of articular cartilage and on early diagnosis and treatment of osteoarthritis. The MD recently won the ABC Traveling Fellowship in Orthopaedics. This is the oldest and most prestigious orthopaedic traveling fellowship and recognizes emerging academic leaders. *—Missy Raterman*



Chu



SECOND CHANCES

Amid the beehive-like buzz of the Biomedical Science Tower Lobby, Meghan Wilson explained recently what led her to enroll in the University of Pittsburgh/Carnegie Mellon University Medical Scientist Training Program—aka the MD/PhD program.

She had wanted a career in medicine since she was a kid in Florida, but "after my accident, I didn't think that was still a realistic option for me," she said. A skiing accident during her senior year of high school rendered her quadriplegic 11 years ago.

As an undergraduate at the University of Florida, she discovered an interest in neuroscience research and, with the encouragement of one of her professors, decided to pursue a combined degree. "I wanted to study human disease and help translate basic research findings into improvements in clinical medicine" she said.

Since then, Wilson has graduated with a degree in neurobiology and completed two years of medical school. She is now in the third year of her PhD training in neuroscience, focusing on ALS (Lou Gehrig's disease).

The work, as you might expect, is challenging and time consuming. So was getting the opportunity to do it. Wilson didn't get accepted to med school on her first try (despite a soaring MCAT score and GPA, plus strong letters of recommendation). "Then I sent out letters to medical schools all around the country explaining my situation. I wanted to gauge who was willing to give me a chance and work with me to develop appropriate accommodations."

Only one school was. Pitt.

"They talk about the importance of diversity at many schools, but here at Pitt they actually put in the extra effort to support it."

She works with a technician in the lab and plans to hire a physician's assistant when she returns to med school for her third- and fourth-year clerkships.

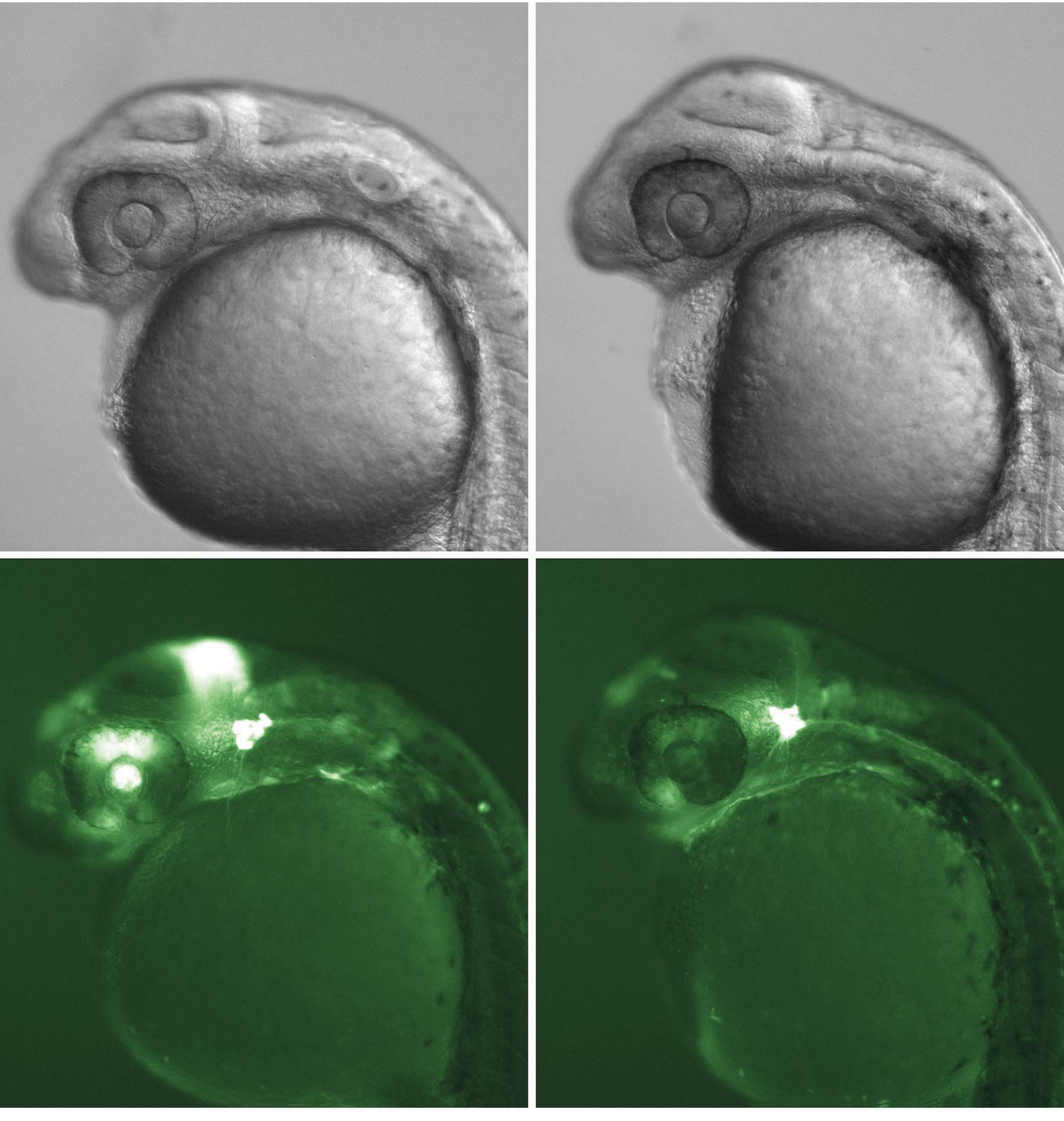
Then residency. Then a postdoc. Then a faculty position at an academic medical center.

"I'm working toward a career where I'll be able to do intellectually fulfilling work and help improve the quality of other people's lives. That is something I wasn't sure would be a possibility for me," Wilson said. "I'm grateful for the opportunity."

—Joe Miksch

Photograph by Cami Mesa

Explorations and revelations taking place in the medical school



ONE BIG HEART
COMING RIGHT UP

TSANG MANIPULATES A GROWTH FACTOR PATHWAY

BY JOE MIKSCH

For many, the utility of fish begins and ends with their estimable service as food. Michael Tsang, University of Pittsburgh assistant professor of microbiology and molecular genetics, uses fish to search for answers, molecule by molecule, regarding how embryos develop.

What he's learned even allowed him to control the size of a developing heart.

Tsang employs the zebra fish, an inch-and-a-half-long striped swimmer, which shares 70 to 80 percent of its genes with humans. Zebra fish reproduce and develop rapidly. The zebra fish embryo—this is key—develops outside the mother, making it easier to examine than, say, a mouse embryo. And the University of Pittsburgh's Biomedical Science Tower 3 hosts one of the largest colonies of the critters in the world.

Tsang, a PhD who previously worked at the National Institutes of Health, developed his novel zebra fish–centric molecular screening model so he could investigate embryonic development via fibroblast growth factors (FGFs). The FGF pathway is vital to brain, heart, and limb formation. FGFs, there are 22 of them, also play critical roles in wound healing and angiogenesis.

Tsang has created transgenic zebra fish embryos that act as biosensors for fibroblast growth factor activity vital to brain, heart, and limb formation. These fish embryos are under a microscope in standard light (top) and blue light (bottom). In the bottom right image, the growth factor isn't active in the eyes or parts of the developing brain.

COURTESY MOLINA ET AL BMC DEVELOPMENTAL BIOLOGY (2007)

When FGF receptors malfunction, diseases such as Crouzon syndrome, which is marked by facial deformities, can develop.

To prevent disease, doctors may sometimes want to block the FGF pathway. Other times, they may find it preferable to ramp it up.

Figuring out which molecules might have an impact on FGF signaling is no easy task.

Tsang's solution was to create a line of transgenic zebra fish. He injected a piece of DNA consisting of two elements, a promoter and a reporter, into the fish.

Promoters, as the name indicates, help facilitate genetic transcription and can switch on gene expression. Tsang's promoter comes from a gene normally regulated by FGF signaling. The reporter, which contains a code for a jellyfish protein called GFP (green fluorescent protein), glows under blue light.

Tsang's lab then bred his genetically unique zebra fish and looked for places where the glow was prevalent.

"This indicates to us where FGF is active in the embryo just by looking at it," Tsang says. "This fish is like a live biosensor for FGF activity."

With his model, Tsang can treat his transgenic zebra fish with molecules, hoping to find ones that increase or suppress FGF activity.

Things go pretty quickly once the molecule being investigated gets into the rapidly growing zebra fish embryo.

"We add our compounds, and we can look for GFP expression in six hours. We add them in the morning, and we'll know what happened by the afternoon," Tsang says.

If GFP doesn't appear, Tsang knows that the molecule blocks FGF signaling. If there's more GFP than normal, FGF signaling is increased. If the embryo dies, Tsang says, "then we know it's toxic, and it's no good to continue on with that compound."

Tsang's collaborators on this project include Andreas Vogt, research assistant professor of pharmacology and chemical biology; John Lazo, Allegheny Foundation Professor of Pharmacology; Ivet Bahar, John K. Vries Chair of Computational Biology; and Billy Day, professor of pharmaceutical sciences and chemistry.

Of the 5,000 molecules Tsang's colleagues have so far screened, they've found one (called BCI) that hyperactivates FGF signaling. It turns out that BCI blocks a particular FGF inhibitor from doing its job. So, Tsang now knows the identity of a molecule that affects FGF function and that molecule's target, as well as the mechanism by which BCI works to augment FGF activity.

He is beginning to use this knowledge to learn how the timing and location of FGF expression modulates embryonic development.

Using BCI and changing the fate of embryonic cells, Tsang's lab has managed to increase the size of a zebra fish's heart.

"By adding BCI, we've seen less blood and blood-vessel progenitors and more cardiac tissue, because we enhanced FGF signaling at a particular time in development.

"If you block FGF signaling, you get the opposite effect," he says. ■

SAYING "HI" TO THE BAD GUY

THE BODY'S SENTINELS COULD PREVENT ORGAN REJECTION

BY REID R. FRAZIER

You might call the task Herculean, or Sisyphean, if you like. How do you get the body to accept a new organ without killing the body in the process? Immune systems attack transplanted organs, but immunosuppression regimens can cause high blood pressure; increase the risk of cancer, heart disease, and stroke; and leave the body vulnerable to infection. In time, the problems they cause take the lives of roughly one quarter of all transplant recipients for many types of organ grafts.

Finding a way for the body to accept a new organ without turning off the entire immune system is the holy grail of transplant immunology. "It's a Nobel Prize, if you can find a way to transplant without drugs," says Mark Hardy, Auchincloss Professor of Surgery and director emeritus of transplantation at Columbia University. Bone marrow transplantation, radiation, and blood transfusions are just a few of the methods scientists have tried to induce tolerance for a new organ.

The University of Pittsburgh's Angus Thomson thinks he's on to a way to make the immune system more tolerant of a transplanted organ. Thomson is known for his work with dendritic cells, sentinel cells that trigger the immune response. He believes doctors can use dendritic cells to make organs feel at home in their new surroundings.

The concept is a little like convincing a snarling Rottweiler guarding a house to suddenly hop up on its hind legs and lick your face.

The Scotland born Thomson, a fellow in the Royal Society of Edinburgh, Scotland's national academy of science and letters, thinks there's a way to train the Rottweiler to recognize your face as friendly.

Thomson, Distinguished Professor of Surgery with appointments in immunology, as well as microbiology and molecular genetics, was among the first to use dendritic cells in transplant immunology in the 1990s. He and his collaborators showed that these cells, particularly immature ones, could be "trained" to regulate the immune response in lymphocyte white blood cells.

Some call this approach a "negative vaccine," because it undoes the immune response.

"If you can program [dendritic cells] the way we want to, they can tell the lymphocytes to switch off rather than on," says Thomson. (Or, as Hardy notes, "You kind of encourage the cell to be stupid.")

This changed the way transplant scientists viewed dendritic cells, Hardy says. Dendritic cells, the thinking went, "were there to be attacked, not to be encouraged," says Hardy, who himself has studied how to "tolerize" dendritic cells by exposing them to foreign tissue.

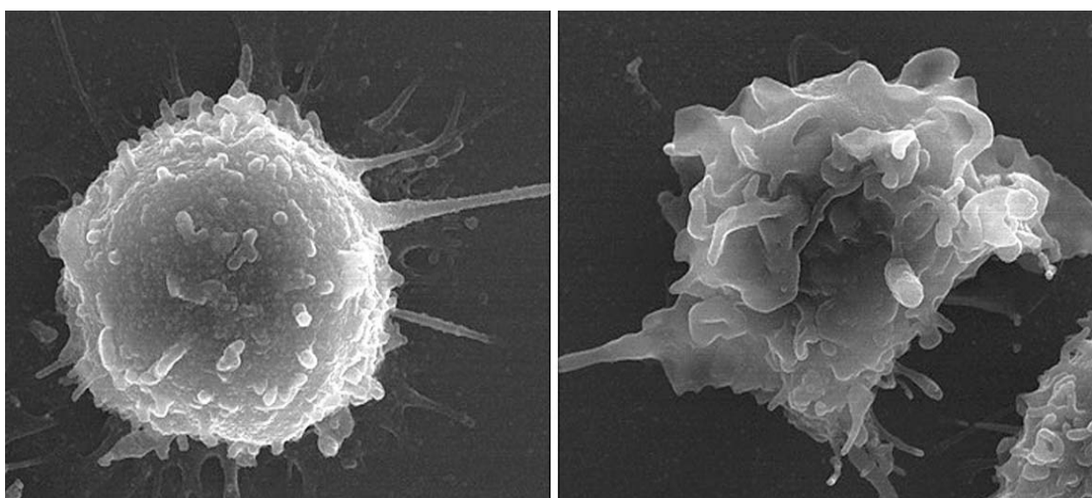
"[Thomson's breakthrough] was very significant and very important and stimulated other people to focus their research in the area," he says.

Transplant doctors had good reason to fear dendritic cells—shape-shifting structures that trawl the body looking for potential invaders, like a virus, bacteria, or a new organ. Once they sense a problem, the cells get excited, extending thousands of tiny protrusions, or dendrites (dendron is Greek for "tree"), to snatch up loose bits of the offending newcomer. The cells then cart their bundles off and present them to the body's T-cells, which attack the intruder.

Since his initial discoveries about dendritic cells, Thomson, director of transplant immunology and associate director for basic research at the Pitt-UPMC Thomas E. Starzl Transplantation Institute, has continued to explore the pathways through which these cells can induce tolerance. In 2002, his group found that exposing dendritic cells to the immunosuppressor rapamycin helped keep them immature. The cells could then be reinjected into the body to regulate immune responses to a transplanted organ.

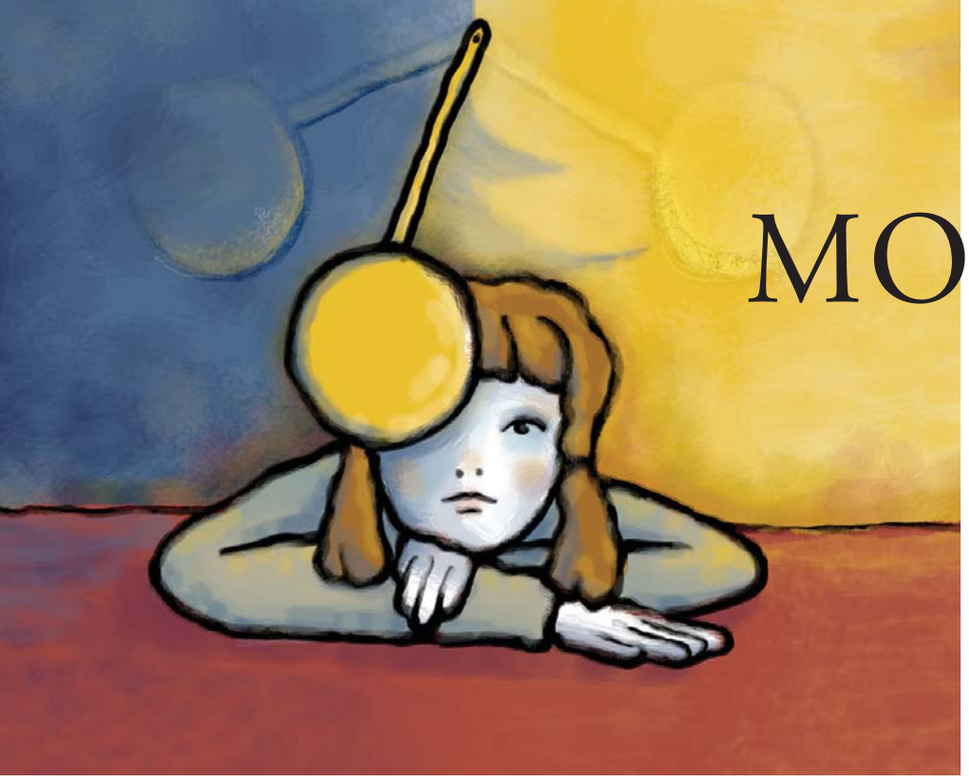
Thomson and his collaborators recently found several molecular signatures for these "tolerogenic" cells. "That's a big question for us and the rest of the field," the immunologist says. "What is the hallmark of a tolerogenic dendritic cell?" And, otherwise "how do you know your negative vaccine cell is doing any good?"

His group found high concentrations of two molecules (ST2 and IL-10) in cells with tolerogenic properties. Thomson is hopeful the FDA will approve human safety trials on tolerogenic dendritic cells in transplantation within the next few years. ■



COURTESY DONNA STOLZ

Thomson has found a way to keep dendritic cells "stably immature" (right image) so they don't attack transplanted tissue. On the left is a mature dendritic cell which is normally highly effective in stimulating the body's immune response.



MOLLY FEUER

MOOD PENDULUM

HELP FOR CHILDREN WITH BIPOLAR DISORDER

BY ELAINE VITONE

Adults living with bipolar disorder—that pendulum of moods that swings from stability, to mania, to depression, and back again—struggle with a range of devastating symptoms. Depending on the severity of the disorder, they might undertake reckless behavior they cannot control, endure strained interpersonal relationships, and even harbor suicidal thoughts.

"If you develop the illness as an adult, it's very hard, but at least you already have your foundation in place," says the University of Pittsburgh's Boris Birmaher, an MD who holds an endowed chair in Early Onset Bipolar Disease and is a professor of psychiatry. "But if you get this as a child, it's much worse. Unless you treat these kids, they don't have the opportunity to develop normally—emotionally, cognitively, socially, or academically."

Unfortunately, diagnosing bipolar disorder is especially challenging. On average, it takes adults 10 years to get an accurate diagnosis (that's from the time they first seek help to the time they arrive at the answer). And for children, the challenge is even greater. After all, it's normal for kids to be fanciful, to believe they can fly. But in adults, the same behavior would be a red flag. And the symptoms of bipolar disorder overlap with those of several other disorders common in children—ADHD, for example—further confounding diagnosis.

To address these challenges, 10 years ago Birmaher founded the Child and Adolescent Bipolar Services Clinic at Western Psychiatric Institute and Clinic. He believes it is the only clinic exclusively devoted to the treatment and study of bipolar disorder in children and adolescents.

"In psychiatry, all you have is the assessment," says MD Associate Professor of Psychiatry David Axelson, the bipolar clinic's current director. "There aren't any blood tests, X-rays, or genetic tests to help with diagnosis. It's all based on the history and mental status that people report to us."

From day one, the clinic has used an exceptionally thorough diagnostic process. It begins with a 20-minute phone interview with the child's caretaker—this step rules out a bipolar diagnosis for about 40 percent of callers. (These callers are then assisted with referrals.) Next, the child and caretaker come in for a detailed assessment with an experienced psychiatric nurse or a master's level clinician. Based on this interview, an attending psychiatrist at the clinic will confirm the diagnosis and meet with the family. All told, the process of diagnosing a single patient can last as long as six hours. "We call it the Cadillac of interviews," Birmaher says.

In the last decade, the clinic has assessed and/or treated many more than 1,000 children and adolescents. Its patient load—which averages around 260 at a given time, many of whom are study participants—offers singular insight into this often-misunderstood disorder. Ongoing studies are investigating early symptoms, long-term outcomes, treatment efficacy, potential biomarkers, and genetics, among other areas.

Perhaps most notable among the clinic's research projects is Course and Outcome of Bipolar Youth (COBY), a study led by Axelson and Birmaher that follows 440 children at UPMC, UCLA, and Brown University. The study is in its seventh year; analyses from COBY have been widely published. It is the largest study of its kind.

COBY helped Axelson elucidate the subtle differences between children with bipolar 1 (the most severe form of the disorder) and children with subthreshold bipolar (in which episodes with two or more symptoms last four or more days at a time). It also allowed Birmaher to explain how mood shifts in bipolar children can differ from those in adults. Mood swings in children with subthreshold bipolar disorder are more frequent than in adults with the same disorder.

Axelson is quick to point out that the clinic has seen a lot of success stories. With proper treatment, many patients have managed their symptoms and done well in college and beyond. Yet doctors need better diagnostic criteria so they can help kids early on—when it counts most. Accurate diagnosis is a major focus of the clinic's studies.

"That's why we have to keep working," says Axelson. ■



HOW A CANCER INSTITUTE CAME TO BE

BY JAMES P. SWYERS

INVISIBLE NO MORE

"Embarrassing" is how Thomas Detre describes the landscape for cancer care in Pittsburgh in the mid-1980s—and he would know. In 1984, Detre, an MD, became Pitt's senior vice chancellor for the health sciences with responsibility for the University's six health sciences schools, including the School of Medicine. As such, he also became an unofficial "go-to" person for medical advice or referrals.

"I've never adopted the parochial attitude that we're the best in everything," says Detre, now a Distinguished Service Professor of Psychiatry. "When people would ask me where I thought they would receive the best care, I sent them wherever I thought was the best place possible."

Although Pitt was making great strides at the time in many areas of medicine, for cancer care, the best place to go was usually somewhere else. (The notable exception was work in breast cancer being done by Bernard Fisher, MD '43, who ultimately changed the treatment protocol for the disease and even established a regimen for prevention.) Overall, however, the University was "very thin" in terms of cancer expertise, Detre recalls. Consequently, cancer patients and their families often found it better to travel to Cleveland, Philadelphia, New York, or Washington, D.C., for treatment.



As Ronald Herberman steps down this winter, he ends an era of extraordinary growth for the University of Pittsburgh Cancer Institute.

ILLUSTRATION | TIMMY KUCYNDA

PHOTOGRAPHY | JOHN ALTDORFER

The fact that the University of Pittsburgh Cancer Institute (UPCI) today ranks among the foremost cancer centers in the United States is a testament to how much things have changed in the past 20-some years—as well as to the determination of one man: Ronald Herberman, founding director of UPCI, associate vice chancellor for cancer research, Hillman Professor of Oncology at Pitt, and director of the UPMC Cancer Centers. Herberman will step down this February as director of UPCI and UPMC Cancer Centers. With that act ends an era of astonishing growth.

"I've heard people say that Ron Herberman is made of steel, but I tell everyone he's really made of titanium. … He's one of the most persistent people I've ever met," says Detre.

In January 1984, a University task force concluded that a consortium consisting of Pitt, its affiliated hospitals, and Carnegie Mellon University should work together to establish a regional cancer institute; all of the parties agreed to provide start-up money. Not long after Detre became senior vice chancellor for the health sciences, the Richard King Mellon Foundation gave $3 million to help establish the institute.

With initial funding in hand, Detre appointed a search committee to find a director, but viable candidates were reluctant about Pittsburgh, which still bore the scars of a smoky steel town whose heyday had passed. Eventually, the committee found a well-respected expert in chemotherapy who agreed to an interview.

However, as Detre recalls, the candidate "would not do." He wanted someone more in tune with newer, more innovative cancer therapies, someone who could effectively lead the institute into the future. He assembled eminent oncologists and researchers—one of whom later won a Nobel Prize—to identify the credentials such a candidate should have. Like Detre, his advisers believed that molecularly targeted cancer treatments would come to the forefront and that much could be learned about cancer by better understanding the body's immune system.

Gerald Levey, head of the search committee and chair of the Department of Medicine at the time, knew someone who fit that description perfectly. It was Herberman, who had begun a long and notable career at the National Cancer Institute (NCI) in 1966, two years after earning his MD from New York University. Levey and Herberman had been friends since their days as residents at Massachusetts General Hospital. From the outset of Herberman's career, immunology was the focus of his work.

In the early 1970s, Herberman's laboratory discovered that a type of immune cell called a natural killer cell could attack cancerous tumors, and he demonstrated its importance in resisting the spread of cancer. Based on evidence that some people develop a natural immunity to cancer, his lab also organized a national program for improving cancer diagnosis based on immune markers, a field now known as immunodiagnosis. Likewise, the lab developed a novel diagnostic tool by detecting biochemical markers in the blood, urine, and tissue of people with cancer. (He remains engaged in natural killer cell research with close collaborators—though he gave up his own lab years ago because of administrative responsibilities.)

Herberman played a major role in establishing NCI's Biological Response Modifiers Program, which funded research on biological and immunological cancer treatments like immune messenger molecules, vaccines, gene therapy, and bone marrow transplants.

Only after considerable arm-twisting did he agree to an interview.

However, when contacted about the Pittsburgh job, Herberman, like the others, was reluctant.

"The reaction I got from my colleagues at NCI was that I shouldn't even bother going to Pittsburgh because there wasn't much going on in cancer at the time. In addition, the hospitals were too independent and weren't under control of the University. The general consensus was that it would probably be too much trouble, and it probably would fail," Herberman recalls. Only after considerable arm-twisting did he agree to an interview.

Herberman had been to Pittsburgh only once before, and it was a quick trip—no sightseeing. This time, he was surprised to find the city so attractive. However, he remained skeptical. Detre listened patiently to his concerns, assured him they were solvable, and suggested he ask around for input from others.

Herberman did and found that Detre was known as a man of his word—and more. Under Detre's leadership, Western Psychiatric Institute and Clinic had secured tens of millions of dollars in clinical research grants, established three National Institute of Mental Health centers of excellence, recruited top-level researchers and clinicians, and emerged as a research powerhouse with a wealth of groundbreaking studies on topics ranging from psychopharmacology to the genetics of mental disorders. Herberman also was impressed by the collection of University-affiliated hospitals. At NCI, his access to cancer patients was limited; he saw the setup in Pittsburgh as much more feasible for the kinds of studies he wanted to conduct. He finally agreed to take the job.

In September 1985, the fledgling cancer institute consisted of Herberman, a secretary, and a three-room suite in the former Eye and Ear Hospital.

Barbara Duffy Stewart soon joined UPCI as one of its first employees. She recalls that on her first day on the job, while helping unpack a pile of boxes shipped from NCI, Herberman never removed the jacket of his corduroy suit despite the sweltering heat. It was a telling sign, because throughout the early frantic days of the institute, Herberman never lost his cool, says Duffy Stewart, who is now executive director of the Association of American Cancer Institutes.

"Thank goodness for his personality. When something unexpected would happen, and the rest of us would go crazy, he was able to keep everyone on an even keel," she says.

Not long after Herberman arrived, John Kirkwood, an MD and highly regarded melanoma researcher from Yale University, joined UPCI as its clinical director. Another early recruit was Theresa Whiteside, a PhD who was already at Pitt in the Department of Pathology. "Ron wanted me to start an immunological monitoring laboratory for the cancer institute very similar to the one I ran for the Department of Pathology; however, this would be for monitoring patients' immune responses to cancer therapy," she recalls.

With Kirkwood and Whiteside on board, Herberman began aggressively recruiting more basic scientists and physicians. *Places Rated Almanac* had recently named Pittsburgh America's Most Livable City for the first time (an accolade repeated in 2007), and he used this distinction as leverage to convince potential recruits to come and see what the city and its new cancer center had to offer. Come they did, few at first but many more before long. Herberman's concerns grew about the availability of space and resources to support them. In 1986, the Mellon Foundation donated another $3 million, followed by $8 million in 1989 so that two floors of the University's new Biomedical Science Tower (BST) would be devoted to cancer research. In addition, Herberman put a core grant from NCI to work in 1988 to develop infrastructure and to build shared facilities for the institute's research faculty. Nevertheless, for UPCI to become a leading cancer

center, the quest for additional funding and space had really just begun.

In 1990, after only five years, UPCI won a powerful endorsement with its designation by NCI as a comprehensive cancer center—"the youngest center ever to receive that distinction," Herberman says—in recognition of its far-reaching strengths in cancer treatment, research, education, and prevention. UPCI today is one of only 39 comprehensive cancer centers in the country and the only one in Western Pennsylvania.

Throughout the 1990s, while UPCI increasingly incorporated faculty from both Pitt and Carnegie Mellon into its research projects, it was pretty much an "invisible" cancer institute, with clinicians and researchers scattered around the campuses of both universities. What the institute needed more than anything was a home. That opportunity came in 1997 when UPMC wanted to acquire Shadyside Hospital. One condition mandated by the hospital's board of trustees for the merger was that UPMC establish a center of excellence there.

Although Herberman was intrigued by the prospect of relocating UPCI's inpatient program to Shadyside, he didn't want to leave the outpatient and research activities in Oakland, fearing that would fragment the institute even more. So, before agreeing to the move, he wanted a commitment for a new outpatient facility and space for the institute's research labs. UPMC initially bristled at the idea; "shocked" is how Herberman describes the reaction he got. Disappointed but determined, he set out to build a case for more space. Building lab space at Shadyside would not only allow UPCI to move all of its personnel to one location, but also free up two floors of space in BST. Finally convinced, UPMC officials announced plans in 1998 for the cancer center's new facility to be built adjacent to Shadyside Hospital and launched a capital campaign to fund it. Pittsburgh philanthropists Henry and Elsie Hillman provided the lead $10 million gift for the project and a name for the building. The Hillman Cancer Center today serves as home to UPCI as well as the flagship of the UPMC Cancer Centers, a network of 45 clinical care facilities in Western Pennsylvania and the surrounding region. The $130 million clinical and research complex opened in 2002. An adjacent facility, the UPMC Cancer Pavilion, houses administrative offices and a 400-seat auditorium.

In 2005, the Hillmans gave $20 million more—at the time, the largest single gift ever to Pitt and UPMC—to create the Hillman Fellows Program for Innovative Cancer Research, which provides seed money to stimulate collaborative and novel cancer research, and to launch a major five-year initiative to raise $200 million for UPCI's future growth and development.

Through the years, UPCI has become more closely associated with the nation's older, more established cancer centers. In addition, UPCI and the UPMC Cancer Centers now constitute one of the largest clinical cancer operations in the country and provide cancer care to nearly half of the patients in the region, including more than 30,000 new ones each year. The influence extends far beyond the region now; among UPMC's most recent ventures are two new cancer centers in Ireland.

UPCI's stature has grown, and so has Herberman's. Among his honors in recent years are the Governor of Pennsylvania's Award for Excellence in Science and Medicine and a Lifetime Science Award from the Institute for Advanced Studies in Immunology and Aging.

Colleagues speak of his vigor and energy. Herberman is also a reserved, intensely personal man not given to idle rhetoric. He has a permanent loss of peripheral vision as the result of surgery on his pituitary gland. Herberman is himself a cancer survivor. Six years ago, he was diagnosed with chronic lymphocytic leukemia. "It was quite disconcerting until I got reassurances that things could go well for me," he says. His leukemia has progressed very little and may well continue in that state for some time. "Fortunately I'm still feeling good," he says.

His leadership at Pitt has made a difference for untold other cancer patients.

For example, one of his first recruits, Kirkwood, has significantly advanced the treatment of melanoma, the deadliest form of skin cancer. Using a naturally occurring immune-stimulating protein called interferon, Kirkwood's group has demonstrated the regression of disease in some patients along with dramatic improvements in long-term survival.

UPCI is making significant advances in the diagnosis, prevention, and treatment of many other cancers, including breast cancer, head and neck cancers, lung cancer, and cancers of the blood and lymphatic systems. For instance, Whiteside's Immunologic Monitoring and Cellular Products Laboratory assesses patients' immune response to therapy; it can measure multiple parameters, including immune-cell types and functions as well as the cells' ability to manufacture cytokines. "We now can detect cancer and cancer progression much earlier because we can look for 10 to 15 markers rather than the one or two we were able to study 20 years ago," says Whiteside.

She also oversees a facility for generating cells and cellular products for cancer therapies like vaccines. "We're developing products for as many as nine clinical trials, not only for cancer but also for other conditions such as HIV and diabetes," she says.

And Herberman is excited about his own research partnership with Michael Lotze, a Pitt professor of surgery and bioengineering and director of strategic partnerships for UPCI. That work is unveiling how natural killer cells collaborate with dendritic cells (which are key to the body's immunity).

An institute that began with a couple of employees in 1985 now employs approximately 500 people, many of them highly respected scientists and physicians in more than 30 disciplines who have come from some of the world's leading academic research centers.

UPCI's latest headline-grabbing recruit is Nancy Davidson, who will assume Herberman's directorship duties on March 1. (See story p. 16.) Davidson, a renowned oncologist, comes from the Johns Hopkins Sidney Kimmel Comprehensive Cancer Center's Breast Cancer Program, which she directed, and is known for her work identifying the role hormones, including estrogen, play in gene expression and cell growth in cancer.

"I'm very pleased we were successful in recruiting Nancy Davidson," says Herberman. "She has the breadth of vision and background that prepares her to take on a large and complex cancer institute."

Looking back at how that institute grew, he says, "Overall, it was a terrific experience. Something I'm extremely proud of—to be given a chance to build a cancer institute and have so many terrific colleagues." Building a home for UPCI, the Hillman Cancer Center, was the cherry on top for Herberman—"It's much more than I'd first envisioned."

And these days, when Pittsburghers ask Detre where to go for cancer care, he advises them to stay right here. ■

This article, which has been updated, first appeared in Excellence Defined*, the University of Pittsburgh School of Medicine's 2007 report.*





At the Hillman Cancer Center, research takes place down the hall from clinical care.



BREAST CANCER EXPERT NANCY DAVIDSON TO LEAD UPCI | BY ELAINE VITONE

A CHOICE CHOICE

On a bitter cold, windswept day in November 2008, Nancy Davidson is packing all she can into a whirlwind trip to the city that will, in a few months, become her home. At 1:30, she has an interview with the *Pittsburgh Post-Gazette*; at 2:10, with the *Pittsburgh Tribune-Review*. At 2:30, she'll pose for a photo shoot. Her mission later this afternoon: Find an apartment.

Davidson wears no trace of fluster on her face, no falter in the strides of her Michelle Obama–tall frame, despite the excitement building around her. Just days ago, Davidson, an internationally renowned breast cancer researcher, was named the new director of the University of Pittsburgh Cancer Institute (UPCI).

"Are there any plans to move any of your research here?" one reporter asks.

"This decision is pretty fresh—I only made it last week," Davidson says. "These discussions are ongoing with my colleagues at Johns Hopkins. But we're hopeful that we'll be able to set up a collaboration."

Davidson's reputation precedes her: As a physician scientist. As the director of the Johns Hopkins Sidney Kimmel Comprehensive Cancer Center's Breast Cancer Program, one of the National Cancer Institute's Specialized Programs of Research Excellence, or SPOREs.



Nancy Davidson assumes the directorship of the University of Pittsburgh Cancer Institute on March 1.

(Her husband, Tom Kensler, a basic scientist who studies liver cancer at Hopkins, heads one of the subprojects of this grant.) As a former president of the American Society of Clinical Oncology, the largest and most prominent society of cancer physicians in the world.

In the coming weeks, Davidson's colleagues back in Baltimore react to the news with grace and good humor, despite their disappointment. "It's a win-win for everyone—except us," says her mentee Ben Ho Park, assistant professor of oncology at Hopkins and one of several who gave up time they didn't have for these bittersweet discussions. In stolen moments—while boarding a plane, taking a lunch break, driving home from the hospital late in the evening—they gush about what an exceptional director UPCI is gaining.

Park likens academics to professional sports—turnover and trades are just part of the game. Still, he says, losing a strong leader and team player like Davidson isn't easy.

"It's a shame for us and a huge, huge gain for you all," Park says. "The only reason I'm doing this is I feel like you all should know how lucky you really are."

Breast cancer research has come a long way since Davidson began her career in the early 1980s. At that point, lumpectomy as an alternative to radical mastectomy was a relatively new development, as was tamoxifen, a drug that is still widely used today. Much of the research that convinced doctors of the usefulness of these paradigm-shifting treatment strategies was spearheaded by Pitt's own Bernard Fisher (MD '43), Distinguished Service Professor of Surgery.

"It is an honor to take the lead at the University of Pittsburgh, where Bernard Fisher has led so many practice-changing clinical trials," says Davidson.

About 70 percent of breast cancers produce a protein called estrogen receptor, or ER—meaning they're dependent on the presence of estrogen to grow. Drugs that were designed to capitalize on this need—either by decreasing estrogen levels, decreasing ER expression, or stymieing the interaction between the two (like tamoxifen does)—were among the first cancer treatments of any kind that homed in on a particular, critical biological signaling pathway of a cancer cell in a relatively safe, nontoxic way.

For much of her career, Davidson has focused on how hormonal therapies worked for premenopausal women with breast cancer. She also ran one of the major clinical trials on the efficacy of hormone therapy when combined with chemotherapy in younger women.

Unfortunately, not all women respond to hormone therapy. Some have tumors that do not express ER. Others have ER-positive tumors that respond to hormone therapy for a while, but then, after a time, the treatment stops working.

"I was distressed by that in the clinic," says Davidson. "So I went back to look at this in the laboratory. I think that bidirectional flow is really important."

In work published in several journals since 1994, Davidson found that one of the reasons certain cancer cells stopped producing ER was because of epigenetics—the environment, events, and mechanisms that contribute to the gene's silencing. That is, though the structure of the DNA remains intact, other changes are introduced that prevent the gene from being expressed.

Other laboratories have begun to develop two new types of therapies, which Davidson's team has begun to test in her lab and clinic: DNA methyltransferase inhibitors (drugs that prevent epigenetic changes to the DNA itself) and histone deacetylase inhibitors (drugs that counteract the epigenetic changes to certain proteins that work closely with DNA and directly influence its functioning).

"The notion of restoring the ability to treat these breast cancer cells with tamoxifen is very exciting," says Bill Nelson, director of the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins. "That's been a major discovery of the basic biology of the disease."

"This is the next level of understanding the complexity of cancer," says Pitt's Allegheny Foundation Professor John Lazo, who cochaired UPCI's search committee for a new director.

The story of hormone therapy illustrates something Davidson describes as one of the more "insidious" characteristics of the disease she's spent decades fighting—or we should say "diseases."

"Although we call it one disease," she says, "breast cancer is in fact a whole bunch of different diseases. A lot of things have to go awry in a cancer cell, and they may be very different depending on the cell of origin. Increasingly, [research] is going to be very focused on specific biological subsets of breast cancer."

Davidson has contributed to numerous clinical trials that illustrate this biologically based approach. One was for a study of trastuzumab (Herceptin), an antibody that interferes with the tumor growth receptor HER2. This trial led to FDA approval for the drug to treat early breast cancer.

She was instrumental in a large international trial of aromatase inhibitors, agents that decrease the body's production of estrogen. The study was initially intended to last five years, but its results were so promising so early on that organizers discontinued the placebo group after three.

Davidson also led several studies of an angiogenesis inhibitor—a drug that chokes off cancer's blood supply. Most recently, she published in *The New England Journal of Medicine* her findings on one in particular: bevacizumab (Avastin), a drug that the FDA approved last spring. She found that, though bevacizumab did stave off breast cancer recurrence, it offered no advantage in actually prolonging life. Given the side effects of this toxic agent—not to mention the high costs associated with it—the study brought controversial issues of oncology to the fore.

Clinical research is by nature a slow process. And in the case of breast cancer, it takes a long time to compare one course of treatment to another. It's the best possible problem: Patients are living longer, healthier lives now than ever before.

"It's a shame for us and a huge, huge gain for you all."

"It takes a lot of patience," Davidson says as she recalls one large clinical trial she began working on more than 20 years ago. It studied what hormone therapy might add to chemotherapy for premenopausal women with certain kinds of breast cancer. "I remember I wrote [the clinical protocol for the trial] around Christmas 1987—because that was the year my son was born," she says. "And I had the chance to actually publish [the results] in the month that my son went to college."

The paper, which was published in the *Journal of Clinical Oncology* in 2005, got its start with the support of ECOG (Eastern Cooperative Oncology Group), a collaboration between multiple clinical cancer research organizations. Like its Pittsburgh-based counterpart, NSABP (National Surgical Adjuvant Breast and Bowel Project, of which Fisher was the founding chair), ECOG was established to allow researchers to pool their most precious and critical resources—patient volunteers.

Davidson is a big believer in the value of collaborative efforts—particularly when it comes to

PREVIOUS PAGE AND RIGHT: Scenes from the Hillman Cancer Center

the earliest stages of clinical trials, where blood and tissue sample results can help researchers triage potential therapies in the pipeline.

To this end, she helped organize the Translational Breast Cancer Research Consortium. As the consortium's chair, Davidson hopes that eventually the 15-member consortium will add Pitt.

"There are a lot of ideas and opportunities," she says, "and a finite amount of resources. Financial resources are even more constrained right now. We want to make sure we've used patients who volunteer in the wisest path possible."

"It is a pleasure to succeed Dr. Herberman, the founding director of the UPCI," Davidson says. "Ron is revered by all because of all that he has accomplished. He has put UPCI on the cancer landscape map, making it one of the top NCI-funded institutes in the country." (See story on p. 12.)

Davidson has her own admirers. Colleagues marvel at how she's able to wear so many hats with such apparent ease. "Physician-scientists are kind of a dying breed," says Park. "But Nancy has managed to do both—and do both extremely well. She doesn't do anything halfway."

Eric Winer, director of the Breast Oncology Center at Harvard University's Dana-Farber Cancer Institute, has known Davidson for 18 years and most recently worked with her through the Translational Breast Cancer Research Consortium.

"All of this is done in this very calm and quietly confident way," says Winer of Davidson's role with the consortium. "She leads very large efforts without making a fuss."

Davidson has honed a particular skill as a unifier. Lazo notes that after years of large-scale collaborative efforts, she's been able to bring together surgeons, internists, basic scientists, geneticists, biochemists, surgeons—you name it—and learned to speak everyone's language.

She doesn't panic or get overwhelmed, her friends and colleagues say. And Davidson knows when she needs help and isn't afraid to delegate. When she does, people don't mind.

"As long as I know what the plan is, I'll do anything for her. I'll do back flips," says Carol Riley, a nurse practitioner who's known Davidson for 20 years and worked with her for 10.

Davidson's mentor Marc Lippman—former head of the Medical Breast Cancer section of the National Cancer Institute and current chair of the Department of Medicine at the University of Miami—calls her knowledge of breast cancer "encyclopedic." In Davidson's leadership roles, scientific sleuthing, and one-on-one interactions with patients, she's known as a reassuring, neutral voice, a wise mediator who can systematically take apart even the most dauntingly complex problem and formulate a plan.

For instance, when patients come to Davidson's clinic, it's not uncommon for them to feel paralyzed by all the forks in the road: Radiation or not? Chemo or not? Standard of care or clinical trial? And how on Earth to manage working *and* taking care of the kids *and* undergoing treatment?

"She has a way of cutting through all the nonsense and getting right into the issue," says Riley. "She'll give them a time frame and say, 'Okay, for the next five days we'll think about this decision only,' or 'You need to decide that in three weeks you will have made this decision and put it behind you.' She's very methodical."

But as people point out all of this, they're quick to add that Davidson is no robot. She inspires loyalty in her colleagues and forms close bonds with her patients. "As we've been announcing to her patients that she's leaving," says Riley, "several have cried."

Davidson has a delightfully wry sense of humor, people say again and again with knowing laughs. Funny thing, though: They all have trouble coming up with examples.

"Nancy is not a stand-up-in-front-of-the-room-and-crack-10-jokes kind of person," says Nelson. "You'll share a more private exchange with her that will leave you chuckling."

Perhaps her indifference to the spotlight plays a part in why she's become so accomplished—and, ironically, so lauded.

"From the top down," says Park, "Nancy has always impressed upon all of us that our mission is not winning awards or money or accolades.

"It's really about making a difference across the street, where our patients reside."

Carolyn De Wilde Casswell was 34 when she was diagnosed with late-stage breast cancer. It had spread throughout her bones, from her head to her pelvis. And yet she felt no pain.

When it was time to choose an oncologist, De Wilde Casswell chose carefully—in all, she met with seven doctors. "And it was a team approach," she says, recalling that day in 2002 when she first met Davidson. De Wilde Casswell brought her entire family—her husband, parents, brother, and sister.

"We had to keep bringing in more chairs," she says with a laugh.

"On that first day Nancy met me, she had to tell me I don't have a normal life expectancy, that I can't have children, and that I needed to be thinking about breast cancer as a chronic illness. The only good news—I was an excellent candidate for hormonal therapy.

"She looked me straight in the eye, even with my whole family in the room, and said, 'This is what you're up against.'"

De Wilde Casswell felt like she was getting the absolute truth and best possible care from an expert. At the same time, Davidson was able to deliver the very worst imaginable news with kindness and a sense of hope.

That was it. Davidson was drafted to the team. De Wilde Casswell began a hormonal therapy and years later added a phase I vaccine clinical trial, all recommended by Davidson.

Every month, when De Wilde Casswell leaves Hopkins after her treatments, she makes a point to do something special. She started this tradition purely by accident. On the day of her first treatment, as she was leaving the hospital, she noticed that just down the street, her alma mater, Cornell University, was playing in the NCAA women's lacrosse championship semifinals. De Wilde Casswell had played lacrosse in college. She took a place at the sideline.

"It was incredible," she says. "Seeing those running, vibrant athletes and all the cheering and the exertion. It reminded me how hard I needed to work, given what I was up against."

And as she cheered, her own voice becoming part of a chorus, perhaps she was also reminded of who was on her side. ■









What looks like a mountain on top of a huge worm is actually a fluorescent quantum dot attached to a DNA repair protein as the protein scans a segment of DNA. Attaching the relatively huge quantum dot (about 20 nanometers) to the protein (about 3 nanometers) is like appending a boulder to a pebble.

DNA REPAIR LIVE AND IN REAL TIME

BY JOE MIKSCH

HOW DOES IT DO THAT?

If our DNA cannot repair itself, we are well and truly sunk. Dead, actually.

With each lesion, whether caused by ultraviolet light, other radiation, additional insults, or even normal metabolic doings, the damage mounts. Without a mechanism by which cells can identify the harm and call in a repair crew to remedy the disruption, cells can die or reproduce with rabbit-like rapidity, causing tumors. Inheritable diseases can be passed on.

Scientists know there are proteins that monitor the health of our DNA, locating errors and fixing them. One big question, though, is "How can a small team of proteins find and undo damage efficiently enough?" Human DNA contains 3 billion base pairs. An organism whose DNA we know more about, *Escherichia coli*, has a few million base pairs. For every 188,000 or so *E. coli* base pairs, there's likely to be just one DNA repair protein.

On the surface, that ratio is as absurd as having only a handful of highway workers to repair every pothole in Pittsburgh. There's just no way they can get the job done quickly enough to be effective. Right? There's no way one pothole can be filled before a dozen others crop up.

Enter Bennett Van Houten.

COURTESY BENNETT VAN HOUTEN

Not only has he solved the mystery of the apparent labor shortage, he's also managed to find a way to watch the DNA repair process happen live and in person and to identify the tools by which these molecular road crews get the job done.

His work may one day allow scientists to rescue the DNA repair process when it fails and open up new treatments for DNA-damage-related disease.

Van Houten, a PhD, leads the University of Pittsburgh Cancer Institute molecular and cell biology program and is the Richard M. Cyert Professor of Molecular Oncology and a professor in the Department of Pharmacology and Chemical Biology at the University of Pittsburgh. He came to Pitt from the National Institute of Environmental Health Sciences (NIEHS, where he held a precedent-setting joint appointment in both its intramural and extramural research divisions).

At his PC in his office at the Hillman Cancer Center, Van Houten sets up a running slideshow on DNA repair, specifically nucleotide-excision repair (NER), a DNA-mending pathway that employs proteins to identify and cut out damage and to fill in gaps. Van Houten works with *E. coli*, but the process is similar, though more complex, in mammalian cells. In fact, NER is universal among all biological organisms. It's kind of a catch-all repair mechanism in that it addresses a wide range of insults to DNA. In humans, NER is the major mechanism used to protect DNA from damage from ultraviolet light.

Van Houten is one of those guys who seems larger than he is. It's probably his ebullient personality that creates the illusion of physical hugeness. Van Houten, who arrived at Pitt in September, is "there."

His gestures are sweeping. His enthusiasm is engaging. He is a rhetorical question machine. He is very willing to spend nearly two hours explaining the minutiae of DNA repair proteins, their function, and his novel method for watching them in action in real time—an exercise that involves frequently interjecting terms such as "cool," "really cool," "very cool," and "super impressive." And that's just what half of his lab works on. (Van Houten is also pursuing studies that demonstrate how mitochondrial DNA become damaged from oxidative stress.)

Caroline Kisker, a PhD and chair of structural biology at the Rudolf Virchow Center for Experimental Biomedicine in Wuerzburg, Germany, has collaborated with Van Houten on this DNA repair work. She says that Van Houten has an outsized passion for his work, a passion so strong that a spirited discussion can sound like a confrontation.

"It is wonderful to talk to him about science even if we disagree," says Kisker. "It may even sound sometimes like a fight when we try to convince each other about our ideas, but at the end, even if we disagree, we are always best friends and have learned from each other a lot.

"The way he talks about science clearly reveals how deeply he thinks about it but also how much he is excited about it."

With his floppy mop of blondish hair, Van Houten swings in his swivel chair, turns to this reporter, and—after saying, "I'm really big into visualization"—begins to paint a picture in PowerPoint of a professional obsession: the machinery of the system that prevents injuries to DNA from killing us.

"Imagine being on a road crew, and your job is to fix potholes," he says as images click by. "Unfortunately, there aren't many of you, and you have to drive from California to New York and fix every road in between. That's what these repair proteins [in an enzyme group called Uvr] are doing."

That's not fast enough if you'd like to see all of your DNA

"They're basically looking for any perturbation in the structure of the DNA. I don't know how many miles of roads there are in the United States, but if you think about this problem, you've got to ask, 'How do you even attempt to do that?'"

The road crew consists of UvrA, UvrB, and UvrC. UvrA is the dummy of the bunch. It sees a lesion in the DNA first, but then it's stumped.

"I call it big and stupid," Van Houten says. "It says, 'You know, there's something wrong with the DNA, but I can't tell you what it is.'"

UvrA is not a particularly discerning worker, so it calls upon UvrB, the road crew supervisor, kind of. UvrB's job is to confirm that, yes, there is something wrong here, a pothole in the DNA, if you will.

Here's where UvrA, that dim bulb, lends a hand. It helps B bind to the DNA so smarty-pants can confirm A's suspicion. Such DNA damage can thoroughly bollix transcription and replication and cause irreparable damage—fatal damage—to a cell.

So in comes UvrC. C cleans crumbling asphalt from the DNA pothole by snipping out the lesion with the aid of a DNA helicase (a master at pulling apart double-helix strands). Then two colleagues, other proteins, visit the work site to fill and seal the gap.

But in an *E. coli* cell, there are between 25 and 200 UvrA molecules to 4.7 million base pairs of DNA. The ratio is similar in human cells. And the generation time of *E. coli*, even under the best of circumstances, is no more than 20 minutes. That's a lot of road to monitor in very little time. So how does the Uvr crew get the job done?

"Think about how you would go about searching every road in the United States," Van Houten says. "One way would be to fly around in a helicopter and just randomly come down on the road in certain places. But that's a three-dimensional search, and that would take a long time," particularly with all that surveying from the sky, landing, checking, and launching again.

How about a surface search? Like an "intelligent" car that could travel the DNA highways. It could trundle along each road and, when a flaw is found, notify the repair system. That might be faster, but not by a huge margin, Van Houten says.

Or, what if the smart car could hop along like a hovercraft, bounding over good DNA? Maybe it would be more like the Tarzan—"I can't come up with a good road metaphor here," Van Houten says—of the DNA highway repair crew, swinging from strand to strand, never still or in the "air" for long?

You could guess and hypothesize all day long and, with the aid of the scientific method, come up with a rational, falsifiable idea of what's going on. Or, you could just take a look.

How? Call on the quantum dot.

Quantum dots may sound like something used to help the Starship Enterprise rend the fabric of the space-time continuum, but in actuality they are little beacons of light. Consisting of semiconductors, they absorb light of any wavelength and then emit a bright band of a discrete color. The biggest quantum dots—about 20 nanometers—emit red. The smallest ones—around 12 nanometers—give off blue light. "And they're super bright," Van Houten says.

Attaching quantum dots, as small as they are, to much smaller individual proteins is kind of like appending a boulder to a pebble. But Van Houten and his colleagues found a way to mate the dot with the protein. At least they thought they did. Van Houten's lab colleague Hong Wang, PhD and master of atomic force microscopy, was able to confirm this.

Atomic force microscopy uses a tiny probe with a sharp tip (only 50 nanometers) attached to a cantilevered arm. Like a stylus on a record player, the arm sweeps across the mica surface. As it bumps over molecules, it causes a laser to deflect off the arm. The instrument captures this deflection and converts it into an image.

Van Houten pulls up a movie on his computer that's part of the PowerPoint show. Neil Kad, a lecturer in biophysics at the University of Essex, made the movies with Hong's help. "Neil worked out a way to stretch the DNA," says Van Houten, "which usually resembles a hopeless mess of spaghetti, into a tightrope, [allowing us] to watch the proteins do their stuff.

"So now we can watch proteins move," he says.

checked for damage and repaired before you're singing with the choir invisible.

Stretched out strands of DNA resemble a green spider web. A bunch of little red blobs, which are the UvrA-affixed quantum dots fluorescing, engage in a spastic dance. Some pause along the DNA web while others flash and move. No one had witnessed this life-saving dance until Van Houten's team came along. "This is a huge breakthrough," Van Houten says.

But something didn't make sense.

"The UvrA is just doing a three-dimensional (helicopter) search," Van Houten says. "But jumping from strand to strand is going to take a while. Over some pints in a pub, Neil and I calculated that with the amount of protein and the amount of DNA, it would take the proteins about four generations of *E. coli* to search all the DNA."

That's not fast enough, obviously, if you'd like to see all of your DNA checked for damage and repaired—what's supposed to be a never-ending process—before you're singing with the choir invisible. Van Houten and colleagues then suspected that UvrB might contribute to the search. So, B gets added to the mix with A, and …

"What UvrB has done here, and I don't know of any examples of this [described] in the literature, is take a protein that moves in three dimensions and turn it into a one-dimensional search," Van Houten says. That's A and B together, kind of sliding randomly on a strand of DNA. How about B on its own?

Van Houten says he would have bet a lot of money that UvrB wouldn't move at all without being told to by chemical signals from its buddies. That's a bet he would have lost. After confirming the damage first recognized by UvrA, sometimes UvrB seems to get tired of waiting for UvrC. At that point, with C already having been signaled for, B strikes out on its own, moving along one axis but somehow directed.

It's not just one protein moving in one way trying to identify DNA damage, Van Houten realized. A, by itself, does what Van Houten calls a three-dimensional search, swinging around strands of DNA. A and B together randomly walk around. And B occasionally heads out on its own to what seems to be a predetermined destination.

"Together, these three types of motion allow Uvr to clearly see all the roads in the United States," says a satisfied Van Houten.

There is, of course, a next step. And, Kisker says, Van Houten wouldn't be Van Houten if he weren't eager to take it. "He is always driven to understand different topics and will not hesitate to analyze them from all different angles to obtain a more complete picture," she says.

At the moment, as Van Houten notes, he and his colleagues can only see the Uvr proteins with the aid of quantum dots. What interests Van Houten is unraveling the structure of these proteins. Knowing how they're composed is key to knowing how they work, how they find damaged DNA. Function follows form.

Interpreting a molecular dance is key to damage assessment. "The DNA is wiggling and dancing and the repair enzymes are looking at that wiggling and dancing," Van Houten says. "If you put a lesion in the DNA, it affects the dynamics, and that's a big part of the recognition process."

Okay, but how do the proteins themselves figure out when the wiggling has gone awry? Structural biologists have found that UvrA has "zinc fingers," structures that look and act like fingers and bind to zinc. What they do, says Van Houten, is function like chemical probes. The fingers insert themselves into the DNA, poking around for chemical signals that indicate damage.

UvrB then gets into the picture. It has a structure called a helicase fold, which Van Houten says acts like the "jaws of life" emergency responders use to extricate crash victims from their cars. The fold spreads open the DNA, allowing another structure called a beta hairpin to go into the DNA and probe to confirm UvrA's suspicion of damage.

"The UvrABC system had long resisted structural analysis until Ben teamed up with Caroline Kisker to achieve a sophisticated breakthrough," says former National Institutes of Health colleague Jan Drake, a PhD who is chief of the NIEHS laboratory of molecular genetics in North Carolina.

This breakthrough, says Kisker, may have wide-ranging benefits for human health. "Maintenance of the correct genetic information is crucial for all living organisms," she says. "Mutations are the primary cause of hereditary diseases, as well as cancer, and may also be involved in aging. Eighty to 90 percent of all human cancers are ultimately due to DNA damage."

The bacterial Uvr proteins have human analogues, Van Houten says: "I think these are fundamental findings that are going to be true for the same system in human cells."

Sorting this out, says Drake, could open a window through which scientists can manipulate the DNA repair process for the better.

"Understanding key cellular systems allows [us to] recognize when mutations or environmental impacts have disabled them," Drake says. "This work provides the foundation for a new generation of studies, which have the potential to manipulate or fix repair systems to our advantage."

"I tell people that before I retire or expire, I want to change these little blobs [which represent proteins on a PowerPoint slide] into structures," says Van Houten. "My goal, and I'm really serious about this, is to make a molecular movie of how all these proteins work."

And he says this with a big smile. ■



Charlee Brodsky dedicated her book to her daughters (shown here several years ago). Her family knows the anguish brought on by bipolar disorder. One of her daughters experienced early onset of the disorder at age 10 and was hospitalized at Western Psychiatric Institute and Clinic for eight days.

MENTAL ILLNESS IN THE FIRST PERSON

PHOTOGRAPHY | CHARLEE BRODSKY

ESSAYS | CHARLEE BRODSKY AND ANONYMOUS CONTRIBUTORS

I THOUGHT I COULD FLY

These essays are excerpted, with permission, from I Thought I Could Fly … Portraits of Anguish, Compulsion, and Despair *(2008 Bellevue Literary Press, New York), which is edited and with photographs by documentary photographer Charlee Brodsky. The book was published with support from UPMC's Western Psychiatric Institute and Clinic. Some facts have been changed and identities obscured to protect privacy.*

I am a mom who has a daughter with bipolar disorder. I am also a documentary photographer. Because I live with someone who is mentally ill and have strong feelings about how mental illness is misunderstood by many, I wanted to create a body of work that would communicate the complexities and gravity of psychiatric disorders to others.

When I show people this project, they ask, *Who lives such lives?* Almost all the accounts in this book are from people I know. Finding participants was surprisingly easy. I learned that mental illness is pervasive. Some form of mental illness exists in most every family, school, and workplace, among both rich and poor, and across all ethnicities and all ages. As a friend writes, Winnie the Pooh has an eating disorder, Tigger is manic, Eeyore is depressed.

I believe it is healthy to share stories of mental illness so that the culture becomes more tolerant of the differences in how our brains work. My hope is that these stories will be comforting and educational. For those newly afflicted, I hope they learn that they are not alone. Also, I want them to learn that mental illness encompasses a wide spectrum of disorders from mild to severe, that it is physiologically based, that there are resources, and that life can be lived well even with a mental illness diagnosis. For those more knowledgeable, I hope these accounts make a contribution to the field by acknowledging the importance of simple storytelling and the sharing of everyday experiences. —*Charlee Brodsky*



Her ex-boyfriend controlled her thoughts through a bangle.

I hated the meds, the fuzzy thinking, the 20 pounds I gained. But, gradually, I began to feel more like my normal self. We began to wean me off the medications I had been taking. Things went well for a while.

Then, again gradually, in the spring of 2005, about a year after I had been off medication, I began having paranoid thoughts again. I again began to feel watched. At work, they were on to me. The light behind me concealed a camera. My computer was being monitored. Again I began to have the distorted thoughts about the lights. Where had I been? And what had really happened? Surely I could find the answer on the Internet! As I searched, I began to wonder why I had not received credit for inventing the cell phone. I had given the idea to my Uncle Curtis, a real radio whiz, who worked for Motorola. Motorola knew. They had designed their logo based on the cabbage-rose print of the dress that Auntie Lynn had given me! How could I get the credit I deserved? Surely there was money I was owed; this would help pay college tuition!

I didn't understand why Andrew and his girlfriend emptied a Baggie of aphids onto my hibiscus, or why they had done it in plain sight, as we were sitting down to dinner at the table. What had I done that would make them want to hurt my favorite plant?

And why was the little white car following me? Everywhere I went, it seemed to be there. It was becoming a little unsettling. And that pickup truck belonged to "John Turner, Plumber"—I knew that name. He had been accused of abusing his daughter.

What did that creep want with me? Was it safe to drive my truck? Hadn't he loosened the lug nuts? Someday I would be driving along and the wheels would fall off. I was conflicted when I realized that Debbie DuMont, our assistant pastor's wife, was actually my daughter. I had become pregnant long ago with Sarah's father's child, and I was sent back to the States to have this baby, who was given up for adoption. I was so young at the time. Should I tell her?

And the gold bangle that Lewis, my ex-boyfriend, had given me that I still liked to wear—take that thing off! Of course! It was the item that he needed in order to maintain control of my thoughts. The man was a witch. And so was Bridgette's high school art teacher, Miss Bentley. Struggling against me for control of my daughter's mind. But the last straw was when I realized that George was planning to kill me. He and Amanda were going to go fishing in Cuperas Creek, which was contaminated by copper; it was all over the news. And I was deathly allergic to copper; it was a rare condition, but he knew about it.

After George had fed me the fish (which he wouldn't eat, because he didn't like fish), he would be rid of me. And he and Amanda's mother could be together again. No more wicked stepmother.

I couldn't let him know that I knew. On my way to church that Sunday, I struggled for control. As I pulled into the parking lot, I saw the vehicles that concealed the men who were after me. I should have kept going: to New York City, to my sister Mary's, to get away from George. But could I trust Mary? After all, she had stolen my identity years before and had been using it to get around in Europe. She would take little side jaunts away from her psychology conferences, and my identity was her cover when she connected with the others in her network, moving drugs. Would the men believe me when I told them I hadn't known anything about it?

I had to give myself up. Tim DuMont, our assistant pastor, was the first person I saw. Should I tell him that Debbie was my daughter? I didn't. But I did ask him to take me someplace safe. I didn't think that I should be teaching Sunday school that day. This was a first for Tim, but he did just fine. He took me to his office. Later, our pastor came. They called George. When I got home, he was waiting for me. The little white car followed me home. I went out into the garden. It was hard to pull weeds and remain calm, knowing that there was a satellite up there that was taking pictures.

Back on the drugs. Permanently this time, George said.



When Rebecca's daughter returned, she had numerous new piercings up and down the curves of her ears, a belly button piercing on the verge of infection, and uncombed hair.

REBECCA'S DAUGHTER COMES OF AGE

My daughter put me in one of those moods again. It was morning, and her meds hadn't kicked in. She had attitude—the kind I don't like—and it was aimed at me. Better seen in Scorsese films than experienced firsthand. Her rudeness was unnecessary. It made me mad and hit in my gut. It put me in an emotional space where I live often because of her. But for once, I thank her for the cheek because I've decided to use that inconsequential incident to introduce my story. Jamison, a beautiful 18-year-old, was diagnosed with attention deficit hyperactivity disorder (ADHD) when she was 7 and bipolar disorder when she was 10. At 10, she experienced a year-long manic episode that may have been brought on by a drug she was prescribed for anxiety. She had been a difficult child, but it was hard to understand her destructive behavior as a matter of an odd but "within the range of normal" personality. She was shoplifting, leaving home in the middle of the night, and was dangerously aggressive toward her younger sister. We learned that she was sick, that she had a psychiatric illness, and that her brain worked differently from ours.

When I learned that Jamie had a mood disorder, the diagnosis did not at first convey the seriousness of the illness to me. "Mood disorder" sounded normal—after all, I go in and out of moods all the time. But Jamie's illness could jeopardize her life. Sixty percent of all suicides are committed by people with mood disorders. As a 10-year-old, Jamie was admitted to Western Psychiatric Institute and Clinic (WPIC) because she really thought she could fly. She had been racing everywhere, climbing on everything, and could not be contained. After an especially bad fall, I watched the pediatrician dig gravel from her knees. After Jamie's discharge from WPIC, she was put on a "cocktail" of daily medications and began a regimen of cognitive behavioral therapy. There was still a tumultuous period of many months, but her explosions became less frequent. We started having small successes. I could get her up, dressed, and out the door to catch the school bus without the tantrums. But Skittles were still close at hand if I needed a bribe.

As Jamie's health improved, I wondered if, upon meeting her, others could sense her past. Jamie has a winning smile. She is lovely to look at. She is sweet when in her proper mind. But would something in her manner betray her—would there be something not quite right? Was the illness even still there? We were told that Jamie could be a poster child for good outcomes for those with this illness. The doctor even questioned if she was truly bipolar. Few children in a WPIC study, we were told, could match her steadiness. But rather than taking comfort in this observation, I wondered what lay ahead. If all those others were in the trenches wrestling with the disease, was it just a matter of time? Jamie is 18 now. In the eyes of the law, she is an adult. In her eyes, 18 means she can do as she pleases. Full of hormones, adolescent rebellion, and a history of both stable and difficult times, she acts much younger than her age. In the past year, she's stolen large sums from our wallets and told acquaintances that she lived in California and gave up a baby girl for adoption. In the past two months, she has left home five times, once for as long as a week without her medications. On one of the returns, she had numerous new piercings up and down the curves of her ears, a belly button piercing on the verge of infection, and uncombed hair. At one point, she told us, she hadn't eaten in two days. She is in her last semester of high school but no longer goes to school and will not receive her diploma this June.

Mental health practitioners advised us to increase her biweekly therapy sessions to the more intense family-based therapy where two clinicians come to your home two to three times a week for many months. When that therapy failed, Jamie entered an intensive outpatient five-day-a-week "partial" program on the clinicians' advice, but she stopped going there, too.

A friend who survived her children's tricky adolescence asked if Jamie's behavior of the past year was "teenage stuff." I replied that it probably adds to the mix. Yet adolescence doesn't explain what appears to be a major developmental delay, a major inability to connect her actions with consequences, a major sense of entitlement, a major inability to take comfort in and enjoy her family's love, a major inability to tell right from wrong, and a major inability to set even one goal. I believe what we are seeing is Jamie's illness. But sometimes it is unclear to me what is Jamie and what is the illness. Jamie is being treated with medications prescribed for bipolar disorder and ADHD, but perhaps we're seeing a different mental disorder emerge? Or might this be a set of symptoms that, as of yet, remains undefined as an existing disorder in the DSM IV, the bible of psychiatric disorders?

Jamie has left home yet again, and I can only watch her go. Perhaps some day in the future, Jamison and I will be snuggling together on the couch, reflecting on that time when she turned 18. She will remember the thrill of the wave while I recall the darkness of the water.



He insisted that his work pants and shirts be pressed each day and that his black boots be highly polished.

A FATHER'S ODD BEHAVIOR

My earliest memories of my father's battle with Tourette's, with OCD ... I remember lots of hugs and kisses, and that he always grabbed our arms as we walked by. He grimaced and on occasion made a high-pitched grunt.

He insisted that his work pants and shirts be pressed each day and that his black boots be highly polished. My mom and grandmother starched and pressed his clothes. We helped by polishing his boots, and all the men working for him in the foundry called those boots his "lamp blacks." Those boots would be worn to almost nothing, yet every Monday they were shiny and black.

I always wondered why he checked the doors so much at night. He would go up to the front and back doors, lock them, and then turn the handle several times to check to see if it was really locked. He would walk away, grimace, grunt, and then check each door again. I felt safe that the door was really locked.

Whenever we drove in the car, the steering wheel made jerky movements, and he blinked a lot. I loved riding in his truck early on a Saturday morning because we would go into the downtown produce market and pick up cases of fruits and vegetables. We would wander through the stalls, and he would try to talk the men into selling a case of produce for a lower price. When he pointed at the produce, he would point at it several times. I thought he was making his point.

Every flower bed was perfect, with not a weed to be found. His roses always were neatly trimmed, and we learned to trim the spent buds off at the leaf stem that had five leaves and not three. This would help the rose bloom again on the same stem. He had more than 70 orchids. They were all the same kind, cymbidiums.

He loved photos of flowers and the family. The flowers were always close-up and of one bloom. Family photos were with groups of the children, and we always waved. When he used his camera, he would stop grimacing and hold very still. I wondered how he could be so still when he took photos.

He expressed love in almost overwhelming ways all of our lives. His eyes looked at you, almost straight through you. Your arm always got grabbed. He fiercely defended me. There was once an attempt upon my life, and he slept with a loaded gun under his bed for more than a year. His eyes followed me wherever I was, in and about the house. I felt comforted that he would save me if something more happened.

When I got older, I noticed these types of things in me. I play the flute and had to practice always in the morning at about 6 a.m. and then late at night if I were traveling.

I live in fear of playing badly if I do not practice.

I don't grimace, but I shake. I used to blink a lot, but I got over that as a teenager.

I iron everything. I need to have everything neatly pressed. I even iron my T-shirts. I am bothered when I do not see neat creases. I love gardening. I live in a place where I cannot do much outdoor gardening, so I have many orchids, too many orchids. I tend to take photos of flowers and people. I always take close-up photos of one flower at a time.

I love almost overwhelmingly. Sometimes my friends wonder how I can have so much love. I am overly compassionate. I feel the need to check if my friends are okay.

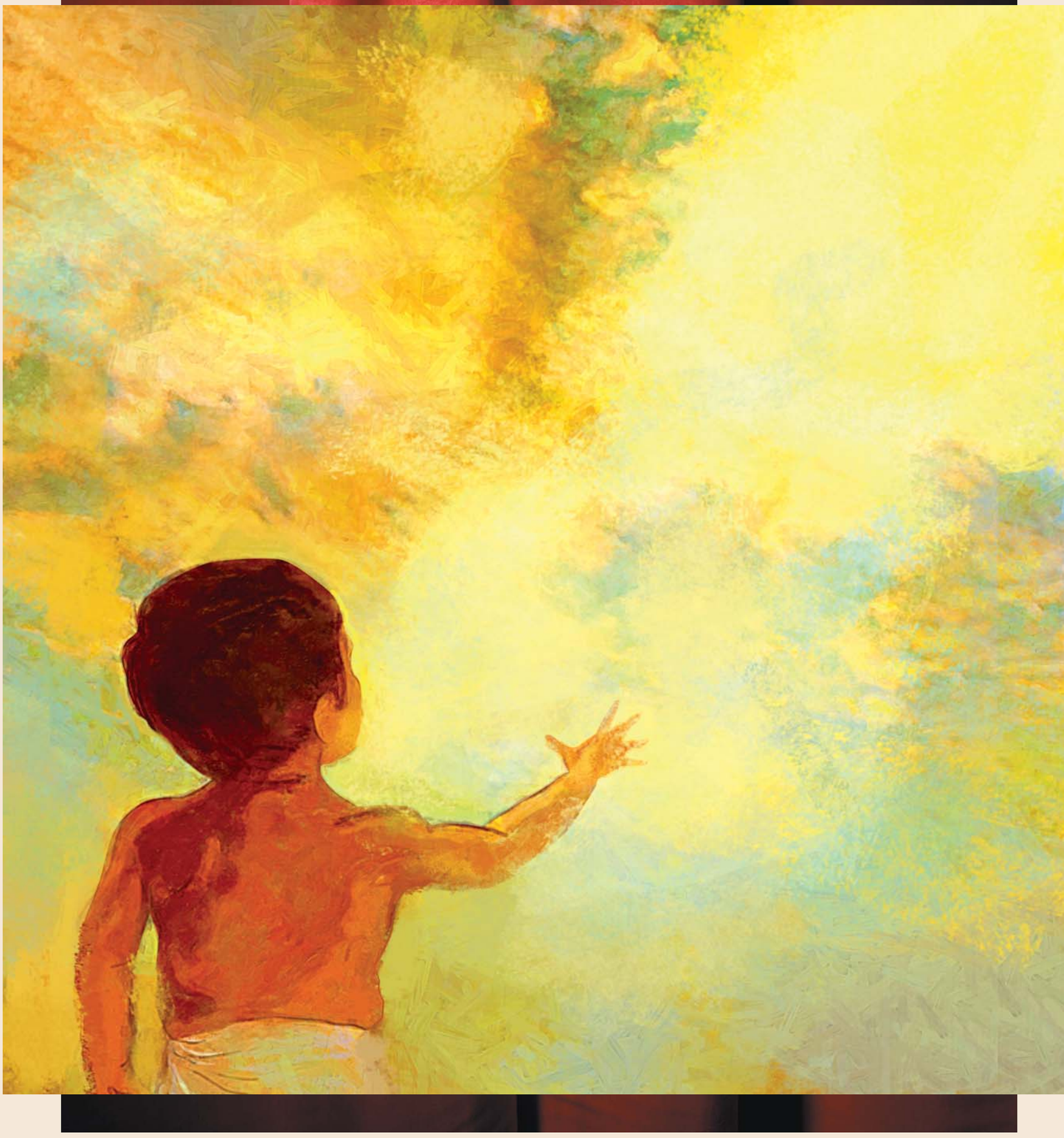
I have learned that not everyone is like this. ■

NOTE TO FAMILIES AND CLINICIANS:

For information on Services for the Treatment of Early Psychosis, Western Psychiatric Institute and Clinic's intervention program for people who may be experiencing early signs of psychotic illness, call 412-225-STEP (24 hours a day).

To learn more about the Child and Adolescent Bipolar Services Clinic at WPIC, call 412-246-5238 or see story p. 11.

For information on WPIC's Obsessive-Compulsive Disorders program and its outpatient program for children and adolescents (which recently won an award from the Substance Abuse and Mental Health Services Administration), call 412-488-4186.



ARGUMENTS FOR AND AGAINST THE EXISTENCE OF GOD

A SICK CHILD AND ALBERT CAMUS

BY TIMOTHY STOKER LAUX

ILLUSTRATIONS BY FRANK HARRIS

Author's Note: This story comes at an intersection—where the true memories of others and the imagination of the writer meet. Simply put, I recount here a tale from a time well before my brain finished wiring all its synapses. It's told with only a few known facts, but written under the mindful eyes of the protagonists—or at least a photo of them. My parents watch carefully from inside the frame as I share this story.

Their young son had been very sick—blue lips, a lack of appetite, and an overall listlessness that made my dad think that he was perhaps the only man alive who had more energy than his toddler. A spate of doctor's appointments had occurred and would occur. My dad, head bowed, would pad down the opaque halls of IBM, wondering how long his bosses would empathize as he answered every question about my condition (except the one about how much time he needed off) vaguely and in the third person.

Never one for fashion, he begins a system where, to bring a measure of stability to his life, he wears the exact same outfit every Monday, every Tuesday, and so on through the end of the workweek. The system falls apart when he occasionally must go in on Saturdays to make up time. And one day he looks down, thinking it is Friday only to be reminded it is Wednesday, and he almost tears up, realizing how much all of this is completely outside of his control. Shortly after he takes to absent-minded drumming—he is a drummer—on anything that will hold still long enough for his fingers to settle on: his desk, the steering wheel of a gray Chevrolet station wagon. He even drums the large containers of pressurized gas that line the hallways of the T.J. Watson Research Center. His coworker and closest friend, Max, is able to learn more about my father's mental state each day listening to the rhythms coming from the hallway than by taking in the words coming from his mouth.

My mom is at home with me and one, almost two, graduate degrees and her professorial knowledge of biology. She knows something is terribly wrong with me. She pays too much attention to unimportant details and finds herself thinking I am making a turnaround when, at lunch, I take nine spoonfuls of food instead of my usual six or seven. But these events signal no meaningful change.

She envies her husband for his ability to take a daily break from this reality, even though he calls home on his lunch hour every day. Only years later does she realize how terrible it is to have a reality call in the middle of the day. She sits with reality—her hands in its hands, her head on its shoulder—all day long.

Even though she never speaks it aloud and even dances around the idea in her silent prayers, some days she wonders whether getting pregnant again was the best idea; she is a few months pregnant with their second child. My kid sister lies hourly in a sauna of tears. For weeks my mom cries—for herself, for me, for the child within her, for the overall state of the world. Eventually she becomes deeply suspicious of crying. Years later, one of her hallmarks will be how she saves her tears for seasons of joy.

The blood and pathology work come back. The boy has a condition with a long name, erythroblastopenia. Those with training in the classics can readily deduce its meaning. The body has stopped producing red blood cells. This means, among other things, that the baby isn't growing, and that, because the problem hasn't fixed itself, we—Dr. Cat, the family pediatrician, always says "we"—we are looking at a bevy of treatments involving the bone marrow and perhaps a steady stream of blood transfusions as long as the anemia continues. Dr. Cat looks into the eyes of Mr. and Mrs. Laux and says, yes, in bad cases, this disease does result in the one event, besides war, which encourages some to claim human experience as their strongest evidence against the existence of God—namely, when parents must smart over what succinct phrases to put on an undersized headstone.

She sits with reality—her hands in its hands, her head on its shoulder—all day long.

Dr. Cat reaches into his white coat and takes out a map. My mom and dad know that the doctor walks to work, so for him to have a map in his pocket that belongs in his car's glove box means he saw this coming. My parents are Midwesterners; and New York City, with buildings so tall they block out a prairie-based sense of direction, is not someplace they go of their own accord. Dr. Cat realizes this, so on the map he has highlighted the route he recommends to get to Presbyterian Hospital on the West Side of Manhattan. They must go to begin the final stages of a diagnosis that cannot wait. He has already contacted the hospital to let the doctors know they are coming.

My parents make a Saturday appointment. Dad wears his Friday clothes. The family cat sees us to the door, and we gently press into the gray station wagon and head for the interstate. For the only time in her maternal career, my mother insists on holding me as we ride. She notes joyfully that her pregnant belly allows her to support and cradle me easily, and I sleep well the entire way despite her constant barrage of love talk.

This trip is the first occurrence, among many, where my unborn sister gets to support me, as she would throughout our lives, beating me to all of life's major rites of passage—including meaningful education, marriage, and, in all likelihood, parenthood, despite my two-and-a-half-year head start.

My parents budget way too much time for the journey. They arrive at the drab office before the three appointments scheduled prior to theirs. But in that waiting room, with me still sleeping, they are able to be in each other's presence in a way that has been impossible in recent months.

The time passes so quickly in small talk that the nurse has to say my name twice before they hear it. My mother stands with such gravity that I immediately wake up.

This appointment is like other appointments, only this doctor speaks a lot more and a lot louder than Dr. Cat. My parents are smart enough to keep up with him, but his ramblings unearth their weariness. They manage to stammer only a few questions at the end, but none of the ones they had discussed asking on the drive down.

The doctor says that a bone marrow sample must now be drawn, and, as if on cue, because they are on cue, a few medical residents and interns materialize in the room. One of them, the most senior, gives the speech explaining what will occur and that it is best for the parents to leave the room and wait nearby.

On the way out, my father is able to glimpse the needle—as long as my young forearm and very sharp—they will use to puncture my spine. Both he and my mother know how the procedure is done. But as they wait in a side room and nurses check on them, he vows to himself not to give away the sheer size of the instrument. Instead he tries to pick up the earlier waiting-room conversation but surrenders to silence amid the curtain of blood pressure cuffs and sterile instruments hanging from the walls. He and my mother writhe in silent, still horror as they hear two screams in the next room, one for the insertion and one for the extraction. My mother swears to this day she felt both.

I am placed in the car seat on the way home. It's a quiet ride. My dad adjusts the rearview mirror between me and the road. Other than that, the only noises are his gloved hands tapping the steering wheel and my mom turning around in her seat and tickling my feet a hundred times to make sure I still number among the living. My parents reach home as the winter sun sets and only realize then that they haven't eaten since the night before.

My mother and father never had cause to visit that hospital again. I got back there eventually, for a medical school interview in early 2008.

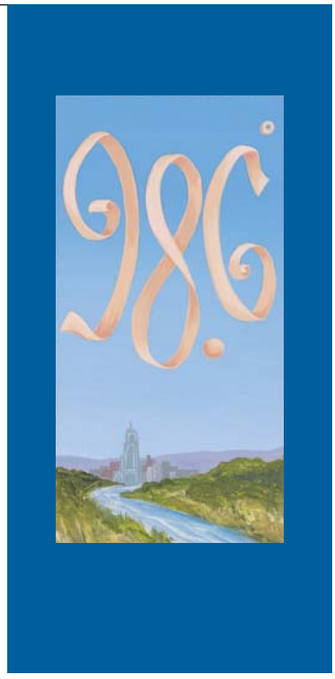
In the ensuing weeks after their trip, even my father, who didn't want to get his wife's hopes too high, had to admit that I did seem to be much more comfortable and in better health. And soon Dr. Cat was able to conclude, with exquisite joy, that it appeared as though I would be rejoining the ranks of the chronically healthy. This turnaround remains the event that, to this day, will be my parents' counterbalance to Camus' challenge that the proof against God's existence is the death of children.

Steven and Kooki Laux gave birth to a healthy baby girl, Kathleen, in December of 1983. ■



Timothy Stoker Laux, author of this piece of fiction based on his life, is a first-year medical student at the University of Pittsburgh.

People and programs that keep the school healthy and vibrant



GENETIC TIME BOMBS

GIFT TARGETS CANCER CULPRITS

BY REID R. FRAZIER

Say there's a problem inside the nucleus of a breast cell. The DNA has broken because of radiation, a carcinogenic chemical, or a naturally occurring insult. A pair of genes, BRCA1 and BRCA2, come to the rescue. They produce proteins that survey the broken double helix and put it back together, like a team of carpenters after a hurricane.

At least that's what's supposed to happen. For people who carry a mutation in BRCA1 or BRCA2 (pronounced "bracka one" and "bracka two" around the lab), the damage isn't repaired properly. This can be a serious problem. The disturbed DNA might code for cancer-fighting proteins; if the "broken ladder" is never repaired, the proteins might never get deployed. In time, many of the women who carry this mutation will develop breast or ovarian cancer. Men who carry the mutation are more prone to prostate, breast, and pancreatic cancer. The mutation can be passed on to children.

The BRCA mutations are sometimes thought of as genetic time bombs for the one out of every 345 Americans who carry them. Among Ashkenazi Jews, approximately one in 40 carry the mutation. Relatively little is known about the biological pathways that lead from BRCA mutation to cancer. Why are only certain cancers associated with the mutation, when every cell in the body carries the BRCA gene? Scientists don't know yet. However, thanks to a gift from a local family foundation, Pitt researchers might soon have some answers.

The David S. and Karen A. Shapira Foundation has announced a $1 million gift to the University of Pittsburgh Cancer Institute to establish the Frieda G. and Saul F. Shapira BRCA Cancer Research Program. With additional donations from UPMC, the local community, and matching funds from the Shapira Foundation, the gift will total $5 million.

With Shapira program support, Pitt scientists will conduct research into how BRCA genes work and continue to pursue early diagnostic tools for people with the mutation.

"The Shapira family has recognized this is a major problem, particularly for members of the Ashkenazi Jewish population," said Ronald Herberman, the outgoing director of UPCI and the UPMC Cancer Centers.

Among the projects researchers will undertake is a comprehensive epidemiological study of more than 100 families with BRCA mutations to determine what roles environmental exposures and personal behaviors play in the development of cancer. Another project will examine the role other genes play in expressing the BRCA mutations.

Developing better diagnostics is critical, because some women with the BRCA mutation have radical mastectomy or have their ovaries removed to prevent cancer. These are extreme surgeries with profound effects on a woman. "We certainly only want to do them when they're necessary," Herberman says.

The program will support research into new imaging technologies and the study of proteins that may serve as biomarkers to better detect the early stages of cancer.

"How these mutations play out or how they result in development of cancer, all of that is very poorly understood right now," Herberman says. "But we believe that with the constellation of expertise we have and with these new resources, we can make a quite substantial impact in the overall field." ■

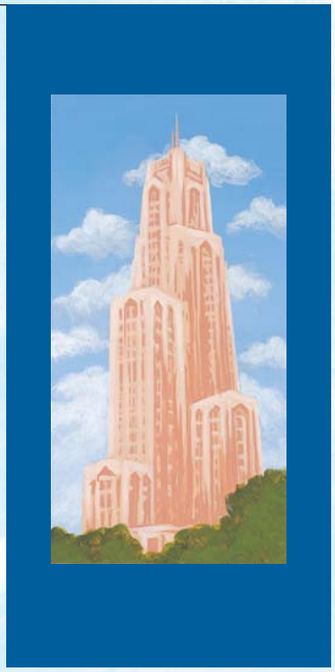
BOOSTER SHOTS

Henry Mankin (MD '53) and his wife, **Carole Mankin**, have given regularly to the University of Pittsburgh School of Medicine through the years. In 2008, they increased and put a name to their continuing philanthropy at Pitt: the Henry and Carole Mankin Endowed Fund for the School of Medicine. Mankin, the Edith M. Ashley Professor of Orthopaedics at Harvard Medical School, has a great appreciation for the research at Pitt and, as a longtime member of the School of Medicine's Board of Visitors, he has been witness to its exponential growth. Duly impressed, the Mankins have left the use of the funds at the dean's discretion.

Last summer, several Pitt med students could be found in clinics afar—in Mexico, Haiti, Malawi, Tibet, and elsewhere—where they put their skills to use and gained new ones while caring for patients and carrying out clinical research projects. Originally funded by the **Medical Alumni Association** through **Beth Piraino**, professor of medicine, who donated honoraria from speaking engagements, Pitt's summer enrichment program is now supported by donations from medical alumni through the MAA general fund. In March, medical students will have an opportunity to submit applications for 2009 service projects.

–Chuck Staresinic

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



CLASS NOTES

'60s

Barry Brenner (MD '62) has spent a long and successful career characterizing kidney disease and developing ways to combat it. (The eighth edition of his tome *The Kidney* was published in 2007.) Lately, he has turned to epidemiology, identifying risk factors that he hopes will lead to ways to prevent kidney disease. Brenner argues that the reason many newborns weighing less than 4 pounds develop kidney disease as adults is that they are born with half the number of filtering units that a typical-weight baby has. They may have normal kidney function for decades, but they are at risk for high blood pressure and kidney disease later in life. Brenner is the Samuel A. Levine Professor of Medicine at Harvard University and director emeritus of the renal division at Brigham and Women's Hospital. He was named a University of Pittsburgh Legacy Laureate in 2008.

'70s

By the time they reach age 40, one out of every 100 women suffers from premature menopause or what is now more properly referred to as primary ovarian insufficiency (POI). **Lawrence Nelson** (MD '73), who heads the Unit on Integrative Reproductive Medicine at the National Institute of Child Health and Human Development, has seen teenagers with this diagnosis. Although 90 percent of women with POI are never given a definitive cause for the disease, Nelson's research has proven that autoimmunity is at least one cause. Nelson has received a number of awards for his research, including the U.S. Public Health Service Meritorious Service Medal and the Hagerman Award of the National Fragile X Foundation. Nelson was recently awarded patents for his discovery of MATER, a human gene critical for female fertility.

Before medical school, **William Sonis** (MD '74) studied theater arts at Pitt. He says his office is his theater now: "What else do you do with kids but play?" Sonis is director of the residency program in child and adolescent psychiatry at Drexel University and was recently awarded the Parker J. Palmer Courage to Teach Award by the Accreditation Council for Graduate Medical Education (ACGME). "I don't teach; I facilitate learning," he says. "Teaching is passive. I set up the structures and provide the courses, but it's the resident's job to learn. Learning is active."

In his 20s, **Stephen Dummer** (MD '77, Infectious Diseases Fellow '84) worked as a reporter for *Newsweek* and befriended a number of physicians. This reawakened his interest in science, and at the age of 30, he began medical school at Pitt. After a surgical residency at Stanford University, he pursued a Pitt fellowship, where Monto Ho, then chief of infectious diseases, encouraged him to specialize in treating infectious disease in transplant patients. Dummer is now the director of the transplant infectious disease program and a professor of medicine at Vanderbilt University.

'80s

According to the National Psoriasis Foundation, more than half of the patients living with psoriasis report that the disease plays a debilitating role in their daily lives. Psoriasis is a chronic autoimmune disorder most often characterized by lesions on the skin. It's associated with other serious health conditions, such as diabetes, heart disease, psoriatic arthritis, and depression. **Cynthia Guzzo** (MD '82) ran the psoriasis center and dermatology clinical studies unit at the University of Pennsylvania for 10 years before transitioning to work in the pharmaceutical industry. Now, in her role as vice president of Centocor, a subsidiary of Johnson & Johnson, she leads teams of clinical study investigators at sites around the world. One of the studies she led resulted in the development of Remicade, a drug that has been approved to treat six diseases, including psoriasis, and has been used by more than a million patients worldwide.



Guzzo's teams run clinical studies worldwide.

CLARION CALLS

THIS SURGEON WANTS TO CHANGE A FEW THINGS

Timothy Eberlein (MD '77) has some concrete ideas about what surgeons can change about their work that would make a world of difference for cancer patients.

In speeches and papers, Eberlein has issued some clarion calls to his fellow oncological surgeons. The 2003 Hench Awardee is member of the Institute of Medicine, director of the Siteman Cancer Center at Washington University in St. Louis and Barnes-Jewish Hospital, Bixby Professor of Surgery, and chair of the Department of Surgery.

For one thing, he says surgeons should design more clinical trials for cancer. Otherwise, they are leaving a hole in cancer care, he believes.

"Traditionally, in most cancer centers, surgeons aren't very active in clinical trials as the principal investigator. In most institutions, it's probably the medical oncologist," he says.

Yet surgeons see things that other doctors may not, Eberlein explains. Imagine a surgeon in the middle of what was originally thought of as a routine procedure to relieve gastric reflux who then begins to suspect a cancer of the gastroesophageal junction. "A medical oncologist may have never seen that patient if there wasn't [an initial] diagnosis of cancer," Eberlein points out.

FRANK HARRIS

'90s

While watching a scene in the film *My Tale of Two Cities* alongside 1,200 others at Pittsburgh's ornate Byham Theater, **Doug Kress** (Dermatology Resident '93, Pediatric Dermatology Fellow '95) leaned over to his wife and whispered, "Honey, I filmed that." Years earlier, Carl Kurlander—a friend, Visiting Distinguished Senior Lecturer in Pitt's film studies program, and Hollywood producer and screenwriter—described his vision of a film about Pittsburgh. "Make it," Kress responded. "I'll get you started." Kress was the first backer for Kurlander's project, which evolved into an independent, feature-length documentary that premiered at California's Sonoma Valley Film Festival in 2008.

Kress is chief of the pediatric dermatology division for Children's Hospital of Pittsburgh of UPMC and a Pitt clinical associate professor of dermatology. Through his private practice, he and his partner are developing a teledermatology project with Children's that will allow them to consult on cases remotely.



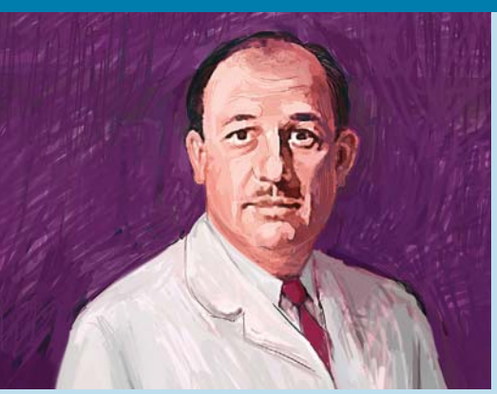
Kress at a screening of *My Tale*.

Ed Kassis (MD '99) completed a general surgery residency at Johns Hopkins University and a surgical oncology fellowship at the National Cancer Institute. He is now one of two thoracic surgery fellows at M.D. Anderson Cancer Center in Houston. "Patients come to us with difficult problems that have no easy solution. There are a lot of nuances to the field, but the majority of the time we are able to help them through a very difficult time in their lives." Kassis will be an attending physician upon completion of his program in June 2009. He'll also continue research in molecular oncology.

Injury is the number one cause of death in American children. In fact, an injury is more likely to kill a child than all diseases combined. As an assistant professor of pediatrics in Baylor College of Medicine participating in its Educational Scholars Fellowship Program, **Karyn Kassis** (MD '99) is developing a pediatric trauma curriculum. "Trauma is generally considered more of a surgical subspecialty, but the pediatricians are the ones working in the ER and often the first to see the trauma patients," she says. After completing her pediatrics residency eight months pregnant, she decided that moonlighting in the ER was the best way to complement the demanding schedule of her husband, Ed Kassis.

How rare is the premature-aging syndrome known as Hutchinson-Gilford progeria? A study published in *The New England Journal of Medicine* last year, with **Sarah Clauss** (Pediatrics Resident '99) as a coauthor, enrolled 15 children, describing them as "nearly half of the world's known patients." Clauss, a pediatric cardiologist at Children's National Medical Center in Washington, D.C., worked with some scientific superstars on the study, including Francis Collins, then head of the National Human Genome Research Institute, who discovered the gene at the heart of this disease. Clauss contributed her clinical expertise in lipids, atherosclerosis, and echocardiography to present the most thorough characterization to date of this disease, which usually leads to death at around 13 years of age. Clauss says that she examined one patient on a weekend and brought her 5-year-old daughter along. "I had explained to her beforehand that the child was going to look different. ... They look kind of wizened." After a couple of hours during which the children played together, Clauss' daughter said, "Mom, I don't know what you're talking about. He was perfectly normal."

—Missy Raterman and Chuck Staresinic



Eberlein speaks up about how surgeons can improve care for cancer patients.

Eberlein would also like to see more cold, hard data collected about whose patients are faring better than others. And he wants to see such data applied to practices. (He notes the American Board of Surgery already requires some outcomes-based criteria for recertification.)

So once you have this data, how do you approach individual surgeons about how they measure up statistically—without ego and pride getting in the way?

"It's most important not to be punitive," Eberlein says. "There are ways you can sit down with knowledgeable people. You can say, 'Here's the way I do liver resections. I tend to lose less blood.'" That's the kind of information surgeons are interested in, he says.

Has this approach worked for him?

"Surgeons are competitive," Eberlein says. "If I find out that your [patients'] length of stay is shorter than mine, I want to know, 'Why is that?' It doesn't take very long for me to replicate that so my patients get out of the hospital sooner." *—Erica Lloyd*

THE WAY WE ARE
CLASS OF '79

The fabled Nephron Art Contest has been democratized, says Pitt professor of medicine **Jamie Johnston** (MD '79). One student this year was inspired to build a *papier mâché* dragon in the shape of the basic kidney unit, but the number of entries has dropped through the years. So Johnston now provides each student with a fill-in-the-blanks nephron. And he went retro: Drawing on the chalkboard, he talked kidney physiology. Then, he worked through scenarios such as dehydration, high salt, and low salt—"running the nephron," as he calls it.

Johnston is a past winner of a National Golden Apple. High attendance and enthusiasm seem to be the norm among his students. Despite the old-fashioned chalk talk, he's been an early adopter of new technologies in the

continued on p. 38

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continued from p. 37

classroom. He notes that all of Pitt's first- and second-year lectures are available as online videos and podcasts. In 2008, Johnston was elected the director of Pitt's new Academy of Master Educators—a collective that he describes as "very solid evidence on the part of the administration that they support the development of medical educators."

"I'd be surprised if there are five or six medical schools in the country that have anything like this," he adds.



Johnston



Rubash



South-Paul

For a guy who says he doesn't get back to Pittsburgh much, **Harry Rubash** (MD '79, Res '84) sure has a lot of nice things to say about the place. (He'll be here for the 30-year reunion of his class in May, by the way.) Rubash, an expert in reconstructing failed hip and knee replacements, is chief of orthopaedic surgery at Massachusetts General Hospital and professor of orthopaedic surgery in Harvard Medical School. He looks back on his years of training here and says, "To this day, I regard the physicians and the teachers [at Pitt] as the best in their field, because they instilled in us an incredible love of the profession and a dedication to our patients."

Shortly after leaving Pittsburgh for Boston, Rubash created a full medical scholarship at Pitt in his late father's name.

After two decades at Johns Hopkins University, where she was most recently director of prevention programs at the Sidney Kimmel Comprehensive Cancer Center, **Kathy Helzlsouer** (MD '79) is now director of the cancer prevention center at Mercy Medical Center in Baltimore. She remains a Hopkins professor of epidemiology. In 2007, Helzlsouer received a National Cancer Institute award for outstanding service and scientific leadership. She is now leading an effort at NCI to study ways that vitamin D can reduce the risk and recurrence of certain rare cancers.

At Mercy Medical Center, she studies cancer survivorship. "We are doing well with treatment of many cancers," she says, "but now we're finding problems that are contributed to by the treatment. Since people are surviving, we need to know more about what happens next to help patients have the maximum quality of life as they survive their cancer."

Jeanette South-Paul (MD '79) spent several years serving at the Uniformed Services University of the Health Sciences before becoming the Andrew W. Mathieson Professor and chair of the Department of Family Medicine at Pitt. She's won a number of awards for community service, research excellence, teaching, and mentoring, including the prestigious Joy McCann Foundation Mentoring Award.

Her focus, she says, has been community work that eliminates health disparities.

She recently completed a four-year study revealing that women in minority populations suffer from dramatically higher incidences of depression, high blood pressure, and other risk factors for heart diseases. Data gained during this project led South-Paul, who established the first ambulatory center in the UPMC network to provide care to uninsured patients, to organize an effort in which behavioral health services and primary health services are delivered in one location. "For me, research is of no value if it doesn't create change in the community where people sit," she says.

Jeffrey Milsom (MD '79), section chief and Jerome J. Decosse Professor of Colon & Rectal Surgery at Weill Medical College of Cornell University, has received international acclaim for improving laparoscopic techniques in colon surgery. Under his leadership, his section now performs 90 percent of surgeries using such minimally invasive techniques. He is now exploring a new approach for endoscopic surgical procedures. "We are redesigning how endoscopes are used to make procedures much more therapeutic than diagnostic." Milsom is also partnering with bioengineers and neurosurgeons to advance the development of surgical devices and rethink operating room design to accommodate new technologies.

—MR & CS

MITCHELL B. MAX

JULY 10, 1949–OCT. 22, 2008



Max

While on a sabbatical in Israel in the late 1990s, pain researcher Mitchell Max worked with scientists who inspired him to delve into genetics, thinking that might lead to new strategies and new drugs for pain relief. Years later, he was key to the discovery of genetic variations that help to explain why people have different pain sensitivities.

Max, a professor of anesthesiology at the University of Pittsburgh and senior investigator in the Center for Pain Research, died in October at age 59.

A neurologist, Max was a graduate of Harvard Medical School. He conducted research for more than 20 years at the National Institute of Dental and Craniofacial Research and was chief of its clinical pain research section and medical director of its Pain Research Clinic. He also served as a captain in the U.S. Public Health Service. Publishing in journals such as *Nature Medicine, Pain*, and *Nature Reviews Drug Discovery*, he was an authority in the field. In recent years, by identifying the genes and proteins involved in pain, Max and others were opening the door to understanding the molecular events that lead to the sensation of pain. Shortly after his death, *The Journal of Pain* published his editorial, "Addressing the Decline in NIH Pain Research Funding."

—CS

IN MEMORIAM

'30s

RUTH S. MASTERS
MD '35
DEC. 9, 2008

'40s

CHARLES MATTHEWS SWINDLER
MD '40
OCT. 18, 2008

JAMES STANTON TIPPING
MD '41
NOV. 22, 2008

EARL KEENEY WALLACE
MD '47
NOV. 14, 2008

'50s

NICHOLAS CARROLL CHUBB
MD '51
OCT. 20, 2008

CHARLES M. REEL
MD '51
OCT. 23, 2008

CHARLES ROBERT SLOAN
MD '55
AUG. 2, 2008

DENNIS HOEFFLER
MD '57
SEPT. 2, 2008

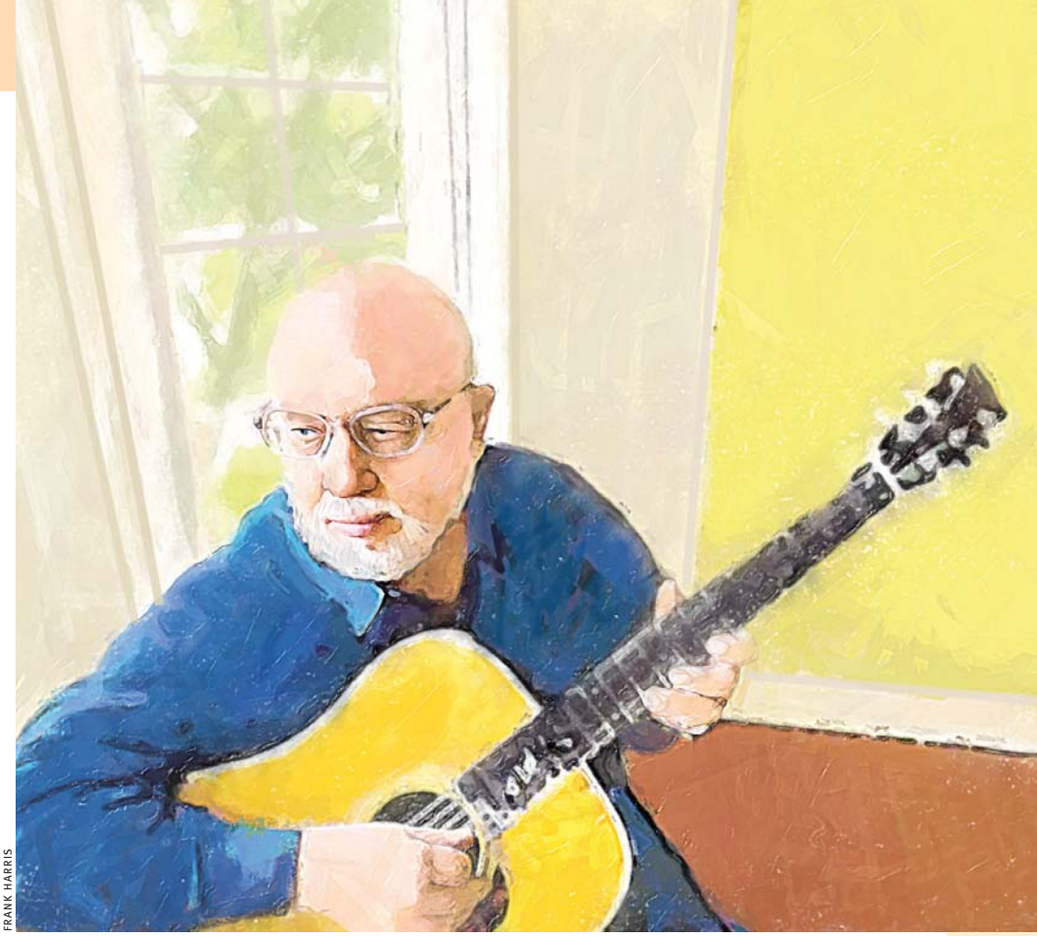
JOSEPH FRANCIS MCKERNAN
MD '57
JULY 24, 2008

'80s

C. STEPHEN JEFFRIES
MD '83
OCT. 16, 2008

RICHARD BERGMAN
A MIND OF HIS OWN

BY SHARON TREGASKIS



FRANK HARRIS

In Pittsburgh, Bergman played blues gigs at Shadyside's Loaves and Fishes. He often carries his guitar to conferences to jam with other scientists.

Richard Bergman's beard very nearly cost him his PhD.

Pittsburgh in 1965 was on the cusp of a cultural revolution. Reproductive endocrinologist Ernst Knobil, then professor and chair of Pitt's physiology department, hewed to the European model of academia—strictly hierarchical and exceedingly formal.

"Well, Bergman," said one professor offended by the 20-year-old grad student's new look, "if you can't be an intellectual, you should at least look like one."

John Urquhart, professor of physiology and Bergman's adviser, stepped in.

"John had to intervene [with the faculty] and tell them I could do whatever I wanted," says Bergman, who still sports some whiskers. "They finally capitulated."

But Urquhart didn't really mean his protégé could do anything. Soon after, Bergman bought a motorcycle, and Urquhart offered him a choice: the bike or the PhD.

"I don't want to train someone only to have his brains splattered over a curb in Pittsburgh," Bergman recalls being told.

"So I had to sell the thing."

Now the chair of physiology and biophysics at the University of Southern California's Keck School of Medicine, Bergman (PhD '71) serves as editor-in-chief for the journal *Obesity* and has more than 300 scholarly articles to his credit. A 2006 recipient of the American Diabetes Association's Banting Medal for Scientific Achievement, the 64-year-old scientist is perhaps best known for the eponymous model that predicts which patients are likely to develop type 2 diabetes. Bergman's minimal model was dubbed "the gold standard" by then-ADA president Robert Rizza when announcing the Banting award. To build the model at the University of Southern California in the '70s, Bergman deployed his undergraduate engineering training, marrying quantitative and qualitative analyses of glucose metabolism.

"He's got a very broad-based approach to interesting scientific questions," says University of California, San Diego Professor of Medicine Daniel Porte, who collaborated with Bergman throughout the '70s and '80s.

"It was his mathematics and model and our physiology and data, but fundamentally, it was a lot of fun. We could look at the same data, argue about it pretty vigorously, and then go out for a drink."

It took more than five years for Bergman's model to catch on with other scientists, and Bergman credits Porte's collaboration for bringing the systems approach to the mainstream.

He's doubtful that young scientists would take such a route today.

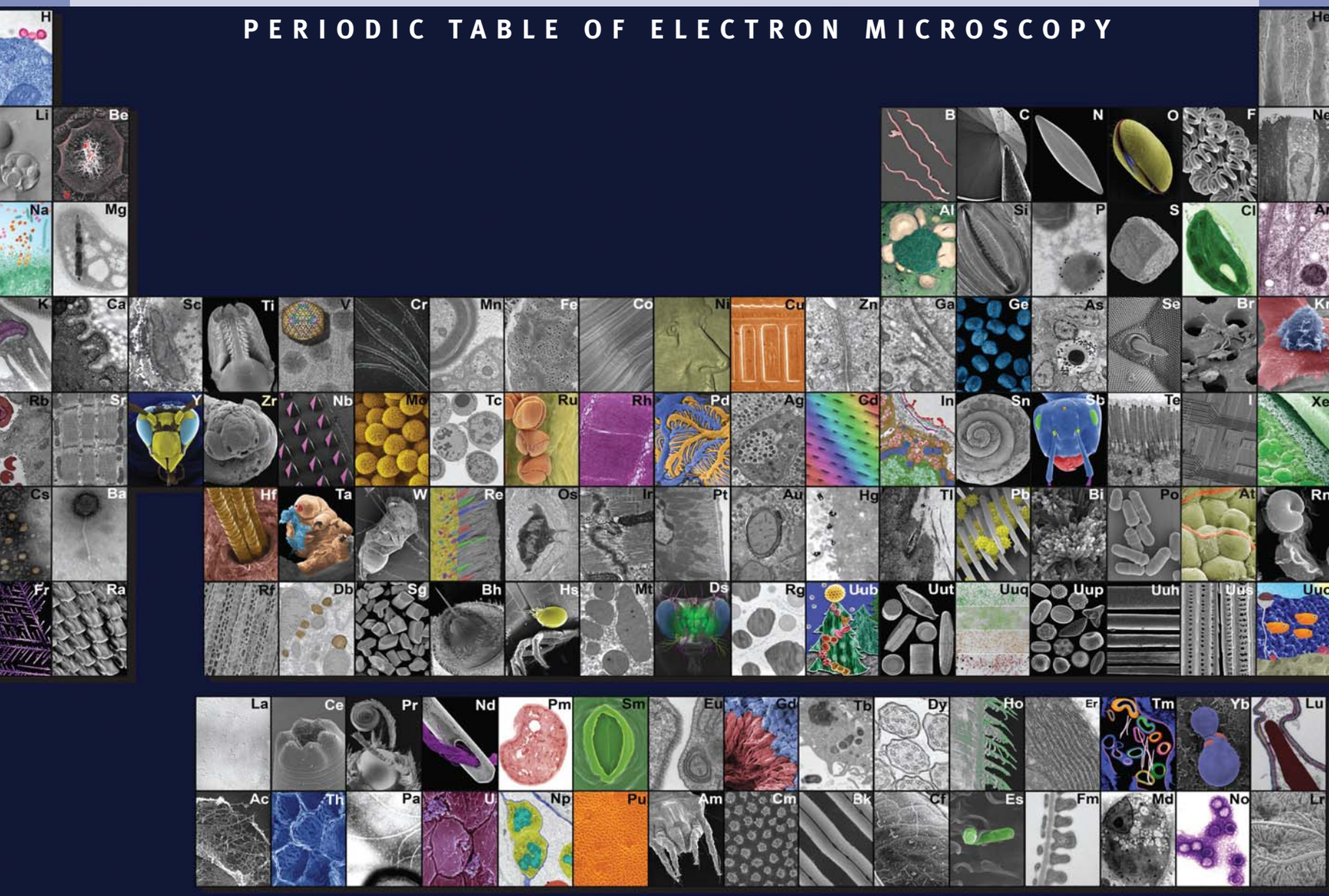
"When I came up, people realized you had to develop something, and it might take some time," says Bergman. "Now everyone's looking for something to be in *The New York Times*, which means it has to be in *Science*, *Nature*, or *The New England Journal of Medicine*. Taking the risky approach I took—doing something arcane and not understood by a large fraction of the community—is probably suicide for a young scientist."

An adviser to more than 30 graduate students and nearly two dozen postdoctoral fellows throughout the course of his career, Bergman credits Western Psychiatric Institute and Clinic Research Director Arthur Mirsky, a psychotherapist and physiologist, with cultivating his interest in diabetes and Urquhart for honing his capacity for independent research. "Science is one of the few institutions left where you still train people on a one-on-one basis," he says. "It's incredibly fulfilling."

Diane Finegood, founding scientific director of the Institute of Nutrition, Metabolism and Diabetes at the Canadian Institutes of Health Research, earned her PhD in Bergman's labs at Northwestern and USC.

"Dr. Bergman was critical in cementing for me the importance of thinking of the mentee as a total person," she says. He also taught her the value of "giving people you train a lot of rope," she adds. "Some students get tangled up in the rope, but with smart ones, it's a lot better than telling them what to do." ■

PERIODIC TABLE OF ELECTRON MICROSCOPY



WHAT WOULD MENDELEEV DO?

Donna Beer Stolz, research assistant professor of cell biology and physiology and assistant director of Pitt's Center for Biologic Imaging, somehow got it into her head last summer to take on an art project—more specifically, she decided to create the Periodic Table of Electron Microscopy. Her idea was to find something that would represent each elemental square and put it under the microscope.

"There are lots of periodic tables," Jonathan Franks, artistic and scientific collaborator at the center, explains—like the Periodic Table of Mixology, a college student's cocktail guide, or the Periodic Table of Fishing Lures and Flies, which Stolz remembers seeing on a T-shirt. "But they don't try to match their periodic table to the elements." Stolz didn't realize the challenge the task would present. (What do you do for Rf, anyway, when you can't acquire any single-celled rotifers? Up against the deadline for the display at this year's science festival, Stolz ran to a fabric store, snatched a handful of raffia, then handed it off to Franks, saying, "Hurry up and take the photo!") One hundred eighteen donated and gathered samples later, she had her creation.

Every square has a story. An undergrad working with Professor Graham Hatfull isolated a virus and named it. His image of "Awesome the Bacteriophage" replaced Ba (barium). Stolz's favorite is an image of a tardigrade for Ta (tantalum). This clawed microscopic invertebrate, commonly referred to as a water bear, can enter a state of cryptobiosis and survive for years before being introduced back to life through rehydration.

You've probably been wondering about Bk (berkelium), to Stolz aka broken record. "That is actually the track 'Black Country Woman' from the Led Zeppelin record *Physical Graffiti*," says Stolz. "You can see the grooves even though it was warped from spending the summer of '78 in the back of an old boyfriend's truck. Jonathan, who is a musician, had a terrible time breaking that record." *—Missy Raterman*

THIS PERIODIC TABLE IS THE COMBINED WORK OF PAST AND PRESENT STAFF MEMBERS FROM THE ELECTRON MICROSCOPY UNIT OF THE CENTER FOR BIOLOGIC IMAGING FROM 1997 TO 2008: DONNA STOLZ, JONATHAN FRANKS, MARA SULLIVAN, ANDREW BARCHOWSKY, ELIZABETH IANNONE, MING SUN, DORIS CLAY, MARC RUBIN, ANA LOPEZ, FENGLI GUO, KATIE CLARK, FRAN SHAGAS, AND SIMON WATKINS. ADDITIONAL IMAGES AND SAMPLES WERE KINDLY PROVIDED BY DOZENS OF OTHER RESEARCHERS, BOTH AT PITT AND OTHER INSTITUTIONS.

CALENDAR

OF SPECIAL INTEREST TO ALUMNI AND FRIENDS

For information on an event, unless otherwise noted, contact the Medical Alumni Association: 1-877-MED-ALUM, 412-648-9090, or medalum@medschool.pitt.edu. You can also visit the Web site at www.medschool.pitt.edu/alumni

WINTER ACADEMY
FEBRUARY 21
Ritz-Carlton Resort
Naples, Fla.
For information or to request an invitation:
Pat Carver
412-647-5307
cpat@pitt.edu
www.winteracademy.pitt.edu

FISHER LECTURE
FEBRUARY 25
4 p.m.
Lecture Room 6, Scaife Hall
Nancy Davidson, MD, Speaker
For information:
www.surgery.upmc.edu

BAHNSON LECTURE
MARCH 18
8 a.m.
Lecture Room 5, Scaife Hall
Mark Orringer, MD '67, Speaker
For information:
www.surgery.upmc.edu

STARZL LECTURE
APRIL 1
4 p.m.
Lecture Room 6, Scaife Hall
Clyde Barker, MD, Speaker
For information:
www.surgery.upmc.edu

PHOENIX HEALTH SCIENCES ALUMNI RECEPTION
APRIL 18
Phoenix, Ariz.
For information:
Pat Carver
412-647-5307
cpat@pitt.edu

MEDICAL ALUMNI WEEKEND 2009
MAY 15–18
Reunion Classes:
1949 1954
1959 1964
1969 1974
1979 1984
1989 1994
1999

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

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

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

REUNION DINNERS
MAY 15
Class of 1959
7:30 p.m.
Concordia Club

Class of 1949
Class of 1954
7:30 p.m.
Scaife Hall

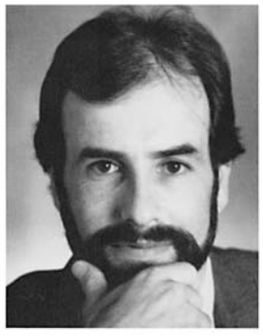
ALUMNI CHAMPAGNE BREAKFAST
MAY 16
9 a.m.
Herberman Conference Center
UPMC Cancer Pavilion

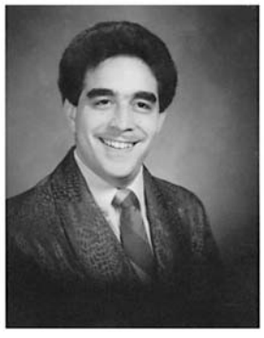
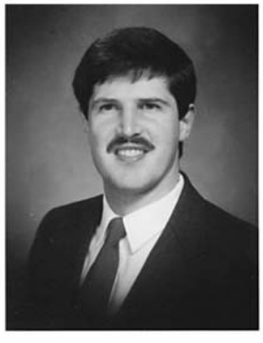
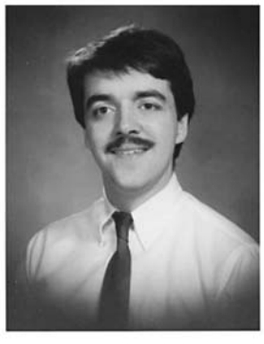
REUNION GALA
MAY 16
7 p.m.
Carnegie Science Center

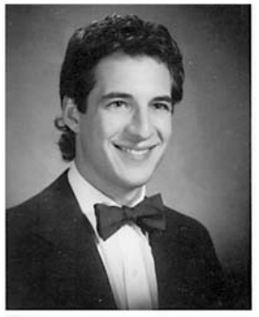
SCOPE AND SCALPEL'S "HOW TO SUCCEED IN MEDICAL SCHOOL WITHOUT REALLY TRYING"
MAY 16
4 p.m.
MAY 17
2 p.m.
Carlow University
For information:
www.scopeandscalpel.org

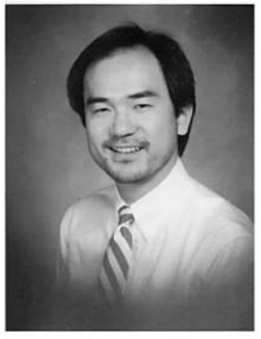
CLASS OF 2009 COMMENCEMENT
MAY 18
10 a.m.
Carnegie Music Hall

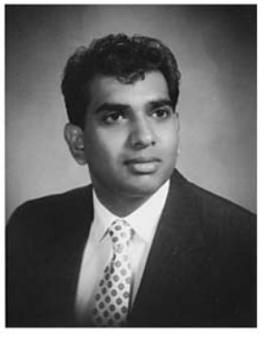
TO FIND OUT WHAT ELSE IS HAPPENING AT THE MEDICAL SCHOOL, GO TO www.health.pitt.edu





GUESS WHO?

Time to warm up for Medical Alumni Weekend 2009. Dust off your copy of the *Hippocratean*—as we did here with the 1989 edition—and reminisce. Extra credit for anyone who can tell us a good med school story about these or any other members of the Class of '89. Send your stories to medmag@pitt.edu, or

Pitt Med
University of Pittsburgh
400 Craig Hall
Pittsburgh, PA 15260

Medical Alumni Weekend
May 15–18, 2009
For a list of classes having reunions this spring, turn to the other side of this page.

FOR MORE INFORMATION:
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medalum@medschool.pitt.edu
www.medschool.pitt.edu/alumni

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