UNIVERSITY OF PITTSBURGH SCHOOL OF MEDICINE | SPRING 2011

PITTMED

“None of my memories are my own. They’ve become memories of mine since they are from people I trust. But what about all those little things that only I would know about? I don’t have anyone who can give that back to me.”

LIVES CHANGED IN AN INSTANT

TRAUMATIC BRAIN INJURY

COFFEE TALK

A little brouhaha has been brewing since we first ran this photo on the back page of our Summer 2009 issue. Several 1950s alums have called to tell us the young docs pictured here are not, in fact, all from the Class of 1955 like we said. That much they agree on. What they can't agree on are the names of these Joes enjoying their java. Robert Yanchus (Class of '50) says the guy on the far left is him. Anthony Bruno (Class of '55) says it's really Gene Bouch (Class of '55). And Robert E. Lee (Class of '56) says nope, that's Walter Dukstein (Class of '56). And that's just a sample of the clouds in our coffee. We give up and plan to take up easier pursuits, like memorizing the Krebs cycle. The haze may never clear on this, but we've enjoyed the feedback and catching up with everyone. You all really should get in touch with us more often (medmag@pitt.edu or 412-624-4152)!



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Pitt Med
400 Craig Hall
University of Pittsburgh
Pittsburgh, PA 15260
Phone: 412-624-4358
Fax: 412-624-1021
E-mail: medmag@pitt.edu
pittmed.health.pitt.edu

For address corrections:

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



YOU CAN'T MISS

A staggering debt is par for the course for many med school graduates. So, head out to the course and make par (or birdie, or bogey, or double bogey, or, well, let's not go any further) in an effort to lighten the financial burden borne by Pitt's newly minted docs.

Come on out to the 12th annual Pitt Med Golf Outing, which supports the school's Scholarships and Loans Fund.

8:30 a.m., Saturday, April 30
Quicksilver Golf Club
Pittsburgh

Suggested donations:
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Residents: $100
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PITTMED

UNIVERSITY OF PITTSBURGH SCHOOL OF MEDICINE MAGAZINE, SPRING 2011 (FEB/MAR/APR)

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A devastating auto accident stole Derrick Gaines' memory. He and his wife, Pitt med alum Anna Gaines, have learned to navigate a new life and have fallen in love again.

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Pitt people are finding out what treatments work best and for whom. Can they help solve a $2.3 trillion question, too?

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How Thomas Detre's skills as a talent scout, as well as a visionary, helped transform a medical school and a hospital system.

BY JOE MIKSCH

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In her 20-year career as a photojournalist, MARTHA RIAL ["None of My Memories Are My Own" and "Take a Moment"] has shot many moving scenes. Her work documenting the genocide in Rwanda in 1998 earned her journalism's highest prize, a Pulitzer. In the past year, Rial has become an independent photographer, artfully documenting health-related issues around the world. She recently produced a photo essay, commissioned by the Global Campaign for Microbicides, on HIV prevention efforts in Zimbabwe. (The women she photographed were all participants in the University of Pittsburgh School of Medicine–based Microbicide Trials Network.) This project will be exhibited in the U.S. Capitol rotunda on March 8, International Women's Day.

A visiting lecturer in Pitt's English Department, KRISTEN COSBY ("None of My Memories Are My Own") turned to writing, in part, out of boredom. She grew up on a 39-foot sailboat. Her seafaring family docked on the New Hampshire coast throughout most of the school year and spent summers sailing to Bermuda, Nova Scotia, and Newfoundland. There was no TV on board—just a small collection of saltwater-warped books. "You end up reading the same things over and over again," she says. "Eventually you start writing your own stories." Her current project: a memoir about her nomadic beginnings.

Cosby received her MFA in creative nonfiction from the University in 2006. This summer, she and her husband are moving to Austin, Texas, where Cosby hopes to write full-time.

COVER

Derrick Gaines has built a life with no memories after a terrible car crash.
(Cover: Typography by Elena Gialamas Cerri © 2011.)

PITTMED

PUBLISHER
Arthur S. Levine, MD

EDITOR IN CHIEF
Erica Lloyd

ART DIRECTOR
Elena Gialamas Cerri

SENIOR EDITOR
Joe Miksch

ASSOCIATE EDITOR
Elaine Vitone

CONTRIBUTING EDITOR
Chuck Staresinic

PRODUCTION MANAGER
Chuck Dinsmore

STAFF CONTRIBUTORS
Kelsey Ballance, Maureen Passmore

OBITUARIES CONTRIBUTOR
Macy Levine, MD '43

CIRCULATION MANAGER
Crystal Kubic

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There is, it seems to us,
At best, only a limited value
In the knowledge derived
from experience.
The knowledge imposes
a pattern, and falsifies,
For the pattern is new in every moment
And every moment is a new and shocking
Valuation of all we have been.
—T.S. Eliot, *Four Quartets*


JOSHUA FRANZOS

In a recent *New Yorker* article, Jonah Lehrer delves into a puzzling issue: Many well-established scientific findings look increasingly uncertain. The reproducibility of the results—reproducibility being the keystone of modern science—wanes over time. The truth seems to turn soft. This problem has been witnessed in a wide range of fields, from psychology to ecology—even physics. We can point to a few factors that, in all likelihood, have led us to this uncomfortable place.

For one, results that seem statistically sound in a sample of 100 may look very different when the hypothesis is tested again among thousands. You might, for example, give 100 carefully selected patients Vioxx and find that it is a safe and excellent painkiller. But when released in the general population, trouble arises if it's taken by a small cohort of people carrying a genetic mutation or polymorphism that puts them at risk for cardiovascular disease when exposed to the drug. (This takes the drug off the market even though it may be very beneficial for most people.) In medicine, such statistical hiccups can mean unexpected deaths. Alternatively, if the hiccups appear first in the smaller sample, they skew the results to the negative until you approach the mean—which may well be positive.

We also know there is publication bias. As a finding becomes popular and establishes a new paradigm, momentum builds in the community of scientists to find more such results. Further, positive results are the ones that tend to get published—and not just when the results are from pharmaceutical companies with a strong interest in favorable results. As Lehrer noted, one statistician in 1959 revealed that 97 percent of all published statistically significant psychological studies found the effect they were looking for!

Scientists themselves contribute to this selection bias, even when they have the very best of intentions to be rigorous in their studies. Consider the preeminent Linus Pauling (with two Nobel Prizes), who was convinced that megadoses of vitamin C prevented colds, having so dosed himself and being free of colds. Yet Dr. Pauling overlooked the fact that he had reached an age whereby he was hardly ever exposed to cold viruses.

Just as people with a heroic view of themselves may go to medical school, people may get PhDs to "cure cancer" or contribute to our body of knowledge in some other "evangelical" way. An investigator's own desires and beliefs can subtly shape the way he or she measures a mouse's whisker or chases statistical significance.

This is not so different from what happens at the bedside. Doctors tend to give more optimistic prognoses than is warranted. Our patients are, unintentionally of course, complicit in this. When breaking the news to a patient with cancer that he is likely to die in a few months, a doctor might hear a response like, "Between you, me, and God, I'll beat the odds, won't I?" We may find ourselves interpreting our patients' deaths, at some level, as personal failures, rather than happenstances of biology.

Though we cannot immediately explain all of the statistical conundrums that contribute to what seems to be a decline in reproducibility across fields, we can become stricter with ourselves as scientists, deeply questioning our biases, especially when they are not explicit. We should also come to terms with the idea that it is not only okay to report bad (or mundane) news—nonconfirming results—it is crucial if we hope to better understand our world.

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



Devoted to noteworthy happenings

at the medical school

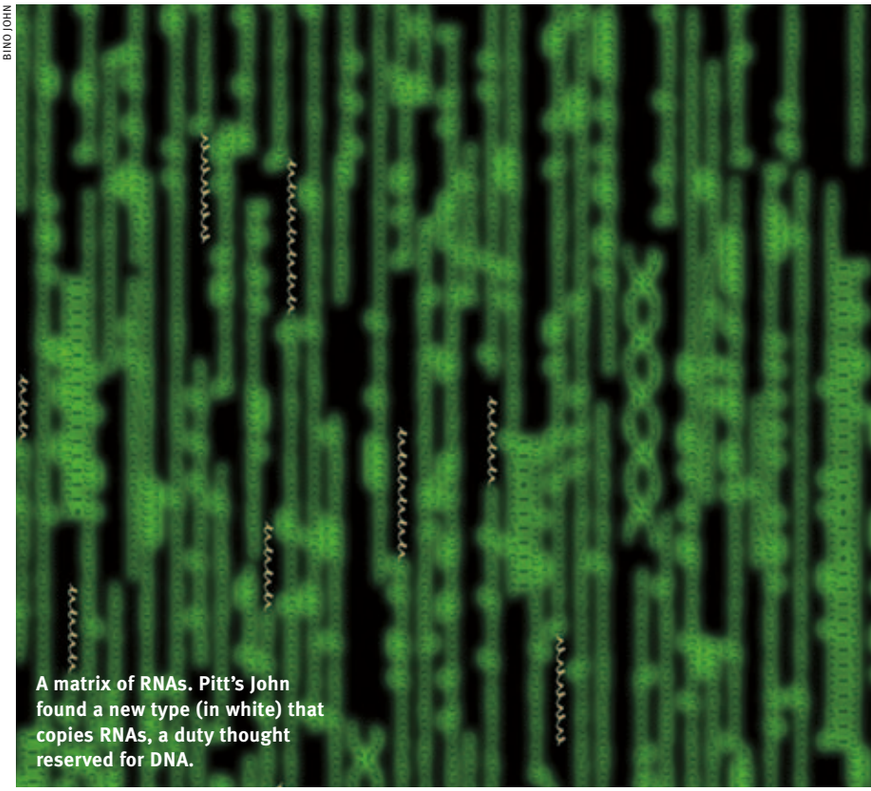
How Mammals Make RNA: Take 2

It's gospel in the scientific community that all RNA in human cells was copied from the DNA template. It's also wrong.

Along with collaborators at Helicos BioSciences Corporation and Integromics, the University of Pittsburgh's Bino John used single-molecule sequencing technology to confirm that mammalian cells can synthesize RNA by copying RNA molecules directly.

Some had suspected this was possible, but John's letter to *Nature* (July 29, 2010) is the first to confirm these suspicions. John, a PhD assistant professor of computational and systems biology, says that his findings show that single-molecule sequencing is vital for "accurate and comprehensive genetic profiling." The work also has implications for diagnosis, because scientists now have another place to look for causes of disease. —*Joe Miksch*

BINO JOHN



A matrix of RNAs. Pitt's John found a new type (in white) that copies RNAs, a duty thought reserved for DNA.

FOOTNOTE

You look tired. Why don't you rest your head on my spleen? Er, pillow. Um, actually, both, in this case. During Science 2010, Pitt's annual celebration of all things science-y, a display called "Translational Art: From Bench to Bed Top" featured a slew of soft pillows in designs inspired by hard science. The aforementioned pillow now shares space in the waiting area of Pitt's Center for Biologic Imaging with others, including one festooned with an image of a dendritic cell and a T-cell interacting; you could also cozy up to a plush white mouse wearing appliqué organs.

Aspirin for Cancer

Sometimes the simple things can be as valuable as the highest of high technology.

For years, doctors have known that nonsteroidal anti-inflammatory drugs (NSAIDs)—such as that old medicine-chest staple, aspirin—can lower the risk of colon cancer. The University of Pittsburgh's Lin Zhang, a PhD associate professor of pharmacology and chemical biology, thinks he finally knows why this is the case. In an article published in the *Proceedings of the National Academy of Sciences*, Zhang reports that NSAIDs target cancer stem cells that have accumulated mutations that may lead to cancer.

Zhang found that when their feed was augmented with NSAIDs, a line of mice predisposed to colon cancer experienced a marked increase in apoptosis—programmed cell death—in these cancer stem cells within one week.

Down the line, Zhang says, scientists can use this knowledge to develop agents that will further sensitize abnormal stem cells to NSAIDs while assessing the effectiveness of cancer-prevention drugs. —*JM*



CAMI MESA

A&Q

David K.C. Cooper: Surgery's Revolutionaries

David K.C. Cooper, who won the TTS-Roche Award for Excellence in Translational Science in 2010, was part of the team that did the U.K.'s first series of successful heart transplants in the 1970s; he also worked with Christiaan Barnard (who performed the first heart transplant in 1967) in Cape Town, South Africa. Now a University of Pittsburgh professor of surgery, Cooper has since put down his scalpel to pursue xenotransplantation research. He is working toward a future where genetically engineered pigs will supply needed corneas, hearts, and islets for transplant.

Cooper marveled at the bold and visionary surgeons, many of whom he knew, who made modern heart surgery possible. His hobby for the past 20 years was researching and writing his latest book, *Open Heart, The Radical Surgeons Who Revolutionized Medicine* (Kaplan, 2010).

Some of these men were establishment figures and some were mavericks. [For example], by putting patients in a hypothermic bath to drop their body temperatures for surgery, [Minnesota's] F. John Lewis gave himself six minutes instead of four to operate on the quiescent heart. He was the first person who was able to actually see what he was doing in the heart, rather than just operating blindly by inserting a finger. Yet he walked away from surgery soon after and developed computers for the ICU. He eventually became disenchanted with academic medicine and retired at 59. He took up residence in Southern California, where he kept busy developing physical fitness, studying mathematics, reading, and trying his hand as an artist and musician. He told me someday he'd like to sing and play piano in a bar, although he admitted he couldn't sing and playing the piano was "difficult enough." This is the man who initiated open heart surgery!

Able to push ahead despite high mortality rates. Christiaan Barnard told me, "Some weeks, we would operate on one patient every day, and by the end of the week we would have five dead patients." It took tremendous fortitude on the part of the surgeons to persevere against such a high mortality. They had to believe that what they were attempting would eventually prove successful.

His question for us. If there was a realistic chance that a pig heart would keep you alive for a number of years, sustaining a good quality of life, would you be prepared to have a pig heart as a transplant? *—Interview by Erica Lloyd*

Faculty Snapshots

It takes brains to be number one. A study published in the September 2010 *Journal of Neurosurgery* places Pitt's Department of Neurosurgery the overall leader, tied with the University of Virginia, in the academic impact of its publications. The journal counted the number of times a department's publications—113 American and Canadian residential neurosurgery departments were included in the survey—were cited in other academic neurosurgery papers. The journal counted citations from 2000 to 2009. Pitt's L. Dade Lunsford—Lars Leksell Professor of Neurological Surgery, Distinguished Professor of Neurological Surgery, and an MD—headed the department during many of those years. Robert Friedlander, an MD professor of neurological surgery and current chair of the department, says what makes the ranking impressive is that the study takes into account not only the volume of a department's work, but also its quality. "We have different colleagues at the highest levels all working with each other," says Friedlander. "It's a statement about the community as a whole."


Lunsford


Friedlander

George Michalopoulos is the recipient of the American Liver Foundation's Distinguished Scientific Achievement Award for 2010. The award honors scientists who undertake novel work, mentor other researchers, and attract substantial funding over the course of their careers. A professor in and chair of Pitt's Department of Pathology, Michalopoulos specializes in liver regeneration and was the first to identify hepatocyte growth factor and its receptor, c-Met. Michalopoulos, an MD/PhD, says it's an "acrobatic balance" to do his own work while mentoring others and managing the department. *—Kelsey Ballance*


Michalopoulos

No Time or Money

A whistle blows, and about 75 medical students leap out of their chairs and scatter, scrambling to be first in line to cash a check, make an appointment with social services, and get to work. They have a limited amount of time to fulfill a week's worth of obligations. A student waves his hands in frustration when he sees the line at the quick-loan store. Another sighs when she learns that food stamps won't kick in for two weeks. Rent is due at the end of the week, and there is very little money in the bank. On top of that, the bank won't cash her checks, she has no more transportation vouchers, and many of her neighbors' homes have been robbed recently.

This is a poverty simulation exercise, part of the Population Health Course, a class in the University of Pittsburgh School of Medicine's new second-year Patient, Physician, and Society block. Each student is assigned a role, and the exercise's four 15-minute blocks simulate one month in the life of a person in poverty.

"It's important for medical students to understand … that poverty will affect their work. The woman who is late to her appointment may have had to take three buses to get there and drop her child off at day care in between," says Hollis Day, an MD associate professor of medicine and medical director of the school's Advanced Clinical Education Center. "We're hoping the students develop empathy for people who … face barriers to health care."

After the exercise, students discuss the experience. Many detail how stressful it was to complete their tasks and that no one cared about their difficulties. Suzie Lee (Class of 2013) says, "I couldn't get anything done at all. I had no money or time to accomplish much. It was overwhelming. And eye opening." *—Maureen Passmore*



GETTY IMAGES

SELF-REPORTS IN QUESTION

There's an old saying among the ink-stained wretches of newspaper journalism: "If your mother says she loves you, check it out." Recent work done by Miguel Regueiro shows that the same sentiment can be applied to Crohn's disease patients who say they feel just fine after corrective surgery.

The Crohn's Disease Activity Index, which uses patient self-reporting to assess recurrence of the disease, might need to be replaced with more objective monitoring, such as endoscopy, suggests Regueiro.

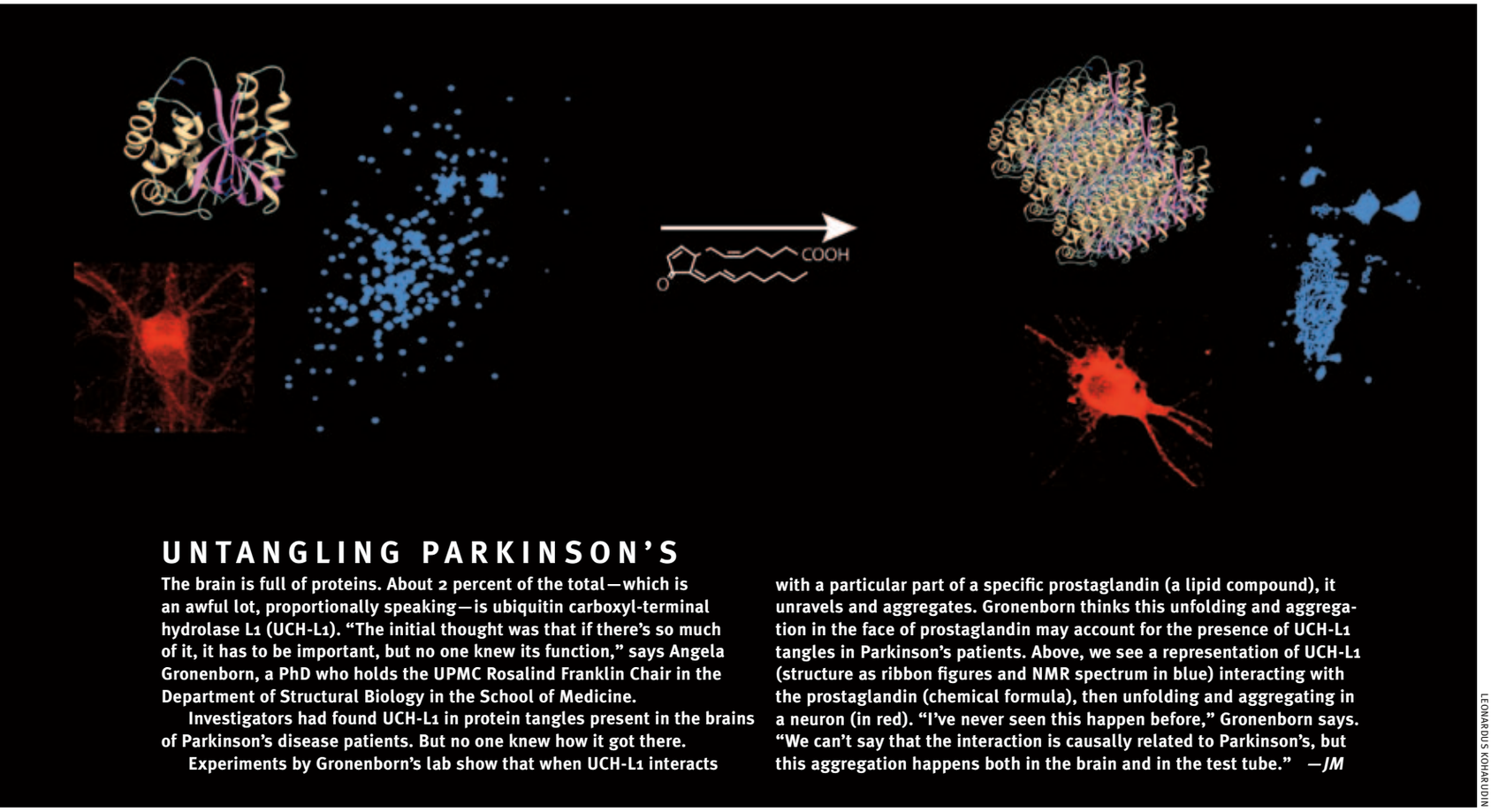
Regueiro is an MD associate professor of medicine and codirector of the Inflammatory Bowel Disease Center in the School of Medicine. He has found that even though many patients report they're symptom-free, sometimes even years after surgery, the disease may have returned and started wreaking havoc in their intestines. A delay in treatment, Regueiro says, may necessitate a second surgery. ***—JM***

POWER COUPLE JOINS PITT

The School of Medicine is set to welcome a heavyweight husband-and-wife team to Pittsburgh. Jeremy Berg, a PhD and current director of the National Institute of General Medical Sciences, will become Pitt's first associate senior vice chancellor for science strategy and planning for the schools of the health sciences in July. His wife, Wendie Berg, an MD/PhD, is a renowned expert in breast cancer screening and has led major, multicenter clinical trials to explore the efficacy of adding ultrasound and aspects of nuclear medicine as adjuncts to mammography in breast cancer screening. Formerly on the faculty at Johns Hopkins University and director of the breast imaging program at the University of Maryland, she is expected to arrive in Pittsburgh in March and will be a professor of radiology.

Wendie Berg says that Pittsburgh offered her opportunities she couldn't find elsewhere. "It's interesting and dynamic and well-positioned for the future," she says. "There's a can-do atmosphere, and it's clear that breast imaging is a top priority."

Jeremy Berg's research portfolio includes advancing the understanding of how zinc-containing proteins bind to DNA or RNA and regulate gene activity. In addition to serving as associate senior vice chancellor—as such he will help direct and expand the University's contributions to biomedical research—he will be a professor of computational and systems biology in the School of Medicine. *—JM*



LEONARDUS KOHARUDIN

UNTANGLING PARKINSON'S

The brain is full of proteins. About 2 percent of the total—which is an awful lot, proportionally speaking—is ubiquitin carboxyl-terminal hydrolase L1 (UCH-L1). "The initial thought was that if there's so much of it, it has to be important, but no one knew its function," says Angela Gronenborn, a PhD who holds the UPMC Rosalind Franklin Chair in the Department of Structural Biology in the School of Medicine.

Investigators had found UCH-L1 in protein tangles present in the brains of Parkinson's disease patients. But no one knew how it got there.

Experiments by Gronenborn's lab show that when UCH-L1 interacts with a particular part of a specific prostaglandin (a lipid compound), it unravels and aggregates. Gronenborn thinks this unfolding and aggregation in the face of prostaglandin may account for the presence of UCH-L1 tangles in Parkinson's patients. Above, we see a representation of UCH-L1 (structure as ribbon figures and NMR spectrum in blue) interacting with the prostaglandin (chemical formula), then unfolding and aggregating in a neuron (in red). "I've never seen this happen before," Gronenborn says. "We can't say that the interaction is causally related to Parkinson's, but this aggregation happens both in the brain and in the test tube." *—JM*

Appointments

In September, Edward Chu was appointed chief of the Division of Hematology/Oncology in the School of Medicine and deputy director of the University of Pittsburgh Cancer Institute (UPCI). Chu is an internationally recognized MD in the biology and treatment of colorectal cancer. He says that UPCI attracted him because it is well-designed for translational research. Before his arrival at Pitt, Chu was a professor of medicine and pharmacology at Yale University and the chief of medical oncology and deputy director of the Yale Cancer Center. Chu is now planning a clinical trial to study how the Chinese herbal remedy Huang Qin Tang might boost the effectiveness of chemotherapy.


Chu


Lee

UPCI and Magee-Womens Research Institute recently joined forces to found the Women's Cancer Research Center, which will help breast and gynecological cancer researchers translate promising findings for use in the clinic. Pitt attracted Baylor College of Medicine breast cancer researchers Adrian Lee and Steffi Oesterreich, husband and wife PhDs, as center leaders. Lee codirects the center with Robert Edwards, an MD professor in and vice chair of the Department of Obstetrics, Gynecology, and Reproductive Sciences. Oesterreich, an expert in estrogen-receptor biology and action, is the director of education. Lee, whose own work focuses on growth factor pathways, says he expects the new center will have "a rapid and major impact on reducing the burden of [women's cancers]."


Oesterreich

The School of Medicine's new Department of Cardiothoracic Surgery has found its leader. James Luketich will be the founding chair. An MD and the Henry T. Bahnson Professor of Cardiothoracic Surgery, Luketich has pioneered minimally invasive surgical techniques for esophageal and lung operations. His other specialties include multidisciplinary management of several types of thoracic cancers and Barrett's esophagus. Luketich was formerly the director of Pitt's Heart, Lung, and Esophageal Surgery Institute.


Luketich

Although he has served as a professor at Harvard and then at Carnegie Mellon University, D. Lansing Taylor has spent the most recent part of his career as an entrepreneur. Taylor developed fluorescent light microscopy techniques to give scientists a new perspective on living organisms and ended up founding several biotechnology companies, including Cellomics, that produce equipment for drug discovery and systems biology. He is now the director of Pitt's Drug Discovery Institute and is Allegheny Foundation Professor of Computational and Systems Biology. Taylor aims to balance pure science with focused drug development and wants to encourage other promising scientists to embark on their own spin-off and licensing ventures. *—KB*


Taylor



THE LAST REUNION?

Seated in the Pittsburgh Athletic Association's comfortable lobby, Joe Novak, Rupert Friday, and Paul Rike (shown left to right) share a laugh. These three—a retired ophthalmologist, ob/gyn, and cardiologist, respectively—are the last standing among the 61 graduates of Pitt med's Class of 1938.

With Friday on the eve of snowbirding to sunny Arizona to escape a long Western Pennsylvania winter, the men trade jokes and memories during a Sunday brunch that doubles as a potential final "class reunion" because, as Novak bluntly says, "We'll probably never see each other again."

The trio started their careers during an eventful year. President Franklin Delano Roosevelt signed into law a bill establishing the nation's first minimum wage—25 cents an hour—and Adolf Hitler's army goose-stepped into Vienna to annex Austria. At New York University, Jonas Salk was a year away from earning his medical degree.

Now, with nearly three centuries of life between them, the men swap fond stories about instructors and classmates, all departed. "Joe did his best to keep everyone connected, even if just by phone," says Friday. As for their longevity, he playfully chalks it up to brainpower.

"We were the only members of our class to be accepted in Alpha Omega Alpha," Friday says, referring to the prestigious medical academic honor society. "I didn't know you had to be smart to live this long."

Friday admits to believing that he "knew it all back then."

"At the time, I thought there couldn't possibly be anything more I could learn. But over the years, I learned that wasn't true. My grandson is a doctor. What he knows now, I couldn't even imagine when I graduated."

The men plan to pass along a well-aged legacy to future physicians.

"We bought a bottle of 50-year-old Scotch and promised that the last living member of our class would present it to the next incoming class at the Pitt medical school," says Novak. Let's offer a toast to keeping that bottle in storage for years to come.

—Story and photograph by John Altdorfer

Explorations and revelations taking place in the medical school



Women with postpartum depression show a decreased connectivity in some neural circuits and unusually low levels of activity in areas of the brain that are associated with emotion.

IT'S NOT JUST THE HORMONES TALKING

THE PATHOPHYSIOLOGY OF POSTPARTUM DEPRESSION

BY REID R. FRAZIER

A new mother's brain is like a house undergoing renovation. The work crew consists of hormones pouring in to promote new cell growth and rewire neural circuits. There's a lot of commotion. This has led to a common perception that when women undergoing dramatic fluctuations in hormone activity—as in premenstrual syndrome, menopause, and pregnancy—get depressed or moody, "it's the hormones talking."

But new evidence from a University of Pittsburgh researcher is showing that postpartum depression is considerably more complicated than that. Eydie Moses-Kolko and her collaborators found that women with the disorder had noticeably different levels of activity in parts of the brain associated with emotion; additionally, these women had a decreased connectivity in certain neural circuits. They published these findings in a recent issue of the *American Journal of Psychiatry*. (Scientists have also reported different patterns of brain activity and connectivity in women with garden-variety depression; however, no studies directly comparing postpartum and nonpostpartum depression have been completed, says Moses-Kolko.)

For the 15 percent of new mothers who experience postpartum depression, the first few months after birth can feel like grief. A mother might grow despondent, lose sleep, have difficulty connecting with her baby, and worry that she isn't being a good mom. She can feel like the infant is deliberately trying to make life hellish. Pangs of aggression toward the baby can creep in.

A little over a decade ago, Moses-Kolko began wondering why this happened in some new mothers. As a resident in psychiatry at Pitt in the 1990s, she saw women who had managed to cope with prior depression or anxiety suddenly wanting to drown their newborns.

"I've been really struck by how ill women can get in the postpartum period, particularly in cases of postpartum psychosis, when there might have been little evidence of prior mood disorder," says Moses-Kolko, an MD assistant professor of psychiatry. The stakes of this question have been heightened by studies suggesting a mother's postpartum depression can have long-term ill effects on her child's mental health.

What sets off the depression in some women remains a mystery. Some think it's simply sleep deprivation causing havoc; insomnia is certainly a risk factor for depression. Women with poor social structures or stressful relationships are at greater risk for postpartum depression, which suggests an environmental role. But so are women with mood disorders, which points to some kind of genetic or epigenetic determinant. Treatment can be as simple as talk therapy, an antidepressant, and a sleeping aid.

To dig deeper into the pathophysiology of postpartum depression, Moses-Kolko used functional MRI to study two groups of new moms—some with postpartum depression and some who were healthy—under functional MRI. She gave them two tests, one that matched shapes (a control task) and another that matched faces.

In the face-matching test, each mother saw a face in an emotional state—perhaps a worried expression—then was asked to find its match between a pair of faces. When attempting to find matching faces, postpartum-depressed women had significantly lower activity in their dorsomedial prefrontal cortex (DMPFC for short), a part of the frontal lobe that is involved in control of emotional responses and empathy. These women also had lower levels of activity in the amygdala—another important region in emotional response—when looking at fearful faces.

Moses-Kolko says these findings suggest a dampening of the emotional response in postpartum-depressed women. "It could be a protective mechanism to just shut things out in order to cope day to day, to be able to take care of a potentially noxious stimulus—the baby," Moses-Kolko says. "Maybe their shutting down is protective, so they don't throw the baby across the room."

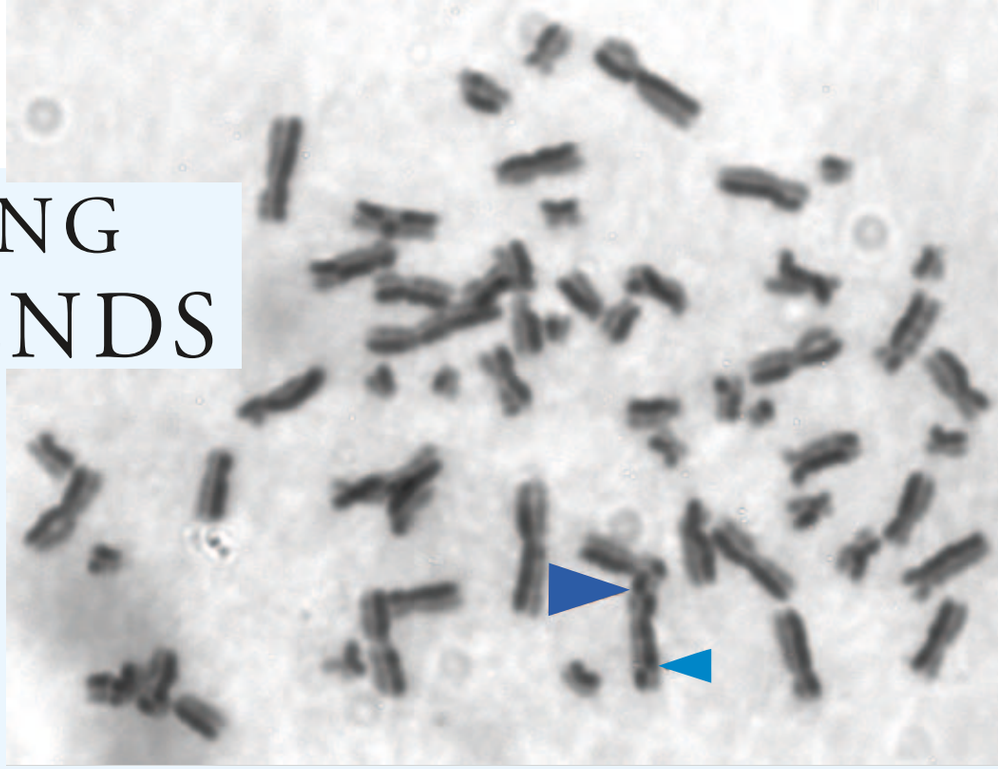
The tests also showed women with postpartum depression had less connectivity between the DMPFC and amygdala than did healthy women. This is significant, says David Rubinow, Assad Meymandi Professor and Chair of Psychiatry at the University of North Carolina and a leader in the field of reproduction-related mood disorders. The prefrontal cortex is believed to regulate brain regions and neural circuits, acting "a bit like a traffic cop," he says. Rubinow adds that Moses-Kolko's work is part of a wave of research that's getting closer to a biological marker for the disorder, which would make early detection—and better treatment—more likely. He says that knowing what to expect before a baby arrives would be a great help for these mothers and their newborns. ■

PHOTO RESEARCHERS INC.

CANCER-KILLING DIVIDENDS

A DNA-REPAIR PROTEIN YIELDS SURPRISES

BY MELINDA WENNER MOYER



CHRISTOPHER BAKKENIST

ABOVE: Here, we see a process known as sister chromatid exchange, which is believed to be a manifestation of a DNA-repair pathway. Pitt's Bakkenist believes that disrupting this pathway could be a potent means of killing cancer cells while saving normal cells, especially in cases of lung and pancreatic cancers. (The smaller arrowhead indicates an exchange near the telomere, i.e., the chromosome end. The larger arrowhead indicates an exchange near the centromere.)

Cancer may be a tough adversary, but Christopher Bakkenist, an assistant professor of radiation oncology based at the University of Pittsburgh Hillman Cancer Center, has a surefire tactic: Defeat the disease using wits, not muscle. "It's really only in the last decade that we've tried to be smart with cancer therapies," he says—meaning using approaches that specifically target the cancer without inadvertently harming healthy cells. Now, thanks to insights gleaned from a certain DNA-repair protein, he may have one of the cleverest solutions yet. And in the meantime, he has uncovered some surprising details about cell biology that could change how scientists study drug effects.

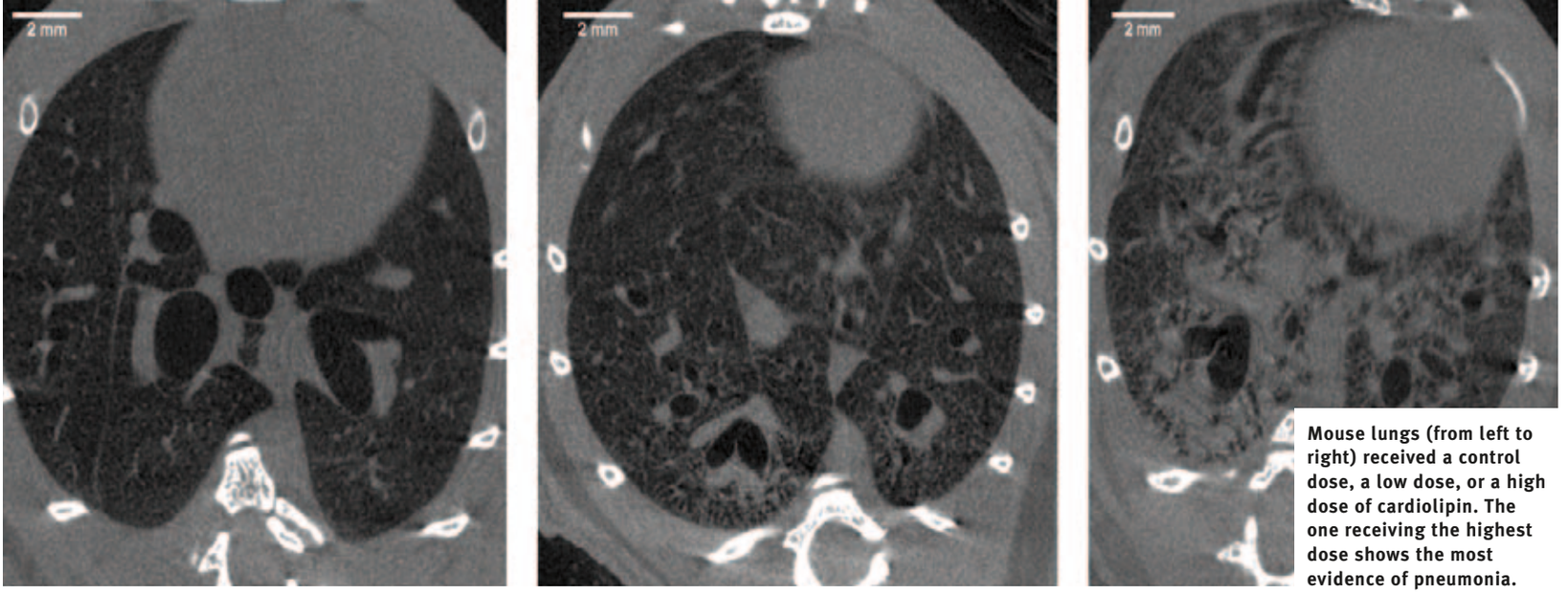
Bakkenist owes his breakthroughs to ATM kinase, a protein the body turns on when exposed to ionizing radiation and other insults to DNA. Although researchers have known that the protein helps repair DNA damage, it has been unclear how, exactly, ATM kinase works its magic. To find out, Bakkenist treated human lung cells with small molecules that inhibit ATM-kinase activity and hunted for the mechanism through which DNA damage accumulated. He had some hints for where to look: People with a rare disease called ataxia telangiectasia (AT)—who suffer from neurodegeneration, sensitivity to ionizing radiation, and predisposition to cancers—are born with mutations in the gene for ATM kinase and are therefore unable to make the protein. Yet they can still repair DNA through a process known as sister chromatid exchange (SCE), a type of genetic recombination in which lesions are mended during DNA replication.

Bakkenist guessed, then, that ATM kinase probably wasn't involved in SCE, so he looked to other repair pathways for his answer. But his guess didn't pan out. "We had eliminated every other possibility we could look at, so we ended up looking at SCEs," Bakkenist explains. Much to his surprise, when he inhibited ATM-kinase activity in normal cells, the cells were unable to conduct SCE—a finding that, to say the least, was "not anticipated," Bakkenist says, because the cells of people who cannot make ATM kinase can conduct SCE just fine. His team published its findings in June 2010 in *Science Signaling*. By shedding light on how ATM kinase functions, Bakkenist's work could help researchers develop better cancer therapies. Cells that are destined to become cancerous often acquire defects in DNA-repair pathways early in development that allow them to accumulate cancer-causing mutations. If cancer cells are later hit with another blow to their DNA-repair mechanisms—through drugs that inhibit ATM-kinase activity, for instance—they will be far less likely to survive radiation therapy than healthy cells, which have redundant repair pathways. "ATM kinase may well be essential for the survival of that cancer. So if we inhibit ATM, it will kill cancer cells," Bakkenist explains. Lung and pancreatic cancer cells, he says, might be particularly vulnerable to ATM-kinase inhibitors because of the specific mutations they accumulate.

Bakkenist's findings could have big implications for pharmacological research overall. Scientists often try to predict the effects of protein-inhibiting drugs by deleting the gene for the protein in animal models. Yet Bakkenist's work shows that cells that cannot make ATM kinase behave differently than cells in which ATM-kinase activity has been inhibited (that is, the protein is still made by cells, but it simply cannot do its job properly). Bakkenist's work suggests that sometimes, cells can maneuver around the loss of a gene in unexpected ways to get a biochemical task done, which means that scientists may want to reconsider using genetic deletions to predict the effects of protein-inhibiting drugs.

Why might these differences exist? Impaired proteins, Bakkenist speculates, may get in the way of important cellular activities such as SCE and essentially "prevent things from happening," he says. In contrast, people who are born without the ability to make the protein at all may adapt to the loss early in development through biological rewiring.

"It's going to be hard to tease these things out," he says. Nevertheless, "it's a bit surprising and a bit exciting." ■



RAMA MALLAMPALLI

Mouse lungs (from left to right) received a control dose, a low dose, or a high dose of cardiolipin. The one receiving the highest dose shows the most evidence of pneumonia.

A VISCOUS CYCLE

STEPPING UP THE "MOTOR OIL" OF THE LUNGS TO TREAT PNEUMONIA

BY JOE MIKSCH

Under the best circumstances, typical bacterial pneumonia can be a rough road. In the course of about two weeks, a person with pneumonia will cough, have trouble breathing, and develop shaking chills and fever. For the lucky ones, antibiotics and rest will restore health over time.

But for some people—particularly those with weakened immune systems, smokers, the very old, and the very young—pneumonia can require hospitalization. And, in more than 10 percent of cases, it can lead to death. The Centers for Disease Control and Prevention reports that in 2007, 1.1 million people in the United States were hospitalized with pneumonia and more than 52,000 died.

But why does pneumonia hospitalize or kill some and spare others, regardless of these risk factors? Rama Mallampalli—Pitt professor of medicine, chief of the pulmonary division of the VA Pittsburgh Health Care System, and director of the Acute Lung Injury Center of Excellence at the University of Pittsburgh—thinks a process involving a structural molecule called cardiolipin might be key.

Mallampalli, an MD, and Pitt colleagues Bill Chen, Bryan McVerry, and Valerian Kagan—along with faculty from the University of Iowa School of Medicine—recently published a paper in *Nature Medicine* that reports that cardiolipin is found in unusually high concentrations in the lung fluid of mice and people infected with bacterial pneumonia.

Under normal circumstances, cardiolipin plays a role in mitochondrial-energy metabolism—a good thing, obviously, because mitochondria provide the power that keeps our cells, and therefore us, alive. So the questions become: Why is there so much cardiolipin in the lung fluid of pneumonia sufferers? And why does it seem to be such a bad actor when let loose in the lungs? "You and I normally have very low concentrations of [cardiolipin] in our lung-fluid secretions," Mallampalli says. "We hypothesized that there may be a protein that basically eliminates or removes [cardiolipin], and there might be a problem related to it."

As the investigation progressed, Mallampalli and his team identified a carrier protein called Atp8b1. They learned it transports cardiolipin, essentially acting as a pump that controls levels of the molecule.

With cardiolipin and Atp8b1 in his sights, Mallampalli traced their interaction: As pneumonia progresses, lung cells die. And as they perish, these cells release their components, including cardiolipin, into the lung fluid. At a point, Atp8b1 is faced with much more cardiolipin than it can process. As cardiolipin levels build, the molecule begins to disrupt the function of surfactant, a lubricant that is essentially the motor oil of respiration. As surfactant fails to work properly, respiration falters, and lung cells acquire even more damage—and a conventional case of pneumonia becomes more severe.

Mallampalli says he intuited that Atp8b1 might play a role here because of earlier work done by others on a rare and very serious liver condition called Byler's disease. Byler's disease patients have a mutation in Atp8b1 and an unusually high incidence of pneumonia in addition to liver failure.

Mallampalli is optimistic that this discovery offers the potential for new anti-pneumonia drugs. "All treatments for pneumonia are antibiotics," Mallampalli says. "This has been a good thing in that we've saved a lot of lives; but on the bad side, this has led to the emergence of drug-resistant bacteria."

Now, Mallampalli says, it may be possible to design drugs that either bind to cardiolipin, rendering it impotent, or that activate Atp8b1, making it a more robust cardiolipin "pump."

"For the first time, we have a new paradigm or model for pneumonia, and it will lead to a nonantibiotic approach to alter the host response to the infection," he says. ■



GETTY IMAGES

Researchers at Pitt are shedding light on the shadowy field of traumatic brain injury. Their work is helping athletes, soldiers, accident victims, and others.

THE REPERCUSSIONS OF TRAUMATIC BRAIN INJURY ARE BECOMING CLEARER

BY CHUCK STARESINIC

WHAT HIT HER

Katy Korber knew exactly what hit her. It was a volleyball—a blistering spike from the outside hitter on the opposite side of the net. Katy, 15 years old and starting her first season on varsity, had gone straight to the net for the block, timing her jump with arms extended, palms flat and braced for impact. When the ball blazed past her hands she had only a fraction of a second to react. She turned her head and took it in the right temple, hard.

In another, very real sense, Katy didn't know what hit her, and neither did her parents. She crumpled to the hardwood. The game stopped. Everything stopped. Eventually, she wobbled off the court with teammates and coaches supporting her. Her mother came down from the bleachers to help her home. By the next morning, it was clear that this wasn't just a pain that would go away with aspirin. The headache was intense. She was fatigued. She couldn't think clearly and was unsteady on her feet. Her mother called the doctor.

Traumatic brain injury (TBI) is a broad category describing any blow or jolt to the head that disrupts normal mental function—everything from the sports concussion that leaves a player seeing stars and momentarily dizzy to the high-speed collision on the highway that renders a victim profoundly and permanently disabled.

The Centers for Disease Control and Prevention estimates that 1.7 million people per year in this country suffer a traumatic brain injury. Katy's injury was the most common type—a concussion, which is also described by the rather oxymoronic term "mild traumatic brain injury."

"We're in the golden age of traumatic brain injury [research and awareness]," says Patrick Kochanek, a critical care medicine physician and researcher at the University of Pittsburgh. This statement summarizes a reality full of contradictions. Scientists know more than ever about injuries to the brain, and they are finding ways to help patients regain lost function. At the same time, they are learning that there are significant risks even with mild TBI—especially if a patient resumes activity too soon and suffers what is known as "second concussion syndrome." In people who suffer severe TBI, there is increased risk of later developing neurodegenerative diseases like Alzheimer's. At Pitt and other institutions, researchers are gleaning eye-opening details about exactly what is going on in the injured brain and what dangers might lie ahead. And they are showing us how doctors might one day treat patients so that they can avoid many of the often menacing short- and long-term consequences of these injuries.

Confoundingly, the more that airbags, seatbelts, helmets, and body armor are successfully deployed (and the longer the country remains at war), the more survivors there are struggling with moderate to severe TBI. The math is simple: As the death rate goes down, the number of patients goes up.

Thirty percent of severe TBI patients had Alzheimer's-like plaques, even the young people.

Your brain is suspended inside your skull like an oversized yolk crowding the confines of an egg. This yolk is exceedingly fragile, of course, but it does come with significant protective systems. The most obvious is your shell: the aforementioned skull, which is a quarter-inch thick. Less obvious is the dura mater, a leather like covering surrounding the brain and spinal cord (there are two other thinner coverings as well). Filling the space between the dura mater and the brain is the clear cerebrospinal fluid, which slows and cushions the motion of the brain in the skull as you move about.

Your brain does not sit inside your skull—its weight would impede blood flow just as sitting in a chair for too long does to other parts of your anatomy. Neither does the brain float like a duck, which would create the same problem up top as it pressed against the roof of the skull. The brain has neutral buoyancy, like a densely compact jellyfish suspended in the sea. The result of neutral buoyancy is that the human brain, which might weigh 1,400 grams when the coroner sets it on the scale, effectively has a weight of 25 grams or so when it is properly suspended in its bath of cerebrospinal fluid.

All of this is well and good, right up until the moment you slip on the ice and your head whips backward to meet this unforgiving surface. Same goes for the sudden blast of a volleyball to the side of the head or the unsettling deceleration from 65 mph to 0 mph in a split second, even when the impact is cushioned by an airbag. For soldiers clad in body armor and bullet-proof helmets, the blast wave produced by the detonation of an improvised explosive device turns out to have its own unexpectedly sinister fluid dynamics. The blast is a wave of energy that rolls across the skull, compressing the bone as it travels across the surface—even beneath a helmet. It squeezes the skull with forces completely out of proportion to what one would expect based on the actual movement of the head because of the blast.

Today there is increasing public awareness of and research funding for these injuries, especially in sports medicine and in the care of soldiers returning from Iraq and Afghanistan. And Pitt has emerged as a TBI center with few peers. The reasons for this are multiple and multidisciplinary. Pitt has exploited several points along the broad spectrum of TBI to intervene and investigate—from concussion to blast injury—and individual multidisciplinary teams have grown at each of these points.

"There's been a generation of [TBI] trainees who came in as young faculty and now have their own funding," says C. Edward Dixon, who joined Pitt's Brain Trauma Research Center in 1995 and is now its director.

The result of this decades-long organic process is that the individual domains of multiple investigators, clinicians, and research programs at Pitt now overlap and inform one another, creating a rich research environment. Pitt is home to some of the world's very best people in the arenas of sports concussion, severe TBI, rehabilitation medicine, blast injury, and neurodegeneration. There isn't a single city in the country that has more TBI researchers than there are in this one institution, notes Dixon. That said, these docs have their work cut out for them.

One of the long-standing problems with studying TBI is the difficulty of defining and describing the injury so that you can reach scientific conclusions.

"When we talk about severe brain injury, we are usually talking about injury severity as measured by the Glasgow Coma Scale (GCS)," says Joseph Ricker, a clinical neuropsychologist and associate professor of physical medicine and rehabilitation in the School of Medicine. "A score of 3 to 8 is severe. Moderate is 9 to 12, and mild is 13 to 15. … But even with severe TBI, there is a huge range of presentation and outcome. Initial severity doesn't predict outcome perfectly. I've had patients with severe TBI at initial presentation with surprisingly good results. And I've had patients with injuries classified as mild that had outcomes that were much poorer than you'd expect."

Kochanek, an MD professor of critical care medicine, director of Pitt's Safar Center for Resuscitation Research, and noted researcher in severe TBI and blast injury, points out that the *Journal of Neurotrauma* once published a cover showing six CT scans of humans with brain injuries and a GCS of 4. Each looked completely different, illustrating that TBI may need to be considered as a complex of multiple diseases in the same way that cancer is now understood as multiple diseases. In TBI, one patient may have a contusion, another diffuse injury, another diffuse swelling. Then there are those who are bleeding into various spaces between the three membranes surrounding the brain: One has a subarachnoid hemorrhage, another has a subdural hemorrhage, and another has an epidural hemorrhage. Each flavor of TBI means different symptoms, prognosis, and treatment. To complicate matters further, TBI often occurs in tandem with shock and trauma to the limbs and trunk. Were a particular course of treatment given to all six of the TBI patients featured in the journal, it may help some, harm some, and have no effect on others. How is a researcher to study TBI in animals, or even describe symptoms of TBI, in such a "messy" disease?

"Scientists like total control," says Kochanek, "so, for many years, [articles on] traumatic brain injury couldn't get into higher-tiered journals."

One person who played a major role in opening avenues for laboratory-based TBI research is Dixon, a Pitt professor of neurological surgery, vice chair for research in that department, and codirector of the Safar Center for Resuscitation Research. After earning a PhD in psychology at the Medical College of Virginia in 1986, Dixon began a postdoctoral fellowship at General Motors research laboratories in Warren, Mich.

"They had a crash-injury biomechanics group studying the relationship between TBI and mechanical forces relevant to automobile crashes," says Dixon. "The ultimate goal was to develop computer models of brain injury, and they were doing large-animal research to validate their computer models."

At Pitt, Dixon joined a blossoming TBI program. Founded in 1991 as a sort of minicenter with a modest grant from the National Institutes of Health, the Brain Trauma Research Center was designated a full-fledged NIH center of excellence for TBI less than five years later. Through a combination of laboratory research and clinical trials, it has advanced the science and treatment of TBI in several ways. Pittsburgh was one of the first clinical sites to show clear benefits of using therapeutic hypothermia, which is now the standard of care for control of intracranial pressure. (TBI often leads to brain swelling and a deadly rise in pressure inside the skull.) Dixon and colleagues have published a large portion of the studies looking at neurostimulants such as methylphenidate (Ritalin) and amantadine, which are commonly used in TBI and show some promise (though a large clinical trial hasn't been conducted).



GETTY IMAGES

Confoundingly, the more helmets and other prudent safety measures are used, the more cases of moderate to severe TBI occur. As death rates go down, the number of injured goes up.

Dixon was interested in more than biomechanics. He wanted to understand the behavioral consequences of TBI, so he developed one of the first rodent models which is now the most widely used model of head injury in laboratories worldwide.

"Ed's contributions were enormous in that regard," says Kochanek. "It's simple. It can be done in any credible lab, and it's not terribly expensive." The animals remain stable afterward and can then be studied for important metrics like memory and learning. When Dixon joined the Pitt faculty in the '90s, he brought that expertise in developing laboratory-based functional-outcomes assessments with him.

With better understanding of the mechanisms of TBI and recovery, researchers are increasingly turning to a big frontier in TBI research—the question of long-term consequences.

Two-and-a-half months after she suffered a concussion during a high school volleyball match, Katy Korber was back at the UPMC Sports Medicine Institute. She sat beside her father at a small conference table. On the wall behind her was an autographed poster of Merril Hoge—a former Pittsburgh Steelers running back who retired from football after a series of concussions and persistent postconcussion symptoms. The sign outside the closed door read, "Sports Concussion Room." Katy and her father had become familiar with this room. Between her regular appointments here, she'd missed weeks of school and pared down her activities in an attempt to rest and recover from nagging postconcussion symptoms like headaches and difficulty concentrating. Katy and her dad were hoping for good news.

When she arrived that morning, Katy sat down at a computer screen in another room and took an online test called ImPACT—Immediate Post-Concussion Assessment and Cognitive Testing. It's the same baseline test required for athletes in the National Hockey League, the National Football League, and college football. It's one of several tools used to evaluate a player's injury and recovery before he is cleared to return to play.

A series of words was displayed on the screen, and Katy was instructed to remember them. Using a standard keyboard, she completed interactive tasks measuring reaction time and comprehension. Then she was asked to recall the words shown to her earlier. ImPACT includes a series of activities like this. It takes about 30 minutes, and it immediately provides scores in memory, visual motor speed, reaction time, and impulse control. Katy had taken the test every few weeks since her injury so her scores could be compared over time. If her cognitive function was improving, it would show. Even better, Katy took the test at the start of the season (hers is one of many school districts that tests all athletes), so every subsequent test could be compared to her performance before the concussion.

Outside the concussion room, Pitt's Mickey Collins, a PhD neuropsychologist and associate professor of orthopaedics and neurological surgery, stands with one hand in his white coat pocket and reads from Katy's chart: "Took a spike to the right temple in September. Persistent headache, nausea, fogginess, fatigue, concentration difficulty, sensitivity to light and noise, blurry vision left eye, pain. X-ray of neck, CT of head—all normal. Next day, she had migraine and proceeded to sleep most of the next several days."

He points to Katy's scores in verbal and visual memory, motor speed, impulse control, and reaction time. Here she is at baseline, he says, then postinjury, three weeks postinjury, and six-weeks postinjury. "She's normal, then grossly impaired, grossly impaired, grossly impaired." Measured as a percentile relative to others free of injury, Katy's baseline scores were average to above average. After the concussion, she was lower than the first percentile. "She was grossly impaired. But look here," says Collins, pointing to today's results. "She's getting back to normal. Still a little low in visual motor speed and reaction time, but not bad."

Collins was a collegiate athlete, and he still looks the part. He played baseball for the University of Southern Maine in the 1989 NCAA Division III World Series. Like a lot of clinicians in sports medicine, he's a big fan and a fervent believer in the benefits of competitive sports. Few things make him happier than telling a young person that she can go back to the field. "She's probably going to be a happy girl," he says before going in to talk with Katy and her father. "She's doing much better."

"When I started doing this in the mid to late '90s, 'How many fingers am I holding up?' and smelling salts predicated return to play," says Collins. He was beginning his neuropsychological graduate work at Michigan State when he realized that he missed athletics. He made his first trip to Pittsburgh in 1995, when the city hosted the first major sports concussion conference, and met brain trauma researcher Mark Lovell and Joseph Maroon, a neurosurgeon and Pittsburgh Steelers team physician who was goaded into a neurocognitive epiphany by the team's head coach, Chuck Noll. Maroon describes Noll as "a well-read Renaissance man" and "a Socratic gadfly."

Part of Maroon's job was to make sure that players were medically cleared to play after injury. One day, he asserted to Noll that the quarterback, who had suffered a concussion a week earlier, wouldn't be ready for Sunday's game.

Noll wanted to know why.

He has a concussion, said Maroon. *The guidelines say he should sit another week.*

Who wrote the guidelines?

Well, I was on the committee that wrote the guidelines, said Maroon.

Noll pressed on: *And what data did you use to draw up the guidelines? What objective data do you have that says he should rest two weeks instead of one?*

Maroon grudgingly admitted he did not have data. But it was his feeling that the quarterback needed another week.

The thing that got under Maroon's skin was that Noll was correct. There was no reliable way to test injury severity or recovery. This story marks a critical point in the prehistory of the ImPACT test. Maroon, a Pitt professor of neurosurgery (who's competed in six Iron Man triathlons), huddled over the problem with Lovell, a PhD. Their starting point was the only sort of test available at the time—a doctor sitting across the table from a patient with paper, pencil, and a series of exercises to test memory and cognition. Important metrics like reaction time couldn't be measured very closely and couldn't be compared from one test to another.

They concluded that they needed to develop a repeatable, computer-based test that would work for NFL players and young athletes alike.

When Lovell relocated to Henry Ford Hospital in Detroit, he continued to collaborate with Maroon on neurocognitive testing for athletes. After meeting these two in Pittsburgh, Collins returned to graduate school and applied early versions of the test to the Michigan State football team. After completing his PhD, he started a postdoctoral fellowship in Lovell's lab.

Maroon pitched the early version of ImPACT to Noll and the Steelers organization, which became the first NFL team to adopt baseline neurocognitive testing of players. Today, ImPACT is required by the NFL for all players. It's used in collegiate athletics, recreational sports leagues, and school districts throughout the country.

In 2000, both Collins and his mentor Lovell relocated to Pittsburgh for the establishment of the sports medicine concussion program at UPMC, with Lovell as its founding director. In the ensuing 10 years, with Maroon and other colleagues, they have solidified Pittsburgh's place as the premier center for sports concussion. The center trains hundreds of physicians a year in treating concussion.

"We recently tested 30,000 special ops forces who are being shipped out to Iraq and Afghanistan," says Maroon. "We're also developing ImPACT for use in doctors' offices with patients [without brain injury] who might develop mild cognitive impairment, which is a very common thing in people after age 50. … We're working on a test that can be done in 15 to 20 minutes."

"Concussion, in my opinion, is the next Agent Orange for the army," says Maroon. "I say that in the sense that it was the long-term effect—one year, two years, five years afterward—that members of the military in Vietnam developed a syndrome. If these guys suffering concussions in Iraq and Afghanistan start developing dementia, it could come back on the army as a postconcussive injury."

A man or woman who has survived a TBI may look okay outwardly. Yet returning soldiers and other TBI victims may be dealing with cognitive and emotional issues—including poor memory, decreased concentration, impaired executive functioning, irritability, anger, and depressed mood, "making it difficult for many individuals to live alone or even with others," notes Pitt's Rory Cooper, professor in the School of Health and Rehabilitation Sciences, in a recent paper.

Maroon brings up a question that is still unresolved. A small number of NFL players with a history of concussions or even subconcussive blows to the head have been found to suffer from what looks like chronic traumatic encephalopathy (commonly found in boxers). But the number has been too small to make a definitive connection.

Concussion experts like Collins say there probably are long-term risks that go along with concussion, but large epidemiological studies have to be done before we can understand the nature of the risk, who is at risk, and how to minimize it.

Unlike the potential link between concussion and later neurodegeneration, an epidemiological link between severe TBI and Alzheimer's has long been known—if you suffer a severe traumatic brain injury, you have a greater risk for developing Alzheimer's down the line, even before old age. But the mechanisms behind this risk are not fully understood. But several years ago, Pitt researchers realized a last-resort surgical technique provided a rare opportunity to study brain tissue after TBI.

Because the skull is a tightly closed system, brain swelling after TBI has the potential to cause death or devastating damage to the brain. In some cases, surgeons will remove a section of the skull to give the injured brain room to swell. In other cases, small sections of brain tissue are removed for the same purpose. These bits of tissue present a rare opportunity to examine brain tissue from someone who'd survived severe TBI just hours or days prior.

Milos Ikonomovic, an MD associate pro-

fessor of neurology, explains what he and colleagues in Pitt's Brain Trauma Research Center found: About 30 percent of the severe TBI patients had Alzheimer's-like plaques. This was the case even in young people, which is very unusual. The plaques that neuropathologists evaluate to establish a diagnosis of Alzheimer's disease are called neuritic plaques, says Ikonomovic. "The plaques that we saw in brain trauma patients were of a diffuse type, an early form of amyloid deposits, as opposed to these mature plaques seen in Alzheimer's disease. This supports the idea that the pathology that we detected after severe trauma was a very early form and most likely developed subsequent to brain injury within hours to days of the insult."

Subsequent studies by Ikonomovic and colleagues are beginning to reveal the mechanisms responsible for the development of the amyloid plaques that are linked to Alzheimer's. "We have shown that trauma not only induces upregulation of the amyloid precursor protein but also increases the accumulation of amyloid beta and amyloid beta peptides, which are thought to be neurotoxic."

In mouse models of TBI, Ikonomovic and colleagues are looking into potential therapies that will block neuronal cell death linked to trauma-induced increases of amyloid beta peptide. They have achieved success with caspase inhibitors, which block a protease involved in cell death, and with statins, which reduce amyloid beta concentration and improve neuronal survival and functional recovery.

Basic science research from many areas provides a springboard for clinical advances. Faculty members in Pitt's Department of Physical Medicine and Rehabilitation research and implement new and refined treatments for TBI. They include MDs exploring the effects of neurostimulants on patients in sports medicine and clinical neuropsychologists like Ricker, who takes traditional psychosocial and cognitive approaches to treating brain trauma. Ricker and collaborators are taking advantage of the University's leading-edge imaging capabilities to conduct extensive imaging of brain-injured patients. "What we hope," says Ricker, "is to use this diagnostically in the clinic someday, to do a scan to determine which areas of the brain were injured and how much."

Kochanek is a believer in the future of TBI treatment. From the NIH alone, support for TBI research at Pitt is very strong—Dixon is the principal investigator on a large TBI program project grant that is now in its 18th year, and the Brain Trauma Research Center has been continuously funded since 1991. But NIH money is matched or exceeded by funding from the Department of Defense. The military, says Kochanek, wants answers and wants them now. DOD-funded projects include blast injury research designed to identify new drug therapies. Pitt research projects with potential implications for both the battlefield and the ball field include a project to detect biomarkers of head injury in blood (or other bodily fluids) with a strip of paper. Also with DOD support, Kochanek is leading a five-year project aimed at identifying new drug therapies for TBI. For this multicenter project, researchers have identified 10 promising agents that they will rigorously test in multiple labs in multiple ways. Five are what Kochanek calls "low-hanging fruit." They are FDA-approved for other uses; some are off-the-shelf neutraceuticals like resveratrol. The other five he calls "high risk, high reward"; these are not FDA-approved and only have a few promising studies behind them, but they could dramatically change the status quo if they pan out.

"Concussion, in my opinion, is the next Agent Orange for the army."



CORBIS

As it passes through a skull, a blast wave turns out to have its own unexpectedly sinister fluid dynamics.

The ranks of those who could benefit from such advances are wide ranging. They include victims of automobile accidents and falls, soldiers shipping out today and in the future, and the future Hall-of-Famers that now inspire such admiration on the field.

And then there are those high school athletes, like Katy Korber, who just want to have a good game, be a part of a team, and be a better person for having given it all. These are the same things Katy's parents—and her physicians—want for her. Despite the obvious concerns about injuries to the head, there's no evidence that a single concussion is a risk factor for any long-term consequences, provided the person fully recovers. One could make the argument that the health risks of not participating in a team sport like volleyball are as great or greater than the risk of participation.

Katy, incidentally, is one young athlete who can expect to have many opportunities to have the game of her life.

Her final visit to the sports concussion room ended with an enthusiastic fist-bump from Collins and an "all-clear-to-play." ■



Anna and Derrick Gaines on a date night. After Derrick suffered a traumatic brain injury, the two have rebuilt their relationship around a new and deeper investment in one another.

AN INJURY THAT ERASES SELF

TEXT BY KRISTEN COSBY

PHOTOGRAPHY BY MARTHA RIAL

"NONE OF MY MEMORIES ARE MY OWN"

Anna Gaines (MD '08) last spoke to the man she married on the morning of June 9, 1999. Readying for the office, her husband, Derrick Gaines, donned a cream-colored suit, a bright blue shirt, and a blue tie.

"You look handsome," Anna said.

Derrick picked her up, gave her a hug, and kissed her. They were both 24 and had been married for not even two years. In college, they'd been racquetball partners at the University of North Carolina, Chapel Hill, and then friends, before falling in love—their partnership secured deeply within their admiration for one another.

That morning, they spoke via cell phone as Anna tailed Derrick's Camry to the Pennsylvania Turnpike. She could see him talking to her through the rear window of his car. They'd been discussing their future. Anna—who'd graduated Phi Beta Kappa from UNC in three years—planned to apply to medical school. Derrick—who'd distinguished himself as one of a couple hundred high school students selected for the accelerated North Carolina School of Science and Math and had been offered several academic scholarships—hoped to get his doctorate in physical therapy. They both wanted children.

"I have a lunch meeting at noon, but I should be back in the office at one," Derrick said and hung up.

The memory of those last moments within the shared vision of their past and future as a couple is precious to Anna. Now, she alone carries their history, their vision. Derrick cannot remember any of it. Nor can he remember the truck tire that hurtled through his windshield as he was returning from his lunch meeting, or the subsequent six months he



By viewing snapshots repeatedly, Derrick has been able to rebuild some of his own history and the experiences he and Anna have shared.



spent in hospitals and rehabilitation facilities recovering from the severe traumatic brain injuries (TBI) he suffered during the resulting crash. He cannot remember their racquetball games, the letters he wrote Anna every day when they spent a year apart, their wedding, their married life before the accident, or even their experiences together during the 11 years since.

The truck tire struck Derrick in the head and chest and knocked him unconscious before peeling off the roof of the Camry. The car spun across the median and collided, head on, with another vehicle. Derrick's heart stopped. His brain began to suffocate.

He was flown by emergency helicopter to Allegheny General Hospital. When Anna arrived, he was strapped to a gurney, covered in blood, and comatose.

"Please," she said to the doctors, "do everything you can. He is such a special man."

Derrick had suffered diffuse axonal injury, the shearing and tearing of delicate conducting filaments that transmit signals from neuron to neuron; multiple focal contusions, bleeding into brain tissue; and anoxia, cell death from lack of oxygen. The impact also broke his right scapula, right leg, and several ribs and shattered his left hand. Over the next few days, the swelling and bleeding in his brain destroyed yet more tissue. Anna and Derrick's parents stood at his bedside and prayed for his life.

Three weeks after the accident, Derrick's eyes flickered open for the first time.

Four weeks after the accident, Anna realized Derrick didn't know who he was.

Eleven years later, there is little evidence of the trauma to Derrick's body—a V-shaped scar on the right side of his head, a few others elsewhere. His physical person is almost fully functional. But there is also little evidence of the man Derrick Gaines was before the accident. His neurons are wired differently; his brain functions differently. Derrick and Anna have reconstructed his person.

In the six months immediately following the accident, Derrick spent 12 hours a day with Anna and various teams of rehabilitation specialists relearning how to swallow, walk, speak, eat, groom, go to the bathroom, read, and use ordinary objects. He progressed in minute steps. Derrick's procedural memory remained intact. He could learn—memorize—by repeating tasks over and over until they became reflexive. Instead of hitting "save," committing information to his hard drive, he had to wear a groove into a record.

As he healed, Anna waited for her Derrick to recognize her. He recovered core autobiographical information: He had a brother; he was from North Carolina; he was born on July 30, 1974. Later, he seemed to know the faces of his mother, his father, his brother, and his college roommate. Though he couldn't remember their names or their shared experiences, he retained these deep emotional connections.

But Anna remained anonymous to him, a nameless woman with whom he had to be reacquainted each day—until he began to understand, vaguely, that she was his primary caregiver.

"Hey, girl," he'd call to her. "What's your name?"

Then he began to call everyone "Anna": his mother, his therapists, his brother. Everyone except Anna.

She gave up waiting for him to remember her and began waiting for him to accept the stories







OPPOSITE PAGE AND ABOVE: Derrick and Anna at home with their three children: Justin, 7, Mariah, 5, and Sean, 3. Parenthood has brought more chaos and love into the couple's lives. "The kids are such a blessing," says Derrick. **RIGHT:** Anna at work in UPMC's Rehabilitation Institute based at UPMC Mercy where she often sees patients who've suffered traumatic brain injuries. Anna notes, "I know the current-day 'snapshot' of my life with Derrick is nothing like the typical outcome of severe TBI in a young adult. Our success has been very hard fought, and the road continues to be very fulfilling, albeit anything but smooth."



Anna has learned that rehabilitation requires faith, hope, and the ability to understand that one's beloved may not return.

she and his family were telling him about his life. Ritually, almost every waking hour, Derrick, Anna, and Derrick's doctors would review his information from the front page of his orientation log: *He was Derrick Gaines. He was 25 years old. He was married.*

Three months after the accident, he responded to his name.

Four months after the accident, he began using Anna's name correctly.

In December, after half a year in various brain injury rehabilitation centers, Derrick and Anna returned to their house. With the help of ReMed, a community-based brain-rehabilitation program, Anna tried to re-integrate Derrick into their home life. He needed supervision at all times. He believed he was 14, his home was North Carolina, and Anna was just some woman preventing him from returning there.

He still needed to fill in blanks. Four times a day, Anna helped Derrick complete his new orientation log: *My name is Derrick Gaines. I am 25 years old. I am married. . . .* Photographs of him as an adult distressed him. He had no sense of life portrayed by the images. When Anna played a video of their wedding, he left the room. "I don't remember that," he said. "I don't believe it."

A year after the accident, Derrick accepted that he had a brain injury.

A year and a half after the accident, he accepted that Anna was his wife.

But their relationship felt neither tender nor unified. Derrick fought Anna as she helped him dress in the morning. Like many TBI patients, he was often aggressive and inappropriate. These acts were not conscious. Derrick had yet to relearn to control his impulses, and he was often agitated by his limitations.

Additionally, Derrick couldn't remember conversations from one hour to the next, even important conversations, like when Anna wanted to know whether he still wanted to be a parent, or whether she should go to medical school. The man she'd married had wanted children and wanted her to become a doctor. She assumed those sentiments still prevailed within Derrick. He said yes more often than not. So she applied to medical school, and they conceived.

As Derrick's schedule and routines were disrupted by Anna's pregnancy and their move to a house near the University of Pittsburgh, he became more agitated. Anna realized she could not keep them both safe. She moved him into a residential brain-injury care facility near their new home, feeling as if she'd lost her husband again. Their baby, Justin, was born May 23, 2003. In photos, Derrick grins at his newborn son. But Anna had to decide whether Derrick could handle the unpredictability of being a parent. She consulted his doctors. She prayed.

"I have never lost my appreciation for who Derrick was," Anna says. "He was awesome. I loved him even though he wasn't who he had been. And I saw hope in who he was becoming."

From the start, Derrick loved Justin. Fatherhood gave him something to identify with—other than being a brain-injured man. Derrick couldn't remember the birth, but he knew from photos that he'd been there. He worked to develop strategies that would allow him to control his impulses; and, slowly, he integrated into their new life.

Eleven years after the accident, Derrick drives, plays basketball, reads bedtime stories to his three children and helps get them ready for school, does laundry, and vacuums the house—though he can't remember where to put things back when he's done (and jokes about this at times). He volunteers at Children's Hospital of Pittsburgh of UPMC as a chaperone at the sibling center and at Pitt's Department of Physical Medicine and Rehabilitation's research program doing data entry. He jots down notes of important events in his log book and repeats stories aloud again and again, trying to carve them into his memory. His every task is scheduled on a planner that he and Anna compose, and he navigates his world using instruction books that Anna has compiled with him. Every day, Anna creates new systems in which Derrick can achieve, and every day, Derrick engages. Although negotiating that structure still challenges their marriage, their partnership has been re-formed with new intimacy around the injury they've survived, and they continue to survive, together.

"I can't rely on my brain," Derrick says, "I can't do all the things I could do before the accident, but I can do a few things very well. I like that. I like doing things to help Anna. I am lucky that she stayed with me. And the kids are such a gift. I love where we are."

He can recount many of his stories, having heard them enough times that he can retell them, but he hesitates. *Did that happen?* Then he turns to Anna for confirmation.

"It's sad sometimes. I can't tell if I remembered something or if Anna told me. None of my memories are my own. They've become memories of mine since they are from people I trust. But what about all those little things that only I would know about? I don't have anyone who can give that back to me."

Anna graduated from Pitt's med school and is now a third-year resident in physical medicine and rehabilitation at UPMC, where she often counsels families affected by TBI. From her own encounters with rehabilitation, she knows that the most difficult work comes when patients leave the hospital and enter a chaotic society where they appear deceptively uninjured. Rehabilitating someone within that world is a delicate, unending process unique to each injury and each brain.

"The idea of the Self is at the heart of rehabilitation—the most extreme example being patients with acquired brain injuries involving memory deficits—because the Self is a plastic thing," says Margaret Reidy, an MD and president of the UPMC Rehabilitation Network. Reidy, formerly a physician of Derrick's, encouraged Anna to enter the field of rehabilitation medicine. "In rehabilitation, you get to see the human condition at its most desperate and its most graceful—as in 'Amazing Grace.' Derrick is having a life he easily might not have had. He and Anna are lucky to have found one another."

Anna has learned that rehabilitation requires faith, hope, and the ability to understand that one's beloved may not return.

"It's different now, after 11 years," she says. "Derrick, at some point, transitioned into feeling love. He started caring about me; he started caring about his future. Even though I remember how I felt with Derrick when we got married and in those early years, I don't look for that in Derrick anymore. I did go through periods of time when I had to let myself grieve the loss of that relationship so that I wasn't expecting something unreasonable from Derrick now."

The couple sits at their kitchen table, Derrick smiles, crooking the right corner of his mouth higher than the left. Anna smiles back. "You used to smile that way before the accident, when you were saying something funny."

"Really? I don't remember that," says Derrick. Then he listens as she tells the story of how he proposed to her. If she repeats it often enough, it will become his story, too. ■

We have the technology, and the vested interest, to build a better, stronger, fitter health system.



THE DOCTOR DOCTORS

PITT RESEARCHERS ARE FINDING OUT WHAT WORKS BEST IN MEDICINE. CAN THEY HELP SOLVE A $2.3 TRILLION QUESTION, TOO?

BY REID R. FRAZIER

ILLUSTRATIONS BY JESSE LENZ

One night in the 1980s, Mark Roberts phoned a transplant surgeon about a very sick patient in the ICU at what was then New England Deaconess Hospital in Boston, where Roberts was a resident. As a young MD, Mark Roberts had a habit of questioning his betters. A few years earlier, he'd earned a master's degree in public policy and health policy while in medical school. (As a third-year med student, he once drew up a schematic model on the options for a patient with an aortic aneurysm, after watching attending physicians and residents debate whether or not to operate, without basing their arguments on any scientific evidence.)

ILLUSTRATION: JESSE LENZ. PHOTO OF THE 6 MILLION DOLLAR MAN: CORBIS

The subject of the late-night phone call was a woman who'd had liver disease for 15 years and was awaiting a liver transplant. Roberts quizzed the transplant surgeon, Roger Jenkins, on why she hadn't been operated on sooner.

"I said, 'Roger, if you had a *Star Trek* replicator, and you could build an ABO-compatible liver of the right size for this woman, when should you have transplanted her?' And his answer was, 'I have no idea,'" Roberts says. Ideally, would it have been six months earlier? A year? There was no answer. No one had ever researched it, in part because there was no way to study the problem through traditional methods.

The question stayed with Roberts. With the help of Jenkins, he began working on a "virtual" trial to come up with an answer. Roberts produced a computer model of end-stage liver disease. The model took into account life expectancy with or without transplant, the likelihood of organ rejection, and the chaotic ways liver disease progresses in individuals—sometimes slowly, sometimes quickly. Roberts borrowed an algorithm designed for industrial plants. Models like Roberts' are now used routinely to determine which patients should get priority in liver allocation.

Questioning typical care decisions—like when a transplant should be done—might seem like common sense. But in many corners of the medical world, doctors employ remedies without much evidence that a chosen treatment is the best one.

For example, Roberts points out that there are 19 different drugs he can prescribe for high blood pressure. But they haven't been compared to one another across a spectrum of patients. So when he sees a hypertensive patient, Roberts is left without enough data to know which of the 19 drugs are best and for which patients.

Roberts—now a University of Pittsburgh professor of medicine and of industrial engineering, as well as professor and chair of health policy and management in Pitt's Graduate School of Public Health—has spent his career trying to find ways to answer these seemingly simple questions. He's designed models to study antiretroviral therapy for HIV patients, determine the effectiveness of alcoholism interventions, and figure out the optimal time to administer vaccine during an outbreak of flu.

He uses computer models because standard research techniques can't answer many of the questions he would like to answer. Randomized controlled trials, the gold standard for clinical medicine, are costly and time consuming. They work very well when asking how a new drug compares to placebo. But they're ill suited to find out how a drug might compare to 18 others in a diverse set of patients.

"Most of medical science is based on randomized controlled trials, which simply answer, *Is A better than B?* [with B being a placebo, typically]. But many of the questions we have in real clinical medicine aren't that dichotomous," says Roberts, a general internist. "They're, *What's the best time to intervene?* Or, *Under what conditions is this better than that?* It's much more continuous, much more calculus."

Real-life medicine is filled with questions that might appear simple but are, in fact, very hard to answer: What's the best way to avoid health care–associated infection? How do you best address obesity, hypertension, and diabetes in underserved populations? Should you treat back pain with surgery, physical therapy, or some combination thereof? These are examples of problems addressed by comparative effectiveness research (CER), a field that uses epidemiology, biostatistics, and health policy science to compare treatments and assess which work best, when, and for whom. (The field is new enough that it's been assigned several names, including "patient-centered outcomes research" and, in the UK, "clinical effectiveness.")

The many medical questions addressed by CER have taken on new urgency in the past few years as society has come to terms with budget-busting health care costs. Finding out which treatments work best should help us to stop paying for treatments that are inferior. That's why President Barack Obama is trumpeting CER's promise, and why Congress allocated $1.1 billion of stimulus funding to pay for research in CER.

COMMON SENSE GETS FUNDING

Since it was founded in 1990, the U.S. Agency for Healthcare Research and Quality (AHRQ, or "Ark," in the lingo) has been the major source of funding for comparative-effectiveness science. The agency is relatively small—its 2009 budget was about 1 percent of that of the National Institutes of Health (NIH), which funds most basic biomedical research. That will start to change. Congress' appropriation will essentially double the agency's budget.

Why the sudden attention? The biggest reason is economics. The United States spent $2.3 trillion on health care in 2008. With 32 million more people promised health coverage under the Patient Protection and Affordable Care Act, health care costs are expected to climb. Harvard University's Michael Chernew has called the state of health care costs "financial Armageddon."

In this gloomy picture, CER offers a ray of hope that we can eliminate unnecessary or ineffective treatments. For instance, new cancer drugs like cetuximab have been shown to work in colorectal cancer patients who have a normal expression of their KRAS gene, but not in those with a mutation in the gene. By simply giving the drug to only the appropriate patients, we could save $600 million in health care costs, research suggests.

A second, related issue is quality. Several well-known studies by the Dartmouth Institute for Health Policy and Clinical Practice found that health outcomes were no better in the highest-spending regions of the country than in those that spent the least. This phenomenon has been linked to the medical incentive system in America—more procedures, scans, surgeries, and prescriptions mean doctors and health care systems get paid more. Yet when doctors do more, that doesn't necessarily translate to better care. A well-known study of 6,700 patients found that doctors followed "recommended care" only

Roberts points out that there are 19 different drugs he can prescribe for high blood pressure. But they haven't been compared to one another across a spectrum of patients. So when he sees a hypertensive patient, Roberts is left without enough data to know which of the 19 drugs are best and for which patients.



Cleanup in the medicine aisle: A lack of convincing data may cause doctors to follow recommended-care guidelines only 55 percent of the time, according to one study. By revealing the best treatments, researchers think we could cut health care costs, which eat up nearly one-fifth of the U.S. economy.

55 percent of the time. This may be because guidelines are often too vague to be of much use in many care decisions. So doctors rely on their own experience, the advice of colleagues, and other unscientific information when making medical decisions.

The rapid advance of medical discovery is a third area where CER can be of use. New treatments often come online before adequate research establishes how they compare to other options. Drug-eluting stents for angioplasty, for example, were on the market for several years before the completion of any studies comparing them to older, bare-metal stents. Several studies found no difference in mortality. In some studies, drug-eluting stents were associated with slightly higher short-term mortality rates.

Add all these factors together and you get an expensive, inefficient health system. Most disconcerting, patients and doctors often make critical decisions without much help from the scientific data.

Hearing that an expensive test is unnecessary may be fine in the abstract, but when the patient is your wife or son, you're less likely to be receptive to the message.

This is where CER can help, says Wishwa Kapoor, chief of Pitt's Division of General Internal Medicine and vice chair of its Department of Medicine, as well as Falk Professor of Ambulatory Care and a professor of health policy and management. Kapoor has been comparing the effectiveness of treatments and strategies for the better part of 20 years. He has studied the best ways to treat pneumonia, administer antibiotics, and manage ICUs. It is in the gray areas of medical decision-making that advanced statistical modeling and measurement techniques can provide guidance, he notes.

"Sometimes there are no studies available to tell you what to do, but you can look at the evidence, add it all up, and come up with the best strategies for a particular condition," Kapoor says. "We deal with a lack of evidence all the time, but sometimes, you have to make a decision."

A MOVEMENT AFOOT

In the midst of this national CER effort, the University of Pittsburgh is moving quickly to establish itself in the field. Senior Vice Chancellor for the Health Sciences and Dean of the School of Medicine Arthur S. Levine chairs an NIH working group on the emerging field. The University has brought in several high-profile recruits to build up its CER operation. These include Sally Morton, former head of statistics for RAND and vice president for statistics and epidemiology at the research group RTI International. Morton is professor and chair of biostatistics in Pitt's Graduate School of Public Health. The University also recruited Everette James, who recently served as Pennsylvania's Secretary of Health and is an expert on health policy and cost containment. James has been tapped to lead Pitt and UPMC's compliance with health care reform, as well as to launch major research initiatives aimed at CER.

There are already hundreds of ongoing studies at Pitt that address comparative effectiveness, relating to everything from middle-ear infections to chemotherapy. With its access to UPMC's health network and electronic medical records, Pitt is poised to become a health services laboratory, says Steven Shapiro, Jack D. Myers Professor and Chair of Medicine and UPMC's chief medical and scientific officer.

One advantage Pittsburgh has over other academic medical centers, Shapiro says, is the presence of UPMC's integrated health insurance plan. This means that implementing less intensive—and thus less costly—treatments, say, watchful waiting instead of an MRI, won't hurt the system's overall budget.

"Being an integrated payer-provider allows us to focus exclusively on the best outcomes for the patient. That is, we only need to keep the patient healthy without concern for the 'health of our bottom line' in the current and unsustainable system of reimbursement."

CALLED TO SERVE

The daughter of physicians, Morton chose a career that allowed her to use math to solve real-world problems. The PhD is now a nationally recognized expert in using statistics to make health policy decisions. Morton has been asked to serve on several Institute of Medicine panels, including one with the (somewhat ambitious) title, "Knowing What Works in Health Care." Among its recommendations, the group called for the creation of an autonomous organization to evaluate the effectiveness of various interventions. A few months after the report came out, Congress created just such an entity, the public-private Patient-Centered Outcomes Research Institute (PCORI). Morton is quick to point out that "many others" had previously called for the creation of PCORI but admits that when the legislation came out, she felt a sense of pride. "It felt like, whoa—it really mattered what we said, that people were listening. As a statistician working in health policy, I'd never felt so close to decision-making."

Morton's next call from the IOM came during the beginning of the health care debate, in early 2009. The Institute was quickly convening a group of experts to create a list of the "Top 100" problems in health care for effectiveness researchers to address.

The call to serve felt profound to Morton. "Every single person who was asked to sit on that committee said, 'Yes,'" she says. In a few adrenaline-fueled months, the committee crafted a report, convened public hearings, and sent its draft for review. Typically, such a report takes 18 months to prepare. This one took five.

"We really thought the time was now—this was during health care reform," Morton says. "For a lot of us, we'd been working on health care for all our careers. To suddenly feel that things were changing, and we could contribute to that change in a positive way, was very uplifting."

Where is all of this headed? Morton has been watching with great interest the emergence of electronic medical records. She believes they have the power to transform how medical science is undertaken but need to be evaluated with caution. "There are people who have actually said that clinical trials should become obsolete," Morton says. "When you have a hundred million records, why do we need a trial?" Yet observational data like electronic medical records are more prone to bias than randomized experimental data, Morton notes. "The combination of EMRs and randomized data is where the strength lies," she says.

Kapoor and others have already embraced the computational potential of electronic records. He and his colleagues mined electronic records to study the use of spiral CT scans in the diagnosis of pulmonary embolism, a common cause of preventable mortality in

hospitals. The group wanted to know whether the proliferation of the spiral scan, which provides more detailed images than standard CT systems, actually improved outcomes. Combing through millions of medical records, the researchers isolated 38,000 hospital discharges for pulmonary embolism. Their conclusion: Spiral CT scans caught pulmonary embolism earlier, resulting in lower death rates for patients.

FACING UP TO THE COST QUESTION

In its landmark 2010 health care legislation, Congress explicitly forbade its new creation, PCORI, from funding studies that would compare the cost effectiveness of different therapies. The decision was made after extensive lobbying from the drug and device industries, which argued that the studies would reduce incentives for innovation. Some politicians warned that considering cost effectiveness would lead to care rationing.

Yet around the world, countries with national health insurance routinely consider cost effectiveness when deciding whether to pay for treatment. (This is one reason health care costs in most European countries are much lower than in the United States.) Among the most advanced of these systems is the United Kingdom's, whose National Health Service uses cost-effectiveness analyses (yes, there's an acronym: they're CEAs) to approve therapies for coverage. If a treatment cost falls above a threshold, around $50,000 per quality-adjusted life year (essentially an extra year of good health), the system might decide against paying for it. This approach has drawn criticism—the NHS has had to go back on some decisions to deny some forms of cancer treatment. Last year, the UK's new government decided to overhaul the health system and may yet scale back reliance on cost effectiveness.

A national health policy that ignores cost may simply be wishful thinking, says James, Pitt's recently appointed associate vice chancellor for health policy and planning. James ought to know. While leading the Pennsylvania Department of Health, James saw firsthand how hard it was to achieve meaningful cuts in health care costs.

On an overcast fall morning, James drops a photocopy handout on a desk in his sparsely decorated Scaife Hall office. "This is why we can't avoid cost," he says, putting his finger on a photocopy of a graph titled "How High Could It Go?" It shows the cost of health care in the United States from the 1960s until today, with a line graph portraying growth in private insurance, Medicare and Medicaid, and out-of-pocket expense costs. The graph looks like a staircase that gets steeper and steeper as it nears the top.

Under James, Pennsylvania set up a national model to reduce the prevalence of hospital-acquired infections (an effort led by many Western Pennsylvania hospital leaders, including those at UPMC). James tried, unsuccessfully, to enact measures proven to lower health costs in other places, like liability reform and apology legislation, which encourages open dialogue between doctors and patients in the event of medical error. Prior to taking the state post, James worked at a Washington, D.C., law firm, serving as counsel to both for-profit and nonprofit insurance companies. He has been on both sides of the public-private divide in health care and has a perfect vantage point from which to see the system's bottlenecks.

Part of James' job is to guide Pitt as it navigates around those bottlenecks. He will help create a data infrastructure to support CER research, giving investigators ways to access a warehouse of medical data. James acknowledges the difficulties of building the data architecture and legal agreements for CER while preserving patient privacy. But they are worth it, he says.

"It may be a headache, but it's going to be necessary to have a large enough sample size and enough utilization and outcome data to make the findings relevant," he says. First, James plans to reorient the hundreds of CER-related research projects across Pitt's schools of the health sciences under one umbrella for better access to funding, resources, and expertise. He has been logging 15-hour days on the job.

POLITICS AND PROSE

In late 2009, the U.S. Preventive Services Task Force announced new guidelines for mammograms for women ages 40 to 50. It suggested these women should consult with doctors about the need for mammograms, because the data showed the procedures were of limited benefit for women younger than 50.

The announcement came as the health care debate was coming to a boil, and reaction to the guidelines was swift and forceful. Patient advocacy groups opposed them. It seemed to them as though the government was trying to take a preventive tool away from women.

"The guidelines did not say that women 40 to 50 should not have a mammogram," says Morton. But that's not the way it was received after press reports, she notes.

The controversy was an important object-lesson for CER. The data do not always conform to the wants and expectations of patients, doctors, medical systems, or governments.

"I think patients think, *More is better.* And if they're faced with the question, *Should we do the test or not?* they think, *Why not?*" says Morton.

Herein lies a challenge. Hearing that an expensive test is unnecessary may be fine in the abstract, but when the patient is your wife or son, you're less likely to be receptive to the message.

"When people hear about CER, sometimes what they hear is, 'You're going to tell me what I can't get,'" Morton says. "They're not hearing, 'This is what works for you as an individual. This is what's best for you.'"

An area where comparative effectiveness has borne fruit is in cancer research. Nancy Davidson, director of the University of Pittsburgh Cancer Institute and UPMC Cancer Centers, is known for her work comparing treatments for certain kinds of breast cancers in premenopausal women. Davidson has also researched the importance of the HER-2 gene in breast cancer, and its role in treatment response. As a consequence of her studies and studies like them, gene testing is a common practice in breast cancer care.

"As we understand the molecular Achilles' heel for different types of cancers, we're better able to design treatments and make sure we're not exposing patients to treatments that won't work on them," Davidson says.

This kind of progress toward "personalized" medicine is exactly what Roberts would like to see in other areas of medicine. Clinical trials for new drugs are likely to exclude large numbers of patients, often because of age or disease. Yet most of the patients in Roberts' office are there because they are old or sick.

"If you ask the question, 'Would my patient have been included in the studies that were used to make those recommendations?' The answer is—a surprising number of times—'No,'" Roberts says.

"To me, the idea of comparative effectiveness is to try to understand, in real, live conditions, in real, live patients—who look like the patients I see—'How can I make better decisions about what's the best thing to do for them?'

"That's what we're trying to do." ■



THOMAS DETRE: A LEGACY BUILT WITH PEOPLE

BY JOE MIKSCH

THE RECRUITER

When Thomas Detre died, he left behind family, friends, admirers, detractors, and an enormous legacy in the form of the partnership between the University of Pittsburgh School of Medicine and UPMC.

Known as an unstoppable worker and an unapologetic visionary, Detre took what some saw as a good regional medical school with pockets of excellence and helped transform it into an organization that was on the fast track to becoming world-renowned as a center of academic medicine. His chief skill, he said often, was his ability to persuade the right people to come to Pitt at the right time—people who could cross traditional boundaries to build something great. Had he been a college football coach, he would have outrecruited them all and pocketed more than a few national championships.

Detre's career in Pittsburgh began in 1973 when he left Yale University to take the reins of Western Psychiatric Institute and Clinic (WPIC) and an appointment as chair of Pitt's Department of Psychiatry. In the ensuing decades, Detre, an MD, led Pitt's Medical and Health Care Division and was Pitt's senior vice chancellor for the health sciences and interim dean for the School of Medicine. He also served as president of UPMC, and was executive vice president for international and academic programs and director of international medical affairs for UPMC.







Thomas Detre (left), who died in October 2010, was one of Pittsburgh's prime movers whose work created UPMC and helped raise the profile of the School of Medicine. Detre (right, top to bottom) with former UPMC board chair George Taber, who was instrumental in helping Detre create one of America's leading academic medical centers; with David Kupfer, a former student of Detre's at Yale University, who followed him as head of Western Psychiatric Institute and Clinic; and with Lila Decker, an RN who came with Detre from Yale and was his "point lady" throughout their intertwined careers.

OPPOSITE PAGE: REIDER PHOTOGRAPHY. THIS PAGE, TOP TO BOTTOM: BILL REDIC; DETRE ARCHIVE COLLECTION, FALK LIBRARY OF THE HEALTH SCIENCES, UNIVERSITY OF PITTSBURGH; LILA DECKER.





Detre was known as a "European gentleman" by his colleagues and a loving companion by his cat, Marco (left). Continuing clockwise, Detre's med student identity card from the Pázmány Péter University of Science in Budapest, posing with a motorcycle in Europe, and with his parents, Géza Feldmeier and Gabriella Bauer, in Venice in the 1930s.

DETRE WITH CAT: DETRE ARCHIVE COLLECTION, FALK LIBRARY OF THE HEALTH SCIENCES, UNIVERSITY OF PITTSBURGH. ALL OTHER IMAGES: THOMAS DETRE.

Detre's death in October 2010 prompted more than a few fond recollections of the man many considered a friend and a mentor as much as a strategic thinker who ruffled a feather or two on his way to rocketing Pitt's School of Medicine and UPMC to the top.

David Kupfer accompanied Detre in his move to Pittsburgh from Yale in 1973. Detre's influence on the younger MD's career is obvious when you look at Kupfer's job titles: Thomas Detre Professor and former chair of the Department of Psychiatry and director of research at Western Psychiatric Institute and Clinic. He was a student of Detre's at Yale and coauthored papers with his mentor and colleague starting in 1966.

Although Detre published one of the first psychiatry textbooks that endeavored to shift the field's center from psychoanalysis to a more empirical, scientific, and data-driven realm, Kupfer says Detre's primary strength was that of a talent scout, not a bench scientist.

His eye for talent, for example, netted the National Cancer Institute's Ronald Herberman, who became the inaugural director of the University of Pittsburgh Cancer Institute in 1985; Loren Roth, a trainee of Detre's at Yale who served as chief medical officer of UPMC and is now Pitt's associate senior vice chancellor, health sciences, and said of his mentor, "Within 10 minutes of meeting him, I knew I had to hitch my star to that guy"; and Jeffrey A. Romoff, director of what he called "a very small mental health counseling planning group in Waterbury, Conn.," who is now president and CEO of UPMC.



Margaret McDonald—who, early in her time in the School of Medicine, was essentially Detre's writer—is now associate vice chancellor for academic affairs for Pitt's schools of the health sciences. As Detre's role in Pittsburgh expanded, so did hers. But he had to use ample powers of persuasion to get her here. Her story will be familiar to many, if not in detail, then in form.

McDonald was a Washington, D.C.–based science writer in the early '70s and found herself interviewing Detre. They hit it off, she says. "I talked back to him. I just engaged him in very direct conversation, which, apparently, he liked."



By the time Detre and McDonald met again, it was several years later, and he was chair of psychiatry at Pitt. He remembered McDonald, as he did everyone he met, and made an offer. "My response was, 'Oh, well, that's in Pittsburgh, and I live in Washington and have a boyfriend.' So I blew it off."

A year passed, they met at another conference, and Detre made his proposal anew. "He gave me his famous line, 'Vell, vy don't you just come and visit,'" McDonald says, imitating Detre's Hungarian accent.

She did, and she got the typical Detre whirlwind tour: Fly in at night, see the city pop into view—luminescent—as you pass through the Fort Pitt Tunnel, have a nice dinner, have a day of intensive interviews, get on a plane, get home, and get an offer.

This was in 1983. McDonald accepted, obviously, and has this to say of her rising through the ranks with Detre: "People were scared of him, but there was absolutely no reason to be.

If you did what he asked, and you did it well, you would get the resources to do more and get more responsibility."

On a more personal level, McDonald adds, he was never anything but warm and engaging. "All the stories about him being a European gentleman were true," she says. (Even when he was slowed by illness in his last months, he held the door for *Pitt Med*'s contributing editor Chuck Staresinic.) "One of his defining characteristics was that when you were with him, it was all about what you and he were discussing."

Detre was also pretty funny—dry and slightly sardonic. "He smoked and did not exercise," Kupfer says. "He felt that exercising was a waste of time. Many made the argument that somebody might gain years [of] life by exercising, and his comment would be, 'Well, think of all that time you spent exercising, now subtract that from the time you might have gained.'"

You'd be hard-pressed to find anyone who would say Detre wasted a day of the 86 years he lived.

What follows is a series of edited excerpts from *Beyond the Bounds: A History of UPMC*, a book by Mary Brignano that chronicles Detre's creation of UPMC—in concert with Romoff—as well as his life, career, and the growth of academic medicine in Pittsburgh. In many ways, these things cannot be separated. (© 2009 UPMC. Reprinted with permission.)

A Half-Century Ahead

Thomas Detre was born Tamás Feldmeier in Budapest in 1924, the only child of Géza Feldmeier, an MD and Berlin-trained obstetrician-gynecologist, and his wife, Gabriella Bauer. He grew up in the city of Kecskemét, his father's hometown, about 85 kilometers from the capital.

DETRE: *My father was one of the best doctors I have ever known. His instinct for diagnosis was so acute that the public absolutely refused to consider him as only an obstetrician-gynecologist, although he had delivered nearly 4,000 babies by the time he was deported to Auschwitz. My mother loved to dance, and drink, and play cards, and was absolutely outrageous in the best possible way. When my father was drafted during the First World War, she cut her hair, disguised herself in a soldier's uniform, and traveled by train to the Russian front, where he was stationed with the hussars. Because they were newly married, and she missed him.*

I was brought up very liberally. My parents were about half a century ahead of themselves in every respect.

Crossing the Line

Tamás was educated at a private Catholic high school and college, the Gymnasium of Piarist Fathers—"slightly stricter than the Jesuits," he maintains. There, in a moment of appalling irony, he first became interested in psychiatry.

DETRE: *Anti-Semitism in Hungary started to increase in the late 1930s and peaked in the early 1940s. You began hearing anti-Semitic remarks on the streets. One day, even at the Piarist gymnasium, a teacher of cultural history referred to Sigmund Freud as "the degenerate Jew who developed a pan-sexual view of human nature." I am actually grateful for that remark. It made me curious. I was only 14, but my father allowed me to read all his books about Freud. I decided that psychiatry was going to be an interesting discipline for me. My father was upset. He wanted me to be a "decent" doctor, not a psychiatrist.*

Because no Jews were permitted to attend medical school, Tamás continued his education at the Academy of Law in Kecskemét. He also worked as a research assistant in the neuropsychiatric unit of Budapest's Jewish Hospital.

DETRE: *The refugees arriving in Budapest told horror stories about what was going on in Nazi-occupied countries. I was convinced that our family had to get out of Europe. But my father was a highly decorated World War I officer. He said deportations would never happen in Hungary. He said his patients would protect him. I was more skeptical.*

When the Germans occupied Hungary in March 1944, I stayed in Kecskemét for a few days, but I saw it was not possible to remain safe in a small city. I packed some jewelry and went back to Budapest. That was the last time I saw my parents. The following year, I learned they had died in Auschwitz along with 20 members of our family.

Escape

The Russian "liberation" of Hungary in 1945 enabled Detre to attend medical school at the Pázmány Péter University of Science in Budapest. [He earned his MD from the University of Rome in 1952.]

His psychiatric studies crossed into new territory as well. His mentor, "a little known, but very intelligent psychiatrist called Leopold Szondi," believed that psychoanalytic psychotherapy was ineffective in treating most biologically based mental disorders. Detre came to a lifelong conviction: For some illnesses, no amount of talking could make the patient better. "Psychotherapy alone is likely to be of major benefit only when the impairments originate exclusively in the sociopsychological roots and consequences of the illness," he would write in his definitive *Modern Psychiatric Treatment*.

Raised Eyebrows

To pursue academic medicine, Detre came to the United States in May 1953 and began his Yale career in 1955. In 1956 he married Katherine Maria Dreschler, like himself a refugee from Hungary. Katherine Detre, an MD and DrPH (who died in 2006), would build a career as one of the nation's foremost epidemiologists, known internationally for leading large-scale studies investigating the appropriate treatment for cardiovascular disease. Both Detres insisted on the need for evidence-based medical research to evaluate treatments and advance patient care. [The widower later married psychologist Ellen Ormond.]

At Yale Thomas Detre immediately clashed with the psychoanalysts who dominated the Department of Psychiatry. Yale was not unique: By 1962, analysts would head 59 of the country's 82 academic psychiatric departments. "Tom was one of the first to make the leap from psychiatry as an art to psychiatry as medical science," notes Loren Roth, an MD/MPH. [Detre envisioned a future in which psychiatrists would collaborate with biologists, neurologists, epidemiologists, geneticists, and others, to help people with such biologically and genetically based disorders as depression and schizophrenia.]

DETRE: *I think that I was the only person ever promoted to tenure at Yale who was not analyzed. I refused. I told them I was so goddamned healthy, I don't need it!*

Luckily, Yale's chair of psychiatry was Frederick C. Redlich, an MD and pioneer in social psychiatry who was pushing the department toward a multidisciplinary approach and curriculum. Detre describes Redlich as "a shining light of American psychiatry. He thought that I was absolutely right, that psychopharmacology was coming."

The first antipsychotic drugs came into use in the early 1950s, offering patients with schizophrenia and psychosis the first chance to lead more normal and fulfilling lives. Many psychiatrists dismissed these drugs as a way of dealing only with symptoms. But Detre predicted they would both improve lives and transform lengthy hospitalization of the mentally ill.

Detre finished his own controversial, 733-page *Modern Psychiatric Treatment* in 1971. In writing this book, says Loren Roth, "Tom was

're-medicalizing' American psychiatry, putting it in the mainstream of American medicine. His approach could therefore be appreciated by a medical school, so when a medical school picked a new chairman of psychiatry, they were going to pick somebody who was going to reunite medicine with psychiatry."

Rethinking WPIC

Even before he officially became chair of psychiatry on March 1, 1973, Detre began reorganizing WPIC, recruiting researchers and equipping new clinical laboratories. He announced plans to establish specialty clinics. Each would not only improve the quality of and access to patient care, he felt, but also open the doors to more patients—and opportunities for more research.

Accompanying the chair-elect on his whirlwind visits was one of his former students, David Kupfer. After two years on a career-development grant at the National Institute of Mental Health, Kupfer had returned to Yale to pursue research in sleep disorders. In one of the first displays of Detre's legendary talent-scouting, the chair went out on a limb by inviting the young, relatively inexperienced psychiatrist to [become director of research at] WPIC.

KUPFER: *Tom had been told correctly by everybody that one of the first things he needed to do was to find a relatively senior director of research, somebody who had already acquired federal grants. So he goes and recruits someone who is 31 years old and who has had only a career-development grant!*

Kupfer would go on to succeed Detre as chair of psychiatry in 1983 and to build the department into the nation's number-one recipient of NIH funding for psychiatric research.

No Lone Rangers

"When my life started at WPIC," Detre remembers, "what I tried to do was to recruit people from various specialties, even other departments, so we could create a robust clinical and research program." Although in the early 1970s he had only a fraction of the budgets of major psychiatric departments like Yale's or Stanford's, the $5 million endowment from the Mellon Charitable Trusts, the increase in the state appropriation, and the promise of new revenue from patient care and research gave him a toehold for the recruiting and collaborations that became his hallmarks. He sought out "academicians who, in addition to being exceptionally competent, have the temperamental characteristics to operate with ease in a multidisciplinary setting without worrying too much about boundaries."

"Dr. Detre knew how to do things on an interdisciplinary basis when nobody was even talking about interdisciplinary," says Gerald Levey, an MD and the former chair of Pitt's Department of Medicine [who recently stepped down as executive vice chancellor and provost of medical sciences and dean of the David Geffen School of Medicine at UCLA].

DETRE: *It was crystal clear to me that you cannot provide decent patient care without basic multidisciplinary research. The time for lone rangers was over. Science was galloping so fast that no single person could grasp it all alone.*

This is the open-door policy that eventually would shape the University of Pittsburgh Cancer Institute, collaborations with Carnegie Mellon University, department mergers, the integration of separate hospitals into a medical center, and the creation of nearly 75 interdisciplinary centers of excellence developed during Detre's years at the university. "Inter- and multi-disciplinary, of course, characterize contemporary biomedical and behavioral research," Senior Vice Chancellor and Dean of the School of Medicine Arthur S. Levine, an MD and molecular biologist, would say in 2007. But in 1973, such collaboration was far from routine.

Detre pushed psychiatric research into emerging disciplines—biomedicine, neurobiology, social and behavior science, and genetics. His Department of Psychiatry was an early adopter of information technology. He hired electrical engineers and partnered with the Department of Neurology to establish an electroencephalographic unit to provide evidence of how the brain functions. He persisted in breaking through the boundaries between the Department of Psychiatry and the rest of the University, despite resistance from the Departments of Medicine and Surgery and from the basic sciences, where the psychiatry department and WPIC were regarded as second-class citizens. He established collaborations with the Departments of Sociology, Psychology, Clinical Psychology, Neurosurgery, Pharmacology, Biochemistry, and Life Sciences, as well as the School of Law.

"Dr. Detre and Dr. Kupfer would go down to the National Institute of Mental Health, talk, and get involved in various study sections," says George Huber [who served as general counsel for UPMC for 30 years]. "And it wasn't all, 'Give me, give me, give me.' It was, 'How can we help you?' And so they gained their confidence."

Top of the Mountain

Within four years of Detre's arrival, the National Institute of Mental Health designated WPIC a Clinical Research Center for Affective Disorders. The hospital established the John Merck Program for multiply disabled children, the only one of its kind in the country. Within 10 years the University of Pittsburgh Department of Psychiatry would rank as one of the nation's three top recipients of NIH psychiatric funding. Between 1974 and 1982, the department's full-time faculty increased from 36 to close to 150. WPIC's staff grew from 300 to 1,200.

Two roads diverged in 1982 for Thomas Detre: He could stay in Pittsburgh or return to the prestige of the Ivy League. "I'm not a maintenance man," he says. "Once you accomplish about 80 percent of what you want to accomplish, the time must come to exit." Detre's remarkable success at recruiting researchers and attracting research funding had made him a hot academic property. An offer to chair a major New York university's psychiatry department intrigued him in 1982.

Weighing Options

In August 1982, Thomas and Katherine Detre retreated as usual to their summer place in Maine.

That August he thought about the challenges he would face as a university administrator for the health sciences [a job he had just been offered by then-Pitt Chancellor Wesley Posvar]. The federal government was slashing the budget for Medicare and Medicaid, and funding for medical research was not a priority at that time. Detre knew he would have to continue to battle hostile camps within his own university as well as the "fiefdoms" of each independent teaching hospital. [And rival local hospitals were gaining strength.]

But Detre and the WPIC managers believed that by raising the academic quality of the University of Pittsburgh, they could also help the Pittsburgh region. A prestigious academic medical center, they predicted, could bring world-class health care to Western Pennsylvania; attract researchers, clinicians, and research funding; and spin off new companies.

They knew that the Pittsburgh region, stunned in the early 1980s by a hemorrhage of manufacturing jobs, desperately needed an economic transfusion—and it needed hope. Detre knew a lot about loss, and he had a prescription: Move into new territory. Take risks. Cross borders. Dream big and act boldly.

When Detre returned from Maine at the end of August, he had decided to stay—and create a new ecology for Pittsburgh. ■

People and programs that keep the school healthy and vibrant



FUND HONORS WORK OF PETTIGREW

Margaret Larkins-Pettigrew and Vaughn Clagette are Pitt people to the core.

She earned her BSN here in 1976 and her MD in 1994 and completed her residency in 1998. Clagette took his MD the year before Larkins-Pettigrew and graduated from the School of Arts and Sciences in 1989.

Larkins-Pettigrew and Clagette are also African Americans. And, they both say, their time as students at this University was made better, easier, and more engaging by the diversity programs at Pitt, particularly in the School of Medicine.

"As minority students at a majority institution, we felt that people gave us so much support and didn't allow the other stuff going on in our lives to become distractions," Larkins-Pettigrew says. "When we came here as medical students into the summer program introducing us to medical school, the University did what it could to make the uphill battle easier and to make sure we did well."



Pettigrew and Larkins-Pettigrew



Clagette

Larkins-Pettigrew and Clagette are friends, as well as former classmates—"We've stayed close over the years. We've watched each other raise our kids," she says. Recently, they had a few phone conversations about how to show their appreciation for the School of Medicine's efforts to assist underrepresented students. "[Clagette] kept calling and saying he wanted to do something for the institution," she says. "We decided we wanted to make a difference, and we wanted it to be in the area that helped us the most."

That logic led to the establishment of the Dr. Chenits Pettigrew, Jr., Fund for Diversity Affairs in the School of Medicine. Chenits Pettigrew is Margaret Larkins-Pettigrew's husband—he has been for 33 years—and is one of the people who helped guide both her and Clagette through their time as students.

Pettigrew (also a Pitt grad—he received his Master of Education degree here in 1976) has been involved with diversity affairs at Pitt for more than 40 years. Today, he is assistant dean for student affairs and director of diversity programs in the School of Medicine.

"We met when I was an undergraduate," says Larkins-Pettigrew, who has served as program director for global health and reproductive science in the School of Medicine and now holds a similar position at Case Western Reserve University in Cleveland. "He was first a recruitment officer and then in financial aid, but he has always worked in the area of student recruitment, retention, and diversity. He's helped people his entire life."

To honor Pettigrew as a mentor, she made a $50,000 pledge to endow the fund. Clagette pledged an additional $25,000 to the endowment and will donate another $25,000 to the Office of Diversity Affairs.

"This isn't just for scholarships," says Mike LaFrankie, executive director of health sciences development. "This money will be used to support the kinds of programs—like the summer programs that help students be comfortable starting out in medical school—that Margaret and Vaughn consider critical."

Larkins-Pettigrew hopes that others affected by her husband's good works and the programs that he and his colleagues have crafted will consider pledging their support, as well.

"He has helped so many people at this University," she says. "Some of us have come from places where no one else goes to college, and he made sure we felt like we had a second home when we came to Pitt." —*Joe Miksch*

UPCI TURNS 25, WRAPS UP CAMPAIGN

As the University of Pittsburgh Cancer Institute turns 25, it—and the UPMC Cancer Centers—celebrates another milestone: The conclusion of a five-year, $100 million capital campaign to support research, faculty recruitment, and infrastructure projects.

A recent $3 million gift from the Mario Lemieux Foundation was key to the fund drive, which exceeded its $100 million goal. (Officials have not yet released a total; funds are still coming in. In addition, UPMC itself matched the sum with $100 million.) The Lemieux Foundation's gift will be used to establish the Mario Lemieux Center for Blood Diseases at the Hillman Cancer Center.

The campaign began with a $20 million contribution from the Henry L. Hillman Foundation and the Hillman Foundation. That gift created the Hillman Fellows Program for Innovative Cancer Research.

The fundraising effort has also resulted in the establishment of the Arnold Palmer Chair in Cancer Prevention, the Thomas and Sandra Usher Chair in Melanoma, the Jane and Carl Citron Chair in Colon Cancer, and the Stanley M. Marks, MD, Research Fund.

Other money generated by the capital campaign has funded research into nutritional and dietary methods of combating cancer, new treatments for melanoma and mesothelioma, and the identification of blood proteins responsible for the development and recurrence of cancer. —*JM* ■

PHOTO ILLUSTRATIONS BY JESSE LENZ. ORIGINAL PHOTOS COURTESY LARKINS-PETTIGREW AND CLAGETTE.



Lee Strawbridge (left) and Larry Oleksa (right) during the Warhol's celebrity-theme tour.

TAKE A MOMENT

A BREATHER FROM ALZHEIMER'S, ONE PAINTING AT A TIME.

BY REID R. FRAZIER

PHOTOGRAPHY BY MARTHA RIAL

It wasn't the best way for Larry and Stephanie Oleksa to start their visit. The couple was celebrating their 31st anniversary on a tour of the Andy Warhol Museum—a tour designed especially for Alzheimer's patients and their caregivers. Larry was diagnosed four years ago, and since then the number of activities he and Stephanie do together has dwindled. They still go to Steelers games, but he sometimes has trouble following the score.

The theme of this tour was "celebrity." As Warhol educator Joan McGarry lectured to the Oleksas and another couple, Larry Oleksa suddenly put his hands on his knees. Then he collapsed on the museum floor in a sweaty heap.

He quickly revived and sat up. Someone got him a cup of orange juice. Stephanie held an ice pack on his neck. He was fine, apparently, just overheated. A few minutes later, paramedics checked his pulse and blood pressure and asked the 60-year-old man in jeans and a green polo shirt whether he wanted to stay on the tour. He nodded "Yes" and was soon off looking at Warhol's Marilyn Monroe portraits.

The Oleksas' day out was courtesy of the University of Pittsburgh's Alzheimer Disease Research Center and the Warhol. The collaboration gives patients and those who take care of them a break from the disease by taking them to see and make art.

"We wanted to give our patients an opportunity to have this interaction that's just positive, where they're not thinking of Alzheimer's or memory loss," says Jennifer Lingler, director of education for the ADRC and assistant professor of health and community systems and of psychiatry. Last year, participants made studio visits with a resident artist whose work focused on memory. On the docket this year are visits to the Carnegie Museum of Art. The idea is based on other "art and Alzheimer's" projects around the country, including "Meet Me at MoMA," which brings patients to the Museum of Modern Art in New York City.

"You're in an environment where there is no right, there is no wrong," Lingler says. "You're looking at a piece of art; there's no answer key about what's the right thing to say about the piece of art you're examining."

Studies suggest activities like exercise and cognitive stimulation, such as creative expression, may slow the onset of dementia. But these indications are gleaned from large epidemiological studies. For obvious reasons, there are no rodent models that can show the effect of artistic expression on the onset of dementia.

Lingler, who helped design the program, says the visits aren't intended to be therapeutic. Instead, they're a way to offset some of the damage Alzheimer's causes to the social lives of those in its grip. Couples living with Alzheimer's might not get invited to as many social events as in the past. And they may be more likely to decline invitations they do receive. Patients can feel ashamed over not being able to remember a friend's name and might want to avoid embarrassing themselves in public.

"Sometimes it's difficult to find things to go to," says Stephanie Oleksa. "It's too difficult to take him to a show—that wouldn't hold his interest. I took him to the Rockettes, and he enjoyed that. But that wasn't something he had to follow, like a play."

As much as the program may do for the patient, it might be just as important to the caregiver, Lingler says. There is mounting evidence that the stress of caring for a loved one with dementia can actually take years off a person's life. Caregivers have high levels of anxiety and depression. They don't go out as much, and they don't take care of their own health.

"You're in a situation where day in and day out you're exposed to someone who's suffering, and there's little you can do about it," says Richard Schulz, professor of psychiatry and director of the University's Center for Social and Urban Research. Schulz has shown that caregivers had lower life expectancies and higher rates of cardiovascular illness than their noncaregiving counterparts. (One of his postdoctoral fellows, Joan Monin, now an assistant professor of epidemiology at Yale University, showed that heart rates and blood pressures increased among caregivers when they saw a loved one suffer; their reactions were not as marked when witnessing a stranger suffering.)

Any step to improve a caregiver's mental state, Lingler says, is potentially worthwhile.

"If the person has a positive experience during that time, even if it's fleeting, then we've done something positive," Lingler says. "Because it really is a disease where people live moment by moment."

During his first moments at the museum, Larry Oleksa sat in stony silence as his small group gazed at portraits of Judy Garland, Dolly Parton, and Sylvester Stallone. Then, when the group gathered in the museum's basement studios, McGarry opened a box of hats and props. They were going to take "celebrity" portraits, she said. When McGarry asked the visitors to come up and get their costumes, Larry sprang out of his chair and was the first to grab a hat. He chose a black fedora with a white band, à la '30s-era gangster. Stephanie chose a pillbox hat and pink feather boa. A few minutes later, they were getting their picture taken in front of a digitized backdrop of *The Wizard of Oz*. Then they rolled ink on a few screen prints.

This was the Oleksas' second trip to the Warhol. On the first, Larry had gone through the tour, like this one, in near-total silence. But it didn't take Stephanie long to make reservations for their next visit.

On the drive back home to Munhall after that tour, Larry turned to Stephanie. "He said, 'That was good.'" Stephanie recalls. "I said, 'Do you want to go again?' He said, 'Yeah.' I called the next day." ■





TOP: Larry and Stephanie Oleksa view Warhol's Marilyn prints; Donna Strawbridge (far left) sits next to Stephanie. BOTTOM: Lee and Donna Strawbridge pose for the paparazzi.

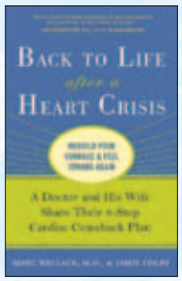


COURTESY OF JIMMEB PHOTOGRAPHY

CLASS NOTES

'70s

During a typical run one day in 2002, surgical oncologist **Marc Wallack** (MD '70) felt pain in his chest. Although he initially dismissed it as acid reflux, the pain persisted. Within the week, he underwent an emergency quadruple bypass, and the hard road to recovery began. Finding the self-help literature less than helpful in the aftermath, Wallack and his wife, Jamie Colbie, a national news correspondent and anchor for Fox News, were inspired to write *Back to Life After a Heart Crisis*, an eight-step plan for overcoming fear and depression following heart surgery. The book was released in February 2010.



Wallack is chief of the Department of Surgery at Metropolitan Hospital Center in New York City and a professor of surgery and vice chair of the Department of Surgery at New York Medical College. He's also an avid runner once again. He returned to marathon racing less than three years after his surgery.

'90s

David C. Seaberg (Emergency Medicine Resident '90), dean of the University of Tennessee College of Medicine Chattanooga, has spent his career planning for the worst. An emergency physician, Seaberg has testified before the House Committee on Homeland Security on how to fight a potential avian flu pandemic. In the fall, Seaberg was named president-elect of the American College of Emergency Physicians. He will assume the presidency of that organization in October.

During his psychiatric residency at Pitt, **Shitij Kapur** (Psychiatry Resident '92) developed an interest in the biological basis of schizophrenia. Today, Kapur is internationally known for his use of brain imaging to understand how psychosis works and how to tame it. Much of Kapur's research has dealt with treatment tactics and dosing issues. In a 2001 study published in the *American Journal of Psychiatry*, Kapur (with Phillip Seeman) argued that what matters most in antipsychotic medications is how they block dopamine receptors, not how much—which pushed the field toward lower dosing guidelines.

Kapur is professor and head of the Section on Schizophrenia, Imaging, and Therapeutics, as well as dean of the Institute of Psychiatry at King's College London. His current research synthesizes imaging, genetics, and sociobiology to develop a "holistic" understanding of psychosis.

Off-the-clock, Kapur studies dosage gradations of another sort; he's developing the perfect lamb biryani recipe.

While a Pitt research assistant professor based at the Thomas E. Starzl Transplantation Institute, **Ruhul Kuddus** (Molecular Genetics and Microbiology PhD '93) saw how patients had to suffer while waiting for suitable organs for transplant. This experience sparked his interest in bioethics, eventually leading to his 2009–2010 fellowship at the Center for the Study of Ethics at Utah Valley University, where he is now on the biology faculty. Kuddus gave the keynote speech at the university's Ethics Awareness Week in September. His talk touched on a variety of topics, including the ethics of organ transplantation through the lenses of Judaism, Christianity, and Islam; the importance of preserving individual lives; and the morality of organ-donation policies. He also discussed the preservation of species. "As much attention as we put to human life," he said, "we should pay as much attention to the well-being of other species."

When **Stewart Anderson** (Psychiatry Resident '94) was in college, he boarded with a young man who'd just been released after his first hospitalization because of hearing voices and other symptoms of schizophrenia. One afternoon, as they were watching MTV, Stewart's roommate turned to him and asked, "Is it me, or did the screen just flash orange and green with stripes sliding across it?"

It was an eye-opening moment for Anderson, who's now a professor of psychiatry and of psychiatry in neuroscience in Weill Cornell Medical College and an attending psychiatrist at New York–Presbyterian Hospital. "I learned throughout that year that many people who suffer with schizophrenia are 97 percent as normal as you and me," he says, "and the 3 percent that's not normal causes them to have perceptual experiences that are intensely disturbing."

Anderson has dedicated his lab at Weill Cornell to uncovering the molecular genetic influences on inhibitory interneurons—work that he hopes will enable researchers to ask more involved questions about this complex illness.

MATTHEW STULL:
THOSE WHO CAN'T WAIT TO TEACH

Recent graduate Matthew Stull (MD '10) is taking an unusual approach to his residency training: He's skipping it. For now, anyway. It's not for lack of enthusiasm about the learning process, though. In July 2010, Stull became the first education and research fellow for the American Medical Student Association (AMSA).

It's an ideal crash course for Stull, who aspires to a career in academic emergency medicine—and eventually, deanship of a medical school.

A first-generation college student, Stull hails from a rural South New Jersey county where "nowhere near 100 percent of [high school] graduates go into a four-year institution," he says. "So for me, college was a really exciting opportunity. It was eye-opening to see what doors education could open, and I became enamored with it. Whatever I could learn, I would learn. Wherever I could teach, I would teach."

At Pitt med, he served for his first two years as the



Stull is AMSA's first education and research fellow.



In September, UPMC Shadyside's family medicine residency program turned 40. One of the oldest accredited family medicine residencies in the country, the program now boasts 242 graduates. To celebrate, dozens of alumni, current residents, and staff came out with their families for a picnic, petting zoo, and pony rides in Schenley Park. The crowd of kith and kin totaled some 220 people. *—KB*

'00s

Lisa (Allenbaugh) Goss (MD '98, Family Medicine Resident '01) craves variety, which is one of the reasons she's enjoying her new position at Washington Hospital in Washington, Pa. "My schedule changes week to week," she says. An assistant director for the hospital's family medicine residency program, Goss splits her time among teaching residents, fulfilling her administrative duties, and treating patients of all ages—a juggling act that suits her. In the past five years, she and her husband have traveled to Italy, Scotland, England, Alaska, and many U.S. national parks.

Lauren Weinberger (MD '06) had an eventful 2010. In July, after wrapping up her residency in emergency medicine at the Hospital of the University of Pennsylvania, she joined its faculty as assistant residency director in the Department of Emergency Medicine. She uses simulators to teach about emergency care for both children and adults—an approach she learned from her mentor, Pitt associate professor of emergency medicine Susan Dunmire (MD '85, Emergency Medicine Resident '88).

In September, Weinberger married **Thomas Conlon** (MD '06, Internal Medicine and Pediatrics Resident '10). Last June, Conlon finished his residency in internal medicine and pediatrics at Pitt. He is now a fellow in pediatric critical care at the Children's Hospital of Philadelphia. Conlon and Weinberger met the week before they began med school and were good friends throughout. They were busy from the beginning—Weinberger served as class secretary, and Conlon was president.

—Kelsey Balance & Kristen Cosby

school's local AMSA advocacy chair, then in his fourth year as AMSA's national chair for medical education. As a fellow, he's been charged with beefing up the association's educational programming, including training on universal health care advocacy, AIDS patient safety and advocacy, and LGBT (lesbian/gay/bisexual/transgender) health issues.

He's also helping med students far and wide advocate to reform their schools' curricula, addressing such issues as the eight-hour preclinical teaching model and the 80-hour resident work week. Stull is on the road a lot, working with students on the local level and representing them at conferences. While working with med students on every continent, Stull has noticed something: "We're all dealing with the same issues. Curriculum reform is everyone's top concern, whether starting from scratch and building a new med school or couched in a highly complex system like ours here in the U.S."

Stull misses the clinic and is itching to get back to it. But in a way, this time away from the bedside could help rather than hinder his skills as a clinician, he says. After all, the word *doctor* is Latin for teacher.

"It's essential that we as physicians recognize that we educate people every day, whether we're academics or not. We teach medical students, other residents, attendings, but more importantly we teach our patients and their families in every interaction." *—Elaine Vitone*

COURTESY LAUREN HUGHES

THE WAY WE ARE

CLASS OF '66

John Krause (MD '66, Pathology Resident '71) was chair of pathology and laboratory medicine at Tulane University in New Orleans when Hurricane Katrina slammed into the city and virtually destroyed the medical school. After sending his residents and most of his faculty elsewhere, he was faced with the trying task of rebuilding the department, starting with several trips through the waterlogged building with a hardhat and flashlight to salvage books and materials. "It was the most difficult period of my professional life," says Krause, a former Pitt professor of pathology and vice chair of pathology graduate medical education.

The experience has not diminished Krause's love of his work, however. Last year, just as he was on the verge of retirement, a former fellow of his clued him in on an opening at Baylor University Medical Center in Dallas as director of hematology. He applied and was offered the job. "As long as I'm enjoying what I am doing, God willing, I'll keep doing it," he says. Over the years, Krause has lectured on hematology at more than 175 workshops across the country. In 2010, he won the American Society of Clinical Pathology's H.P. Smith Award for Distinguished Pathology Educator.



Krause

Another Dallas alum is **Philip Raskin** (MD '66, Internal Medicine Resident '68). After his residency, he served a two-year stint in the U.S. Air Force, then headed to Big D and never left. "I thought the weather was nice," he says. Raskin holds the Clifton and Betsy Robinson Chair in Biomedical Research at the University of Texas Southwestern Medical Center. He is also an attending physician at Dallas' Parkland Memorial Hospital, where he supervises resident education.



Raskin

Raskin, a diabetes researcher who has published more than 270 papers, found new approaches to using the insulin pump. "When I first heard about it, I thought it was the craziest thing in the world," he says, but he later came around. In studying the devices he found that they were as effective as insulin injections for treating type 1 diabetes. His newest project is working with a National Institutes of Health–funded study group, TrialNet, to develop new approaches to preventing the

disease; he's investigating whether anti-inflammatories can fight beta-cell destruction.

Like Raskin (and Krause), **David Maybee** (MD '66) joined the military. He served for 32 years, achieving the rank of full colonel. A pediatric hematologist-oncologist, he has held a range of positions, from director of a fellowship training program to consultant to the surgeon general. Now, he's a medical reviewer at the FDA's Division of Clinical Evaluation & Pharmacology/ Toxicology Office of Cell, Tissue, and Gene Therapy in the Center for Biologics Evaluation and Research. "I feel like I've done everything over the course of my professional life," he says. In his new gig, Maybee checks the safety of clinical trials of all shapes and sizes, many of which deal with gene therapy, umbilical-cord blood, and regenerative medicine. Although he misses seeing patients, he savors the idea that he's helping research and the public at the same time.

A. Richey Sharrett (MD '66) earned a PhD in public health at Johns Hopkins University and then served as an epidemiologist for the National Heart, Lung, and Blood Institute. During his 30 years there, Sharrett was a project officer working on the Atherosclerosis Risk in Communities Study, a comprehensive detailing of the habits and heart health of 16,000 people in four communities. After leaving the institute, Sharrett continued his work on atherosclerosis. Now an adjunct professor in Johns Hopkins Bloomberg School of Public Health, he's focusing on how atherosclerosis contributes to various diseases, including dementia. —*KB*



Sharrett

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ROBERT G. SELKER

JULY 25, 1930–NOV. 1, 2010



Selker

Robert G. Selker (MD '57) spent his life trying to solve the puzzle of malignant brain tumors. In addition, he was such a renowned neurosurgeon and devoted clinician that patients came to him from around the world. "He was a 24/7 doctor," says his wife, Ellen Selker. "Nothing was too much for his patients." Selker died last November at age 80.

A former clinical professor of neurosurgery at Pitt, Selker advanced brain-tumor treatment throughout his career. He taught at Yale University, Emory University, and the University of Chicago. He designed the Selker Reservoir, a device for spinal-fluid sampling and medicine injections, which was more user-friendly than previous reservoirs. His former clinical coordinator, Jeanne Clancey, says that Selker had been pushing for individualized treatment since the 1990s, before personalized medicine became popular. He was a gifted teacher, she says—someone "you couldn't help but learn from." Selker presided over or was a member of many medical societies and received numerous awards. He was the vice president of the Brain Tumor Cooperative Group, a national collaboration sponsored by the National Institutes of Health, for 20 years. Selker also loved to build and fly model planes with his children. Whenever he lectured, he told his two sons his fee was going into the "flying fund." —*KB*

IN MEMORIAM

'40s

WARREN T. KABLE JR.
MD '44
NOV. 3, 2010

'50s

E. DAVID CHERUP
MD '51
NOV. 23, 2010

WALLACE ZERNICH
MD '51
JULY 14, 2010

THOMAS HOHMANN
MD '54
OCT. 26, 2010

JAMES W.G. CARMAN
MD '56
DEC. 16, 2010

'60s

CHARLES PAUL GENNAULA
MD '63
NOV. 7, 2010

ALEXANDER FEFER
RES '66
OCT. 3, 2010

'80s

LONN BRADLEY LOCKHART
FEL '85
DEC. 8, 2010

ROBERT J. STENGEL
MD '85
NOV. 4, 2010

FACULTY & STAFF

SAMUEL L. FLESHER
JAN. 27, 2010

HISASHI SHINOZUKA
SEPT. 20, 2010

PAUL OFFIT: CLAIMING THE HIGH GROUND IN THE VACCINE CONTROVERSY

BY BRIAN G. CONNELLY



ILLUSTRATION FRANK HARRIS/ PHOTO COURTESY AMY SAUL

Offit is co-inventor of the rotavirus vaccine RotaTeq, which was recommended for routine immunizations in infants by the World Health Organization.

When Paul Offit (Res '80) was a resident in the emergency department at Children's Hospital of Pittsburgh in the late 1970s, he had a patient—a 9-month-old infant—who died of rotavirus. Offit was shocked to realize that this common intestinal infection still killed children in the United States. A leading cause of severe diarrhea in infants and young children, rotavirus contributes to more than half a million deaths worldwide each year.

Some three decades later, in 2009, RotaTeq— a vaccine for rotavirus—was recommended by the World Health Organization to protect against the deadly infection. RotaTeq is the fruit of 25 years of labor for Offit, the vaccine's coinventor who is now a renowned expert in virology and immunology. Helping to develop a vaccine that is administered around the world has made him "enormously proud," says Offit. "Professionally, it's the best thing I've ever done, and I did it for the right reasons."

That he would be in a position of defending his intentions has come as a surprise to Offit. Yet he has found himself at the center of a heated debate over whether childhood immunizations—arguably one of the greatest achievements in public health in the past century—are safe.

Offit is the Maurice R. Hilleman Professor of Vaccinology and a professor of pediatrics at the University of Pennsylvania. He also heads the infectious diseases division at the Children's Hospital of Philadelphia and was a member of the Advisory Committee on Immunization Practices for the Centers for Disease Control and Prevention.

Offit's research has led to his becoming a prominent defender of vaccines, which in turn has led to his publication of mass-market books on the topic—most recently, *Deadly Choices: How the Anti-Vaccine Movement Threatens Us All*, which was released in December.

Since the early '80s, some activist groups have advanced the belief that there's a link between vaccines and autism. The suspect vaccines change, but the story remains the same: Citing anecdotes or data taken out of context, activist groups accuse physicians and pharmaceutical companies of concealing what they believe are harmful effects associated with vaccines. These accusations are widely publicized; the epidemiological and other studies that disprove them, however, are not.

It's been wearing for Offit, who has been threatened, sued for libel, vilified on television by actress Jenny McCarthy, and accused of profiteering. (Offit was copatent holder when Children's Hospital of Philadelphia sold the RotaTeq patent to Merck and does not receive payments for subsequent sales.) One study linking vaccines to autism has been widely discredited and recently described as "an elaborate fraud" by the *British Medical Journal*. Yet Offit says the general confusion and controversy won't go away completely until a clear cause for autism is identified.

The contrast between the hype-driven mass media and the stories told by scientists—who work within a very different conceptual framework than the journalists, politicians, and lawyers shaping the vaccine debate—is striking to Offit. His advice: "Scientists and physicians need to claim the emotional high ground. I'm in this because I'm motivated by kids being hurt. We need to show the concern that motivates the science."

Offit, who has testified in congressional hearings on vaccine safety, says the consequences of skipping vaccines are not theoretical. He points to the pertussis outbreak in California this year, which killed 10 infants and infected 9,000 people. "We're past the tipping point," he says. "We're losing the herd immunity, where enough people are vaccinated to protect those who can't be vaccinated."

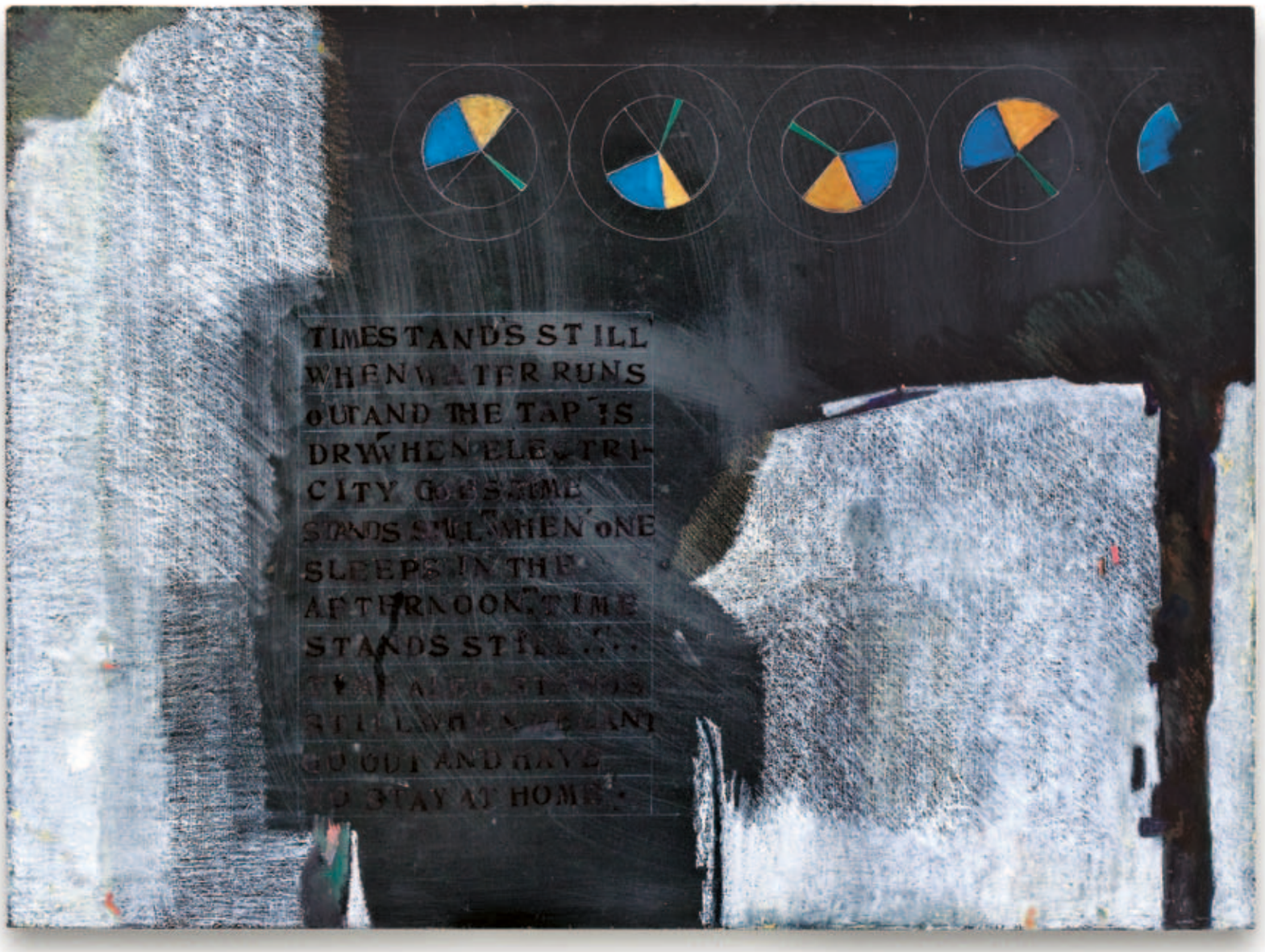
The age of the observer makes a great difference in how the vaccine debate is perceived. Younger people have simply never encountered a child blinded by measles, for instance. But Offit is old enough to remember the toll of childhood diseases.

In 1956, when he was 5 years old, he had surgery for a clubfoot and spent three weeks in a Baltimore polio ward. Jonas Salk and his team at the University of Pittsburgh had developed a vaccine that had been approved the previous spring, following a nationwide clinical trial. New cases were declining—but thousands of victims still lived with braces and iron lungs.

It was a life-shaping experience for Offit, who never forgot the vulnerable children in that ward. Those memories helped drive his choice to become a pediatrician and infectious disease specialist.

"When I take criticism—or praise—I think of those kids and others," Offit says.

"Fear of vaccines causes children to get sick and die." ■



TRUTH IN THE VERY PARTICULAR

Though she stridently abjured the public "wife of the dean" role, Ruth Eleanor Levine's (1936–2010) presence in Pittsburgh was felt widely, particularly in the arts and academic communities. Hers was a life filled with gusto, intelligence, humor, caring, and beauty; that spirit infused those around her.

Ruth E. Levine (née Rubin) met Arthur S. Levine, Pitt's senior vice chancellor for the health sciences and dean of the medical school, when they were both undergraduates. She was studying mathematics at the time (he, Russian literature), yet she ended up pursuing her passion for the arts as a career, becoming an arts administrator and educator. In 1993, Ruth Levine began painting full-time and prolifically. Her paintings hung in museums and galleries in Pittsburgh, Washington, D.C., New York, Chicago, Prague, Venice, and Florence. Her last solo show was proclaimed "miraculous" by Tom Sokolowski, former director of the Andy Warhol Museum.

"We had common ground: I was driven to interrogate biology at its molecular level, and Ruth was driven to interrogate art at its molecular level," her husband notes. "I saw science in her art, and she saw art in my science. I am quite sure that in teaching me how to truly look at a painting, whether a Raphael or a Picasso, Ruth taught me how to look at biology, as well—the truth in the very particular."

In his eulogy, Arthur Levine shared a passage from a scene at the funeral of young Illusha in Dostoevsky's *The Brothers Karamazov*: "And whatever happens to us later in life, even if we don't meet for 50 years, let us remember this time. My dear children, you must know that there is nothing higher or stronger and more wholesome and good for life in the future than some good memory. People talk to you a great deal about your education, but some good sacred memory is perhaps the best education. If people carry many such memories with them into life, they are safe to the end of their days." —*Erica Lloyd*

R.E. LEVINE, *TIME STANDS STILL*, OIL CRAYONS, MINERAL PAINTS, AND INKS ON SLATED BOARD, 29" X 32", 2009. PHOTOGRAPHED BY TOM UNDERINER, PIXEL RIVER.

CALENDAR

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1961	1956

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SENIOR CLASS LUNCHEON
MAY 20
11 a.m.
Alumni Hall, Connolly Ballroom

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MAY 20
Pittsburgh Athletic Association

SCOPE AND SCALPEL'S "INTUSSUSCEPTION"
MAY 20 & MAY 22
May 20, 8 p.m.
May 22, 2 p.m.
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ALUMNI BREAKFAST AND AWARDS PRESENTATION
MAY 21
9 a.m.
Scaife Hall

MEDICAL SCHOOL TOUR
MAY 21
10:30 a.m.
Scaife Hall

REUNION GALA
MAY 21
6 p.m.
Pittsburgh Golf Club

ALUMNI FAREWELL BRUNCH
MAY 22
10 a.m.
Holiday Inn Select at University Center
Pittsburgh

CLASS OF 2011 COMMENCEMENT
MAY 23
10 a.m.
Carnegie Music Hall
Pittsburgh

MUSGRAVE LECTURESHIP
OCTOBER 14–15
Julian J. Pribaz, MD, Speaker

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