UNIVERSITY OF PITTSBURGH SCHOOL OF MEDICINE | SUMMER 2011

PITTMED



OF MED AND MACHINE

ROBOTS AND CYBERSCIENCE

RELEARNED LOVE

Thank you so much for the very moving story of Derrick Gaines and his wife, Anna ("None of My Memories Are My Own," Spring 2011).

Their relearned love is a lesson to all; their story reveals the best of the human spirit.

Barb Woolcott
Department of Neurology
University of Pittsburgh

A VIEW FROM THE ED

I am a former UPMC emergency medicine resident ('98) and currently a physician at Mayo Clinic Arizona. As an expert on the evaluation and management of acute head injury patients in the ED, I was struck by Kristen Cosby's very emotional piece on Anna and Derrick Gaines and their courage.

Keep up the good work.

Christopher Lipinski
Mayo Clinic Arizona

Our last issue also got noticed in the UMagazinology blog. Some highlights:

In the matter of covers, apparently black is the new black.

That Pitt Med *cover story (Erica Lloyd, editor) is part of a powerful two-story package about traumatic brain injury. The science/medical story, Chuck Staresinic's "What Hit Her," is an excellent overview of what TBI is, how it happens, what it does. Some exemplary science writing here. …*

The second piece is "None of My Memories Are My Own" by Kristen Cosby, a poignant story about a young husband and father who survived a truck tire flying into his car and smashing his head. His memories did not survive. Cosby does a great job with delicate material.

Dale Keiger
umagazinology.jhu.edu

RECENT MAGAZINE HONORS

CASE 2010 Circle of Excellence
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We gladly receive letters (which we may edit for length, style, and clarity).

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BE PART OF HISTORY

Big stuff was afoot 125 years ago. The first Coca-Cola was sold in Atlanta. In Germany, Karl Benz drove the first automobile. In Pittsburgh, Alcoa made aluminum a viable commercial product, and … something else … right at the tip of my … Oh, yes, the University of Pittsburgh School of Medicine, then called the Western Pennsylvania Medical College, was founded.

***Pitt Med* magazine, though, has only been around for slightly more than a decade. While we know plenty of interesting things about the school, we're looking for little-known tidbits with which to intrigue and astound our readers as we celebrate 125 years of medical excellence in an upcoming issue. Call 412-624-4358 or drop us a line at medmag@pitt.edu and make your contribution to history.**

PITTMED

UNIVERSITY OF PITTSBURGH SCHOOL OF MEDICINE MAGAZINE, SUMMER 2011 (MAY/JUNE/JULY)

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BY ELAINE VITONE

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Drug discovery at Pitt embraces the complexity of life, rather than running from it, says D. Lansing Taylor, who now heads the effort.
BY REID R. FRAZIER

CONTRIBUTORS

A decade ago, illustrator CARMEN MOK ["Cognitive Cocktail" and "Mother's Math"] was program coordinator for a youth organization in Ontario, Canada. Although the work was rewarding, the hours were brutal. To unwind, Mok blogged about local arts and culture, and, to add interest, she painted images to accompany each post. It was a new medium for her, having studied ceramic sculpture in college. (She'd originally started out as a dinnerware designer.) Mok's paintings were such a hit she decided to take her readers' advice and consider yet another career change.

Mok took a less demanding job, and for the next several years, she spent her evenings practicing and studying the craft. Then, after a bit of moonlighting, the self-taught illustrator took the leap two years ago and went full-time. "This will be my last job," she says. "I'm so thankful for the Internet."

MAUREEN PASSMORE ["That Science Mojo"] fancies herself a "language nerd." So much so that she minored in Ukrainian at Penn State, "because it seemed like one of the more interesting languages I could take … when I wanted some time off from Spanish."

Passmore is also a poet, a mother of two, and a project coordinator in the Office of Academic Affairs, Schools of the Health Sciences, a job that entails working with photographers, taking photos herself, and, of course, writing.

COVER

Okay, robots at Pitt's School of Medicine aren't helping people fly, but they are doing some really cool stuff, like performing surgery and helping people with severely limited mobility. (Cover: Jesse Lenz © 2011.)

PITTMED

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Men are not prisoners of fate, but only prisoners of their own minds.
—Franklin D. Roosevelt


JOSHUA FRANZOS

In his travels to Suriname as a medical student in the 1950s, Baruch Blumberg asked himself the question, *Why do some people get sick but not others?* He eventually became chief of geographic medicine and genetics for the National Institutes of Health, allowing him to explore medicine across peoples.

Blumberg hypothesized that the blood of people who'd received numerous transfusions, like hemophiliacs, would generate antibodies they hadn't inherited. He thought it would be interesting to see whether hemophiliac blood would generate an antibody response to the antigens of people from other geographies. His travels, motivated in part by his interest in the diseases seen in diverse cultures, took him around the globe, often to remote areas. In Australia, he found an intriguing anomaly. An antigen in the blood of an Aboriginal person reacted with antibodies from a New York hemophiliac. Blumberg identified the Aboriginal antigen, which he called the Australian antigen. After several years of research by Blumberg and others, we came to understand that the antigen, prevalent throughout Asia and Africa, is a marker of hepatitis B infection. Blumberg's fundamental investigations into the cultural concomitants of health ultimately led to safer blood banks (which now test for the antigen in potential donors) and to the development of a vaccine for hepatitis B, protecting millions from the disease (and also liver cancer, which may be linked to chronic hepatitis B infection). This little story illustrates compellingly how "chance favors the prepared mind" and how basic discoveries often lead unexpectedly to expansive applications in medicine and commerce.

This is how medicine evolves. Before a significant new therapeutic exists, there must be an advance in fundamental understanding, and many medicines have the most unlikely origins. Consider biophysicist Barnett Rosenberg's investigations into how a strong electric current might influence *E. coli* cell division. When he placed a platinum electrode into his bacterial broth because his usual copper electrode was out of stock, the cells stopped dividing. By adding platinum to the mix, Rosenberg had accidently synthesized Peyrone's salt, also known as cisplatin. From this chance detour would come the astonishingly successful use of cisplatin to treat testicular cancer, curing Lance Armstrong of his widely metastatic disease. This blockbuster drug originated with someone who'd never sought to develop a chemotherapy.

I hope we don't have fewer such stories to share in the future, but support for basic science is threatened, thereby threatening its almost certain—albeit often late—implications for health and commerce. In real dollars, NIH funding has declined to where it was in 2002. As our legislators take on a daunting debt crisis, we are likely to face more such cuts. Yet this work often translates to invaluable treatments, and these, in turn, spur innovations that strengthen our economy and often rein in medical costs, thereby relieving our debt.

Vannevar Bush, FDR's science advisor, once opined that the relation of applied to basic science is like that of a monk's distillery supporting his pure religion. Enlightened corporations reinvest the commercial fruits of a basic discovery or invention back into basic science, and we must encourage them to do so as federal funds decline.

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



Devoted to noteworthy happenings

at the medical school

WISNER LEADING THE WAY

Katherine Wisner's work regarding the treatment of depression during pregnancy and the postpartum period recently earned her the 2011 American Medical Women's Association Women in Science award.

Wisner, an MD professor of psychiatry, and of obstetrics, gynecology, and reproductive sciences, as well as of epidemiology at the University of Pittsburgh, directs the Women's Behavioral HealthCARE program at the Western Psychiatric Institute and Clinic of UPMC and serves as an associate investigator at the Magee-Womens Research Institute.

Her studies include determining the effect that the use of selective serotonin reuptake inhibitors have on the health of new mothers and infants and defining the pharmocokinetics of psychotropic drug use during pregnancy. Wisner is also evaluating novel treatments, including the efficacy of bright-light therapy for depressed pregnant women.

Wisner says she's humbled by the recognition and "very pleased to be named among the many women who have contributed so much to scientific advancement." *—Joe Miksch*

FOOTNOTE

The University of Pittsburgh as a whole published 7,483 research papers from 1981 to 1985. Not bad. From 2005 to 2009, though, that production nearly tripled to 22,457 papers, vaulting Pitt to 10th place in terms of the published academic output of public universities nationwide.

The data were compiled by Thomson Reuters and reported by *Science* and *The Chronicle of Higher Education*.

CARMEN MOK



Dementia and Depression

Older adults who are depressed often experience mild cognitive impairment, as well. And depression in this population can be a precursor to dementia, says the University of Pittsburgh's Charles Reynolds.

Reynolds is an MD, the UPMC Endowed Professor of Geriatric Psychiatry, and director of the Pitt/UPMC Aging Institute. He has found that when older adults with both depression and mild cognitive impairment are treated with long-term antidepressant medication and donepezil, a cognitive enhancer used to treat Alzheimer's disease, they show improvement in their cognitive abilities, notably language, memory, and executive functions. They also have lower rates of conversion to dementia over a two-year period.

The study included 130 depressed adults older than 65 (roughly half took donepezil, the other half a placebo) who were recruited in collaboration with Pitt's Clinical and Translational Science Institute. The results were published in January in *Archives of General Psychiatry*.

Reynolds says the work was a unique collaboration between the National Institutes of Mental Health–funded Late Life Depression Evaluation, Treatment, and Prevention Center, which he directs, and the National Institute on Aging–supported Pitt Alzheimer Disease Research Center at UPMC. *—JM*



CAMI MESA

A&Q

Annie Silk: Reexamining Obesity

Pitt internal medicine resident Annie Silk (MD '08) has been worried about the challenges of examining obese patients since med school. "At first I thought I was just really bad at it," she says. But in comparing notes with her mentors and peers, she realized she was not alone.

It's no wonder. Literature on the topic is scant, she found, and medical texts almost always feature models with helpful bony landmarks. It's a dangerous oversight, given that 35 percent of adults are obese, and excess fat makes everything from hearing heart rhythms to finding tumors more difficult.

Silk brought her concerns to assistant professor of medicine and of epidemiology Kathleen McTigue—who was her mentor in the Clinical Research Training Program and is a national expert on obesity—who suggested she do some field research. Silk interviewed seasoned clinicians to ask for advice, and she came up with plenty of gems. (For example, to get a better listen at the ticker, lean the patent forward so the heart beats closer to the chest wall.) Silk organized these tips into a chart and drafted an accompanying commentary, both of which were published in the *Journal of the American Medical Association* (*JAMA*) in December 2010.

On why this issue is so often overlooked

A lot of doctors don't think there's anything we can do, that the physical exam is just going to be harder with obese patients. I realize medical school is getting more and more condensed, but I think it's worthwhile [to learn to do this better]. We need to meet patients where they are. And now two thirds are overweight or obese.

On the goal of her project

[McTigue] helped me realize that what I wanted was to get other doctors to realize that this is a serious problem—she suggested I submit to *JAMA*. I was happy it was also covered by the *L.A. Times* and CNN.com, because it brought the lay audience's attention to this hidden danger of obesity. It also caught the attention of medical educators, as I'd hoped. A physical-exam-course director in Arizona initiated an e-mail discussion with me and cc'd his colleagues. And [Pitt associate professor of medicine] Peggy Hasley told me she's already using the article in her physical exam course.

Her question for us

Should obese patients be told that their physical exam may be less sensitive than a similar exam on a healthy-weight patient? *—Interview by Elaine Vitone*



Next Generation

During their third year in the Medical Scientist Training Program, a joint MD/PhD program between the University of Pittsburgh and Carnegie Mellon University, all students take a grant-writing class.

The students write a mock F30 grant (technically, a Ruth L. Kirschstein National Research Service Award), which is the National Institutes of Health's individual training grant for MD/PhD candidates. Students critique one another's proposals as though they were on the NIH review committee.

Among the many lessons Corrine Kliment (MD '11/PhD '09) learned in the course was the importance of scope in a successful proposal. "If the project's too broad, somebody will read it and say, 'There's no way you're going to get all that done,'" she says.

Kliment used the class to write a grant to study the antioxidant properties of a protein in the lung.

"None of (the other students) studied oxidative stress or the lung," she says. "The class forced me to be able to communicate my work to people who weren't in my field."

Clayton Wiley, professor of pathology and director of the program, likens the class to a writing workshop "for a very specific kind of writing." It used to be that MD/PhDs like Wiley were trained in "the school of hard knocks." You write a grant application, "then somebody trashes it because you don't know how to write it," Wiley says. "It's like somebody asked you to write a sonnet, and you didn't know what the structure of a sonnet was. We teach them to write the sonnet."

Pitt's MSTP students now lead the country in F30s. (Pitt had 25, at last count, ahead of Washington University's 20 and the University of North Carolina's 18.) The program also trains students in the art of poster presentation, reading research papers critically (and quickly!), and medical ethics.

—Reid R. Frazier

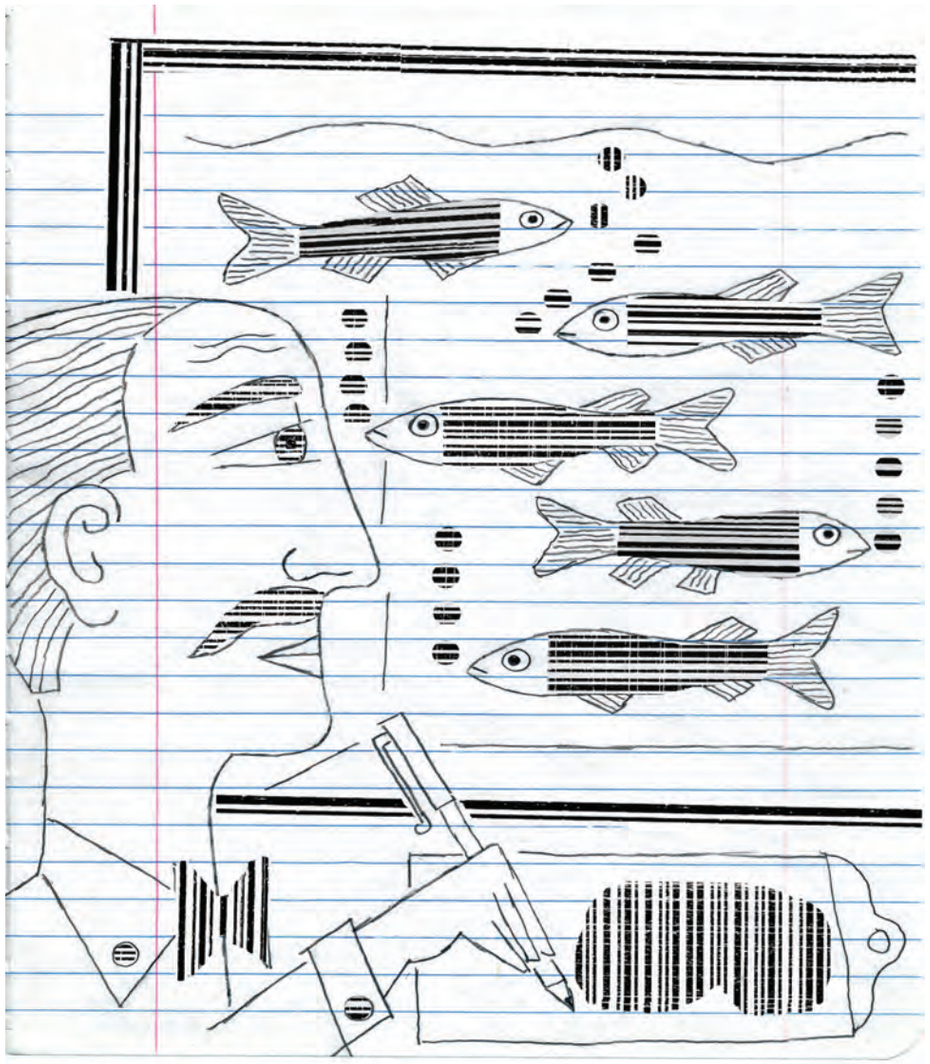
The Fish That Saved Kidneys

Kidneys subjected to acute injury can heal themselves, but do so slowly and often with scarring. In 2008, with the help of Billy Day, a PhD University of Pittsburgh professor of pharmaceutical sciences, Neil Hukriede, a PhD associate professor of developmental biology in the School of Medicine, found and tested a compound that may hold promise for patients experiencing renal injury. The compound, of a class called histone deacetylase inhibitors (HDACi), reversed the effects of acute kidney injury in zebra fish and did so without scarring.

Hukriede, in collaboration with investigators at Vanderbilt University, won a three-year, $2.8 million federal stimulus funding grant to pursue this line of inquiry further, this time in mice.

"It's very exciting," Hukriede says. "So far, we've seen a 30 to 40 percent increase in the rates of renal recovery in zebra fish and mice. We're hoping to find molecules that are more effective and show no toxicity at lower doses."

Hukriede and Pittsburgh colleagues, many of whom are members of the University's Drug Discovery Institute, will identify the compounds that may spur kidney regeneration. Vanderbilt collaborators will use the mouse model to see whether the compounds are hitting their targets and to test their toxicity. ***—JM***



CATHERINE LAZURE

WALK YOUR BRAIN

If you want to stave off Alzheimer's, it probably helps to keep moving, according to Cyrus Raji (MD/PhD '10). While in Pitt's Medical Scientist Training Program, Raji, now a UPMC Mercy intern who begins a radiology residency at UCLA next year, analyzed brain scans from more than 1,000 patients. He showed that high body-mass index correlated closely with a loss of brain volume in the hippocampus, a region implicated in Alzheimer's. (Because many late-stage dementia sufferers don't adequately feed themselves, Raji confined his study to people in the early stages of Alzheimer's, to exclude those who'd lost weight as a result of the disease.) Even when taking other risk factors for Alzheimer's into account—such as education level—the hippocampus was smaller in heavier individuals. Raji also analyzed the effect of walking on brain volume and found that people who walked six miles a week—even those who were obese—had a greater retention of both gray and white matter and a 50 percent reduction in Alzheimer's risk. *—RRF*

FOOTNOTE

Is your 3-year-old daughter's rash something to worry about? There's an app for that, a kind of first-aid kit that fits in your phone.

Children's Hospital of Pittsburgh of UPMC recently released ChildrensPgh, an iPhone/iPad/iPod Touch application available at Apple's iTunes store and the Children's Web site, that helps moms and dads figure out how best to care for their kids' health.

The app features 91 symptom-care guides, which are searchable through an alphabetical index, body-area index, and keyword search. Users can also access pediatric dosage tables for common over-the-counter medications, first-aid illustrations, and images to help identify symptoms, injuries, and common bites and stings.



JOHN ALTDORFER

WHITE CLOUD DAY

Richard Bondi (MD '69) gauges the distance to the green during the 12th annual Pitt Med Golf Outing at the Quicksilver Golf Club on a recent spring day (the first blessedly rain-free tourney day in years). Organized by students, this year's event raised $6,400 for the Dr. Edward Curtiss Leadership in Service Award, presented each year to a Pitt med graduate to offset educational costs. A general surgeon with UPMC, Bondi is a past winner of the foursome team tournament. His team came in second this year. Bondi's prescription for success is simple: "I always bring some young bucks with me." *—John Altdorfer*

Name Dropping

Jennifer Lippincott-Schwartz, chief of the National Institute of Child Health and Human Development's Section on Organelle Biology, shares this thought on her lab Web site: "There's an understandable tendency for researchers to be tempted to extrapolate to grand conclusions. Part of the work of being a scientist, however, is to be disciplined enough to verify hypotheses through a multitude of techniques and approaches." In the spirit of hearing a multitude of perspectives on science, each year Arthur S. Levine, dean of the University of Pittsburgh School of Medicine and senior vice chancellor for the health sciences, invites an elite group of investigators to participate in Pitt's Senior Vice Chancellor's Laureate Lecture Series. This November, Lippincott-Schwartz, a PhD, will join in to discuss how imaging advances are changing scientists' understanding of cellular biology. Lippincott-Schwartz is a member of the National Academy of Sciences. She most recently was named the Keith Porter Lecturer by the American Society of Cell Biology.

Richard Lifton, who is chair of the Department of Genetics, the Sterling Professor of Genetics, and professor of internal medicine at Yale University, as well as a Howard Hughes Medical Institute investigator, will visit in September as a Laureate Lecturer. The MD/PhD's work on the genetics and physiology of cardiovascular and renal disease has uncovered mutations linked to 20 human diseases. His presentation is titled "Genes, Genomes, and the Future of Medicine." Lifton is also a member of the National Academy of Sciences and has been honored with the American Heart Association's Basic Science Prize and the American Society of Nephrology's Homer Smith Award.

The National Institute of Diabetes and Digestive and Kidney Diseases' **Reed Wickner**, an MD, visited in April and spoke about prions, those particles that infect cells and are responsible for such devastating diseases as Creutzfeldt-Jakob and mad cow. Among other things, Wickner's lab discovered that yeast have prions and that yeast prions can code for shape (as DNA molecules, working with RNA, code for amino acids in proteins). Although prions have devastating repercussions in mammalian cells, some researchers suggested that they might actually help yeast cells. Wickner, a National Institutes of Health Distinguished Investigator and member of the National Academy of Sciences, has found that's not the case: "Nature is not all goodness and light, as some people might have you believe." *—Erica Lloyd*



THAT SCIENCE MOJO

David Wheeler's advisor, Guillermo Romero, an associate professor of pharmacology and chemical biology, came into the lab with good and bad news. The good news was that he was nominating Wheeler, a student in the School of Medicine's Medical Scientist Training Program, to go to a meeting. The bad news was that the application was due that day.

The "meeting" would be a week in Germany with other young researchers from around the world. Add 25 Nobel laureates to the gathering, acting as scientific elders, and include informal chats with those scientists over a beer. It was the annual Nobel Laureate Meetings at Lindau, and it sounded too good to be true.

But it was true and very good. Both Wheeler (shown above) and Pitt MD/PhD chemistry student Amir Faraji (not shown here) were chosen as 2010 Lindau Scholars. This year, Kelly Quesnelle (above), PhD candidate in molecular pharmacology in the School of Medicine, was nominated by her advisor, Jennifer Grandis, professor of otolaryngology, to attend the June meeting. She says, "I'm really excited and humbled to be chosen. I can't wait to meet [Edmond Henri] Fischer, who codiscovered the reversible nature of protein phosphorylation, which is essential to the cell signaling that I study. The other students at the meeting have shown a certain scientific mojo, too, and I am excited to meet and interact with them." Only researchers with that "mojo" are invited to attend the meeting. Thousands of applicants from about 70 countries are whittled to approximately 500 attendees.

Wheeler (who studies something about how certain proteins modulate important things that are too complex to describe here) calls the experience "life changing." He not only watched the World Cup and played chess with Nobel laureates, he also found their stories motivating and reassuring. Wheeler says, "You hear the laureates' lab stories, like how they went through five fire extinguishers to get an experiment to work. You realize they were once just like you."

—Maureen Passmore
—Photo by Cami Mesa



Enough with "watchful waiting," says Pitt's Hoberman. There's no reason doctors can't learn to make accurate diagnoses regarding ear infections so children can be treated for this painful condition.

UNCERTAINTY IS NOT AN OPTION

REMOVING DOUBT FROM EAR INFECTION TREATMENT | BY CHUCK STARESINIC

Ear infection is the most frequently diagnosed illness in children. This should come as no surprise to parents, many of whom are familiar with the midnight wailing of an inconsolable child with ear pain. What is surprising is a longstanding question doctors have concerning how best to treat acute otitis media (AOM). Should they prescribe antibiotics or wait a few days and see whether symptoms resolve on their own?

One might think this question had been answered long ago and that antibiotics were recommended for AOM. It is the most-common course of action in this country. But doctors in some European countries follow a strategy of "watchful waiting" for nearly all cases of AOM, reserving antibiotics for those children who fail to improve within two or three days. The Canadian Paediatric Society recommends this strategy for all children older than 6 months of age. A 2004 clinical practice guideline from the American Academy of Pediatrics (AAP) is more cautious, saying watchful waiting is an option for children with mild symptoms and an uncertain diagnosis.

But that doesn't sit well with everyone. Alejandro Hoberman (Fel '92), for one, is no fan of this kind of uncertainty. He is chief of the Division of General Academic Pediatrics at Children's Hospital of Pittsburgh of UPMC. In the 1980s, Hoberman completed medical school and a pediatrics residency in Buenos Aires before coming to Pitt for his fellowship.

"I came to Pittsburgh to work with Jack Paradise and Ellen Wald, who were the leaders in researching and writing about common pediatric problems. There is a history in this institution of landmark studies of conditions that affect millions of children," says Hoberman, who is now the Jack L. Paradise Professor of Pediatric Research in the University of Pittsburgh School of Medicine. (Paradise is a Pitt emeritus professor of pediatrics, while Wald is now chair of pediatrics at the University of Wisconsin.) Hoberman points out that, back in the days when tonsillectomies were more frequently performed, Paradise showed that the operation was appropriate only when there were specific, limited indications. (These criteria were only recently endorsed by the Society of Otolaryngology–Head and Neck Surgery, years after the studies were completed.) Paradise later showed that surgical insertion of ear tubes in many children with persistent fluid in the middle ear did not benefit the children's speech, language, or cognitive development.

In the spirit of these studies, Hoberman and colleagues set out to eliminate the uncertainty around AOM. They were not alone in being irritated by the phrase *if diagnosis is uncertain* in the AAP's language.

"The uncertain diagnosis should not exist," Hoberman says. "One should be able to clear the cerumen [ear wax] in order to be able to see the eardrum and make a diagnosis or not make a diagnosis." With Nader Shaikh, assistant professor of pediatrics at Pitt, and other colleagues, Hoberman created a seven-minute video tutorial for *The New England Journal of Medicine* (*NEJM*), demonstrating removal of wax and detection of AOM's telltale bulging eardrum.

From 2006 to 2009, Hoberman's team conducted a double-blind, placebo-controlled trial of antibiotic treatment for AOM. Unlike the many disparate studies of inconsistent quality used in the meta-analysis that yielded a recommendation for watchful waiting, Hoberman's trial had strict diagnostic criteria. The children, from 6 to 24 months of age, were randomly assigned to receive antibiotics or a placebo.

Before completing the study, the team consulted with outside experts. "We thought antibiotics would have a failure rate of about 15 percent," says Hoberman, "because we had done previous studies with antibiotics. We asked, 'What failure rate for placebo would make you really want to use antibiotics? How much would you like to see before making that recommendation?' Everybody we consulted said twice as much. So a difference of 15 and 30 percent in failure rate would do it for everybody. We found 15 and 50."

Hoberman's landmark paper—with Paradise and Wald among the coauthors—appeared in the January 13, 2011, *NEJM*, alongside a very similar study from Finland, which reached the same conclusions.

"Fifty percent is not an acceptable proportion of children who will continue to have an ear infection," says Hoberman, who is on the committee tasked with rewriting the AAP's clinical guideline for AOM.

The Pittsburgh team saw no change in either the placebo group or the antibiotic group for levels of antibiotic-resistant bacteria colonization in the back of the nose. However, diarrhea and diaper rash were more common among children who received the antibiotic.

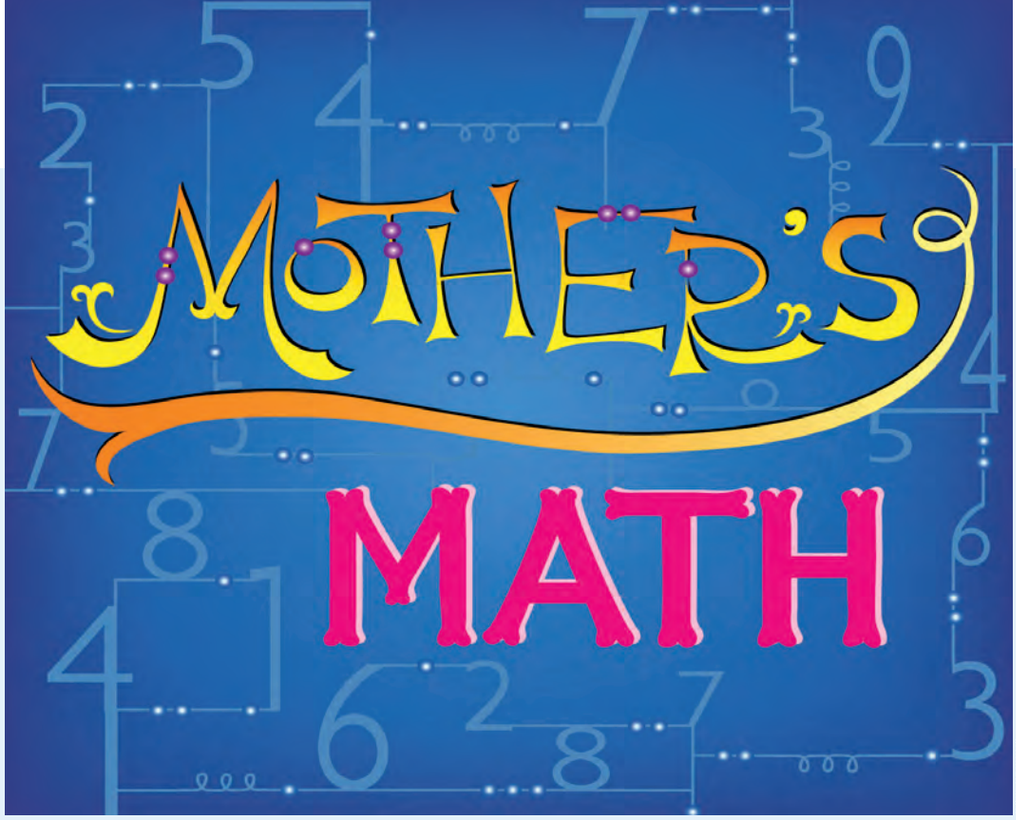
"It's amazing how many areas of the care of children have not been methodically addressed," says Hoberman, who is also pursuing clinical studies in urinary tract infection and other common pediatric problems. "Being able to do that makes me want to wake up in the morning and come to work, filled with energy to take care of patients and ask families to consent to participate in the studies we do." ■

STEPH HOOTON/ PICTOGRAM STUDIO

MOTHER'S MATH

A NEW FETAL GENETIC TEST

BY KRISTEN COSBY



CARMEN MOK

For pregnant women, fetal genetic testing involves a complex and confusing set of calculations of potential risks. Noninvasive screening—typically an ultrasound and a simple blood test—is recommended for all pregnant women in the first trimester. But these tests cannot conclusively determine whether genetic anomalies are present—the detection rate is just 85 percent. Even worse, they have a false-positive rate of 5 percent, so one in 20 women who are screened will be advised to undergo an unnecessary follow-up procedure: either sampling amniotic fluid cells via a needle in the abdomen (amniocentesis) or sampling placental cells via either the same method or a catheter to the cervix (chorionic villus sampling, or CVS). Between one in 100 and one in 1,000 of these invasive procedures—currently the only diagnostic forms of prenatal genetic testing—will result in a miscarriage.

It's a risky venture, says David Peters, a PhD and associate professor in the Division of Reproductive Genetics at the University of Pittsburgh and scientific director of Magee-Womens Research Institute's Center for Fetal Medicine, who first became interested in reproductive genetics when his wife underwent an amnio. "If someone said you had a one in 200 chance of dying of a mammogram or prostate exam, you wouldn't get it."

In the United States, genetic abnormalities account for most deaths that occur around the time of birth. And yet only a few percent of pregnant women opt for invasive testing—typically women who are 35 or older, who have a family history of genetic abnormalities, or whose screening tests show an elevated probability for fetal genetic abnormalities.

Advising expectant parents based on probabilities is extremely difficult. Everyone interprets the odds differently. For some, a one-in-100 chance of an abnormality seems extremely high. For others, it seems minor.

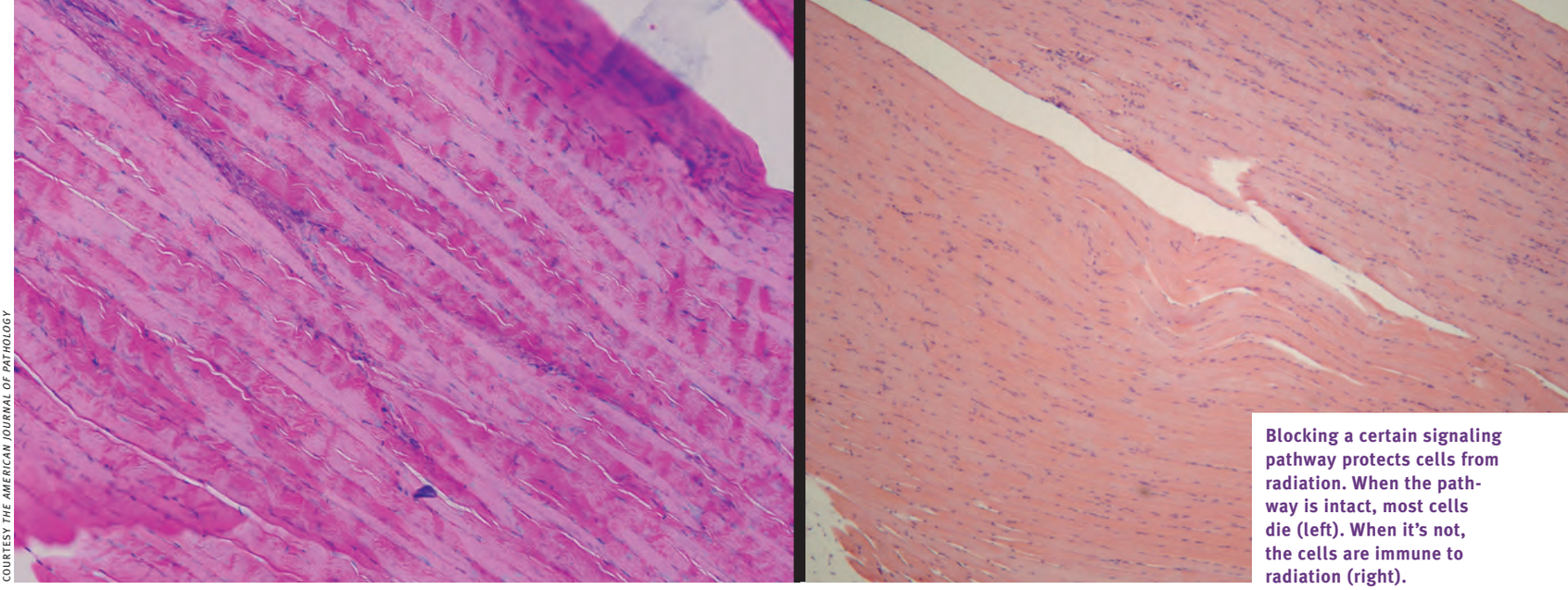
Pitt's Aleksandar Rajkovic, an MD/PhD associate professor and director of reproductive genetics, codirects research for the Center for Fetal Medicine with Peters. The pair hope to develop a new test that detects fetal genetic abnormalities with 95 percent accuracy, using only a blood sample drawn from the mother's arm. They estimate that if they're successful, the number of miscarriages associated with invasive prenatal testing could fall by 80 percent.

Researchers worldwide have been trying to develop such a test since 1997, when it was first discovered that during pregnancy a small amount of fetal DNA escapes the placenta and circulates in the maternal bloodstream. The challenge is that the maternal DNA veils some aberrations in the fetal DNA. In Hong Kong and Boston, researchers are using various methods to enhance, mark, or separate the fetal DNA circulating in maternal blood. The beauty of the Pitt method, says Peters, is that it doesn't require any of these processes. The Pitt researchers have applied a new technology that processes vast quantities of DNA at high resolution, providing a clearer, more complete picture of the genetic makeup of the cells.

Peters and Rajkovic are conducting a National Institutes of Health–funded trial of a testing method that uses "next-generation shotgun sequencing." This sequencing method allows them to analyze large quantities of DNA randomly gathered from maternal plasma, compare that to samples from genetically normal mothers and babies, and tag irregularities that originate in the fetus.

Peters and Rajkovic hope their test will be on the market within five years. "I think that this will lead to a new way of looking at pregnancy and genetic disorders and new ways in which to counsel couples on the uncertainties of undiagnosed disorders," says Rajkovic.

But their vision of the future is much grander. Ideally, they'd like to map the fetal genome with such high resolution that they can begin to look for subtle genetic abnormalities, such as single-gene disorders. (Currently, the technology is limited to detecting additional whole chromosomes.) This higher specificity would give obstetricians new opportunities to treat congenital conditions before birth. The same methods might eventually be applied to the detection of the aberrations that cause certain cancers. ■



COURTESY THE AMERICAN JOURNAL OF PATHOLOGY

Blocking a certain signaling pathway protects cells from radiation. When the pathway is intact, most cells die (left). When it's not, the cells are immune to radiation (right).

COOKING WITH GAS

N.O. STUDIES TAKE AN UNEXPECTED TURN

BY MELINDA WENNER MOYER

As a medical student working in pharmacologist Louis Ignarro's lab at Tulane University in the mid-1980s, Jeffrey Isenberg saw something that changed his life. He watched as his colleagues pumped bubbles of nitric oxide gas—a common combustion byproduct, but also an important cellular-signaling chemical—into contracted mammalian arteries. The vessels instantly relaxed. "That was an epiphany for me," says Isenberg, now an MD visiting associate professor in the Division of Pulmonary, Allergy, and Critical Care Medicine at the University of Pittsburgh. "I figured anyone who can control nitric oxide signaling could really change things for the better, healthwise." (In 1998, Ignarro, with Robert Furchgott and Ferid Murad, won the Nobel Prize in Medicine or Physiology for their nitric oxide work.)

Today, nitric oxide is used in many clinical settings. For example, nitric oxide gas is used to treat neonates with primary pulmonary hypertension. Drugs that release nitric oxide are used as medications for adult hypertension and heart failure. And nitroglycerin, prescribed for coronary artery disease and chest pain since the 1880s, is converted in the body into nitric oxide.

Pitt has made a name for itself in nitric oxide research. Its faculty members have studied pathways that increase nitric oxide levels as a means of treating heart and lung problems and for reducing stress responses during surgery and inflammation in diabetes. Now Isenberg and others have found a way to boost the efficacy of the gas and are hoping to apply that knowledge to treat a number of conditions. Isenberg may have found a way to improve cancer therapies.

After working for several years in academic and clinical practice, Isenberg in 2003 joined the National Cancer Institute, where he began pursuing his interest in nitric oxide under the wing of David Roberts. In 2005, Isenberg found cells extracted from mice that cannot produce a protein called thrombospondin-1 (TSP-1) have exaggerated responses to nitric oxide, which suggested that TSP-1 inhibits cellular responses to the gas. And in 2006, Isenberg and Roberts identified a cell-surface receptor called CD47 that mediates TSP-1-induced nitric-oxide inhibition; by turning off TSP-1 activity or blocking CD47, Isenberg and Roberts showed, it was possible to turn up nitric oxide signaling.

The team found that blocking CD47 activity relieves ischemia—when blood flow is too slow to meet a tissue's needs—which is a hallmark of heart disease and diabetes and a common complication from transplantation and other surgeries. Nitric oxide could benefit patients who get vascular stents, he says: "Maybe you could reestablish flow and then get all new microvascular outgrowth" by introducing a stent that slowly releases a CD47 blocker.

The gas could also have implications for treating or preventing Alzheimer's disease. Research by others has shown that the amyloid beta plaques that are believed to degrade nerve cells in Alzheimer's patients prevent nitric oxide signaling. Blocking TSP-1 or its receptor might heighten the "pro-survival signal from nitric oxide, which could be good for neural health," Isenberg says.

Targeting CD47, however, seems to play a much larger role in cell and tissue response to injury. In papers published in 2008 and 2009—the latter of which was recognized by the National Cancer Institute as one of 2010's top science advances—Isenberg showed that when CD47 activity is blocked in mice with cancer, their healthy cells became more resistant to radiation therapy; the cancer cells in the mice, however, remain vulnerable. Isenberg suspects that blocking CD47 both protects the healthy cells and makes it easier to identify and kill cancer cells. By targeting the receptor, "you could treat cancers more effectively with lower doses of radiation," he says.

The next step is to bring the new therapeutics to patients. Isenberg believes that the best bet is to find small molecules that can block CD47, the receptor for TSP-1, because "it seems to be necessary in all conditions for the inhibitory signal," he explains. He and his colleagues are now developing a screening platform to find possible candidates. "It's turning out to be a rather fascinating story. I think we're just scratching the surface." ■



ROBOTICS TAKES OFF AT THE SCHOOL OF MEDICINE | BY JOE MIKSCH

OF MED AND MACHINE

Robots pique the human imagination.

More than 2,250 years ago, the Greek engineer Ctesibius envisioned many—and created more than a few—self-operating machines that, minus the "intelligence" provided by modern computing, did human work. About five centuries ago, Leonardo da Vinci sketched out a humanoid robot that could sit up and wave. In the 20th century, visions of robots and their possibilities gave Isaac Asimov a career.

On a practical level, in the real-world here and now, robots help us build cars, vacuum our carpets, and defuse bombs. They also, notably in the University of Pittsburgh School of Medicine, are taking a lead role in saving and improving lives.

For instance, Pitt investigators are in the early stages of two clinical trials testing a robotic arm controlled by people's brain impulses. Others at Pitt are perfecting a wheelchair with robotic arms, in the hope that wheelchair users will be able to do even more on their own. And in the operating rooms of UPMC hospitals, surgeons employ a four-armed robot to perform more precise surgery in smaller spaces. The robot's name: The da Vinci, after the man whose imagination led him to ponder robots more than half a millennium ago.

Robotics, cyberscience, and artificial intelligence are changing medicine and people's lives. For instance, Pitt and Carnegie Mellon's PerMMA wheelchair—reimagined on the left—uses robotic arms to allow people with quadriplegia to open doors and feed themselves.

ILLUSTRATIONS | JESSE LENZ

CYBER SNACKING

At the University of Pittsburgh Motorlab, you can see a monkey, its neural activity monitored and recorded by a tiny microelectrode array, feed itself marshmallows using a robotic arm rather than its hands.

When the monkey thinks of grabbing the food—presented to it at the end of a metal spindle—the microarray feeds the monkey's thought of using the robotic arm into a computer, which processes the information and feeds it to the arm. With almost no lag time, the monkey's thoughts cause the arm to reach out, grab the food, and bring it back to the monkey's mouth, at which point the primate stuffs the treat into its maw.

It's kind of nuts to watch. And yet it makes perfect sense: If you can find the neurons responsible for motor activity, you can figure out how these neurons communicate, and then, eventually, find a way to translate the signals to drive motion in a robotic arm. Pretty simple, conceptually. It's not at all simple, though, technologically speaking.

Pitt professor of neurobiology Andrew Schwartz is, in concert with Michael Boninger, Pitt professor and chair of the Department of Physical Medicine and Rehabilitation, edging this technology toward prime time at the University of Pittsburgh.

"We started thinking seriously about this in 1986," Schwartz, a PhD, says. "That was when we could demonstrate that we could decode these signals reliably from the brain. Once we had the data, we knew it could work."

A quarter century since he "knew it could work," Schwartz has surmounted many of the technological hurdles and is pressing ahead.

On a typically inclement early March day in Pittsburgh, technicians assisting Schwartz are less concerned with the weather than the installation and calibration of a remarkably expensive, brand-new robotic arm. The $400,000 device (the Defense Advanced Research Projects Agency—DARPA—has spent tens of millions of dollars on this research and technology so far) was built at the Johns Hopkins University Applied Physics Laboratory.

Looking like it might have fallen off RoboCop, the arm is mounted on a floor-to-ceiling pole in a small room, off a larger space packed with computers. A group of youngish men studying under Schwartz and a rep from the Applied Physics Laboratory surround it, fiddling with the device.

"This project was designed to be a prosthetic arm that goes on an amputee," Schwartz says as the work goes on. "It weighs nine pounds, so it weighs as much as a regular arm. It has the size of a regular arm and hand, and it can do things like lift 50 pounds." Also, Schwartz adds, the fingertips of the device have sensors that will offer users tactile feedback. Eventually. That's something that still needs to be sorted out.

(The technology Schwartz has developed has been featured on *60 Minutes* and in *The New York Times*, among other media outlets. This magazine ran a February 2005 feature, "Cyborg Medicine.")

While Schwartz is the lead brain behind the arm's technology, Michael Boninger, an MD and director of the UPMC Rehabilitation Institute, will lead the about-to-begin clinical trials.

Boninger is recruiting people with quadriplegia from spinal cord injuries for the trial. The group considered others with no use of their arms, such as people with amyotrophic lateral sclerosis, but thought the progressive nature of the disease would complicate the study.

The first trial, Boninger says, will further investigate the most effective way to record electrical signals from the brain. Each patient will have an array of 16 electrodes laid on the brain surface and then be instructed to move a cursor on a computer screen and, eventually, manipulate a prosthetic arm in a simple way while the array records neural activity. The trial will last about a month.

The second trial will last one year and will study how well participants can perform functional tasks with the arm, which will be mounted to a wheelchair. More sensitive arrays—each with 100 electrodes—will actually be implanted into the patient's brain rather than laid on the surface.

"We'll have much more time to train them and much more time to get participants to use the arm with multiple degrees of freedom," Boninger says. "I would hope that by the end of the year, they'll be able to do things so well with the arm that it will be of some practical assistance to them."

The trial is expected to begin late this year. It and the briefer trial are supported by $6.8 million in grants from DARPA and the National Institutes of Health.

No matter how well the trials work and how much is learned, Schwartz says, there's much to be done before his group can offer a commercially viable product.

"Well, it's one thing to demonstrate this in a lab, but will it be reliable enough to use every day? The machinery can break down a lot, then there's the issue of how long the [microarray] implants can stay in; the brain tries to reject them and encapsulate them," Schwartz says. "We'd like to have bilateral control [the ability for the brain to control two robotic arms simultaneously], but we don't know how that's going to work, and we're not sure how well you'd be able to move individual fingers …

"And one of the most critical factors is the patient's ability to learn. What I mean is that we're recording their neural activity, and they're trying to get their neurons to work this device. So they're trying to make their neurons fit our expectations."

THE THINKING WHEELCHAIR'S WHEELCHAIR

Equipped with robotic arms, which can lift a few pounds each and have dexterity enough to lift a magazine off a table, the Personal Mobility and Manipulation Appliance (PerMMA) is being prepped for clinical trials—and is being continually refined—at the Human Engineering Research Laboratories (HERL) at the VA Pittsburgh Healthcare System–Highland Drive. (The lab, affiliated with the University's School of Health and Rehabilitation Sciences, is moving to new space at Pittsburgh's Bakery Square development, also home to a Google campus, in July.)

Early one morning, Garrett Grindle, a graduate student researcher at HERL, and Juan Jose Vazquez, a research associate, were sitting with PerMMA in lead developer Rory Cooper's office, prepared to put it through its paces. Cooper is professor of orthopaedic surgery in the School of Medicine and FISA & Paralyzed Veterans of America Chair and Distinguished Professor of



A brain-controlled robotic arm may one day mean independence for those who can't use their own.

Rehabilitation Science and Technology in the School of Health and Rehabilitation Sciences. (He holds a number of other appointments, as well.)

PerMMA looks like a souped-up conventional electric wheelchair with side-mounted robotic arms terminating in pincers. It's about 3 feet wide, though it can get much smaller when the robotic arms are retracted behind the wheelchair base. It's the same height as just about any other wheelchair you'd see, except that it can lift its human partner a couple of feet in the air to grab something from, say, a kitchen cabinet or otherwise out-of-reach place.

"There are three modes of running it," Grindle says. "In some cases it's automatic. The 'big' task we have been able to do automatically is open a door." "Automatic mode" employs video cameras and Carnegie Mellon University–crafted software to tell PerMMA that it's at a door. The chair's user confirms that what PerMMA has detected is indeed a door and gives it the command to perform the task.

"We've also been able to write little programs to move the robots to a certain pose," Grindle adds. "The robot's pose is almost always the same for picking up a cup, so we move the joints automatically to a generic pose for picking up a cup. It is not that fancy from a software/algorithm point of view, but it is practical and works really well. Then we have direct user control: There are buttons people can manipulate, and we have a touch pad and voice control. The third option is a remote-control mode."

With that, Vazquez, who was sitting quietly at a desk, grabbed hold of two joysticks and made PerMMA's arms move and pincers contract and expand.

"See those two Web cams on the chair?" Grindle asks. "[Vazquez] can see what the person in the chair can see, but it's streaming over the Internet. What we think we might be able to do here is have a call center, like OnStar [the service that allows motorists to get help in an emergency just by pushing a button]. If a person is having a little trouble, they could call someone up—maybe a professional at a call center or a family member or other caregiver at home—and say they need

help getting a bowl out of a cupboard." The person on the other end of the call could then take over control of PerMMA and help its user do what needs to be done.

Grindle hops into PerMMA to demonstrate. A magazine is on a round table in the middle of the office. Grindle powers PerMMA over to the table and reaches out, controlling one of the robotic arms with a joystick, and tries to grab the magazine. He's having trouble.

This is where Vazquez (or, in the future, perhaps a technician at a remote call center) comes in. Sitting at a desk a few feet away, he peers at a computer screen, which shows the table from Grindle's perspective. He grabs hold of one of the two joysticks on the desk (one for each of PerMMA's arms) and causes an arm to slowly move forward. With the arm extended, he opens its pincer-style hand, closes it on the edge of the magazine, and lifts it. Then he gently deposits it onto Grindle's lap.

Done—without the need for a visit from a caregiver.

PerMMA has some limitations. Its arms can only lift about 5 pounds, which is less than a gallon of milk weighs. Hence the Strong Arm project. Grindle says the team is very close to completing a working prototype of a robotic arm that has the ability to help PerMMA's user get in and out of the chair or lift a pot of boiling water off the stove.

"We're going with a 'lobster strategy,'" Grindle says. "We'll have one big arm on one side and a smaller, more dexterous arm on the other. The big arm will be slower (because of the care necessary when moving a person or something potentially dangerous like a pot of scalding liquid), but we've done some attitude surveys, and people say that even if it takes longer for the robot to do it, that's okay, as long as it can be done."

PerMMA and much of what HERL does are personal to Rory Cooper. When he was 20 years old, he was in the U.S. Army. While stationed in Germany, Cooper took advantage of some free time to go bicycling and was hit by a truck. His spinal cord was seriously damaged. Although he has use of his arms, he's been in a wheelchair ever since.

Cooper, a PhD, remains an athlete, having raced in and won the hand-cycle race in the 2009 Pittsburgh marathon. One of his goals as a researcher, engineer, and advocate is to make it easier for those with disablilites to lead full, active lives. PerMMA, he says, has the potential to allow people with severe physical impairments, such as those with quadriplegia, previously unheard of degrees of independence.

Cooper and his collaborators at the joint University of Pittsburgh–Carnegie Mellon University Quality of Life Technology Center, which is funded by the National Science Foundation, say that PerMMA is, "not just a wheelchair with 'added intelligence' and arms; it is a mobile robotic manipulator with a seat for a person."

In essence, PerMMA should become part of the person using it.

"If you're going to be using robots to assist people," Cooper says, "then you should take advantage of human intelligence. It's easy to create a robot that works in a fairly fixed structure or fixed location. But there's a lot of randomness in the world, and that's why I'm very excited to have a human in the loop."

In 2010, PerMMA was named one of *Popular Science*'s 10 most promising robots. Cooper thinks it deserves the honor. "This has the potential to really transform lives. Where we need to go is to improve the interaction between robots and humans, and that's what I'm working on."

THE ART OF SURGERY

In an operating room at UPMC Shadyside, Pitt surgeon Herbert Zeh sits at a console, peering into an incredibly high-resolution, three-dimensional viewfinder. His hands on two delicate-looking joysticks, he makes small, precise motions with his fingers.

His patient, a woman in her 60s with a large tumor growing on her pancreas, is several feet away from him. Above her is a four-armed robot. The arms are outfitted with a camera and surgical instruments inserted into the patient through tiny incisions.

Zeh cuts and cauterizes and ties off blood vessels from a distance. After about three hours, the tumor has been cut loose. It's 7 centimeters in diameter. The robot picks up the tumor, the patient's spleen, and a portion of the pancreas and inserts it all into a plastic bag, which it pulls it out of the patient. Zeh walks the bag to the pathology lab.

The pathology tech slices a section of the pancreas removed with the tumor to see whether there are any cancer cells in the margin of the organ. (Surgeons want to make sure that the margin is clean, reducing the chance that the cancer will regain a foothold in the part of the pancreas that remains in the patient.) Some cancer cells are visible in the slide the tech prepared, so Zeh heads back to the OR to remove a bit more of the pancreas.

In a way, what just happened is a good bit like laparoscopic surgery, a well-established minimally invasive surgical method. What's different here is, of course, the simple fact that a robot—the da Vinci Si, made by a California company called Intuitive Surgical—is doing the job.

But what makes da Vinci better than just a shiny, new toy, Zeh says, is it allows the surgeon greater dexterity (the robotic instruments have a much wider range of motion than the essentially straight-forward ones used in laparoscopic surgery), greater precision (thanks to the three-dimensional, high-definition camera, calibration of the da Vinci's arms, and the fact that robots don't suffer from the slight hand tremors even the calmest surgeon exhibits), less scarring post-op, and much less blood loss.

"It's night and day" compared to open and even laparoscopic surgery, Zeh says, while waiting for the pathology results. "One of the things people have considered a drawback with it is that you don't have that tactile sense. But after many hours at the robot, it's like we can 'feel' through our visual feedback."

It's "like [how] some visually impaired people describe enhanced tactile sensation," adds James Moser, MD Pitt professor of surgery and codirector of the UPMC Pancreatic Cancer Center (and a frequent collaborator with Zeh on da Vinci–related research).

Pitt surgeons are far from the only ones using the da Vinci—there are 1,752 of them in operation worldwide, 1,285 in the United States, 55 in Pennsylvania (including five at UPMC hospitals). But Zeh and Moser are among the earliest adopters and innovators, having performed more robotic major pancreatic resections than any of their peers.

In 2010, Zeh and Moser published a paper in *Archives of Surgery* that was the first to



The da Vinci surgical robot (playfully illustrated here) allows a surgeon greater dexterity and more control than other minimally invasive methods.

establish that the da Vinci is safe and effective for major pancreatic resections. They believe further research will show that the robot improves patient outcomes.

Marshall Webster is executive vice president of UPMC and president of its Physician Services Division. He formerly served as Pitt's Mark M. Ravitch Professor of Surgery. He has long been an advocate of robot-assisted surgery. "This has been a profound advance," he says. "I've never done a robotic procedure—I've been out of surgery for eight years since I've been in this [administrative] role—but the results we've seen have allowed me to be very effective in selling the administration here on buying these $2 million machines."

UPMC, Webster says, sees about 160,000 operations per year, "and we're doing about 1,000 cases a year with robots. All of [the robots] are very busy, it's hard to get time on them now, and there are very few places in the country that have five da Vinci Si machines."

Pitt has 22 surgeons in nine specialties who use the da Vinci regularly. Each year, Webster says, that number will grow, as will the number of procedures performed.

"And, down the line, we're going to be able to do something like this," Webster says. "There'll be one console at Presby and another console in Bedford, Pa., where the patient is. Maybe the surgeon in Bedford needs assistance or a second opinion, and the surgeon at Presby can help wirelessly.

"Things are advancing so rapidly that it's not a matter of if, it's a matter of when."

And it's something that even da Vinci himself never envisioned. ■

To see the da Vinci doing origami and more, check out our Web Extra: pittmed.health.pitt.edu/Summer_2011/web-extra.htm.



At a Greater Pittsburgh Literacy Council classroom in Prospect Park, Schweitzer Fellow Aditya Iyer (right and opposite page) teaches health literacy to refugees. Since 1997, more than 200 graduate students from a variety of fields have volunteered as Schweitzer Fellows to address health disparities in Pittsburgh.



SCHWEITZER FELLOWS PREPARE FOR A LIFETIME OF SERVICE | BY ELAINE VITONE

"WE'RE HERE BECAUSE WE WANT TO BE."

"Are you getting a grade for hanging out with us?"

It was a fair-enough question. At that tense dinner last September when Alison Levine and Lindsay Proud first met the residents of Girls Hope—a Pittsburgh nonprofit that runs two group homes for at-risk adolescent girls—they knew they'd have to earn the girls' trust. The two second-year University of Pittsburgh medical students had planned all sorts of fun health-education activities for the houses (one is in Baden, Pa., and the other is in Coraopolis), which between them had nearly 20 girls at grade levels ranging from fifth to 12th. But first, they had to answer the girls' simple question: Why are you here?

"We told them," says Levine, "'We're not here for school. We're here because we want to be.'"

Each year, the Albert Schweitzer Fellowship selects some 200 students from top professional schools in 11 U.S. cities; Pittsburgh's program, hosted by Southwest Pennsylvania Area Health Education Center, is one of the longest-running, having started in 1997. Partnering with community-based organizations, the fellows design and complete one-year service projects that address health disparities. These fellows continue the legacy of physician-humanitarian Albert Schweitzer.



PHOTOGRAPHY | MARTHA RIAL

Schweitzer Fellows benefit from the experience of designing a service project from scratch and carrying it out from beginning to end. Working with faculty mentors and armed with $2,000 in stipends for their projects, they serve year-round—so that they can learn to build service into their everyday, hectic schedules.

Andrea Fox, chair of Schweitzer's advisory board, associate professor of family medicine at Pitt, and medical director at Squirrel Hill Health Center, has helped this year's and several other crops of School of Medicine Schweitzer Fellows shape their projects. These often end up looking quite different from the original proposals, she notes. "I call it action research," she says. "It's hard to go into a community and know what to do. You have to figure out what it's really about first."

For their project, Levine and Proud wanted to enable girls to take charge of their own health. They designed a series of workshops that allowed plenty of time for open discussions. On the day they talked about relationships, they chatted about the differences between healthy courtships and not-so-healthy

And if you ask a teen how school is going, of course you're going to get a one-word answer: "Fine." But if you ask about what she is reading in English class or who's her favorite teacher, you're much more likely to get a sense of the kid's level of engagement.

"Teenagers know how to answer questions correctly," says Levine. "'Do you smoke?' 'No.' 'Do you wear a seatbelt?' 'Yeah.' But if you ask, 'Are there people in your class who have experimented with alcohol? And if so, how do you feel about that?' then you're more likely to get a real answer."

It's been rewarding watching the girls' progress over time, she says. During the addiction workshop, Levine and Proud asked them about risk factors, and the girls brought up mental health. *Hadn't they talked about how people with depression or anxiety sometimes turn to substances for self-treatment?* they asked.

Levine recalls, "We were like, 'Yes we did, and that was two months ago, and you remembered!' It was great."

Proud spearheaded the lunchtime nutrition workshop/cooking class. The girls weren't sure about the menu at first: stir fry. (*Ginger powder? What's that? I don't like green peppers. Broccoli? Meh…*). But soon they warmed up to it. They split into two groups to divide the labor, which was made all the more enjoyable by a little friendly banter. Levine, a vegetarian, led Team Veggie, and Proud led Team Chicken. The trash talking between the groups was "all in good fun," says Proud.

While the bird was marinating, Proud taught a lesson on the basics of metabolic biology. They had a lively discussion while the girls did their nails—the big homecoming dance was that night. After class, a high school student who's been struggling with her weight approached the Schweitzer Fellows. "Um. Since you're, like, crazy health freaks and stuff, do you think you could help me figure out what to eat and what exercises to do?" Another girl overheard and asked if they'd help her, too.

Before everyone dug into lunch, they said a prayer.

Dear God, Thank you for this food. Please bless Ali and Lindsay for coming here and teaching us about nutrition and for spending time with us. And please let there not be any drama at homecoming tonight.

"So not only did we make it into grace," recalls Levine, "but we made it in before homecoming."

Proud says, "That was when we knew we were in."

Tiffany Behringer, too, has found herself showing up at the homes of complete strangers and hoping to gain their trust. These "homes" are a sharp contrast to the historic townhouses in Pittsburgh's Mexican War Streets, where she lives. They're camps beneath the freeways or aside fire pits near the railroad tracks.

Behringer, a fourth-year student, first started working with Pittsburgh's homeless population two years ago as a volunteer with Operation Safety Net, a local organization that provides mobile medical care and other services to people who live on the street. Struck by the demand for mental health and drug rehabilitation services, she decided to spend her Schweitzer year helping identify the barriers to filling these needs.

Working with small teams—generally a formerly homeless person and an EMT—Behringer makes "street rounds" to the camps in Pittsburgh's North Side, providing basic necessi-

"They also need to realize there are barriers that get in the way of doing good."

ones—and later made care packages for residents of a battered-women's shelter. On mental health/self-care day, they talked about loss and grief—things that many of the girls are no strangers to—and enjoyed a yoga lesson courtesy of Levine, who's a certified instructor. On the afternoon of the nutrition workshop, they talked about the difference between whole foods and processed foods. Afterward they prepared and sat down to a healthful lunch. For the substance-abuse workshop, they talked about how advertisers target young people in marketing addictive substances, from soda to beer and cigarettes, through flashy commercials set to earworm. ("[The girls] remembered that old Britney Spears Pepsi commercial," notes Levine, "and she hasn't been cool for a long time.")

The nights at the Baden and Coraopolis houses have been eye-opening for the young clinicians-in-training, who both plan on working with pediatric/adolescent populations. They've learned a few tricks, like: When you have a group of kids who are different ages, the youngest kids aren't going to know as much, so ask the older kids to explain. That way you can gauge their knowledge and perceptions, too.

ties like socks, Gatorade, food, and wound care.

"The first thing I do is smile at them," she says. Then, if and when the time is right, she conducts informal interviews. At the end of her project, she plans to present her findings to service providers.

It takes patience to work with people who are living on the street. Some don't want to share their last names or even their first names because of legal issues, feelings of wariness after bad experiences with health care workers, or just plain shame. Some have mental illness or drug problems they're not ready to confront. Behringer finds that, all too often, these individuals feel marginalized—but once she earns their trust, they're open to sharing their stories.

"People are so thankful just to have someone be nice to them," she says.

Behringer is learning a lot as a future clinician in emergency medicine. There are basic assumptions that won't always apply if the patient happens to lack very fundamental resources. To further complicate matters, many people who are homeless don't consider themselves as such—untold numbers are "couch surfing."

"[Before this experience], I would've never thought to ask someone, 'Is your home environ-

ment stable? Can you pay your heating bill?'" But working with this patient population, she says, is building her awareness of these largely invisible people and their dire predicaments.

There is a woman—we'll call her Sue—who's become one of Behringer's regulars. She's round-faced, maybe 50-something, with kind, green/gray eyes. She and her partner live under a bridge on the North Side, and when the volunteer team comes around, she's often intoxicated and not always coherent. She talks a lot about a faraway time and place—her childhood in Ohio, where she grew up in a big house and had a mother who used to brush her hair.

"She sits there most of the day, bundled up in front of a scrap-wood fire. I'm amazed how she talks about that time in her life when she used to play with other children. She's not crying. Her face is so peaceful and calm."

Behringer often finds herself thinking of Sue when she's in her own comfortable home, not so far away.

On the second service day of Aditya Iyer's project—a health-literacy course for refugees from Burma, Nepal, Bhutan, Burundi, The Democratic Republic of the Congo, and Somalia—he brought a shopping bag full of over-the-counter and prescription medications to show his students. Sitting there in the classroom—a small apartment where the Greater Pittsburgh Literacy Council's Prospect Park location is housed—he showed the group nasal sprays, eye drops, capsules, and chewable tablets and asked them how each should be taken.

"Almost all of the students believed that the eye drops had to be swallowed," he recalls. "It was shocking to them that people would be expected to drop strange chemicals into their eyes."

Before he began his project, Iyer had been working with refugees in Pittsburgh for more than a year. Still, he would experience moments like this, when it becomes clear how staggering the need is for such work.

Last year, Iyer's girlfriend, Mamie Thant (Class of 2013), completed a Schweitzer Fellowship running drop-in centers for Burmese refugees, and Iyer had gone with her numerous times to help bring people to their doctor appointments. There's a precedent for Pitt med students working with these populations. The 2009-10 Schweitzer Fellows included Ben Meza (Class of 2011) and Mirat Shah (Class of 2012), who did similar work with the Bhutanese community in Prospect Park. Together, Thant, Meza, and Shah organized a health forum on the Pitt campus, inviting members of refugee communities, as well as case workers and health care providers. More than 100 people attended.

By volunteering with the communities, Iyer quickly learned that there are many things we take for granted that simply aren't part of a newcomers' reality. For example, what should you wear during a Pittsburgh winter? "They just don't know," says Iyer. "They just moved here—a lot of times unwillingly—and have no idea what to expect in terms of the climate." He has seen people wearing sandals when there are two feet of snow on the ground.

The federal government views Pittsburgh as a good place to send refugees, Fox explains. The city is big, but not too big, and there's affordable housing and good health care. Pittsburgh has a very low rate of secondary migration—meaning people don't arrive here and have such a terrible time making ends meet that they're forced to move on to another city. As a result, the city's refugee populations are growing. A surge of Russians arrived in the 1990s, then some years later came Somalis. More recently, newcomers have arrived from Burma, Bhutan, and Nepal.

Case workers from resettlement agencies work with the refugees their first year. After that, they're pretty much on their own. The newly minted Pittsburghers are expected to get jobs, learn to get around on the bus, and get their kids into a school. The transition is overwhelming. "As miserable as the conditions can be in the refugee camps," says Iyer, "there is a certain sense of security because meals are provided and some sort of housing, as well."

Many of the refugees Iyer works with know very little English and work 10-to-12-hour days in factories. (In recent months, union workers and community groups have alleged that some of these workers are being exploited.) The language, cultural, and financial barriers leave these individuals extremely vulnerable to health problems. Iyer and his friends have seen that toll. Last year, one woman made repeated trips to the ER—she didn't understand the dosing instructions for her antibiotics. Another woman suffered a miscarriage: She'd been diagnosed with gestational diabetes, but didn't know what it meant, didn't know she wasn't supposed to drink so many sodas. And another refugee committed suicide—Iyer believes he may have had a history of depression that went unrecognized.

Iyer is teaching his students how to name the parts of the body, articulate common complaints, read medicine labels, and respond to emergencies. His curriculum is heavy on images, videos, and activities; and it seems to be working well, thanks to the commitment of his students, he says.

"They are very eager to learn and have a remarkable tenacity to sit through classes before and after long days of work. Every class inspires me to overcome seemingly impossible tasks with enthusiasm and diligence."

"This is a humbling experience," says Fox. "A lot of the fellows want to go out to do good, and that's what they should want to do," she says with a laugh. "They also need to realize there are barriers that get in the way of doing good. That's the singular experience most of them learn. There's this overwhelming need, and it's scary to confront it. But you do what you can."

On a chilly November morning, second-year Pitt med student Adia Kelly introduces herself to the Alvarez family (we've changed their names)—a young couple with one child and one on the way. They meet in the hallway outside the patient rooms of Squirrel Hill Health Center. The Alvarezes are just leaving their appointment with their obstetrician.

"*Mucho gusto*," Kelly says, shaking their hands.

"*¿Hablas español?*" they say, smiling, incredulous.

"*¡Sí!*" she says, and they all laugh. Kelly gets this a lot, she explains later. She's not Hispanic, so she's not someone the center's Spanish-speaking clients expect when they're told they're going to meet a fluent Spanish speaker.

Kelly leads the couple and their almost-3-years-old, pig-tailed daughter to a round table in a back office. Mrs. Alvarez just passed the 13-week mark and is still experiencing morning sickness, she says in Mexican-accented Spanish. Kelly offers her some tips, her Spanish consonants more softened—Kelly studied in Spain as an undergraduate.

Eat several small meals with plenty of carbs, Kelly advises. Take your B6 vitamins. Avoid sweets and… (*Como se dice? Comida con grasa?*) greasy foods. And if none of this



Adia Kelly (gesturing in photo) provides educational sessions on prenatal care for Spanish-speaking patients.



Kelly is one of four Schweitzer Fellows from the School of Medicine; next year's class of fellows will include eight Pitt med students.

works, she says, the doctor can prescribe something for the nausea.

Having finished the ob/gyn exam and wrapped up their chat with Kelly, the Alvarezes proceed to the office of Cheryl Cappurccini—a BSN and, until recently, a case manager for the center—who schedules their next appointment; Cappurccini is also a fluent speaker. We'll see you again December 28th, she says.

"*Es todo?*" Mrs. Alvarez says. (That's it?) Perhaps it's a bit unexpected that the visit has gone so smoothly.

Everyone laughs.

"*Si. Todo!*" Kelly says. "*Chao!*"

Helping to address the health care needs of Pittsburgh's fastest-growing demographic group, Latinos, has been a perfect fit for Kelly. Previously, she'd done service work in Zambia and in Brazil. "That was interesting," she says, "but I know the culture here, and a lot of people from other countries are coming here and need help. So I decided to work with underserved populations in the U.S."

Squirrel Hill Health Center's ob/gyn doesn't speak Spanish, but one in three of the Center's obstetrics patients do. So for her Schweitzer project, Kelly offered to provide educational sessions on prenatal care and also translate as needed.

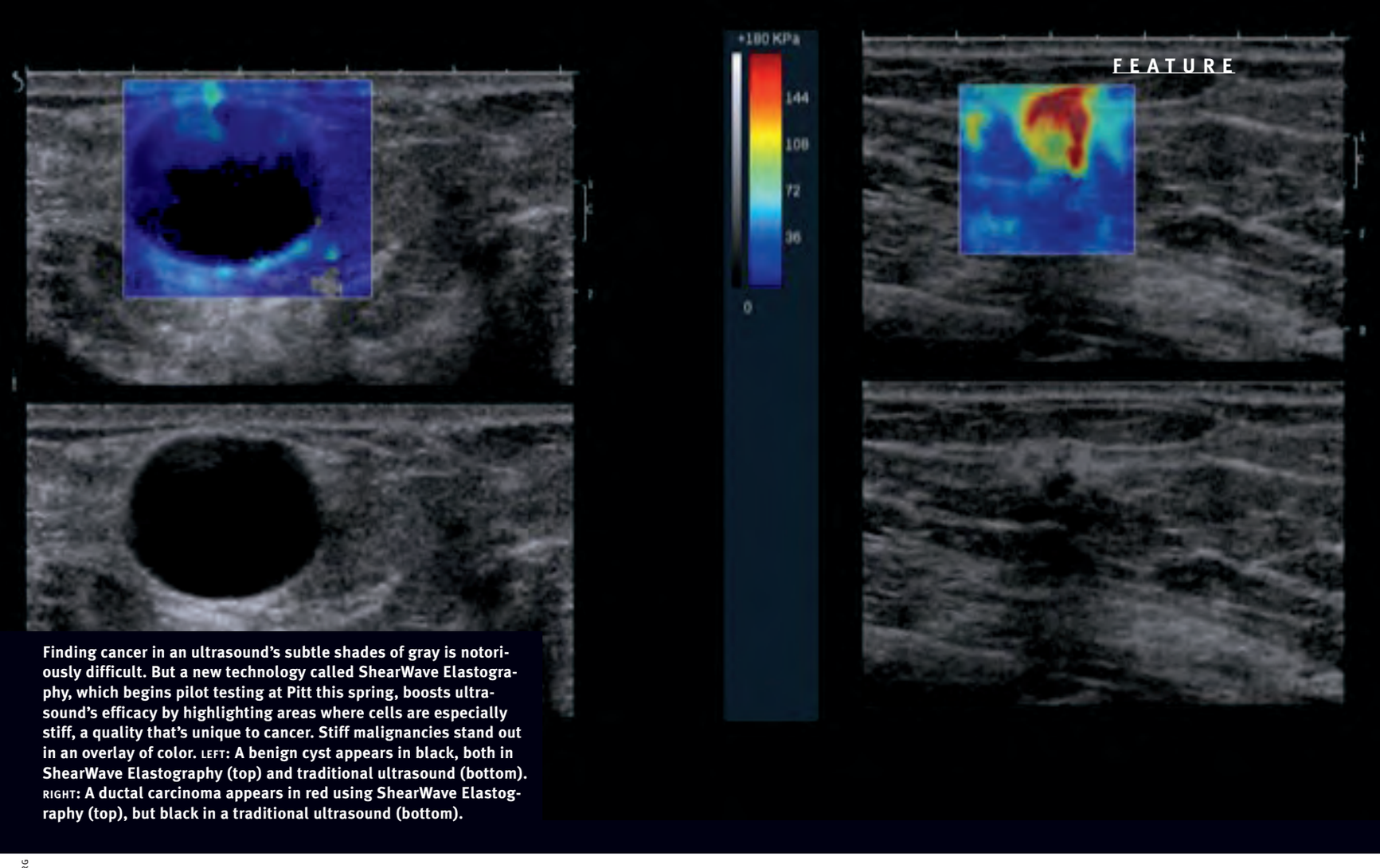
It's a win-win-win. In addition to helping the patients, Kelly is learning all kinds of bonus lessons on prenatal care: For instance, one lesser-known method of predicting Down syndrome is ultrasound—a noninvasive, less expensive alternative to amniotic- or placental-tissue sampling (though it's not diagnostic). Also, if you can't stomach your supplements, chewable children's vitamins go down—and stay down—much easier. And yes, you absolutely must have a car seat in your car, or the hospital won't let you take your newborn home.

"It's been great," Kelly says. "I'm teaching the patients, but I'm learning things, too. And we're doing it all in two different languages."

Around Kelly's neck hangs a nametag on a green lanyard with the words SCHWEITZER FELLOWSHIP in white letters. It was given to her in an initiation ceremony at the beginning of the school year. In attendance were Schweitzer Fellows from previous years, who serve as mentors and motivators, as well as this year's Schweitzers from Pitt's Graduate School of Public Health, School of Nursing, School of Dental Medicine, and School of Social Work. The fellows tend to stay in Pittsburgh—the service year has a way of strengthening ties, building collegial relationships and friendships across disciplines, encouraging roots to grow. The big, burgeoning brood of current and alumni fellows gets together each year—Schweitzer Fellows are considered fellows for life. Next year's 22-member Schweitzer class will benefit from the energy and inspiration of eight Pitt med students, including Veronica Jarido (Class of 2012), who will be an inaugural environmental fellow.

"This experience takes students who came into medicine or health care for the right reasons, and it keeps them glued to those ideals for just a little bit longer," says Fox, joking.

"But seriously. They carry the experience with them wherever they go." ■



Finding cancer in an ultrasound's subtle shades of gray is notoriously difficult. But a new technology called ShearWave Elastography, which begins pilot testing at Pitt this spring, boosts ultrasound's efficacy by highlighting areas where cells are especially stiff, a quality that's unique to cancer. Stiff malignancies stand out in an overlay of color. LEFT: A benign cyst appears in black, both in ShearWave Elastography (top) and traditional ultrasound (bottom). RIGHT: A ductal carcinoma appears in red using ShearWave Elastography (top), but black in a traditional ultrasound (bottom).

COURTESY W. BERG

LESSONS IN SURVIVAL

BREAST CANCER RESEARCH HAS PAVED THE WAY FOR RESEARCH ON OTHER CANCERS, BUT WE STILL HAVE MUCH TO LEARN ABOUT THIS HEADLINER.

BY ELAINE VITONE

Pink isn't just for ribbons any more. There are breast cancer–awareness batteries, rugby balls, even buckets of chicken. In the past 25 years, the efforts of the Susan G. Komen for the Cure Foundation and many others have succeeded in far more than destigmatizing the disease—they've made the fight against breast cancer a headliner. Today, our understanding of breast cancer surpasses that of all other common cancers. Screening and treatment continue to improve, and the research dollars keep coming. The vast majority of women diagnosed with breast cancer in 2011 will survive it.

It can seem inequitable at times—you don't see, for example, M&Ms repackaged in teal, the official color of breast cancer's rarer yet far more lethal sister, ovarian cancer. But those suffering from such so-called "orphan diseases" stand to gain from the rosy renaissance, too. Breast cancer is a trailblazing sort of disease. The more we discover about it, the more clues we gather about how molecules can mutiny to form tumors throughout the body—and how to stop them.

Of course, anyone who's been affected even tangentially by breast cancer will tell you we have a long way to go. Each year, it kills more than 40,000 women, 18 percent of whom were diagnosed during their 40s. Additionally, confusion abounds about how best to screen for breast cancer (more on that later). Nonetheless, it's far and away the cancer that's closest to becoming a chronic disease.

"I have to give the surgeons credit for this," says Adam Brufsky, professor of medicine and codirector of the Comprehensive Breast Cancer Center at Magee-Womens Hospital and the University of Pittsburgh Cancer Institute (UPCI). "Many years ago, surgeons here in the Pittsburgh area realized that this is a multidisciplinary disease that they couldn't take care of alone."

Namely, Brufsky credits Bernard Fisher (MD '43), Pitt Distinguished Professor of Surgery, who led the first clinical trials for breast cancer. (See our July 2002 story "Bernard Fisher in Conversation" online.) Bothered by the lack of scientific evidence justifying the radical-mastectomy paradigm that ruled the day, Fisher put it to the test and disproved it for good in 1974. Lumpectomy plus radiation, he found, was just as effective as the disfiguring, even disabling surgery that took women's entire breasts and chest-wall muscles.

This February, the American College of Surgeons carried on his legacy in a new study, finding that many women with breast cancer can be spared aggressive lymph-node surgery, as well. Current guidelines state that if any nodes are affected at all, the whole adjacent lot should go—a procedure that often causes devastating, permanent damage to the lymphatic system. But as it turns out, removing just the affected nodes might be enough. And Gretchen Ahrendt, associate professor of surgery at Pitt and director of Surgical Breast Services at Magee, is leading the University's part of a multicenter trial to determine whether more limited lymph-node surgery can be performed in women who received chemotherapy prior to surgery. She's hoping they will be able to offer women a less-invasive procedure with fewer long-term side effects.

Perhaps even more important than Fisher's contribution to breast surgery was his ushering in an era of cross-disciplinary, cross-institutional cancer research. As he launched his landmark trial, he founded the National Surgical Adjuvant Breast and Bowel Project (NSABP), a co-op supported by the National Cancer Institute (NCI). The project is still based in Pittsburgh and includes nearly 1,000 sites worldwide. More recently, Pitt joined the Translational Breast Cancer Research Consortium, a 14-center collaboration chaired by Nancy Davidson, director of UPCI and UPMC Cancer Centers. She is also Pitt's associate vice chancellor for cancer research and professor of medicine.

Brufsky explains that UPMC's medical oncology program in breast cancer started small and has grown steadily since he arrived in the 1990s. In that time, he's studied, among other things, the baffling way that bone-loss-prevention drugs also seem to prevent breast cancer recurrence in postmenopausal women—one of the disease's many enigmas. "We've pushed our clinical trials pretty far. But we realized we really needed to beef up the basic science part of our group."

As an MD/PhD, Brufsky would have loved to have done it himself, but that wasn't possible with his patient load. He and his colleagues realized that what they needed were people who "lived and breathed" the study of cancer at the cellular level and thought endlessly about how to apply those insights to treating patients. To this end, Pitt and UPMC have recently brought on a number of new recruits, beginning with Davidson, who joined UPMC two years ago. "They're the missing piece of our program that's really going to take us to the next level," says Brufsky.

In recent decades, we've learned that breast cancer is not one disease, but several—one for each specific biological misstep that can turn breast tissue into a hospitable home for tumors. Heterogeneity is proving to be the case in other cancers as well and is perhaps the most powerful example of breast cancer teaching us about cancer biology in general.

Some breast cancer cells have nuclear molecules that bond to and react with estrogen—they're estrogen-receptor (ER) positive, that is, dependent on estrogen to grow. Starting in the late '70s, Fisher conducted groundbreaking studies on tamoxifen, the first cancer treatment to exploit a biological vulnerability. It is still widely used.

Sixty percent of breast tumors are ER positive and can be treated with this life-saving drug. But puzzlingly, two-thirds of those become resistant to tamoxifen.

STAGS TO RICHES

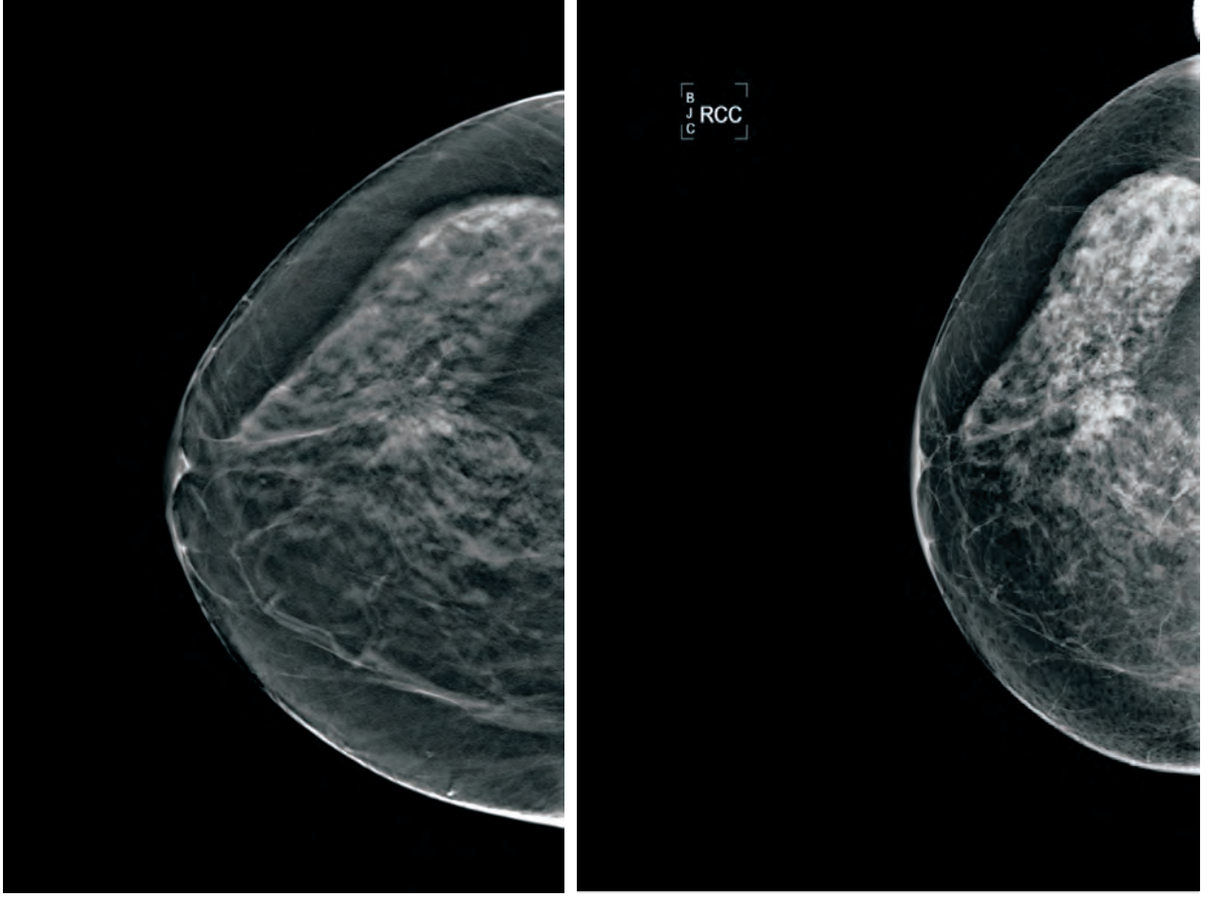
Modern cancer therapy got its humble start more than a century ago in a dairy stable in rural West Scotland. George Beatson, a physician-in-training, was on an extended house call, and on his down time he worked on his MD thesis—a lactation study—using the animals on the patient's estate. Beatson learned that in some countries, farmers removed the ovaries of their cows after calving, a procedure that left them producing milk indefinitely. *This fact seemed to me of great interest*, he wrote, *for it pointed to one organ holding the control over the secretion of another.*

(Similarly, he noted, if a stag loses his left testicle, his left horn ceases to grow.)

Beatson figured that the reason some women's breast cells turn cancerous must be that their ovaries told them to. So, years later, he tried removing the ovaries of two women who had breast tumors, and the disease quieted down. Following Beatson's 1896 paper, physicians adopted ovariectomy for the treatment of breast cancer, and the procedure remains in use for this purpose today.

Only now we know who might benefit from it and who won't.

"When I look into the future, tomosynthesis is [the new] mammography."



COURTESY M.L. ZULEY

For several years, Pitt has been testing digital breast tomosynthesis (DBT), a new imaging technology that received FDA approval this February. Instead of two, two-dimensional images of the breast seen in mammography, DBT creates dozens of higher-resolution, three-dimensional, images—one-millimeter slices of the breast—which radiologists can glide through with the slide of a computer mouse. Here, DBT (left) shows the irregular margins and spicules of the cancer more clearly than the standard mammogram (right).

"We don't know why," says Steffi Oesterreich, a PhD visiting professor of pharmacology and chemical biology. "That's one of the questions we want to answer."

Oesterreich's lab is using cellular techniques, mouse models, and specimens from UPMC's sizeable tumor bank to better understand this particular breed of hormone-hungry tumor.

Adrian Lee, Oesterreich's husband and visiting professor of pharmacology and chemical biology at Pitt, helped to classify another breed. It's fueled by insulin-like growth factors (IGFs), chains of amino acids that regulate glucose levels. Lee has had promising early clinical trials of a drug that targets this mechanism, and he's now working to refine a second-generation version.

Oesterreich and Lee met in the lab of William McGuire, who headed the top U.S. breast cancer translational-science group in the 1980s; it was based at the University of Texas Health Science Center, San Antonio. The group then moved to Baylor College of Medicine in Houston, where Lee and Oesterreich spent 10 years at Baylor's renowned Breast Center. They also helped establish a translational biology and molecular medicine program there. Oesterreich hopes to establish a similar program here at Pitt.

Last year, the couple was recruited for the launch of the Women's Cancer Research Center, a joint venture of UPCI and Magee-Womens Research Institute. Lee codirects the center with Robert Edwards (MD '84), professor and vice chair of the Department of Obstetrics, Gynecology, and Reproductive Sciences at Pitt; Oesterreich is the center's director of education.

Another especially aggressive subgroup of breast cancer feeds on a protein called human epidermal growth factor receptor 2 (HER2), which plays a role in cell growth and differentiation. Some 15 to 20 percent of breast tumors are HER2 positive. Most of these patients respond to the popular drug trastuzumab (the brand name is Herceptin), which targets HER2.

Before coming to Pittsburgh from Johns Hopkins, Davidson began pursuing the first drug that targets what are called the epigenetics of breast cancer, which she's shown to be implicated in trastuzumab resistance. Epigenetics are the nongenetic factors that interfere with gene expression. Davidson now continues this work with Pitt's Yi Huang, an MD/PhD research assistant professor, in collaboration with colleagues back at Hopkins. They've won several grants, including one from Stand Up to Cancer. It's a "very high-profile, Hollywood sort of grant," she says—it's funded by the Entertainment Industry Foundation.

About 20 years ago, scientists learned that mutations in BRCA1 and BRCA2, two genes involved in DNA repair throughout the body, increase the risk of cancer of the breast and ovary, as well as certain types of skin and pancreatic cancer. But only in these organs and nowhere else. No one knows why.

BRCA mutations foul up the DNA-repair mechanism known as homologous recombination; so the cells resort to their plan B, which, in this particular case, is what's called base excision repair. This repair mechanism makes use of a protein called PARP (ADP-ribose polymerase), which helps to ensure a cell's normal cycle of life and death. Unfortunately, the products of plan B are not always so good at the dying part.

Shannon Puhalla, assistant professor of medicine at Pitt and breast oncologist with Magee-Womens Cancer Program, is conducting a series of clinical trials of ABT-888, a drug designed to treat cancer in people with BRCA mutations. By blocking PARP, it shuts down plan B. Instead of replicating their

DNA again and again unchecked, the cells die like they're supposed to.

Puhalla's team started with a study that treated patients with BRCA mutations with ABT-888 alone. About 40 to 50 percent had responded to a similar drug; it's too early to say how effective ABT-888 is. They're also working on five phase I trials for ABT-888 plus chemo (looking for the best regimen and dosage), which includes trials for patients with pancreatic, lung, ovarian, and bladder cancers. In addition, they are conducting the first-ever trial of the effect of ABT-888 plus chemotherapy on women who have what are called triple-negative breast tumors, which are molecularly similar to tumors with BRCA mutations.

Triple-negative breast cancer is the disease's great unknown. It does not have receptors for HER2, ER, or progesterone receptors (PR). For these patients, who account for 15 to 20 percent of all breast cancer cases, there are no biologically based therapies, no options other than chemotherapy. Cruelly, in addition to being difficult to treat, triple-negative breast cancer is the most aggressive form of the disease.

So far, it appears that about 28 to 38 percent of the team's triple-negative study participants are responding to the drug.

Puhalla came to Pitt because of "all the good people who were already here," she says. "And the fact that Dr. Davidson, a world-class breast cancer researcher, and now Adrian and Steffi have come here since then, that's reinforced the fact that this is a great place to study breast cancer. And I'd heard wonderful things about Dr. Egorin, too, but I didn't realize what a wonderful impact he'd have on my career until I got here."

Merrill Egorin, former codirector of the Clinical Pharmacology Analytical Facility at UPCI, led the phase I program before his death last August. Because of Egorin's expertise in pharmacology, in spring 2008 the National Cancer Institute (NCI) had sought his help in developing new drugs through the Cancer Therapy Evaluation Program.

Puhalla recalls, "He used to have a saying: 'Our job is to be rich and famous'—rich enough in terms of grant funding to do the research you want, and famous from publishing your work and helping patients." Puhalla had been at Pitt for about six months when Egorin called her, told her about the good news from NCI, and asked whether she'd come onboard. "He said, 'Do you want to be rich and famous?' and I said, 'Of course.'

"What's great about phase I research is that these drugs and concepts either work or they don't, but either way you learn something about cancer."

READY FOR A CLOSEUP

If you have a mammogram, there's about a 10 percent chance your doctor will need to clarify the results with more imaging tests, such as an ultrasound or MRI (magnetic resonance imaging). In that event, there's a 15 percent chance you'll be called back in for a biopsy. And if you have a biopsy, there's a one in five chance it will confirm that you have cancer.

In November 2009, the U.S. Preventive Services Task Force (USPSTF)—a panel of independent experts in breast cancer prevention appointed by the U.S. Department of Health and Human Services—released new recommendations for breast cancer screening. The panel recommended against screening mammography for healthy, symptom-free women in their 40s.

For breast-imaging specialists, the idea was appalling; USPSTF itself acknowledged that breast cancer is a leading killer of 40-something women, and regular mammograms significantly reduce risk. After a weeks-long firestorm, the task force tweaked its language, advising women to speak with their physicians, consider their family histories and general health, and decide for themselves. Still, confusion persists in both the medical and lay communities.

USPSTF had used statistical models to compare potential harms of annual screening against potential benefits. They concluded that regular mammograms should not be routine until age 50; the incidence of breast cancer rises with age. But even then, USPSTF found, these women need only screen every other year—tumors grow more slowly as women age. With biennial screening, women 50–74 could still get most of the benefits of this test, while their false-alarm biopsies would be cut in half. (For women 75 and older, the task force found the data insufficient to draw any conclusions.)

"I understand the point they were making," says Margarita Zuley (MD '91, Res '96, Fel '97), visiting associate professor of radiology at Pitt and director of Breast Imaging at Magee-Womens Hospital of UPMC. Yet, "I don't know that we should reissue guidelines based on a statistical model when we have population-based studies showing real survival rates that are higher with annual screening."

Some cancers are biologically bound to follow a swifter and deadlier course. For the small subset of women with aggressive, fast-growing tumors, USPSTF stated, even annual screening is not likely to confer a survival advantage.

The problem with that reasoning, says Zuley, is that there is still no way to be sure who will fall into that category. Until there is, she says, "we are still recommending annual screening mammography for everyone 40 and over"—a recommendation that's been steadfastly supported by the American Society of Clinical Oncology and others throughout the debate.

So, what if screenings were more accurate?

In mammography, low-dose X-rays are used to create two, two-dimensional, black-and-white images of the breast, with all of the tissues overlapping. Fatty tissue appears darker. Tumors and their byproducts—little specks of calcification—appear much lighter, but unfortunately, in about half of women, so will much of their breast tissue, because the cells of their breasts are much closer together. To make matters worse, dense breast tissue is significantly more cancer prone.

"The task force downplayed [screening],

There are other challenges: Lighter areas also mark benign lumps, cysts, and fine ducts where the seeds of cancer can hide. Looking for tumors in a mammogram has been likened to hunting for a polar bear in a snowstorm.

On the first morning of spring, Zuley and Breast Imaging Research Coordinator Linda Lovy demonstrate digital breast tomosynthesis (DBT)—a technology recently approved by the FDA that Pitt has been testing for the past

few years—using a gelatinous model breast, "Betty" to her friends. DBT is similar to computed tomography (CT), but involves only a partial rotation around the patient rather than a full 360. Once Betty is compressed and ready for her closeup, we stand behind a leaded piece of glass in the corner of the room where a touchscreen is set up. Lovy initiates the X-ray tube, and it starts to beep, snapping 15 images as it glides along an arc over Betty. Next, the software compiles the images to produce dozens upon dozens of two-toned images representing one-millimeter slices of our patient.

Before Betty is unsqueezed, the scanner quickly switches filters and snaps two mammogram images, too—it's designed to allow researchers to compare these technologies. But there's hardly a comparison, Zuley explains later as she opens a real patient's files in an office across the hall. Sliding her mouse, she takes a virtual tour through the woman's breast, pointing out knobby, irregular shapes and other hallmarks of tumors.

All of this detail, but with only about the same, low radiation dose as a mammogram.

Zuley and colleagues Jules Sumkin (Fel '86)—a DO, chief of radiology at Magee, and professor of radiology at Pitt—and David Gur—an ScD and professor of radiology at Pitt—have shown that DBT reduces recall rate. Right now, it's used only as a second-line technique, but Sumkin is optimistic that will change. "When I look into the future, tomosynthesis is [the new] mammography."

DBT was just approved by the FDA for clinical use this February, and Pitt is well positioned to bring it to the region. Zuley says, "We probably have more experience with [DBT] than anyone else in the country."

CT scans aren't generally used for breast imaging—the radiation level is too high. But recently, the team acquired a prototype unit that's designed for the breast—it's called cone-beam CT, or CBCT, and it uses the same low radiation dose as a mammogram. This technology shows not only the anatomy of the organ, but also its functional activity—invaluable data normally available for breast imaging only through an MRI. But CBCT does the same job with what will likely be a smaller price tag and footprint, to boot.

With grants from the Shapiro and Komen foundations, the team is working on a blind study of biopsied cases, measuring their detection accuracy using CBCT, MRI, tomosynthesis, mammography, and ultrasound.

Yet another budding technology coming to Pittsburgh is a new-and-improved version of ultrasound, thanks to Wendie Berg, professor of radiology, who joined the School of Medicine in March.

Right now, ultrasound is the most-common additional test to follow a mammogram. It uses sound waves to image tissues subtly differentiated in shades of gray. A lot of the shadowy shapes that imagers worry about in these scans are later proven harmless in a biopsy. But this unit will include an extra measure to make things easier: elasticity. Most cancers are much stiffer than benign masses. If any abnormally stiff areas are in the ultrasound wand's sight, it will appear on the screen in an overlay of color.

Berg expects to begin implementing ShearWave Elastography and supplemental screening with ultrasound in women with dense breast tissue in the near future. Before Berg moved to Pittsburgh, she reviewed cases and results of a multicenter, multinational trial for the technology's developer and was very encouraged by its potential.

but that's like telling an ostrich to put its head in the sand."

"There are lots of reasons to be optimistic," says Berg. "The task force [USPSTF] downplayed [screening], but that's like telling an ostrich to put its head in the sand. There's no reason to stop looking. I think what we should be doing is demanding better of what we do right now.

"We can do a lot better—and should."

For a peek at cone-beam CT, see this Web Extra:
http://pittmed.health.pitt.edu/Summer_2011/web-extra.htm.

SISTER ACT

On March 16, 2007, DeDee Rawlins, an RN from Bridgewater, Mass., learned that the enlarged ovary she'd been worrying about for months was no fibroid. This was before Rawlins, who was adopted, tracked down her biological father's family and learned they had all the hallmarks of BRCA mutation. She was diagnosed with stage 4, grade 3 ovarian cancer.

It's an orphan disease, but, fortunately, it has a very powerful sister in breast cancer.

After her surgery, Rawlins spent years on various biologically based therapies and chemotherapies, and though she was able to quell the tumors' growth, the side effects were too much: nausea, high blood sugar, numbness, joint pain, and hypertension at potentially fatal levels.

She desperately wanted to get on a PARP-inhibitor trial—she'd done her homework and was impressed by its success in breast cancer patients—but she didn't quite fit into the criteria of any of the studies in her area. She was looking at straight chemo or nothing.

And then she found Shannon Puhalla.

Last October, after completing her qualifying physical for the study, Rawlins began a series of trips to Western Pennsylvania for her new regimen. By the holidays, a scan confirmed that both of her masses were shrinking and absorbing less dye. "Which means those cells are dying," she says. "It was a fabulous Christmas present."

The kindness of her new friends in Pittsburgh, which she calls her second home, has been overwhelming—the manager of her hotel cried for her good news. "Everyone is so nice," she says. "I don't know what you guys eat for breakfast."

On this treatment, Rawlins' cancer continues to shrivel, and her side effects are minimal: occasional pain, nausea, fatigue, and odd cravings for pickles. But for the most part, she's living a normal life, even helping out in her son's law office. It's almost as though she's merely maintaining a chronic disease.

"I forget I have cancer," she says. ■



HOW TO NAVIGATE THE MAZE OF DRUG DISCOVERY

BY REID R. FRAZIER

THE LABYRINTH

Pick a disease, any disease. Head and neck cancer? Fine.

Let's say you have a pretty good idea about its major mechanisms. You know one or two of the thousands of proteins inside a cell go "off the tracks," producing cell signals that, unimpeded, will result in a tumor.

How do you stop this from happening?

A logical choice is a drug. Perhaps a pill.

So you look for a chemical compound that will bind to that protein and block the bad signaling pathway from starting up in the first place. It's like slashing the tires of cancer's getaway car before it has left to rob the bank. And this is how many of our drugs work. Statins, the most lucrative drug class in the world, bind to an enzyme that produces cholesterol.

PHOTOGRAPHY | JIM JUDKIS

The Drug Discovery Institute is "embracing the complexity of life, not running from it," with models like zebra fish. By the way, Pitt has up to half a million of these transparent swimmers in its research reservoir.

There are more than 1 billion known chemical compounds, and 25 million of these are kept in vast chemical libraries owned by pharmaceutical companies. About 25 years ago, drug makers began screening millions of these compounds for "hits" on various biological targets—usually enzymes and other proteins critical in the pathogenesis of a disease. Thanks to robots that could fill hundreds of microtiter wells in a few minutes, large-scale testing became the industry standard. This method is called high-throughput screening. The idea is to scan as much of the known chemical universe as quickly as possible to find potential drugs. Many new drugs were found in this way.

High throughput is a breakthrough technology, but it's not perfect. The majority of molecules that record "hits" don't become viable drugs. They may be toxic, or will not necessarily interact in a human the way they will in vitro. So, while our ability to find suitable drug candidates has grown, the "pipeline" of promising drugs in development has, if anything, shrunk in the past few years.

This problem has stuck in the craw of D. Lansing "Lans" Taylor for several decades now. In 1982, Taylor, a cell biologist who was among the first to use digital technology, microscopy, and fluorescence imaging, started up Carnegie Mellon University's Center for Fluorescence Research. A few years later, he began consulting with a handful of pharmaceutical companies. He'd never seen how drug discovery worked. "I was appalled," says Taylor. "I thought the pharmaceutical industry had over-industrialized and simplified the process, reducing the human being to isolated proteins in wells."

Taylor thought that, in their rush to do rapid screens for new drugs, big pharma had missed an obvious, critical point: There's no drug that interacts with only one molecular target. Most interact with many, in ways that scientists are only now beginning to understand.

To Taylor, the answer was to find out what the chemical was doing not just to the particular target protein, but to the whole cell, or a group of cells. In essence, to get more and better information about the drug's effect on the animal up front.

To do this, he thought, drug discovery needed better tools, and he coined the term "high content" screening to describe the process. The concept was to test a drug not just against an isolated, purified protein, but inside a cell, or a whole organism, and report the drug's effect with as much detail and specificity as possible. This took longer than a screen built for speed, but it could help make better decisions about how to order research priorities. Taylor left Carnegie Mellon in 1996 to start a series of biotech companies that used fluorescence to look at drug interactions more deeply. In so doing, he changed the way experimental drugs are investigated.

After a decade and a half away from the academy, Taylor took the helm of Pitt's Drug Discovery Institute in November 2010. Founded in 2006, the institute has been one of about a dozen academic high-throughput screening centers around the country. But in recent years, its researchers in biomedicine, public health, pharmaceutical science, and chemistry have made significant inroads into the kind of high-content areas Taylor has been espousing for a quarter century.

"The old paradigm was one drug, one target, one disease," says Pitt's Ivet Bahar, John K. Vries Professor and chair of computational and systems biology and a Drug Discovery Institute associate director. "You look for a specific drug targeting a specific protein. It's widely understood this paradigm is invalid."

Drug discovery is more complicated than that. It's not a hill to climb, nor a path to follow. It's a labyrinth. Taylor wants to navigate it. He thinks Pitt is the place to do so.

IN THE FISH LAB

At 3:30 on a brisk winter afternoon, it is time to look at the zebra fish. A research assistant in Michael Tsang's developmental biology lab pulls four plastic trays wrapped in heavy duty aluminum foil out of an incubator the size of a mini-fridge. Inside the trays are 96 shallow wells. Each well is filled with day-old zebra fish embryos, each treated with a different chemical compound. The fish have fluorescent tags (green fluorescent protein) from jellyfish embedded in their DNA. The transgenic fish make the fluorescent protein in response to fibroblast growth factor, or FGF. FGF is implicated in a number of important biological pathways, including wound-healing and cancer. Tsang is looking for a drug that will ramp up FGF to aid with healing in heart patients. His test: Wherever an embryo expresses FGF, its will fluoresce under UV light.

Zebra fish are a valuable model. For starters, their eggs are fertilized outside of the mother, enabling researchers to take control of embryos a few hours old. They share 70 to 80 percent of their genetic makeup with humans, and they develop many organs within 24 hours of fertilization. So Tsang can do a high-content drug screen on the embryos in a reasonable amount of time. (Another similarly elegant and helpful model is *C. elegans*, the tiny nematode. It's helping Pitt pediatric researchers look at ways cells clean up toxic proteins in an effort to prevent cellular necrosis.)

A few years ago, Tsang's screening of zebra fish showed a chemical called BCI increased FGF activity. Since BCI proved to be toxic at higher levels, he's been searching for other FGF promoters. So he's been putting hundreds of chemicals into the wells every week, looking for some light. On this afternoon, Tsang's research assistant, Manush Saydmohammed, takes the trays up a few floors to a room inside the Drug Discovery Institute in Pitt's Biomedical Science Tower 3. The trays go inside a fluorescence laser scanner, and a few minutes later, the first zebra fish embryo appears in black and white on a nearby monitor. The embryo consists of a yolk and the beginnings of a fish body starting to grow around it. Magnified, it looks like a shrimp trying to crawl on top of a pea. A pair of bright white areas show up on the scan: one at the larva's eye, another a little further back, toward the dorsal area. This is the fish's mid-hind brain. In both areas, the fish is expressing FGF.

The scanner records images from all 96 embryos. Each image will be analyzed by an algorithm Tsang and his collaborators designed to quantify FGF expression. In some of the wells, the embryo is nothing more than a gray shadow, a likely sign that the compound was toxic. In one of the screens, a larva has spots as bright as those of its BCI-laced brethren.

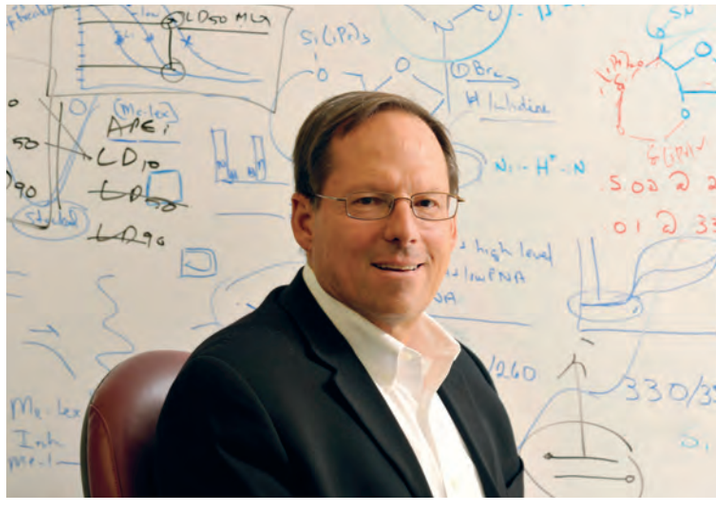
"That's positive," Saydmohammed says.

When Tsang pops into the room a few minutes later, Saydmohammed tells him, "We found one that looks like a hit."

"As much as BCI?" Tsang asks. Tsang has a look of pleasant surprise. It could be promising, but Tsang knows that the experiment will have to be duplicated. If, indeed, it is a potent FGF promoter, a whole new chapter in the work of creating a drug begins.







The University of Pittsburgh's Drug Discovery Institute leadership team includes D. Lansing Taylor, its director (in red tie), and associate directors (clockwise from left) Ivet Bahar, Peter Wipf, Barry Gold, and Edward Chu (not shown).

THE TRIAL AND ERROR OF OUR WAYS

Of an estimated 320,000 plant species on Earth, perhaps as many as 25,000 have been used for some type of folk medicine. Plants were a mainstay of drug discovery for much of human history, usually involving a process of trial and error. Scientists began isolating different plant and mineral chemicals, but finding ones that are safe in humans was remarkably difficult. Only about 120 plant-derived chemicals are in use around the world today.

Plants produce many of their chemicals as toxins to ward off predators. Minerals, another source of early medicine, are seldom able to penetrate the body's biological membrane barriers. Those that do are often highly toxic. Modern imaging, chemistry, and genetics have made drug discovery—whether through plant- and mineral-derived or synthetic compounds—much, much faster, but the process remains riddled with pitfalls.

To be both effective and safe, a molecule must be somewhat water soluble, have suitable places for hydrogen bonds to form, and be small enough and the right shape to "squeeze" into the archipelago of structures on a protein. If a compound isn't metabolically stable, the body will degrade it before it has a chance to reach its cellular target.

"You're talking about many years of optimization, follow-up assays, animal models," says Pitt's Peter Wipf, a Distinguished University Professor of Chemistry with a joint appointment in pharmaceutical sciences and chemistry. "You have to study pharmacodynamics, pharmacokinetics, toxicity, metabolism, absorption, solubility, formulation," before you can think about putting it into humans.

"It is an extremely complex pipeline," says Wipf, who is director of Pitt's Combinatorial Chemistry Center, as well as an associate director of its Drug Discovery Institute. "In fact, it's not really a pipeline. It's more like a maze of different possibilities."

The time between when a compound produces a "hit" on a large chemical screen and when it gets tried in humans is what Barry Gold, professor and chair of pharmaceutical sciences, affectionately calls "the Valley of Death." Gold is a Drug Discovery Institute associate director along with Wipf, Bahar, and Edward Chu, a professor of medicine and deputy director of UPCI.

"Chances of success," Gold admits, "are low. We can't really predict toxicity accurately. Small changes to a molecule can have major changes to its activities." A small methyl group, for instance, can alter the shape of a molecule and, therefore, its activity.

Advanced computational analysis of DNA, molecular and protein structure, and polarity help rule out some types of compounds, but most must be tested either in vitro or in vivo.

Ongoing research in Gold's academic home, the School of Pharmacy, focuses on metabolic stability, predictive models for protein binding, and speeding up ways to synthesize drug compounds. All of these are ways of identifying compounds that may be toxic.

"It's important as early as possible to get that type of information, because you really don't want to be developing a molecule that's going to be toxic down the road in animals," says Gold, whose lab focuses on an inhibitor of protein interactions critical in cancer drug resistance.

Even with the rise of genomics and our new understandings of how proteins work, drug discovery involves one element no scientist likes to rely on: luck. Take the platinum-based cancer drug cisplatin. The biophysicist who found it wasn't looking for a cancer drug. He was studying DNA synthesis in *E. coli* when he observed the bacteria weren't dividing when exposed to a platinum electrode.

"Cisplatin was discovered by pure accident," says Gold. "Someone discovered trace amounts of cisplatinum would inhibit DNA synthesis and induce toxicity. It just came out of the blue."

The researcher who discovered cisplatin may not have been looking for an antitumor agent, but he knew what to do with it once he found it. "In a way, drug discovery is a lot like fishing," says Gold. "A lot of it is luck. But the key in fishing is: Don't fish in vacant waters."

Ivet Bahar is exploring what she believes are bountiful waters.

Bahar is one of the world's leading thinkers in protein biomechanics. Her lab has gained renown for creating computer models for protein movement. Parts of proteins, called domains, can act like spring-loaded door hinges. During cell signaling, they can swing open or slam shut. Each position alters the activities of the protein. In the digital movies she and her collaborators have made to model protein movement, proteins look like balls of yarn and ribbon, bobbing up and down underwater. The models help predict a protein's "druggable sites" for which a chemist can design a compound.

On a recent afternoon, Bahar leaned over a laptop. A video on the screen showed a 3-D, computer-generated form composed of blue and white spheres. It looked more or less like a cloud as seen from an airplane.

"What you see, like a cloud, is the protein, the surface of the protein," says Bahar. The spheres are parts of the protein, colored according to hydrophobicity, polarity, and other chemical characteristics. A series of geometrical shapes jump around the blue and white protein quickly, kind of like Mexican jumping beans. These are small molecules interacting with various sites on the protein.

Among the proteins of interest to Bahar's lab is DUSP6, which Tsang is trying to block because it inhibits FGF expression. Bahar's lab is helping Tsang model the protein and find out what molecules are most likely to interact with it.

When he analyzed a crystallography image of Tsang's protein, Bahar's postdoctoral fellow, Ahmet Bakan, created a dynamic model of the protein. The model revealed that Tsang's FGF-promoter and drug candidate, BCI, made for a pretty weak binder. The model predicted another site where a much tighter bind could occur. Tight binds are preferable, because they increase the chances that a compound will only bind to that site, rather than other, "off-target" sites. This results in fewer side effects.

Bahar says her group can predict internal motion in a protein in the same way one can predict how a door hinge or human elbow moves. "These are motions that the structure favors. Its structure has evolved to favor particular motions that are needed for its function," she says. "This is evolutionary selection."

BUILDING A (DRUG) SEARCH ENGINE

Taylor arrives at Pitt as the world beneath drug discovery is shifting. Big pharma's drug pipelines are thinning, and the industry faces a "patent cliff" as many of its blockbusters are soon to go off patent. Consequently, the industry as a whole has started to scale back, laying hundreds of thousands of employees off around the world. National Institutes of Health funding isn't likely to increase for research that feeds drug discovery anytime soon, Taylor reckons. He sees partnerships between academia and the private sector as necessary in drug discovery.

He is quick to point out there are caveats—the University needs to maintain academic autonomy, avoid conflicts of interest, and recoup an equitable share of any proceeds from drugs developed in its labs. "I think it's important we not just become the front end of a pharmaceutical company," he says.

Each side, he says, stands to gain from such an arrangement. Industry can gain expertise in basic biological sciences. Academia can gain access to the industry's vast chemical libraries, equipment, and money.

Taylor's own experience gives him a unique vantage point from which to view the academic-industry divide. Taylor says he caught "the entrepreneurial bug" while at Carnegie Mellon. In 1996, he left that university to start a biotech company called Cellomics. The company made imaging equipment, imaging software, information management software, and reagent kits for the high-content screening Taylor thought crucial to drug discovery.

This was during the height of the push for high-throughput screening, and Taylor's ideas were met with doubt. "Always in the front row, somebody from the screening facility would say, 'What's the throughput? How long does it take to read?'" The first generation of his screening tools was slow. He told the lab folks it would take 25 minutes to measure a 96-well plate. A high-throughput system took less than a minute. People walked out in the middle of his presentations, Taylor recalls.

But he persisted, and Cellomics was eventually successful enough that it was acquired by Thermo Fisher Scientific.

"I always thought he was a visionary," says Alan Waggoner, whom Taylor recruited to Carnegie Mellon to start its fluorescence research center. "He could see things that could be done with fluorescence detection way ahead of a lot of people—sometimes before it was really practical." (Taylor and Waggoner started Biological Detection Systems in the early 1990s; it is now part of GE Healthcare.)

Taylor's ideas about fluorescence originated when he was a grad student in the 1970s under the famed microscopist Robert Allen at the State University of New York–Albany. Taylor was interested in cell movement. He thought fluorescence could help study this. He stuck fluorescent dyes on proteins involved in movement and watched them under ultra-low light conditions.

"The first image (created in 1974) was from a recently declassified night-vision camera I got from the military," Taylor says. He also began linking cameras to computers, allowing his lab to quantify what the camera saw.

Taylor went on to found a total of three companies based on high-content concepts. His career as an entrepreneur was rewarding, yet he decided to re-enter the academic world last year.

"I want to take some risks here and do some things in academia that pharmaceutical [companies] can't afford to do now," he says. "We're taking this concept of complexity a step further. We're embracing the complexity of life, not running from it."

"I think everyone realizes what we need to do must have practical value and not be just a bunch of neat science," notes Gold. "That's what we're trying to do—to get a drug out." ■



JIM BURKE/CIDDE

Adeola Sadik will go to Massachusetts General Hospital for anesthesiology.

MEET YOUR MATCH

THE ENVELOPES … PLEASE!

TWO PERSPECTIVES ON A VERY BIG DAY

The lecture room in Scaife Hall is buzzing like a nightclub and bumping with bass as the Black Eyed Peas croon *I've got a feeling that tonight's gonna be a good night.* Snapshots of the Class of 2011 flash across the screen, bringing laughter, shouts, and cheers from the actual members of the class, who swarm the aisles. They are glowing, as though lit from within. They embrace, slap hands. Handshakes are firmer than usual. Quiet, knowing nods and pats on the back are pregnant with meaning. It's Match Day. Time to meet the oracle.

Across the nation, more than 22,000 new physicians are poised to learn where they will begin their residency training on this day. Prolonging the suspense here at the University of Pittsburgh School of Medicine's Scaife Hall is Joan Harvey, associate dean of student affairs. *Two-thirds of you,* she says to applause, *matched at top-tier programs (per* U.S. News & World Report's *rankings). … This year the Harvard programs, the University of Washington, Vanderbilt, and Michigan head up the list of other institutions*

(besides our own prestigious UPMC) which will be most populated by our students next year, with Duke, Brown, and Yale close behind.

Encouraging news, but it's all this crowd can do to keep from shouting, "The envelopes, please!" There are babes in arms, couples gripping one another's forearms. Finally, one by one, the members of the Class of 2011 are summoned by Harvey, by Arthur S. Levine, senior vice chancellor for the health sciences and dean of the school, and by Chenits Pettigrew, assistant dean for student affairs.

Cameras flash as students make their way to the front. Attire ranges from nightclub chic to Penguins game day. There are glittering green top hats for St. Patrick's Day. Upon hearing her name called, the owner of a pair of spike-heeled boots takes approximately one half her med school career to descend 36 steps from the back of the auditorium. (What's the point of learning your future if you can't look stunning while doing it?)

Most open the envelope on the spot. Many borrow the mike to share their news.

"I'm staying in Pittsburgh!" someone shouts into the microphone. He commences a vigorous touchdown dance amid a loud ovation and a series of high-fives.

One student reads her letter and pitches forward as she clutches at her throat. She looks at the paper in her hand again, takes the mike, and says, "Massachusetts General Hospital." A student discharges a can of spray confetti indiscriminately as his classmates climb the stairs to their seats holding their letters.

In the back of the hall, a salt-and-pepper-haired doctor stands surveying the scene and grinning. He applauds vigorously each time another fourth-year says, "Pittsburgh!"

Some approach the stage like boxers entering the ring. One quietly sneaks back up the stairs with her still-sealed envelope in hand. A questioning look from a friend causes her to shake her head and mouth, "Not yet." She exits the auditorium. Minutes later, she's back with a grin and a thumbs-up.

One student looks up from her letter and says, "Mom and Dad, I'm coming home."

And that's all you need to know about what's happening here. Classmates are hugged, supported, and caught as they stumble in their emotion. Nobody falls down here. Some will swear their feet never touched the ground.

A woman says, "Radiology at UCSF" into the microphone, then seems to bite her finger in an attempt to hold it together long enough to make it up the stairs to row 14 and pick her way to the middle. She runs a gauntlet of hands—guiding, lifting, reaching out to say, *We're here with you*—until she finally reaches husband and child and dissolves into tears as she is wrapped in the crushing embrace of her future.

—Chuck Staresinic

NO ROMANCE

DOES HER PROGRAM LOVE HIM?

Someone told me once that Match Day is like a wedding. On that day, you and your residency program are bound together, for better or for worse, in a ceremony among friends and family.

Yet, as I learned this year, the Match is not the culmination of a fairy-tale love story. The interview season is like speed dating for the pros. I interviewed with more than 200 people from 27 different programs for 15 to 20 minutes each. I traveled to 10 states and 20 cities in two months. There wasn't even a second date or phone call: Communication between programs and applicants is strictly limited between interview and Match Day.

Lucky for me, I have a fairy-tale love story—with my girlfriend, Tarini. But this put me into a love triangle of sorts, because Tarini matched last year in one of the most competitive programs in the country. I love my girlfriend. She loves me. I desperately wanted to be in the same program as she is. But, did her program love me?

As I looked around Scaife Hall's Lecture Room 6 on the day of reckoning, I found that my situation was not uncommon. Match Day may determine the future of our relationships more than our careers.

After interview season, I ranked the programs, and the programs ranked their interviewees. Then, a computer determined my residency program based on a mathematical formula. Soon, I would find out what the computer had spat out. If Match Day is like a wedding, it's an arranged marriage. I felt like I had no control and that my fate was in someone else's hands.

Forty minutes into the Match ceremony, my palms became sweaty. I was hot and then cold. I was anxious. I was happy when my friends' names were called and they learned of their matches. Then, I was jealous that they already knew. *Where was my name?* Finally, I heard it. My heart skipped a beat. But, nope. Just a classmate with the same first name. I got hotter. *Why do we get our match this way again?* This was torture.

Then, I was called.

I tried not to stumble on my walk to the stage. Dean Joan Harvey was smiling at me. *Was it a pity smile?* She knew I was trying to match with Tarini. As I approached Dean Harvey, pure fear raced through my veins. My hands shook, but I was able to grasp the letter and walk to a corner of the auditorium. I took a deep breath. A calm came over me. I knew my hard work would be worth it. I ripped open the envelope. *Why is this letter folded so awkwardly?* I couldn't find the words on the page. Finally, I saw some words. I refocused, glossed over the boilerplate "Congratulations." There it was, my residency location: I'd matched at Tarini's institution for internship and at another strong medical center (on the other coast) for my advanced program. It was not perfect, but I was happy.

I smiled, and my eyes locked with my friends'. These were the people who had pulled me across the finish line. One had played Rock Band with me for hours to help me relax after a bad day in the hospital. Another had accompanied me on a 1 a.m. trip to the ER for a simple paronychia during board studying. They knew my deepest fears and my greatest dreams. They were family. I hadn't said a word, yet they knew how I felt. They cheered!

This was not like a wedding at all. No church bells. No ritual kiss. Only an aging auditorium and an awkwardly folded letter. There is no good analogy or apt comparison. It's just Match Day.

—Brian Lau (MD '11)

Read another Match story by Brian Lau, on the little-known Scramble: pittmed.health.pitt.edu/Summer_2011/web-extra.htm.

MATCH RESULTS
CLASS OF 2011

ANESTHESIOLOGY
Best, Michael
UPMC/University of Pittsburgh, Pa.
Faulk, Lauren
Univ. of Michigan Hospital
Lee, Christina
UPMC/University of Pittsburgh, Pa.
Nabb, Colin
Beth Israel Deaconess Medical Center/
Harvard University, Mass.
Sadik, Adeola
Massachusetts General Hospital/Harvard University
Shah, Aalap
University of Washington Affiliated Hospitals
Tsui, Becky
Massachusetts General Hospital/Harvard University
Wang, Rachel
Stanford Hospital and Clinics, Calif.
Youngberg, Mark
University of Washington Affiliated Hospitals

DERMATOLOGY
Divito, Sherrie
Massachusetts General Hospital/Harvard University
Pomerantz, Rebecca
UPMC/University of Pittsburgh, Pa.
Yang, Sherry
Henry Ford Health Care System, Mich.

EMERGENCY MEDICINE
Cousar, J'mir
University Hospital/University of Cincinnati, Ohio
De Witt, Benjamin
University of Arizona Affiliated Hospitals
Hougham, Aaron
University of California Davis Medical Center
Lange, Charles
Christiana Care Health System, Del.
Lee, Sean
UPMC/University of Pittsburgh, Pa.
Patel, Dipesh
Harbor-UCLA Medical Center, Calif.
Rajasekhar, Arun
Detroit Medical Center/Wayne State University, Mich.
Staum, Matthew
UPMC/University of Pittsburgh, Pa.

FAMILY MEDICINE
Bemben, Will
Providence Hospital/Alaska Family Medicine
Harbaugh, Matthew
UPMC St. Margaret/University of Pittsburgh, Pa.
Leuenberger, Andrew
UPMC St. Margaret/University of Pittsburgh, Pa.
Lin, Jennifer
Exempla St. Joseph Hospital, Colo.
Ortiz, Veronica
Excela Health Latrobe Hospital, Pa.
Roe, Danielle
UPMC St. Margaret, Pittsburgh, Pa.
Seidel, Ilana
Forbes Family Medicine, Pa.

INTERNAL MEDICINE
Aras, Mandar
Duke University Medical Center, N.C.
Cackowski, Frank
University of Michigan Hospitals
Cheng, Cathy
University of California Davis Medical Center,
Sacramento
Cho, Michael
University of California Irvine Medical Center
Chu, David
Rhode Island Hospital/Brown University
Clark, Alexandra
Duke University Medical Center, N.C.
Dallasen, Renee
Strong Memorial Hospital/Univ. of Rochester, N.Y.
Doan, Daniel
University of Washington Affiliated Hospitals
Donatelli, Christopher
Cleveland Clinic/Case Western Reserve Univ., Ohio
Durst, Matthew
Montefiore Medical Center/Albert Einstein College
of Medicine, N.Y.
Englert, Judson
Brigham & Women's Hospital/
Harvard University, Mass.
Evans, Anna
Yale—New Haven Hospital, Conn.
Fatigati, Nina
UPMC/University of Pittsburgh, Pa.
Hallett, Laura
UPMC/University of Pittsburgh, Pa.
Huynh, Nicholas
University of Southern California,
LAC+USC Medical Center
Kale, Sachin
Ohio State University Medical Center
Kao, Julia
University of California Irvine Medical Center
Kliment, Corrine
Brigham & Women's Hospital/Harvard Univ., Mass.
Kline, Kathryn
Johns Hopkins Hospital, Md.
Komanduri, Paavani
UPMC/University of Pittsburgh, Pa.
Lee, Jonathan
UPMC/University of Pittsburgh, Pa.
Levenson, Joshua
University of Michigan Hospitals
Lo, Nathan
University of Texas Southwestern Medical Center
Morariu, Elena
UPMC/University of Pittsburgh, Pa.
Rivenburgh, Danielle
Ochsner Clinic Foundation, La.
Roberts, Traci
UPMC McKeesport, Pa.
Sriwattanakomen, Roy
Beth Israel Deaconess Medical Center/
Harvard University, Mass.
Tilstra, Jeremy
UPMC/University of Pittsburgh, Pa.
Viccaro, Laura
UPMC/University of Pittsburgh, Pa.
Williams, Gwendolyn
New York Hospital Queens/Cornell University

INTERNAL MEDICINE—PEDIATRICS
Moore, Jaime
Ohio State University Medical Center
Shirilla, Nicole
University Hospitals Case Medical Center/
Case Western Reserve University, Ohio

INTERNAL MEDICINE—PRELIMINARY
Ungar, Allison
University of Massachusetts Affiliates

INTERNAL MEDICINE—PRIMARY
Casas, Rachel
Rhode Island Hospital/Brown University, R.I.
Rauscher, Christine
Bellevue Hospital/New York University

INTERNAL MEDICINE—WOMEN'S HEALTH
Birru, Mehret
UPMC/University of Pittsburgh, Pa.
Sullivan, Sarah
UPMC/University of Pittsburgh, Pa.

MAXILLOFACIAL SURGERY
Bauer, Richard
UPMC/University of Pittsburgh, Pa.
Cudney, Nicholas
UPMC/University of Pittsburgh, Pa.

NEUROLOGICAL SURGERY
Addo-Yobo, Steven
New York Presbyterian–Weill Cornell Medical Center
Atsina, Komli-Kofi
Yale–New Haven Hospital, Conn.
Lee, Philip
UPMC/University of Pittsburgh, Pa.
Zohny, Zohny
Barnes-Jewish Hospital/Washington University, Mo.

NEUROLOGY
Gupta, Vikas
Montefiore Medical Center/Albert Einstein
College of Medicine, N.Y.
Harel, Asaff
Mount Sinai Hospital, N.Y.

OBSTETRICS/GYNECOLOGY
Bregar, Amy
Womens & Infants Hospital/Brown University, R.I.
Brogdon, Linda
University of Tennessee Health Science Center
Fratto, Victoria
New York Presbyterian–Columbia Univ. Medical Center
Joseph, Gail
Sacred Heart Hospital/Florida State University
Kennedy, Margaret
Beth Israel Deaconess Medical Center/
Harvard University, Mass.
Quimper, Megan
UPMC/University of Pittsburgh, Pa.
Racek, Christina
University of Connecticut Health Center

OPHTHALMOLOGY
Abbott, Akshar
UPMC/University of Pittsburgh, Pa.
Way, Amanda
UPMC/University of Pittsburgh, Pa.

ORTHOPAEDIC SURGERY
Eleswarapu, Ananth
University of Chicago Medical Center, Ill.
Greco, Nicholas
UPMC/University of Pittsburgh, Pa.
Jegapragasan, Mithulan
University of Washington Affiliated Hospitals
Komperda, Kazimierz
Temple University Hospital, Pa.
Leigey, Daniel
UPMC/University of Pittsburgh, Pa.
Pan, Tiffany
UPMC/University of Pittsburgh, Pa.
Rayappa, Steven
Albany Medical Center/Albany Medical College, N.Y.

OTOLARYNGOLOGY
Sahu, Nivedita
UPMC/University of Pittsburgh, Pa.
Vosler, Peter *
UPMC/University of Pittsburgh, Pa.

PATHOLOGY
Collins, Ryan
UPMC/University of Pittsburgh, Pa.
McDonald, Thomas *
Beth Israel Deaconess Medical Center/
Harvard University, Mass.

PEDIATRICS
Anetakis, Katherine
Children's Hospital of Pittsburgh of UPMC/
University of Pittsburgh, Pa.
Cosimini, Michael
Children's Hospital Los Angeles, Calif.
Follansbee, Christopher
Children's Hospital of Pittsburgh of UPMC/
University of Pittsburgh, Pa.
Fox, Michael
Children's Hospital of Pittsburgh of UPMC/
University of Pittsburgh, Pa.
Genies, Marquita
University of North Carolina Hospitals
Grant, Abigail
University of Washington Affiliated Hospitals
Harris, Diamond
St. Christopher's Hospital for Children/
Drexel & Temple Universities, Pa.
Holm, Stephanie
Children's Hospital & Research Center Oakland, Calif.
Lopez, Chrissy
University of Michigan Hospitals
Luthy, Sarah
University of Michigan Hospitals
Mehmeti, Anriada
Texas Children's Hospital/Baylor College of Medicine
Meyer, Rebecca
Children's National Medical Center, Wash., D.C.
Ravindra, Anjani
Penn State Milton S. Hershey Medical Center,
Penn State Hershey Children's Hospital, Pa.
Ruffner, Melanie
Children's Hospital of Philadelphia/University of
Pennsylvania
Stevens, Jennifer
Phoenix Children's Hospital/University of Arizona
Taylor, Matthew
Children's Hospital of Pittsburgh of UPMC/
University of Pittsburgh, Pa.
Thomas, Vanessa
Medical College of Wisconsin Affiliated Hospitals
Tkach, Erin
Alfred I. duPont Hospital for Children/
Jefferson Medical College, Del.
Zarit, Jennifer
Children's Hospital of Pittsburgh of UPMC/University
of Pittsburgh, Pa.

PHYSICAL MEDICINE & REHABILITATION
Camacho-Soto, Alejandra
McGaw Medical Center of Northwestern Univ., Ill.
Ramirez, Claudia
Strong Memorial Hospital/Univ. of Rochester, N.Y.

PLASTIC SURGERY
Purnell, Chad
McGaw Medical Center of Northwestern Univ., Ill.
Tuffaha, Sami
Johns Hopkins Hospital, Md.

PSYCHIATRY
Chaiffetz, David
Cleveland Clinic/Case Western Reserve Univ., Ohio
Chou, Justin
Thomas Jefferson University Hospitals, Pa.
Clark, Adrienne
Hospital of the University of Pennsylvania
Cox, Lara
New York University School of Medicine
Drewencki, Laura
Medical University of South Carolina
Faeder, Sarah
UPMC/University of Pittsburgh, Pa.
Kunce, Scott
Jackson Memorial Hospital/University of Miami, Fla.
Nguyen, Caroline
UPMC/University of Pittsburgh, Pa.
Saunders, John
UPMC/University of Pittsburgh, Pa.

PSYCHIATRY—FAMILY MEDICINE
Wong, XiXi
UPMC/University of Pittsburgh, McKeesport, Pa.

RADIATION ONCOLOGY
Rwigema, Jean-Claude
UCLA Medical Center, Calif.

RADIOLOGY—DIAGNOSTIC
Gadwood, Elizabeth
Vanderbilt University Medical Center, Tenn.
Khanna, Vineet
UPMC/University of Pittsburgh, Pa.
Lau, Brian
Yale–New Haven Hospital, Conn.
Raji, Cyrus *
UCLA Medical Center, Calif.
Sheth, Sujay
University of Chicago Medical Center, Ill.
Woodard, Genevieve
University of California, San Francisco

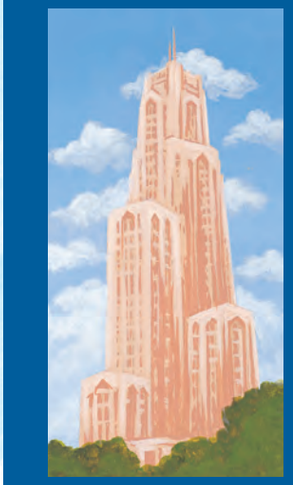
RESEARCH
Scott, Erick
The Scripps Research Institute (PhD Program), Calif.

SURGERY—GENERAL
Craig, Brian
Vanderbilt University Medical Center, Tenn.
Delitto, Daniel
Shands Hospital/University of Florida
Gulack, Brian
Duke University Medical Center, N.C.
Hsieh, Lily
Stony Brook Medical Center and Affiliated
Hospitals/Stony Brook University, N.Y.
Leeper, Christine
UPMC/University of Pittsburgh, Pa.
Lewis, Clayton
Brooke Army Medical Center, Texas
Parent, Brodie
University of Washington Affiliated Hospitals
Stewart, Melissa
Vanderbilt University Medical Center, Tenn.
Waltz, Paul
UPMC/University of Pittsburgh, Pa.

UROLOGY
Jacobson, Deborah
Vanderbilt University, Tenn.
Ogle, Christina
Mayo Clinic/Mayo School of Graduate Medical
Education, Minn.
Ohmann, Erin
New York University Medical Center
Ortiz, Tara
Duke University Medical Center, N.C.

VASCULAR SURGERY
Genovese, Elizabeth
UPMC/University of Pittsburgh, Pa.
Jones, Raquel
University Hospital/University of Cincinnati, Ohio
Teng, Xiaoyi
Cleveland Clinic/Case Western Reserve Univ., Ohio

*December 2010 graduates who participated in this year's match.



CLASS NOTES

'60s

Today, steroid hormones like estrogen and progesterone are targets for treating everything from inflammation to breast cancer. It's difficult to imagine that, as recently as the late '60s, we didn't know what hormones were up to at the molecular level. In 1972, **Bert O'Malley** (BS '53, MD '63) became the first to show that steroid hormones initiate gene transcriptions, regulated by steroid receptor coactivators—molecules that he was also the first to discover. Seeing his contributions to basic science pan out in life-saving clinical developments over the years—like the breast-cancer drug tamoxifen, for example—has been "extremely exciting," says O'Malley. "It's like watching a movie in which you're one of the major actors." In September, O'Malley, the Tom Thompson Distinguished Service Professor and chair of molecular and cellular biology in Baylor College of Medicine in Houston, Texas, will be presented at a ceremony in Berlin with the 2011 Ernst Schering Prize for international excellence in medicine and basic biological and chemical research.

As an advisor to the FDA for 13 years, **Irvin Hirshfield** (Biochemistry PhD '66) developed a taste for food microbiology, so to speak. In his current role—associate professor of molecular microbiology and microbial physiology and genetics at St. Johns University in Queens, N.Y.—Hirshfield studies how bacteria handle environmental stresses like acid and high heat. He has isolated a mutant form of a nonpathogenic cousin of *E. coli* that's extremely tough to kill—1,000 times tougher than the nonmutant, in fact. "We've found some potential reasons why, but more work has to be done," he says. In his preliminary studies, Hirshfield is finding that these mutants behave the same under normal conditions as *E. coli* do in the low-gravity setting of a shuttle mission. And, like *E. coli*, the mutant is "superior" at forming biofilms—sticky aggregates that make all sorts of particularly stubborn infections (e.g., *Staphylococcus*). The possibilities are enough to make a biochemist salivate.



Ciarochi

Throughout the '80s and '90s, **Fred Ciarochi** (MD '69, Endocrinology Fellow '76) served as program director and chief of staff in endocrinology at Dallas' Methodist Hospital, as well as medical director of its Diabetes Management Center. In 2001, Ciarochi launched Project Access Dallas, a nonprofit organization that provides health care services to the working poor and others who cannot afford health insurance. Last year, Ciarochi received the Max Cole Leadership Award from the Dallas County Medical Society, as well as the American Diabetes Association's J. Denis McGarry Award, both in recognition of his volunteer community work.

'70s

For an orthopaedist, **Edwards "Ned" Schwentker** (General Surgery Resident '70) has seen an awful lot of infectious disease cases, namely of what he calls "the working-in-the-developing-world bug." He came down with this bug himself the first time he visited Honduras with a group of fellow health care volunteers in 1995. Schwentker made 26 of these two-week trips to provide treatment for club foot and other childhood deformities, almost all of them with his wife, Bunny Schwentker, who turned out to be a natural volunteer recruiter.

In 2009, the Schwentkers realized a shared dream by founding Hospital de Ortopedia Pediátrica y Especialidades CURE in San Pedro Sula, Honduras, arguably one of the best-equipped orthopaedic facilities in Central America. The hospital has since performed more than 1,100 surgeries. (Just about every one of the residents who has trained there has shown symptoms of The Bug, Ned Schwentker reports.) The experience has been so personally rewarding that he shies away from praise. "In some ways, it's the most selfish thing I've ever done," he says.

Orthopaedics has always interested **Carl Stanitski** (Orthopaedic Surgery Resident '74, Pediatric Orthopaedic Fellow '79), whether he was dealing with his own sports injuries as a teenager or those of the track and basketball athletes he coached in his former life as a high school teacher. In his second career, he's been an associate professor of orthopaedics at Pitt (1980–1991), a team physician for the Pittsburgh Penguins, staff associate at the National Institutes of Health, professor of orthopaedic surgery at the Medical University of South Carolina, Charleston, and chief of orthopaedics at Children's Hospital of Michigan. He has also volunteered for global-health outreach efforts in more than 30 countries. In September 2010, Stanitski and his wife, Debbie Stanitski, were named honorary members of the Polish Pediatric Orthopaedic Society and the Polish Society of Orthopaedics and Traumatology, in recognition of their 15 years of service at American Children's Hospital in Krakow, Poland.

As president of the American College of Emergency Physicians (ACEP), the primary group that represents emergency physicians nationwide, **Sandra Schneider** (MD '75, Internal Medicine Resident '78) is tackling the potentially dangerous practice of "boarding," when inpatients wait in the ER for long periods of time until a bed becomes available in the hospital. "Imagine that people come into your restaurant, and then they never leave," Schneider explains. "They sit there through lunch, and they sit there through dinner. You're trying to serve people, and there's a line going out the door, but nobody's getting fed." Schneider lectures at colleges and hospitals nationwide on the dangers of boarding.

Schneider, a professor of emergency medicine at the University of Rochester, has received numerous awards and honors for her work within emergency medicine, including the Hero of Emergency Medicine Award from ACEP in 2008.

'90s

A third of all women have some form of pelvic-floor disorder, from chronic pelvic pain to incontinence to pelvic prolapse. Women are often told by their doctors that these conditions are just part of getting older—and many of those who are treated have serious complications, says **Pamela Moalli** (Obstetrics & Gynecology Resident '98, Urogynecology & Pelvic Reconstruction Surgery Fellow '99), associate professor of obstetrics, gynecology and reproductive sciences at Pitt and assistant investigator in the Magee-Womens Research Institute. Many of the implants used in these surgeries are too stiff and can cause pain, infection, and injury, she says. "Google *vaginal mesh*, and you will get lawyers' Web sites." With funding from the NIH, Moalli is investigating the biological basis of pelvic-floor failure; potential biomarkers that might predict the likelihood of pelvic-floor descent; and appropriate quality-control guidelines for vaginal mesh, among many other related projects. The insight she's gaining from her laboratory and clinical studies is paying off for her patients. "Once you effectively

treat a person, you can greatly improve her quality of life," she says.

'00s

Last year, **Shawn Fultz** (MD' 97, Internal Medicine Resident '01, Internal Medicine Fellow '03) was appointed director of the Public Health Evaluation Division of the Food and Drug Administration Center for Tobacco Products, which was created as part of the 2009 Family Smoking Prevention and Tobacco Control Act. Fultz's primary goal: to measure the public health impact of the center's initiatives.

Previously, while based at the Veterans Affairs headquarters in D.C., Fultz conducted HIV and liver-injury research as part of the Veterans Aging Cohort Study and advised on a variety of public health topics for the U.S. Department of Veterans Affairs. He also served a three-year term on the national board of directors of the Gay and Lesbian Medical Association. His next move will be a law degree—he's enrolling in the Washington College of Law at American University in Washington, D.C., in the fall. "I realized that the parts of my other jobs that I liked were the parts that involved interpreting regulations or statutes and figuring out how we can do the public health work in those boundaries," he says.

Kelly McCoy (Endocrine Surgery Fellow '07) is a self-described type A surgeon, and she has the resume to back it up. She entered the U.S. Navy after medical school, spending time in Italy before becoming a Pitt fellow. Following three more years of naval service, part of which was spent in Iraq, McCoy returned to Pitt, where she is an assistant professor of surgery.

In conjunction with Pitt professor of surgery Sally Carty, McCoy recently wrote an invited critique to an article titled "Suicidal Ideation Among American Surgeons" for the *Archives of Surgery*. The team's study found that surgeons had suicidal thoughts at a rate one-and-one-half to three times higher than the average American. Even more alarming, only 26 percent sought counseling.

"It's not necessarily surprising, unfortunately," she says. "We tend to be very critical of ourselves. Any sign of weakness is really hard on us." She adds that, given the new work-hour restrictions, the numbers should look better in the years ahead. "We're realizing that a better work-life balance makes for a better doctor."

—Tiffani Emig, Megan Kopke, and Elaine Vitone



CAMI MESA

McCoy

CHRISTINA ALLEN

POWER OF PROPRIOCEPTION



Allen (right) at a Cal Women's Soccer game in Berkeley, Calif., in 2007.

Throughout her training at Pitt, Christina Allen (Orthopaedic Surgery Resident '01, Sports Medicine Fellow '02) loved jogging in Schenley Park in the winter months. "I like running in the snow," she says. "It's good for your balance, your proprioception—the sort of wiring that allows you to know where your body is in space. If you have a bad injury, you have to work on restoring that brain-body connection."

Allen ought to know. As is the case with many orthopaedists, her fascination with the musculoskeletal system began with an injury in her youth. Now, the avid soccer player and associate clinical professor of orthopaedic surgery at the University of California, San Francisco, is helping fellow athletes stay on their toes, and off the bench.

Some anterior cruciate ligament (ACL) grafts fail—and, unfortunately, so do some of the revision surgeries intended to correct them. Allen is co-investigator in the Multicenter ACL Study (MARS), a large trial aimed at discovering why that is. She's also working to develop better treatments for patients with degenerative joint conditions.

Of course, as any athlete will tell you, the ideal scenario is to avoid getting hurt in the first place. She is excited that UCSF recently opened its Human Performance Center to this end. Allen and her center colleagues use video imaging of athletes jumping or cutting to identify those whose balance and alignment might predispose them to injury. They then prescribe appropriate rehab (er, prehab) to strengthen key muscles and hone their powers of proprioception.

Allen doesn't have much time to play soccer herself lately, but she's still kicking around the globe. A team physician for U.S. Women's Soccer, as well as for the men and women of U.S.A. Taekwondo, she has traveled to several countries in Europe, Asia, and the Americas. She has seen the Taekwondo team members take some pretty bad blows, but she's even more impressed by the toughness of the women's soccer players. "If one of them doesn't get up, you know she's really hurt," she says. "Men will take a dive and try to draw a card on another player. But in the culture of international soccer, women are more like American football players. It's: *I'm not gonna let you know you hurt me.*"

If Allen has anything to do with it, there won't be a need. *—EV*

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MARY LYNCH BAILEY

AUG. 21, 1919–JAN. 21, 2011



Mary Bailey with her husband, William Bailey

Mary Lynch Bailey (MD '44, Res '48, Fel '51) attended the School of Medicine when woman enrollees were few and far between. "She commented that she was always treated well," says her son James Bailey, professor of medicine and director of nephrology at Emory University. "She refused to recognize that there was any kind of bias."

Bailey died of congestive heart failure this January. She was 91.

In 1949, while at Mercy Hospital, she coauthored a paper proving the efficacy of oral penicillin in treating pneumonia (injections were the standard at the time). She joined Jonas Salk's lab when he arrived at Pitt two years later. Together, they coauthored a paper on boosting the effectiveness of a flu vaccine.

The lab then began developing a vaccine for polio, and Bailey and Salk made weekly trips to the D.T. Watson Home for Crippled Children to test its safety on infected children. When it was time to expand the circle, Bailey solicited recruits at local schools.

Bailey stopped working to raise her family, but she maintained her continuing medical education credits. And when her children were older, she worked every Tuesday in Mercy's pathology department, attending autopsies and grand rounds and helping residents with their reports.

Bailey is survived by her husband, William Bailey, Mercy's former chief of cardiology, as well as eight children and 14 grandchildren.

—Elaine Vitone

RICHARD H. MICHAELS

FEB. 17, 1928–FEB. 22, 2011

Richard Michaels was the quintessential professor and a role model for what an emeritus could be, says his mentee, Michael Green (Res '86, Fel '89), professor of pediatrics and surgery and an expert in pediatric infectious diseases. In retirement, Michaels continued to attend conferences and work with students, residents, fellows, and junior faculty. "You could always go to him. He didn't tell you what to do. But he helped you think about what you should do." Michaels died this February at age 83.



Michaels

In 1961, Michaels joined the University of Pittsburgh's Department of Pediatrics and Children's Hospital of Pittsburgh of UPMC, where he went on to head the Division of Infectious Diseases, serve as associate medical director, and chair the infection control committee.

Michaels investigated antiviral activity in human milk and the immuno-paresis of congenital rubella. He also made significant contributions to our understanding of the mechanisms and epidemiology of *Haemophilus* influenza infection.

In the '60s and '70s, Michaels helped design and implement Pittsburgh's vaccine campaigns. He also headed Children's Hospital's human rights committee—a precursor to the Institutional Review Board—in the early days of organ transplantation. "He was very involved in assuring patient rights and safety in this brand-new field of medicine," says Green.

Michaels led Pittsburgh's chapter of Physicians for Social Responsibility, which aimed to prevent the spread of nuclear weapons, and codirected the Pittsburgh–West Africa medical scientist summer exchange program, which linked Pitt to Benin Teaching Hospital in Benin City, Nigeria. He also made several trips to Cuba as part of Global Links.

His humility was inspiring, says Marian G. Michaels (no relation) (Fel '92), professor of pediatrics and surgery at Pitt:

"Here was this gentleman who'd held many positions of power within the hospital, and yet, in his later years, he came back as a volunteer to greet people at the pediatric ICU." *—EV*

HARRY E. POPLE JR.

MAY 18, 1934–MARCH 26, 2011



Pople

Widely considered a pioneer in artificial intelligence/expert systems, Harry E. Pople Jr. was a partner in one of the first collaborations between computer science and medicine. Pople, a former assistant professor of neurology and professor in the Katz Graduate School of Business at the University of Pittsburgh, died in March at age 76.

Jack Myers, chair of the Department of Medicine from 1955 to 1970, approached Pople to help him model clinician-thought processes and decision-making. They collaborated to create and direct the Decision Systems Lab and develop INTERNIST-1/CADUCEUS, a computerized medical diagnostic system considered state of the art for its time.

Pople enjoyed his intellectual pursuits but rarely engaged in self-promotion, believing his work should stand on its own, says Sean McLinden (MD '85), a researcher in Pople's lab from 1979 to 1990 who is now a forensics computer specialist—and stand on its own it did. In 1979, Pople served as special advisor to the chancellor for the University Computer Center and chaired the management systems task force. In the 1980s, he created a private company, Seer Systems, that conducted research projects for NASA, the National Security Agency, and the Nuclear Regulatory Commission.

McLinden also remembers Pople for creating what he describes as the "perfect" lab. "Harry created a unique environment where I learned intellectual discipline, critical thinking, and the need to question my assumptions and explore my own ideas," says McLinden. "A lot of people were dabbling in 'artificial intelligence,' but he was the master craftsman."

—Maureen Passmore

IN MEMORIAM

'30s

RUPERT FRIDAY
MD '36
MARCH 16, 2011

'40s

HELEN DENNY CAUSEY
MD '43
FEB. 1, 2011

ROBERT CARROLL
MD '47
MARCH 15, 2011

WILLIAM E. LEBEAU
MD '48
FEB. 11, 2011

'50s

JOHN HOWARD WILKINSON
MD '50
FEB. 2, 2011

GABRIEL A. DEMEDIO
MD '51
APRIL 7, 2011

JAMES WELCH GILLOGLY CARMAN
MD '56
DEC. 16, 2010

'60s

RICHARD FRANCIS LAIN
MD '68
FEB. 23, 2011

FACULTY

GERALD LISOWITZ
MD '55
MARCH 3, 2011

HOWARD HEIT SPEAKS TO AN EPIDEMIC OF UNDERTREATMENT

BY SHARON TREGASKIS



STEPH HOOTON/ PICTOGRAM STUDIO

After a head-on car crash, Heit became an expert in pain medicine, personally and professionally.

One evening in March 1986, Howard Heit (MD '71), a board-certified hepatologist and gastroenterologist and then-chief of endoscopy at Fairfax Hospital, in Falls Church, Va., was en route to a meeting at the National Institutes of Health when a head-on collision changed everything. The resulting axial spastic torticollis left him in constant pain—like "a muscle cramp, multiplied by 100," he says. An offensive tackle and place holder for Pitt's football team as an undergraduate, Heit would spend the next two decades wearing a back brace and using a wheelchair, afflicted by chronic, uncontrollable muscle tremors and spasms. "In my wanderings for diagnosis and treatment, it became apparent that my fellow physicians had no knowledge of pain medicine," he says. "They brushed it off like it was in my head. My life was devastated, my career as an endoscopist was gone. I thought, *If this is happening to me, as a male, a former football player, and a physician, the average person doesn't have a chance.*"

In his search for relief, Heit started studying pain management and addiction medicine. "To do good pain management, you have to know addiction medicine," he says. "And to do addiction medicine, you have to be at least a talented amateur in pain medicine." He went on to earn his diploma from the American Board of Addiction Medicine and become a fellow of the American Society of Addiction Medicine (ASAM).

Heit quickly rose to prominence in the group, serving as founding chair from 2000 to 2005 of the conference Pain and Addiction: Common Threads.

In 2005, Heit published with Douglas Gourlay *Universal Precautions in Pain Medicine: A Rational Approach to the Treatment of Chronic Pain*, a protocol for the assessment and treatment of chronic pain in a way that is consistent and respectful of each patient. The manuscript is one of the most cited papers in the pain and addiction literature.

"Howard has introduced the idea of an agreement between the patient and the physician," says Joyce Lowinson, professor emerita of psychiatry and behavioral sciences at Albert Einstein College of Medicine. "And the consistency of doing this with all patients makes it clear that it's not done because of suspicion that the patient might be deviating. He manages to do it in a way that patients don't feel defensive."

In the late '80s, as HIV emerged, infectious disease specialists began urging health care professionals to don gloves and take other precautions for all exams, simultaneously protecting themselves and their patients. Heit and Gourlay's protocol likewise establishes universal precautions to be used with pain patients, without stigmatizing anyone.

Heit says, "You're using a medicine that can be part of the problem, part of the solution, or both, depending on the relationship between the patient and doctor and the goals that are set up before you write the first prescription."

In 2007, deep brain stimulation rendered Heit's own wheelchairs and back braces obsolete and eliminated 95 percent of his pain. Today he practices yoga and visits the gym daily.

When his wife, Jane Davis Heit (A&S '69), died in April 2010, Heit lost both the woman he'd wed as a second-year medical student and the person who had managed his nearly 300-patient private practice in suburban Washington, D.C. Without her, he decided to stop seeing patients and expand his efforts to educate other physicians and patients about how to practice pain management in compliance with Drug Enforcement Administration regulations.

Before he could shutter his own office, however, Heit had to find colleagues willing to accept his referrals—a process that took four months. "If I had been continuing as a gastroenterologist, it would have taken me less than a week," he says. "Gastroenterologists grow on trees." The experience only reinforced his passion for physician education.

This winter, he signed a contract with Walter Reed Army Medical Center to develop training in pain and addiction for military doctors treating soldiers returning from Iraq and Afghanistan with chronic pain and traumatic brain injury.

"Pain is the most common presentation to a doctor's office, yet more than 50 million Americans are undertreated for pain, and 30 to 40 percent of those with terminal illness die with pain," he says. "We have an epidemic of undertreatment." ■



MUGGLES, MAGIC, AND MEDICINE

There was a lot more to magic, as Harry quickly found out, than waving your wand and saying a few funny words, **J.K. Rowling writes in the first book of the *Harry Potter* series. This idea sparked the interest of National Library of Medicine curators, inspiring them to create the traveling exhibit, "Harry Potter's World: Renaissance Science, Magic, and Medicine." The exhibit, which was on display at Pitt's Falk Library of the Health Sciences this February and March, allowed visitors to learn how Rowling's fictional wizarding world was influenced by Renaissance traditions. The exhibit creators make the case that modern natural philosophy, medicine, botany, and other sciences have their roots in occult and magical traditions.**

"*Harry Potter* had been so popular worldwide, it has sparked some people's interest in the actual traditions and historical people, some of whom were mentioned in *Harry Potter*," Barbara Epstein, director of Falk Library, explains.

Consider for example Nicholas Flamel, a famous alchemist and, in the first *Harry Potter* book, the creator of the philosopher's stone. Flamel believed, both in real life and in the *Harry Potter* series, that the philosopher's stone could turn any metal into gold and create an elixir that gave its consumer eternal life. Many of Flamel's contemporaries thought he had actually created the coveted stone. Although he didn't find the secret to immortality, the alchemist's experiments with metals did help to clear a path to modern day chemistry. (Isaac Newton and Robert Boyle also practiced alchemy.) Harry Potter's universe does seem to be closer to our "muggle world" than we ever thought. —*Megan Kopke*

ILLUSTRATION OF ALCHEMIST'S WORKSHOP BY HEINRICH KHUNRATH, AMPHITHEATRUM SAPIENTIAE, 1595. NATIONAL LIBRARY OF MEDICINE.

CALENDAR

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1961	1956
1951	

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MAY 20
11 a.m.
Alumni Hall, Connolly Ballroom

ALUMNI WEEKEND WELCOMING RECEPTION AND COCKTAILS
MAY 20
5 p.m.
Pittsburgh Athletic Association

SCOPE AND SCALPEL'S "INTUSSUSCEPTION"
MAY 20, 8 p.m.
MAY 22, 2 p.m.
Antonian Theater
Carlow College
Pittsburgh
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www.scopeandscalpel.org

ALUMNI CHAMPAGNE 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 (Oakland)

CLASS OF 2011 COMMENCEMENT
MAY 23
10 a.m.
Carnegie Music Hall
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OCTOBER 14–15
Julian J. Pribaz, MD, Speaker

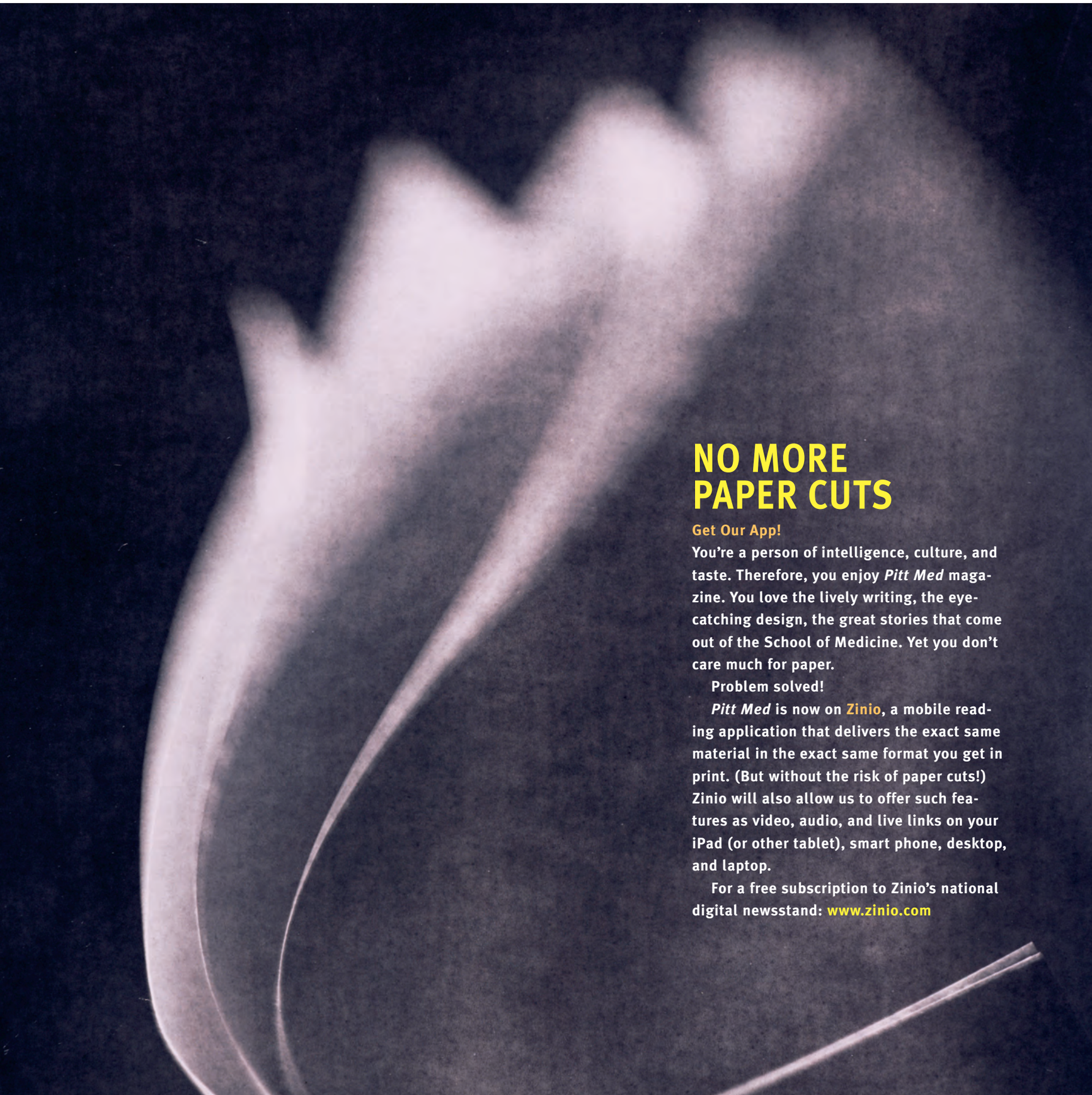
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