UNIVERSITY OF PITTSBURGH SCHOOL OF MEDICINE | SPRING 2013

PITTMED



THESE ARE NOT ICE CUBES

HEAL THYSELF,
WITH A LITTLE HELP FROM BIOMATERIALS

SPIRIT OF '57

I thoroughly enjoy *Pitt Med*. As an endocrinologist, I especially liked the Winter issue cover story, "Out of Darkness," reviewing the exceptional work of Panayotis Katsoyannis at my alma mater.

I do have one complaint, however, about your Class Notes section. I believe several issues ago you stopped including the classes of the '50s. Actually, there are a few of us left. Three of us from the Class of 1957 are alive and well, living in Palm Desert, Calif.: Robert Higginbotham, orthopaedics, Robert McPeake, general practice (our class president), and myself.

John Deller (MD '57)
Palm Desert, Calif.

Editor's Note: We'd love to hear from more alumni from those years. Especially your enduring Pitt memories! Write on.

KINDEST CUT OF ALL

I knew Mark Ravitch, Montefiore Hospital surgeon-in-chief, very well from the time of my Johns Hopkins internship in 1952 to the day of his death in 1989. It would be very difficult to adequately describe the veneration that he deservedly received. Elaine Vitone has succeeded in spades [see p. 18, "The Surgical Curmudgeon"]. Thank you for letting me see the preprint of this masterpiece.

Thomas Starzl
Distinguished Service Professor of Surgery

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

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

CORRECTIONS

In our Winter 2012/13 issue cover story, "Out of Darkness," we noted Pitt alumnus Herb Boyer's degree incorrectly. He earned his 1963 PhD in bacteriology, not chemistry.



WISH YOU WERE HERE

There must be 50 ways to leave your med school. You can go your own way, ride a horse with no name, or take a midnight train to Georgia. Tell us what you've been up to: career advancements, honors you've received, appointments, volunteer work, publications. And we love to hear old Pitt memories, like: What's going on with this scene we found in Pitt's 1975 edition of *The Owl*? Let us know, one way or another. Write a message in a bottle, ring our bell at the number listed above, or friend us on Facebook at www.pittmedfb.pitt.edu/.

PITTMED

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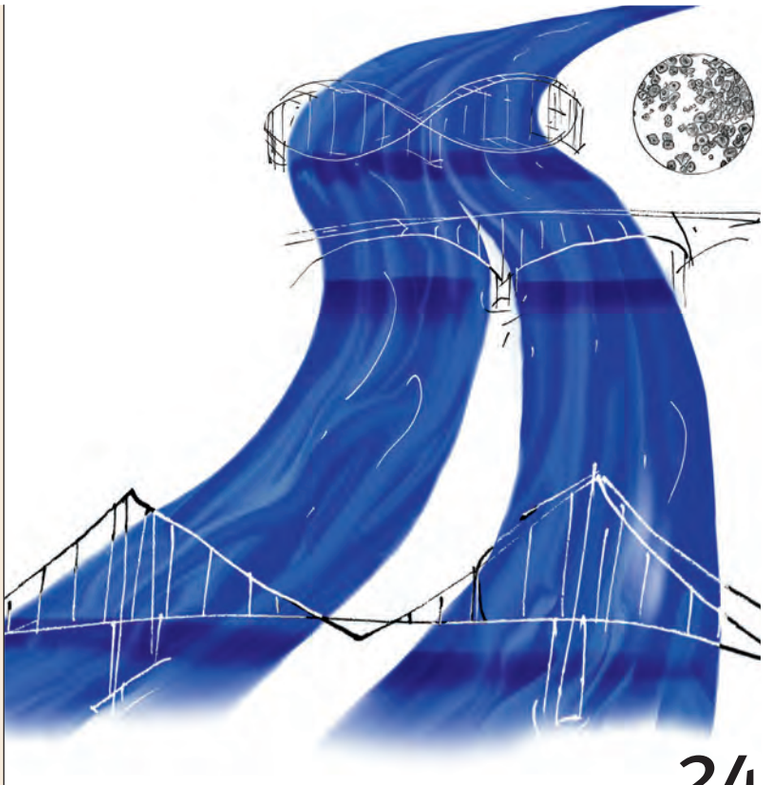
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Can injured hearts and ruined nerves be made whole by something not human being placed inside a human? Pitt investigators say yes, with the help of nature.

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The Surgical Curmudgeon 18

Mark Ravitch introduced America to the surgical stapler, he put Pitt surgeons through trying times at morbidity and mortality conferences, and he left an eternal mark on the art of operating.

BY ELAINE VITONE

A Confluence at Three Rivers 24

The dean's perspective on the next big thing in medicine (make that three things) and how Pittsburgh is poised to make the most of this moment. Also...

In a Maelstrom: health care's stormy front. 29

INFOGRAPHIC: The Pittsburgh Model for transforming medicine. 30

BY ARTHUR S. LEVINE, MICHAEL FITZGERALD, AND ERICA LLOYD

CONTRIBUTORS

A decade ago, MICHAEL FITZGERALD ["In a Maelstrom" and "The Pittsburgh Model"] was burned out. As an editor of a prominent new economy magazine website during the time when, as he says, "the dot-com bubble went pop," he was thinking of switching careers. "I didn't want to be a journalist anymore—or so I thought." But the writing bug bit after a friend asked him to write a short column for a tech website. And it wouldn't loosen its mandibles. A freelancer since 2002, Fitzgerald has been a Nieman Journalism Fellow at Harvard University, a Templeton-Cambridge Journalism Fellow, and a "Prototype" columnist for *The New York Times*. He's won numerous awards; most recently, a piece for *Fast Company* about the music industry won the 2011 Outstanding Business and Technology Article from the American Society of Journalists and Authors.

JENIFER LIENAU THOMPSON ["For Real!" p. 40 1/2] has served as director and curator for the Santa Cruz Museum of Natural History and an exhibition researcher for the Arizona Science Center. For Ocean Conservancy, she developed the Gulf of Mexico "Wildlife Profile" series about species at risk after the BP Horizon disaster, among other stories. And ever since one of her daughters got a skateboard for Christmas, she's been consumed by the urge to thrash. Every member of the Thompson family now has a skateboard and has been Ollie-ing about together. Lienau Thompson is determined to pull a pop shove-it with the best of them.

COVER

The body can heal itself better with a little help from its friends—like these tiny 3-D bioscaffolds designed by Rocky Tuan. (Cover: Photo by Rocky Tuan and Hang Lin © 2013.)

PITTMED

PUBLISHER
Arthur S. Levine, MD

EDITOR IN CHIEF
Erica Lloyd

ART DIRECTOR
Elena Gialamas Cerri

SENIOR EDITOR
Joe Miksch

ASSOCIATE EDITOR
Elaine Vitone

CONTRIBUTING EDITOR
Chuck Staresinic

PRODUCTION MANAGER
Chuck Dinsmore

STAFF CONTRIBUTORS
Katie Martin, Em Maier

OBITUARIES CONTRIBUTOR
Macy Levine, MD '43

EDITORIAL ADVISORS
Jeremy Berg, PhD
Michelle Broido, PhD
Nancy Davidson, MD
Paula Davis, MA
Joan Harvey, MD
Steven Kanter, MD
David Kupfer, MD
Joan Lakoski, PhD
David Lewis, MD
Margaret C. McDonald, PhD, MFA
David Perlmutter, MD
Steven Shapiro, MD
Peter Strick, PhD
Bennett Van Houten, PhD
Simon Watkins, PhD
Marshall Webster, MD, Res '70
Julius Youngner, ScD

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

University of Pittsburgh

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So far, I have not found the science …
—Soul Coughing


JOSHUA FRANZOS

Science is everywhere—in labs, in hospitals, in our food, in our iPhones, and, in fact, in virtually all to which we are exposed and which we experience each day. Yet, somehow, it's not always easy for people to understand the "scientific method"—the process of making an observation, creating a hypothesis to explain that observation, doing an experiment to prove or refute that hypothesis—and relate science to their daily lives. The lack of science literacy in our country is one of our greatest challenges in sustaining our national momentum.

As a young boy, I was fortunate to have a guide. My first cousin Donald Glaser served as my "big brother" as we grew up together in Cleveland. Don, a decade older than me, was driven both to discover and to share the joy of discovery with me, his mentee. Later, Don became a physicist and went on to invent a device called the "bubble chamber," which allowed us to visualize subatomic particles for the first time. In 1960, at 34, he was awarded the Nobel Prize in Physics. Don later moved his interest to molecular biology and biotechnology (an early company that he cofounded commercialized the polymerase chain reaction). Still later, like Francis Crick, he evolved into a neurobiologist. Don died a few weeks ago, and I shall miss my lifelong model and mentor greatly.

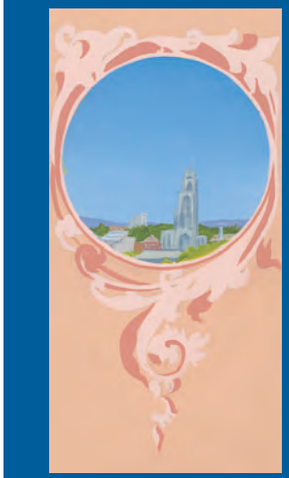
As a university, we have a responsibility and an opportunity to mentor the young and impressionable on an institutional scale. To this end, in 2010 we established the Office of Science Education Outreach in the Health Sciences. This office formalizes and facilitates several long-standing, as well as new, outreach efforts. Through these efforts, we open our labs to youth. These young people—some perhaps future Donald Glasers—learn the scientific method by doing science side by side with our faculty. And each year, we host hundreds of students in our summer science programs. We also have a rewarding relationship with the Pittsburgh Science & Technology Academy, which the Pittsburgh Public Schools opened in September 2009. It's just a few blocks from our home in Scaife Hall. Our faculty serve as mentors to "SciTech" seniors, who also attend many of the lectures held here on research subjects of broad interest.

In addition, thousands of kids have delved into human genetics, developmental biology, and other topics after climbing into our 70-foot-long tractor-trailer, a mobile science lab established by our NIH-funded Clinical and Translational Science Institute. The truck circulates among the public schools and adds substantially to the science exposure offered by those schools.

Others support our efforts as well: Various agencies, foundations, and professional societies fund programs that bring the curious to us and bring science to the curious.

My wife and I visited Don and his wife at their home in Berkeley just a few months ago. I was very moved by Don, after we had had our fill of science talk, grasping his rescue dog's head between his palms and speaking gently, face to face and at some length, to his pet. In that instant, he captured the existence that we share with all of life; it is the interrogation of the mechanisms of this life that fills us with passion as scientists and as physicians. I think that my cousin would have liked the latest addition to this magazine. Flip to the inside back cover, and you'll find our new section—"For Real!"—intended for the Justin Bieber generation. I hope you'll share it with every young person you know.

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



Devoted to noteworthy happenings

at the medical school

FROM LEFT: Kate Bennett (crew chief), Stacie Truszkowski, Anne-Marie Alderson, M. Patricia George, Ryanne Palermo, and Greta Daniels (crew chief/alternate).

UPMC



Pain Eds

According to the National Institutes of Health, approximately 100 million Americans suffer from chronic pain. The cost of treating pain is in the billions of dollars. The University of Pittsburgh School of Medicine established its multidisciplinary Pittsburgh Center for Pain Research in 2006; now it is one of 12 sites to receive the NIH award, Center of Excellence in Pain Education.

The center includes 20 faculty members from Pitt's Schools of Medicine, Nursing, Pharmacy, Dental Medicine, and Health and Rehabilitation Sciences. It will function as a clearinghouse for the development, evaluation, and distribution of pain management curricula for students across these schools. "With better education, I am hopeful that we will achieve better patient outcomes and spend a lot less" on health care in the process, says Debra Weiner, an MD, director of the center, and professor of medicine in the Division of Geriatric Medicine. *—Katie Martin*

OPENING HIV RESEARCH FLOODGATES

Four grants from the Bill and Melinda Gates Foundation—totaling almost $11.5 million—will help investigators in the School of Medicine and in Pitt's Graduate School of Public Health seek and develop new ways to stop HIV.

Pitt's Drug Discovery Institute and Pitt Public Health are teaming up to develop a new test to catch HIV earlier than is now possible. In addition, Ian McGowan, MD/PhD professor of medicine and of obstetrics, gynecology, and reproductive sciences, plans to find out whether monthly injections of rilpivirine, a long-acting anti-HIV drug, will prevent HIV infection. A group led by Sharon Achilles, MD/PhD assistant professor of obstetrics, gynecology, and reproductive sciences, is charged with investigating the notion that hormonal birth control causes changes in genital-tract immune cells, making them more susceptible to infection. And Lisa Cencia Rohan, PhD assistant professor of pharmaceutical sciences in the School of Pharmacy, will study the feasibility of using thin films inserted into the vagina to deliver contraceptives or anti-HIV drugs. *—Joe Miksch*

FOOTNOTE

"Four women on bikes. Nine days to cross America. Devoted to thousands who struggle to breathe." Team PHenomenal Hope—the "PH" is for pulmonary hypertension—will tackle the 2014 Race Across America, a tag-team, continuous bike ride from California to Maryland.

Led by Pitt assistant prof M. Patricia George (Fel '08) and sponsored by UPMC, the gang of four (shown above with their two crew chiefs) will race to raise money for the Pulmonary Hypertension Association.

Follow the team at teamphenomenalhope.org



UPMC

Jan Scheuermann
Cyborg Mom

In 1986, Andrew Schwartz, a PhD and Pitt professor of neurobiology, had an idea he was sure would work: translating signals in the brain, so a person's thought could move a very high-tech prosthetic limb. In December 2012, it worked very well. After months of training, Jan Scheuermann, a 53-year-old mother of two whose ability to move below the neck was stolen by spinocerebellar degeneration, fed herself a chocolate bar with a robotic arm. She bent the arm's wrist and rotated it, closed its hand, brought the treat to her mouth, and took a bite. Schwartz and a team of many others are working on the next step: using this brain-computer interface technology to generate sensation in the brain, allowing the arm's user to adjust grip strength. Below, Scheuermann (a Pitt grad—BA '83) recounts her relationship with Hector, the robotic arm, which is designed to resemble a human arm. ("I name things," she explains. "I had a big, old Dodge; it was so sturdy, I called it the Scheuermann tank!")

On the learning process

Well, the way I control Hector now is so easy. I wonder if I tried too hard at the beginning. Every time I tried to move, I was pushing the muscles in my arm that I would use to move my arm. I was doing that so hard and so concentrated. Now when I train, rather than pretend I'm moving my hand, I just look at the target where the arm is supposed to go and watch it go there. I don't think, "Up and to the right," I think, "There's the target," and go get it. Each new task I got, I knew I would learn. It didn't come real easy, but I didn't get frustrated. I knew it would come eventually.

On the potential of the arm

For people in my situation, who are completely unable to move below the neck, this can help them have a lot of independence and not need someone at home with them all the time. With a Hector mounted to their own [wheel]chair, they could go to the refrigerator, open it, get out some food, put it on their lap, close the fridge, go over to a table, and feed themselves whatever was on the plate. You can use Hector to help you call someone on the phone. You can turn TV channels with him. You know what else it just occurred to me that Hector can do? Turn the pages of a book! That'll be so great because there are some books you can't find on CD!

On the future

We just signed up to go for another four years. I'm allowed [medically] to keep the [electrodes] in my head for five years. As long as I'm enjoying it, and they have new things to learn, I'm game. I am the only one who can do this for right now. I'm so loving what we do every day we go in. And as long as we get occasional tasks where I can feed myself chocolate, I'm there. *—JM*

Faculty Snapshots

The study of tiny viruses can reap huge rewards. **Carolyn Coyne**, PhD associate professor of microbiology and molecular genetics, is one of 10 recipients of the 2012 Burroughs Wellcome Fund Award in the Pathogenesis of Infectious Diseases. Coyne's research proceeds on two fronts: what allows certain viruses to breach physical barriers in the body and how viruses evade the innate immune system. The five-year, $500,000 grant, which is targeted to high-achieving young investigators, is intended to provide the freedom and flexibility to pursue high-risk projects and new avenues of inquiry.



Coyne

The UPMC Rehabilitation Institute has received a five-year, $2.15 million grant and the mantle of Model System of Care for Traumatic Brain Injury (TBI); in this capacity it will collaborate with 15 other TBI model sites. Pitt's **Amy Wagner**, an MD and associate professor and vice chair of research in the Department of Physical Medicine and Rehabilitation, will serve as the center's director. The grant, administered by the U.S. Department of Education's National Institute on Disability and Rehabilitation Research, will help Pitt experts advance research and improve TBI patient outcomes.



Wagner

A porous, cell-free artery graft may be key to acheiving greater success in heart bypass surgery. Within three months of implantation, the graft—made of an elastic polymer—is completely degraded by the body and replaced with a new, 100-percent natural artery. **Yadong Wang**, a PhD professor of bioengineering and surgery, led the development of the graft. The results of his work, published in *Nature Medicine* in 2012, suggest that the porous nature of the material allows cells easy access to the support structure, where they replicate and remodel.



Wang

To see how the eye sees takes some doing. For more than 20 years, **Joel Schuman**, an MD, Pitt's Eye & Ear Foundation Professor, chair of its Department of Ophthalmology, and director of the UPMC Eye Center, has been a vital member of a multicenter, multidisciplinary team that invented and developed an imaging system called optical coherence tomography (OCT) that reveals vivid details of eye anatomy quickly and noninvasively. The five leaders of the long-term project (including Schuman) will share the António Champalimaud Vision Award—worth 1 million euros—from the Champalimaud Foundation in Lisbon. OCT has become the standard tool for early detection of diseases such as macular degeneration, diabetic retinopathy, and glaucoma. *—JM & KM*



Schuman

Infection Now; Asthma Later

Doctors had correlated frequent respiratory syncytial virus infection in childhood with asthma in adulthood. Now Pitt researchers believe they have strong evidence linking the two. The virus seems to harm regulatory T cells (Tregs), which are vital to the development of immune tolerance, says lead author Nandini Krishnamoorthy, a PhD and a postdoc in the lab of Prabir Ray. Ray and his wife, Anuradha Ray, are both PhD professors of medicine and immunology and senior authors on the *Nature Medicine* paper. The researchers posit that this damage to Tregs is not forgotten. It handicaps the ability of Tregs to modulate the body's system of protection against antigens like house dust mites and makes people more likely to develop asthma as they age. ***—JM & KM***



CATHERINE LAZURE

Another Kind of Asthma

Not all severe asthmas are the same, says Sally Wenzel, MD and Pitt professor of medicine. Her lab has uncovered a form of the disease—which is differentiated from other severe asthmas by its difficulty to treat and potential deadliness—that she calls "asthmatic granulomatosis." As the name suggests, this rare form of the disease is marked by small areas of focal inflammation in the lungs. Wenzel's study indicates that asthmatic granulomatosis has hallmarks of autoimmune disease and, therefore, responds better to immunosuppressants than to steroids, the go-to drug class for the treatment of severe asthma. Wenzel says, "If we better understand the underlying mechanisms that are causing [asthma] symptoms, we can offer better treatments." *—JM & KM*

YOU'RE IT!

It crosses all borders: political, geographical, and racial. As though aware of our attempts at surveillance and subsequent destruction, it changes its identity quickly and frequently.

For the past two years, this mutating stalker, influenza, was tracked at one of its favorite hunting grounds: schools. Seasonal flu spreads rapidly among children as they mass for education, and these kids take it home and spread it further.

Shanta Zimmer, an MD and associate professor of medicine at Pitt, and Derek Cummings, a PhD at Johns Hopkins University, are attempting to determine how the flu and other respiratory diseases are transmitted at school and leak again into the community. And children are helping in the research.

The project, SMART (Social Mixing and Respiratory Transmission) in Schools, includes students from the Canon-McMillan school district and Propel Charter Schools in the Pittsburgh area. Organizers gave more than 2,000 children devices to wear throughout the day that sensed and recorded their proximity to other children's devices. Diaries and videos helped flesh out how the children interacted. (Did any of the devices end up on a rooftop or in a toilet, we wondered? Apparently not. "The kids are really engaged in participating and using the equipment," notes Zimmer, "especially the younger ones.")

So far, it appears that, on average, a student interacts with more than 100 other kids per day. This number decreases with age, and kindergartners are much more physically interactive than their older counterparts. Researchers hope that these data will provide insight on how to prevent an epidemic.

SMART is also making kids smarter. Zimmer educates them on how the devices work, the ins and outs of vaccination, and the pathology of disease. *—Em Maier*



COURTESY RMQ SHANKS

BAD FILMS

Bacteria can be bad. Gangs of bacteria living on surfaces (such as lung tissue) as a "biofilm" can be even worse—up to 1,000 times more resistant to antibiotics than free-swimming bacteria. Pitt's Robert M.Q. Shanks, PhD associate professor of ophthalmology and of microbiology and molecular genetics, says biofilms (held together by a polysaccharide matrix) protect bacteria and help render them immune to most antibiotics. Shanks is looking for ways to make the bound bacteria (such as this *Serratia marcescens*) detach and become easier targets for drugs and our own immune systems. *—JM*

Name Dropping

Slated for a June 20 appearance in Pitt's Laureate Lecture Series, Rino Rappuoli, PhD and Global Head of Vaccines Research at Novartis Vaccines and Diagnostics, is expected to expound on the roles vaccines can play in this century. "Vaccines have been the most effective medical intervention ever developed," Rappuoli says. Childhood vaccination has saved lives, extended lifespans, and helped eradicate infectious diseases. In the future, he says, adult vaccines for HIV, cancer, and antibiotic-resistant bacteria will do likewise. "With new technology, genomics, and the application of systems biology, we've gone from this being impossible to being very possible," he says.

In his research career, Rappuoli developed a potent and nontoxic acellular pertussis (whooping cough) vaccine and, with colleagues, helped coin the term "cellular microbiology," reflecting his belief that cell biology and microbiology are inexorably entwined.

In addition to Rappuoli, a sparkling cast populates this year's Laureate Lecture roster:

Helen H. Hobbs, MD professor of internal medicine and of molecular genetics at Texas Southwestern Medical Center, spoke in February. Her work has provided insight into the genetics of cholesterol and fat metabolism and has helped identify new drug targets for atherosclerotic heart disease.

Susan Ferro-Novick, PhD professor of cellular and molecular medicine at the University of California, San Diego, visits September 26 to talk about how vesicles move and deliver cellular cargo.

The lecture series ends December 3 with a talk by the Salk Institute for Biological Studies' Vi and John Adler Professor for Research on Age-Related Neurodegenerative Disease, Fred H. Gage, a PhD. Gage's lab showed that, contrary to accepted dogma, humans are capable of growing new nerve cells throughout life. *—JM*



WHAT WOULD GALILEO DO?

The Pittsburghification of Sicily continues apace. UPMC, with Pitt faculty members and the Italian government, brought solid-organ transplantation to Palermo in 1999. The project got a permanent home in 2004, when the 70-bed ISMETT (Istituto Mediterraneo per i Trapianti e Terapie ad Alta Specializzazione) facility opened.

And now a similar public-private partnership will oversee the latest effort that will make Sicily a medical powerhouse: the pending construction of Ri.MED (Ricerca Mediterranea or Mediterranean Research) Biomedical Research and Biotechnology Center (BRBC) in Palermo-adjacent Carini. A jury of Italian scientists and architects has chosen HOK as the lead architectural firm for the facility after a worldwide design competition among 14 contenders. The winner was announced at a news conference in November, at which Italy's then prime minister, Mario Monti, spoke via teleconference. The president of Sicily and officials from Pitt, UPMC, and Italy's National Research Council also participated (these entitites founded Ri.MED in 2006 with the Italian government).

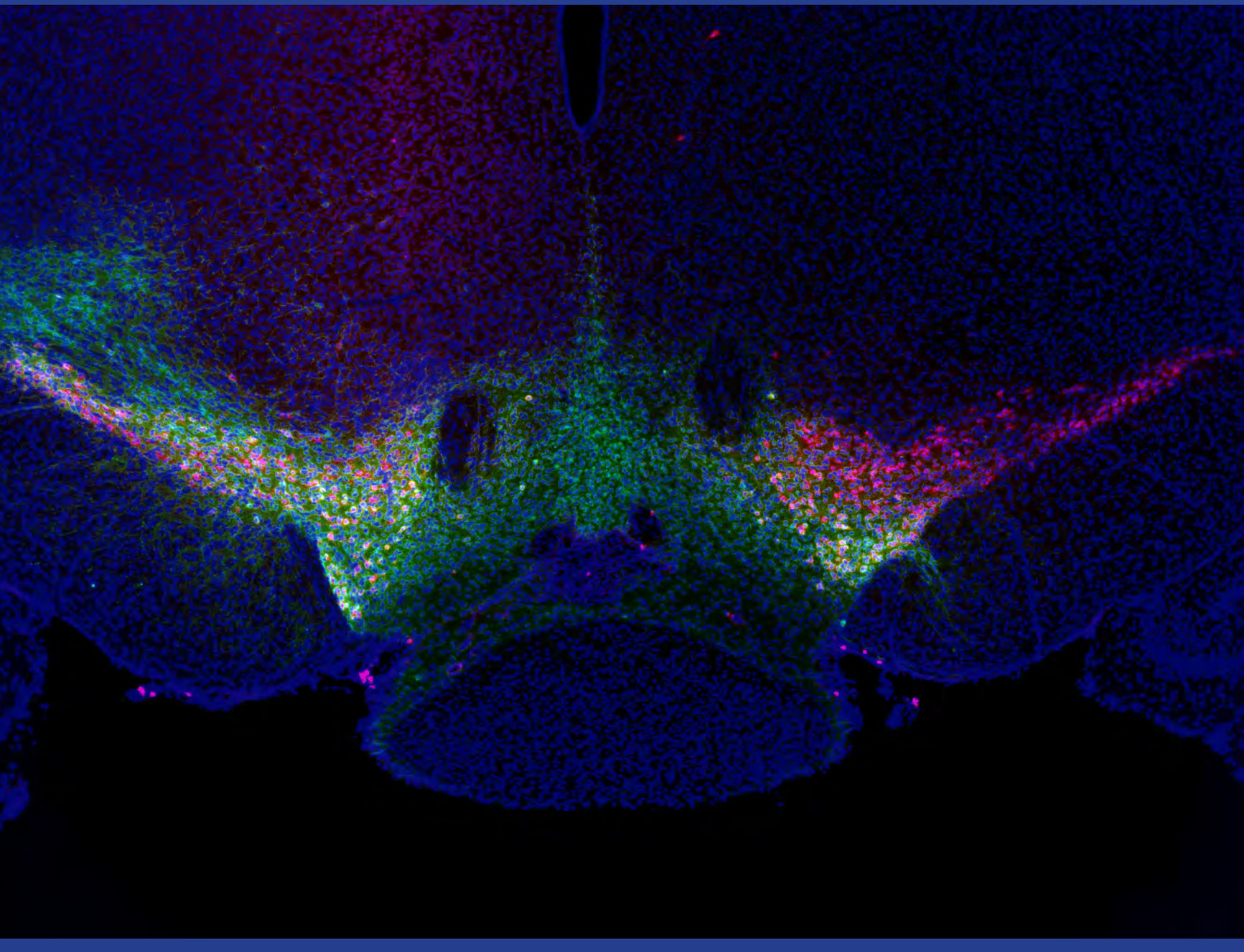
The 334,000-square-foot research facility is expected to open in 2016. BRBC will include a corporate incubator to shepherd its discoveries to market.

Ri.MED's investigators will ply the fields of structural biology, computational biology, drug discovery, vaccine development, biomedical device development, regenerative medicine, tissue engineering, molecular imaging, and neuroscience. If the spectacular views of the Tyrrhenian Sea and mountains are not enough to inspire, researchers can get creative juices flowing by strolling over to the lavender gardens or (we imagine) the campus espresso bar.

Arthur S. Levine, dean of the University of Pittsburgh School of Medicine and Pitt's senior vice chancellor for the health sciences—who also holds the title scientific director of the BRBC—says, "We want to make a substantial contribution to biomedical research globally. The goal is not only to do world-class science, but also to do the kind of science that will lead to the emergence of a biotechnology industry in Southern Italy."

Expansion plans for the Carini site include the prospect of a hospital and the creation of a new medical school. *—Joe Miksch*

—Photo courtesy HOK



McClung has made a direct correlation between the genes that control circadian rhythms and those in the mood-related circuits of the brain. Rodents with a mutation in their Clock gene—a model for mania—behave very similarly to rodents with impaired dopaminergic activity. Here, dopamine neurons, which are regulated by Clock, are shown in green. Shown in red is expression of an ion channel used to directly control dopaminergic activity.

GOODNIGHT (MANIC) MOUSE

MODELING THE LINK BETWEEN MOOD DISORDERS AND THE CIRCADIAN CLOCK

BY NICK CHARLES

It may sound surprising, but like humans, mice can exhibit both depressive and manic behavior. At times, the behavior seems to be linked to the "Clock gene." Humans have the same gene, which is inextricably linked to the "24-hour rhythm in each of us," says Colleen McClung, a PhD associate professor of psychiatry at the University of Pittsburgh School of Medicine.

It's long been known that disturbances in the circadian clock—the master timekeeper of the body's physiological processes—go hand in hand with mood disorders. (See our Summer 2012 issue cover story, "Sleeping's Beauty.")

"However, it wasn't really understood why the genes involved in regulating circadian rhythms also affect mood," says McClung. By using viral gene manipulation and pharmacological approaches, McClung has made a direct correlation between the genes that control circadian rhythms and those in the mood-related circuits in the brain. Her data suggest that new compounds that alter the circadian system might be developed into effective therapies.

Working in the Department of Psychiatry's Translational Neuroscience Program, McClung studies how genes influence circuits of the brain that control mood. She does this by knocking out genes or by breeding mice with different kinds of transgenes—genes that overexpress functional or mutant proteins.

"We've used this method to create mice that demonstrate behavioral responses similar to bipolar mania," she says. "These particular mice have a mutation in the Clock gene (Clock Delta19) that renders this protein inactive."

The method for creating this Clock mutant mouse was developed by other scientists in the 1990s; but it was McClung who characterized its mood-, reward-, and anxiety-related behaviors. Once she discovered that the mutant mice displayed the hallmarks of mania, such as hyperactivity, risk-taking behaviors, decreased anxiety, and lower levels of despair, she began a series of experiments that led to a Rising Star Translational Research Award from the International Mental Health Research Organization, bestowed in July 2012.

"The search for better treatment options for bipolar disease has been difficult due to the lack of suitable animal models," McClung says. "The models that we're working with are appropriate for screening new compounds that might be effective in treating this chronic and debilitating disease."

"It wasn't really understood why the genes involved in regulating circadian rhythms also affect mood."

McClung's team studied responses to stimuli in the Clock mutants compared to healthy mice, measuring behaviors consistent with mania. The Clock mutant mice were then given mood-stabilizing drugs (lithium or valproate) for periods of up to 14 days, and then the tests were performed again. The team found that these medications restore healthy behavior in the mice.

The team also identified a group of enzymes known as histone deacetylases (HDACs) that may present better targets in bipolar disorder treatment. HDACs repress the expression of the dopamine regulator cholecystokinin (CCK), among other genes. McClung found that inhibiting HDACs actually counteracts the effects of Clock mutations.

With her Rising Star grant, she is now searching for the best HDAC to take aim at and the best agent to inhibit it.

"Although [lithium and valproate] have proven effective in treating bipolar disorder, their use has been shown to lead to liver and renal impairment, weight gain, nausea, and tremors," she says.

Her hope is that, by inhibiting specific HDACs, it might be possible "to have the desired results of the drugs without the toxic effects."

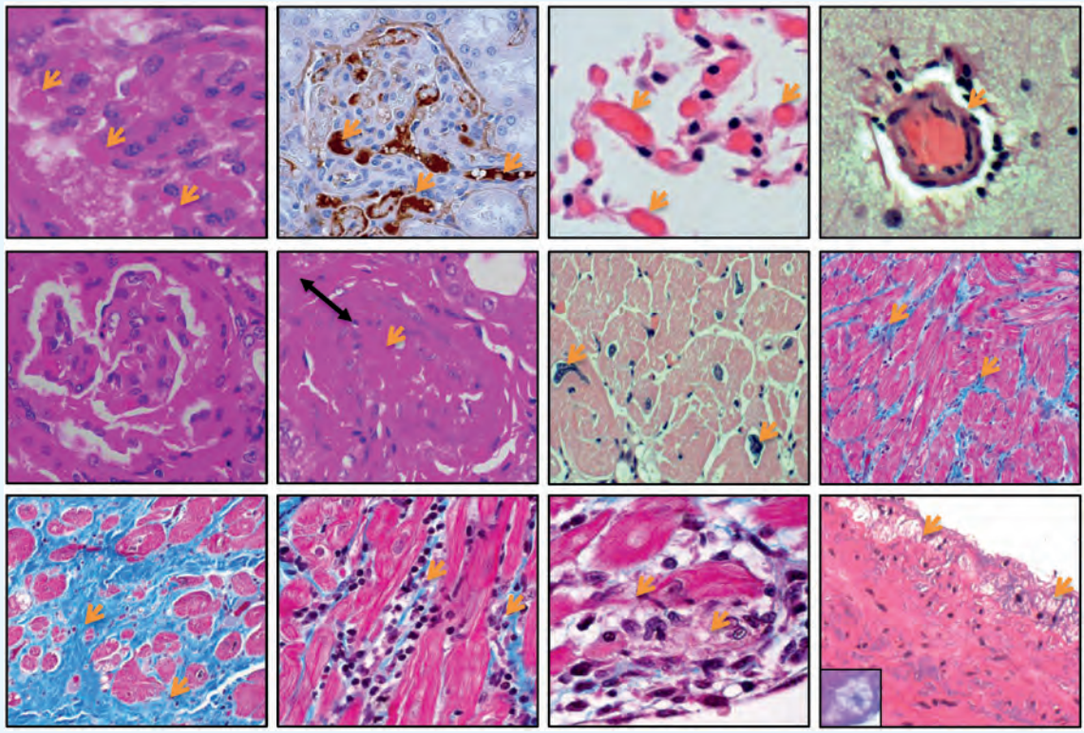
McClung has had several papers on her work with the Clock mouse published, as early as 2007 in *Proceedings of the National Academy of Sciences*. The most recent was October 2012 in the *European Journal of Neuroscience*. Her lab also has current grants from the National Institute of Mental Health and the National Institute of Drug Abuse. ■

COURTESY MCCLUNG LAB

A GUTSY TURN

A CULPRIT FOR EARLY CARDIOVASCULAR DEATH IN HIV PATIENTS

BY MELINDA WENNER MOYER



Pigtailed macaques with SIV, the primate version of HIV, develop serious vascular problems. Here, arrows mark lesions in an infected primate's kidney, lung, brain, and heart, as well as in its aorta.

BLOOD, AUG. 16, 2012; VOL. 120 ISSUE 7: 1357-66 WITH PERMISSION FROM THE AMERICAN SOCIETY OF HEMATOLOGY

It's a conundrum that has mystified virologists for years: Antiretroviral drugs do an excellent job of suppressing viral replication and opportunistic infections, yet HIV-infected patients still die young, frequently from heart problems. Some experts have blamed the drugs themselves; others have fingered unhealthy lifestyle choices common in HIV-infected patients, such as smoking. With so many confounding variables, it's difficult to tease out the true causes. But by studying how an HIV-like virus called SIV affects nonhuman primates, University of Pittsburgh pathologist Ivona Pandrea has found that the complications that afflict HIV patients stem not from drugs or cigarettes but from chronic immune activation—a finding that could have huge implications for HIV treatment.

More than a decade ago, while working in Gabon, Pandrea discovered that African green monkeys and mandrills can get SIV—simian immunodeficiency virus—without ever developing AIDS. Since then, Pandrea has been working to understand how these "nonprogressives," as she calls them, differ biologically from "progressive" primates, like pigtail macaques, which do develop AIDS. In a 2007 study, she reported that CD4+ immune cells in nonprogressive primates express low levels of CCR5, the receptor to which SIV attaches. The reason infection does not progress in these primates, she found, may be that the virus can't enter their target cells.

More recently, Pandrea has turned her attention to understanding how SIV infections unfold in these different primates. People with HIV typically have high incidences of cardiovascular problems like thrombosis and high levels of immune activation and inflammation markers in their blood. In a study published in *Blood* in August 2012, Pandrea reported that progressive primates, including pigtail macaques, also have high levels of these markers and that they develop serious cardiovascular lesions, much as HIV-infected people do. Nonprogressives such as African green monkeys, however, do not have these markers or these symptoms. Considering that primates do not take antiretroviral drugs or smoke, she says, the findings suggest that the virus itself is the cause of the problems.

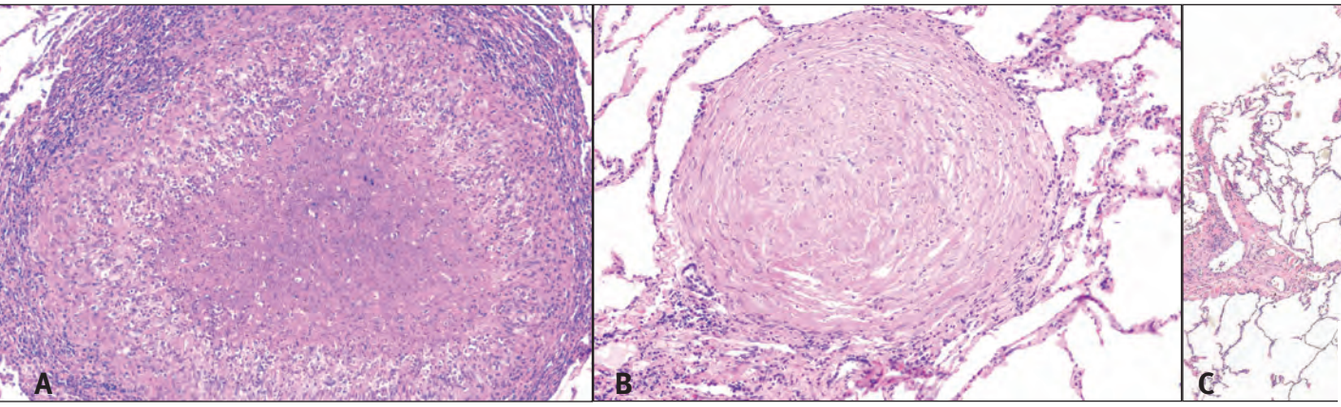
But how? Research by other scientists has shown that one of the symptoms of HIV infection is "leaky gut" syndrome: Because the intestines are home to many immune cells, early in infection HIV damages the gut mucosa, causing pieces of bacteria to "leak" into the bloodstream. Included in this harmful debris is lipopolysaccharide (LPS), a toxic component of some bacterial cell walls that, scientists speculate, causes inflammation and immune activation. When Pandrea injected nonprogressive African green monkeys with LPS for three weeks, she found that, sure enough, there was "an increase in the levels of immune activation and inflammation and coagulation in these animals," she says.

Pandrea wondered whether leaky gut–induced immune activation and inflammation could be a difference between avoiding AIDS and getting it. But perhaps it's not surprising that injecting toxic bits of bacteria would cause inflammation and an immune response. So, to place a final piece of the puzzle, Pandrea and her colleagues wanted to know whether by preventing inflammation and immune activation in progressive SIV-infected primates they might also be able to keep the animals healthy.

In an as-yet-unpublished study, they treated SIV-infected pigtail macaques with a combination of antibiotics and anti-inflammatory drugs, which also prevent leaky gut (also called microbial translocation). "The result was great," she says. Markers of immune activation, inflammation, and microbial translocation dropped drastically.

Pandrea treated the primates early in their infections, before people are typically diagnosed with HIV, so she doesn't know whether the approach would be realistic for humans. Still, Pandrea is excited, and she notes that some of her collaborators are already testing similar treatments in clinical trials: "We identified a treatment that may be useful for HIV patients." ■

KILLING RESISTANT TB



COURTESY EDWIN KLEIN, DIVISION OF LABORATORY ANIMAL RESEARCH

Images of tuberculosis lesions, or granulomas. From left, some granulomas appear caseous ("cheese-like") before medical intervention, then become fibrotic during successful drug treatment. Finally, when the bacteria are eliminated, scarring (interstitial fibrosis) remains.

LOW-OXYGEN PLAYERS ARE A NEW TARGET | BY DANA YATES

Tuberculosis is an intrinsically unpredictable disease. Spread through the air, TB germs cause an active infection in some people and an inactive one in others. And even among those with dormant TB, there is no way of knowing who will always breathe easy and who will end up with the disease (possibly infecting others). Findings derived from studies of monkeys by faculty members at the University of Pittsburgh suggest that reactivation of latent TB could be better prevented if a drug that is effective against bacteria in low-oxygen environments is added to the treatment regimen.

The results of the study by JoAnne Flynn, a PhD professor of microbiology and molecular genetics and an associate member of the Pitt Center for Vaccine Research, and Philana Ling Lin, an MD and assistant professor of infectious diseases, were published online in the Early Edition of *Proceedings of the National Academy of Sciences* last July.

In its active form, pulmonary TB causes people to cough up blood and mucus and experience night sweats, fatigue, fever, and weight loss. Without proper treatment, up to two-thirds of those infected will die of the disease. In fact, according to the World Health Organization, 1.4 million people died from TB in 2011. Among infectious agents, it comes in second, after HIV/AIDS, as the greatest killer worldwide.

A person can become infected by inhaling only a few airborne droplets from a sneeze or cough of someone who has TB. Nevertheless, most people who come into contact with the bacterium *Mycobacterium tuberculosis* develop an asymptomatic, latent infection—one that cannot be transmitted to others. While the bacteria remain in the lungs, they are safely contained in a lesion, or granuloma.

For a small percentage of those with latent TB, however, the disease can stir at any time, and in the early stages of the disease, show no symptoms. In turn, each of these people, who number two billion worldwide, can infect up to 10 to 15 others through close contact throughout the course of a year.

Currently, active TB that is not resistant to antibiotics is treated with two months of the drugs isoniazid (INH), rifampin (RIF), pyrazinamide, and ethambutol, followed by four more months of INH and RIF. Latent TB, meanwhile, is treated with nine months of INH. In either scenario, the treatment isn't easy. INH, for example, can cause liver damage, and people tend to abandon the lengthy regimen before its conclusion.

"No one really knows why people have to be on the drugs for such a long time," says Flynn. "It's just accepted that it's due to the persistence of the bacteria."

Hoping to find a better treatment, Flynn's team targeted the center of the granulomas; these low-oxygen settings are filled with dead cells. Previous work by other researchers had proven that TB bacteria that can survive low-oxygen conditions are resistant to INH.

So, Flynn's team speculated: Could TB bacteria be destroyed by a drug that specifically attacks nonreplicating bacteria in low-oxygen environments? In a project that was partly funded by the Bill and Melinda Gates Foundation, the researchers tested their idea using the antibiotic metronidazole (MTZ) in primate models. Ultimately, the team determined that two months of MTZ alone was just as effective as two months of INH and RIF at preventing reactivation of the infection. Moreover, adding MTZ to an INH and RIF regimen reduced the number and virulence of the bacteria in monkeys with active TB within two months.

One problem: Flynn notes that MTZ isn't safe for humans if taken for an extended time. However, she is excited about what they've learned.

"Low-oxygen bacteria are indeed present in TB, and you can use a drug to treat them," says Flynn. ■



These tiny (the smallest is about 5 millimeters) bioactive scaffolds were created by Rocky Tuan using a 3-D "printer," a mixture of chemicals, and light. (The blue tint was added to enhance visual impact.) Though here they look a lot like something you might drop into a cocktail, they aren't for cooling; the material was designed to form the foundation of new tissue and organs.

COURTESY ROCKY TUAN AND HANG LIN

WITH A LITTLE HELP FROM BIOMATERIALS

BY JOE MIKSCH

HEAL THYSELF



Things fall apart …

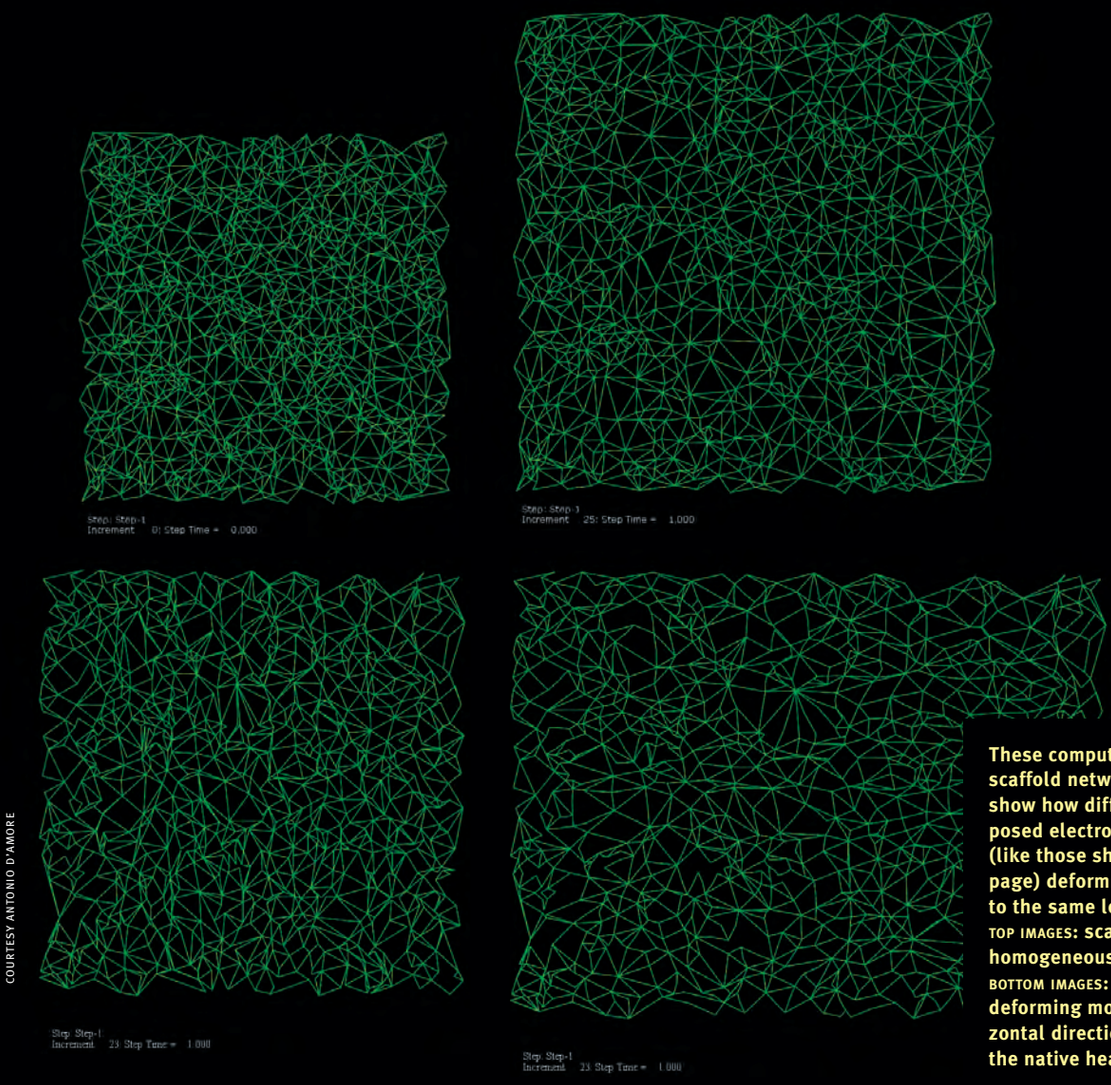
So wrote W.B. Yeats in "The Second Coming." It's safe to say he wasn't talking about the human body, but it's an apt metaphor. Things do fall apart. From injury, from illness, from inborn defects. It's rough out there (and in there, for that matter) for the corporeal being.

We try to fix things, then. Artificial joints, surgical mesh to help heal abdominal damage… In many cases, such interventions work quite well. But there are physical problems that require a more delicate touch. The injured heart. A ruined nerve. Can these things be fixed with "fakery," with something not human placed inside a human? The answer is: It's possible, with the help of nature.

Investigators at the University of Pittsburgh are developing various scaffolds to help with healing, even with regrowth. The key, in the minds of these bioengineers (all the players in this story are School of Medicine appointees who are also members of Pitt's Swanson School of Engineering's mega-multidisciplinary Department of Bioengineering) is to seed such temporary supports with stem cells or growth factors, which focus the body's healing powers on the site of insult or injury. And it's working, showing promise in several concurrent animal studies. The concepts here are not new: *Science* swooned over the nearing prospect of "off-the-shelf replacement parts for the human body" in a 2002 special issue. We didn't get there in the past decade and maybe we won't in the next, but observers say we've made some big leaps forward.

Physician, heal thyself? More like, *Body, heal thyself.*

COURTESY OF ROCKY TUAN AND HANG LIN.



COURTESY ANTONIO D'AMORE

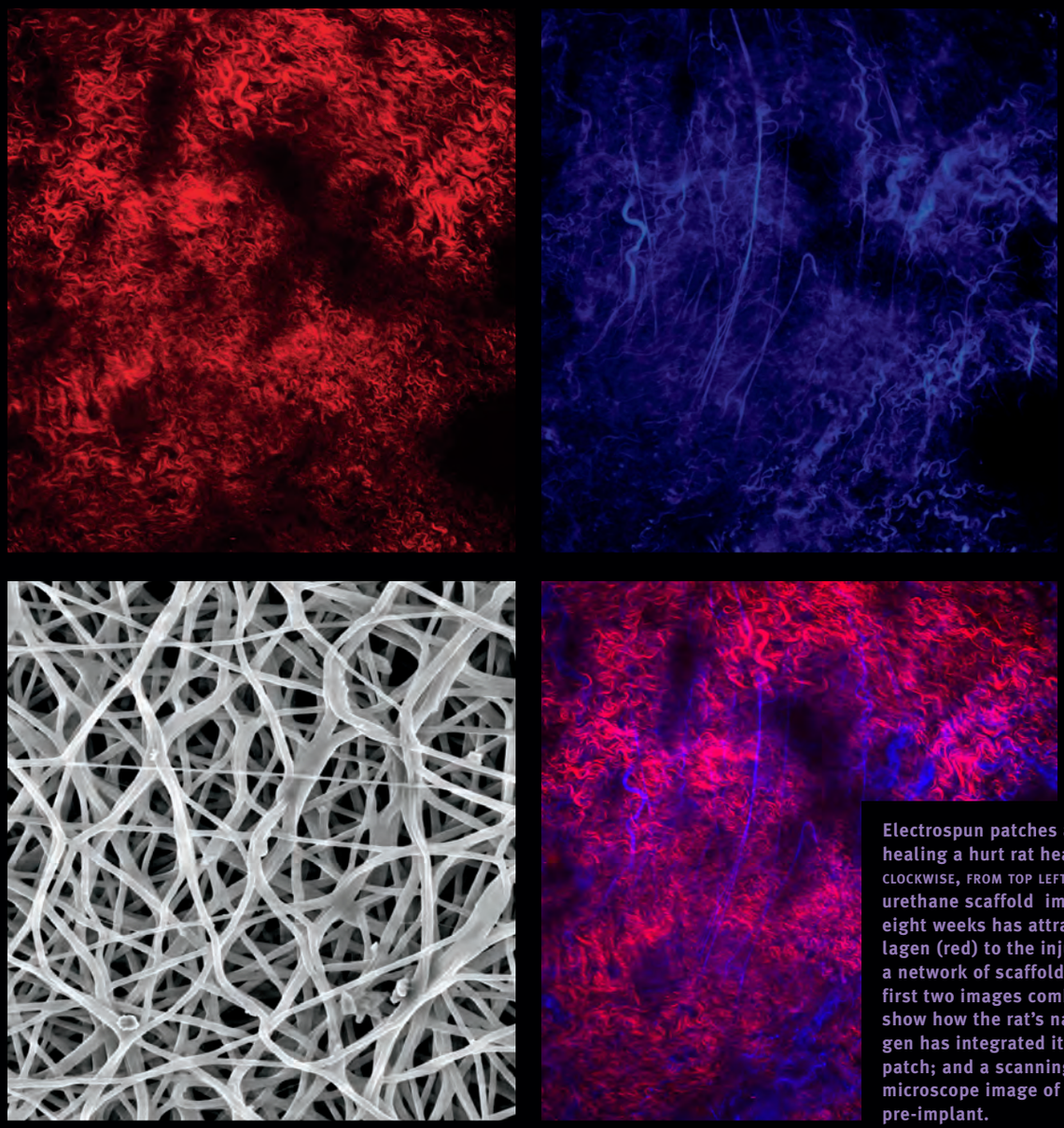
These computer-generated scaffold network models show how differently composed electrospun scaffolds (like those shown on the next page) deform when subjected to the same level of force.
TOP IMAGES: scaffold deforming homogeneously.
BOTTOM IMAGES: scaffold deforming mostly in the horizontal direction, mimicking the native heart wall tissue.

A NEW EAR AT KINKO'S?

What you see on the previous page is not a pile of ice cubes. It's a product of chemistry and visible light that could create a sea change in regenerative medicine.

About a year ago, Rocky Tuan, with the aid of Pitt's Clinical and Translational Science Institute, acquired a 3-D printer. Tuan is a PhD and director of the Center for Cellular and Molecular Engineering in Pitt's Department of Orthopaedic Surgery, as well as director of Pitt's Center for Military Medicine Research. To create this extraordinary material, Tuan starts with a liquid made from a photoinitiator (a compound that decomposes into free radicals when exposed to light; it's necessary for the production of both smog and plastics) and a form of polyethylene glycol (a component of the polymerization process, which creates three-dimensional chemical networks) or gelatin. Tuan uses the "printer" to pass visible light through the material. As the light passes through, layer by layer, the liquid solidifies into shapes as small as 5 millimeters high.

So, that's nifty, being able to make biodegradable, body-friendly solids—down to a micron scale—out of liquid and light. (Tuan says the machine can replicate any body structure, working off computer-aided drafting software.) And the end product needn't be solid; it can have a grid-like internal architecture mimicking that of the tissue it is intended to replace. The truly exciting part is what Tuan includes in his primordial soup: stem cells. By adjusting the density of the liquid, Tuan can ensure that the cells will be evenly distributed throughout the resulting solid. And, most importantly, the cells live. More than 90 percent of them remain viable a week after being polymerized. ("We have an interior hole in here, and it's 50 microns," Tuan says, pointing to an image of his non-ice cubes. "A cell is about 10 microns; so we can have a cell and a bunch of his little [cell] buddies living in there.") If things work as Tuan expects, these stem cells will grow up to become tissue, and the scaffold will melt away. *And, here, Mr. Van Gogh, is your new ear.*



COURTESY ANTONIO D'AMORE

Electrospun patches assist in healing a hurt rat heart. CLOCKWISE, FROM TOP LEFT: **The polyurethane scaffold implanted for eight weeks has attracted collagen (red) to the injured area; a network of scaffold fibers; the first two images combined to show how the rat's native collagen has integrated itself into the patch; and a scanning electron microscope image of the patch pre-implant.**

TAKEN FOR A SPIN

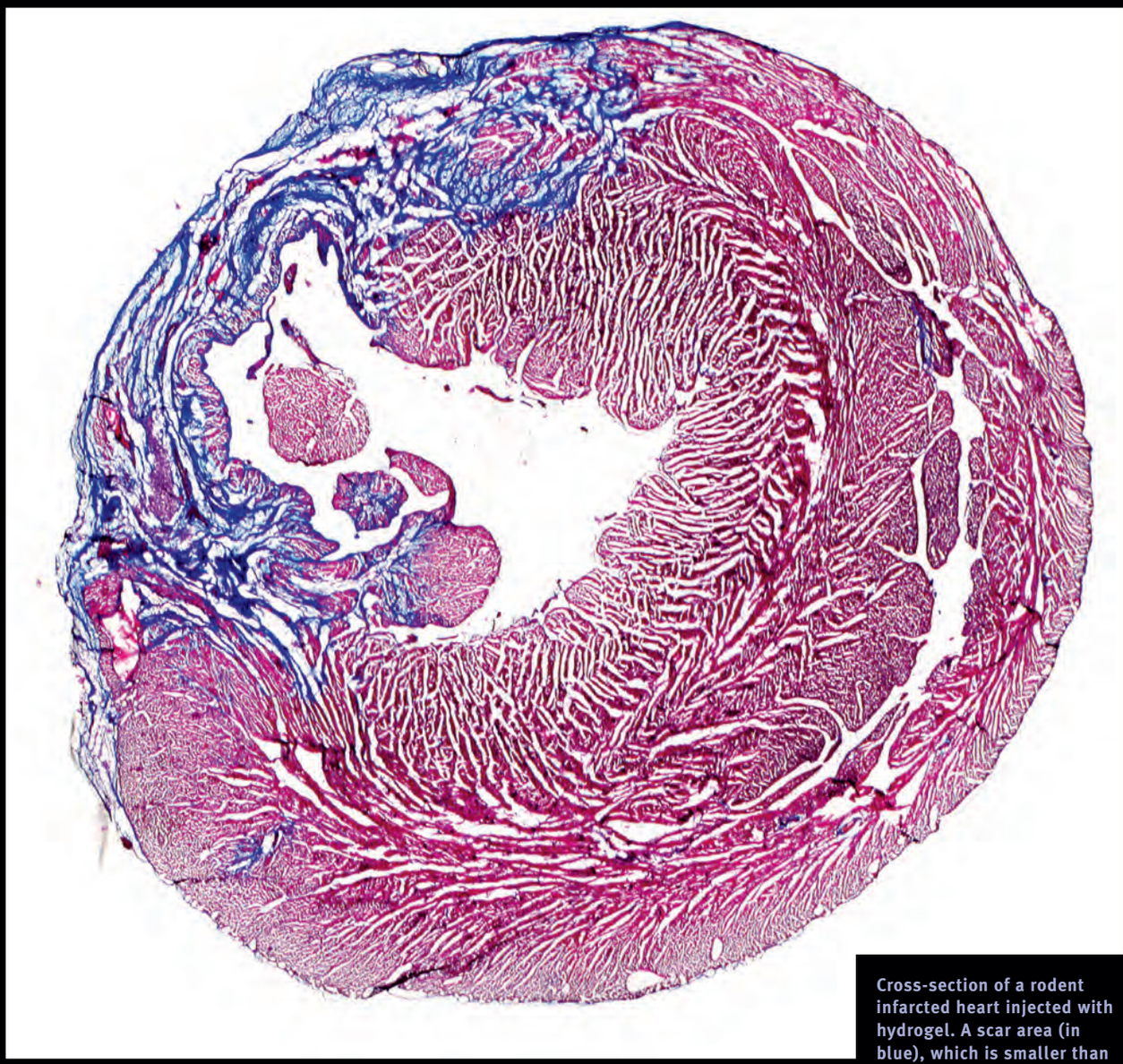
If your abdominal wall became perforated, a surgeon might implant a mesh to reinforce the damaged area. This works, but it can also lead to complications such as a fistula or infection. Pitt's William Wagner, a PhD, director of the McGowan Institute, and professor of surgery and chemical engineering, as well as bioengineering, thinks we can do better.

Using a technique called electrospinning, Wagner and colleagues use a liquid polymer sprayed on a rotating spindle to create small sheets of biodegradable material that can be used to patch anything from injured abdomens to hurt heart walls. The chemistry of the polymeric solution can be adjusted to mimic the tensile strength of the tissue, and the fibers can be arranged to replicate other mechanical properties, such as the direction in which the tissue stretches. These sheets, when properly designed and properly appended to a weakened area, can serve as support while the injury heals naturally. A fine temporary crutch.

Now Wagner et al., with the help of Stephen Badylak (DVM, PhD, MD, and Pitt professor of surgery and deputy director of the McGowan Institute), plan to use their electrospun material to speed up healing. Badylak has created an extracellular matrix (a gel created from pig tissue that has been stripped of cells but which retains growth factors) that Wagner incorporates into the polymeric solution before spraying it onto the rotating mandrel. "So we get these biohybrid composites that have the mechanical qualities of the polymer, but also have tissue ingrowth that's much more rapid than if we didn't have [Badylak's] material," Wagner says.

Essentially, they've created a bioactive Band-Aid.

Wagner cautions that "it's not magic. [We're not] getting new, fully functional tissue. But it is an important step getting the cells to come in [to the site of the injury] rather than just 'walking off.' We're actively trying to figure out how to get more of a positive healing response with these kinds of materials."



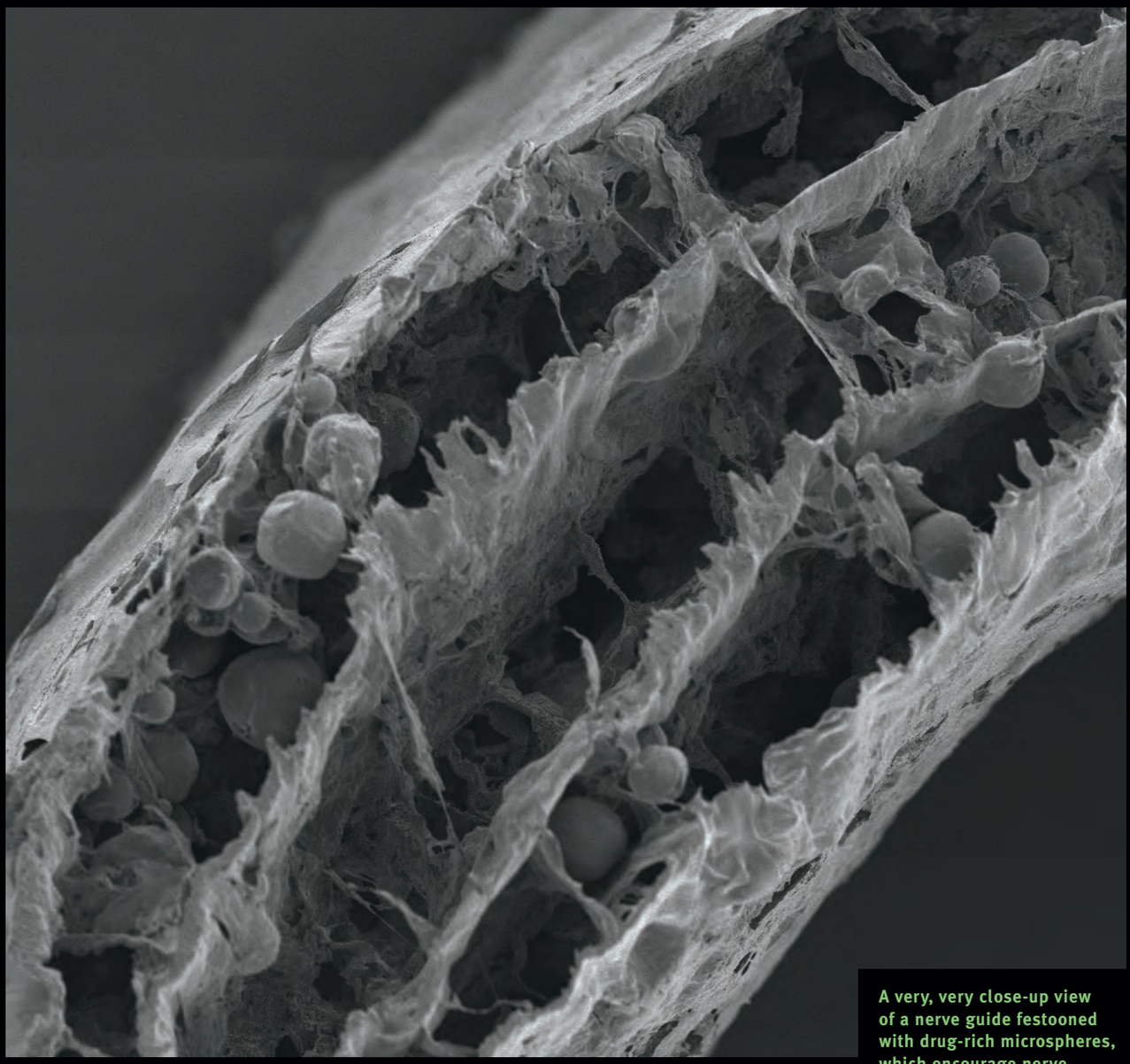
COURTESY WAGNER

Cross-section of a rodent infarcted heart injected with hydrogel. A scar area (in blue), which is smaller than the one observed in untreated animals, indicates early repair facilitated by hydrogel. The gel reduces stress on the heart while the body's own healing apparatus kicks into gear.

A GOO REVIEW

But maybe you don't want a bioactive Band-Aid. In some circumstances, perhaps it would be better to inject the material—replete with growth factors or stem cells—directly into the injured site.

A rat has a heart attack, damaging part of the heart wall. The wall is now thinned out, stretched, and weak; yet heart muscle ought to be strong and resilient. So researchers inject a gel into the heart to thicken it, to reduce the concentration of force on the damaged site, and lower the mechanical stress. Gel? Wouldn't that wash away? It would but for this: Wagner and his team have engineered the gel to be injectable through a small needle and then to solidify at body temperature into an elastic form. In time, as the heart heals, the chemistry of the material changes, allowing it to return to liquid form, still at body temperature, and wash away after doing its job as a structural support.



COURTESY MARRA

A very, very close-up view of a nerve guide festooned with drug-rich microspheres, which encourage nerve growth through the 5-centimeter conduit.

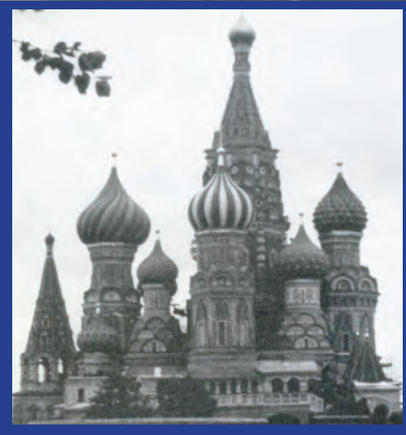
THE NERVE!

Injured peripheral nerves are treatable. One method, which has been tried with varying success since the 19th century, is the autologous nerve graft. This involves taking a nerve segment from another part of the body and inserting it into the lesion to reconstruct the damaged nerve. The technique can restore function (but only about 50 percent of it). It can also result in injury to the donor site or the formation of painful nerve scars called neuromas, among other complications. So, doctors went about creating artificial nerve conduits. But they only work on lesions less than 3 centimeters long.

Kacey Marra, PhD associate professor of plastic surgery in the School of Medicine and McGowan Institute member, has found that treating these scaffolds with a protein called glial cell line–derived neurotrophic factor (GDNF) may be the key to growing new, fully functional nerves that surpass the longstanding 3-centimeter barrier.

"In the walls of the guide [a 5-centimeter nerve conduit], we have microspheres—small, polymeric beads that deliver a drug, kind of like a gel-cap—and they release the drug for over 60 days," Marra says. The nerve endings, attracted by the GDNF, then grow to meet in the middle. "It works in the rat, and we're testing it in the nonhuman primate," Marra says. "If it works there without side effects, we're ready to go to humans."





On a 1958 trip to the Soviet Union, Mark Ravitch learned that Russia had made strides in refining a turn-of-the-century invention he'd been curious about since he was a resident: the surgical stapler. In the following decades, Ravitch worked with United States Surgical Corporation (gratis) to bring this technology to America and train surgeons from around the world to use the devices. ABOVE**: Ravitch (center) with colleague Pavel Iosifovich Androsov and their guide, "Tsintsiper."** RIGHT**: A snapshot of St. Basil's Cathedral taken by Ravitch on his trip.**

MARK RAVITCH BOTH MADE AND WROTE SURGICAL HISTORY | BY ELAINE VITONE

THE SURGICAL CURMUDGEON

MARK M. RAVITCH AND FELICIEN M. STEICHEN, *CURRENT PRACTICE OF SURGICAL STAPLING*, 1991

Each week, the late Mark Ravitch would sit and smoke his pipe in the front row of the surgical conference room in Presbyterian University Hospital, his pale blue eyes and large, gray eyebrows fixed in a stern expression. At the Department of Surgery's weekly morbidity and mortality conferences he led in Pittsburgh throughout the 1970s and '80s, residents held their collective breath as he read the list of all the operations they had performed that week.

If things had not gone well in any of those cases, there was no question that Ravitch would know and call a hapless resident out on it.

And then there you were, answering to *the* Mark Ravitch, surgeon-in-chief of Montefiore Hospital. The one who had introduced America to the surgical stapler—a device that was in those years just beginning to revolutionize surgery—and taught doctors all over the world how to use it. Who had edited nearly 20 medical journals and knew the science, practice, and entire history of surgery backward and forward. The one who had published a paper or book on almost any kind of case you could present to him, from the top of the esophagus to the bottom of the gut.



COURTESY MARSHALL WEBSTER

ABOVE: (From left) an unidentified Chinese colleague with Mark Ravitch, Thomas Starzl, and Henry Bahnson in Shanghai in 1983. The Pitt pack—including Charles Watson and Marshall Webster (not pictured)—visited nine Chinese cities and lectured in five medical schools on this monthlong trip.

No pressure.

How did you manage the patient?, Ravitch would ask, in his low, gruff voice.

Well, Dr. Ravitch, the resident would stammer, *We prepared him for surgery, then we took him to the operating theater and anaesthetized him ...*

Of course you did, he'd say. *You didn't operate on him on the floor. You didn't operate on him without anesthesia.*

He expected you to cut straight to the core problem, think clearly, and speak concisely, recalls Peter Ferson (MD '73, Res '79), professor of surgery at the University of Pittsburgh. Seconds count in the field of surgery, after all. If you wasted them, he would interrupt: *Didn't somebody have a dime to go call for help?* Or worse: *Why didn't you just take a gun and shoot him?*

If he took out his pipe and thumped it in the palm of his thick hand, you knew you were *really* in trouble.

Ravitch cowed his students on purpose, he admitted to colleagues. He used to say he never learned anything from anybody who was just complimenting him.

"I think he understood that we could see through it and recognize that his goal was to educate us and to clear our thoughts from cloudiness," says Ferson.

Ravitch would often pick on residents simply because of the way they had noted their operations on the list. If someone wrote, say, *Billroth Procedure*, he would ask who Billroth was (Christian Albert Theodor Billroth, the Prussian-born father of abdominal surgery and close friend of Brahms, of course) and where he went to medical school (University of Greifswald, naturally). Ravitch's knowledge—not just about surgery, but, by many accounts, most any topic—was encyclopedic, and he expected the same from his trainees. He wanted them both well read and well spoken.

The 45-year-old gentleman presented feeling nauseous, a young surgeon in training would say.

How did you know he was a gentleman? Ravitch would deadpan, glowering over his glasses. *And the patient was nauseated.* You *are nauseating.*

He once wrote, *Be wary of a man who cannot speak his native tongue*—a sensitivity that was probably heightened by the fact that he spoke Russian, German, and French. And a bit of Spanish and Italian. Plus Latin (recalling his high school classes). And he could pretty much wing it through most anything Slavic or Latinate you threw at him.

At first glance, the barrel-chested Ravitch was "incredibly intimidating," says Andrew Peitzman (MD '76, Res '84), a Pitt Distinguished Professor of Surgery, Mark M. Ravitch Professor, and vice chair of surgery, "but once you got to know him, he was just an incredibly good guy. . . . When I was senior chief on service, one of my kids was sick, and this big, gruff guy came to see my kid with a teddy bear in hand. It showed me what the real Dr. Ravitch was like."

For years, a group called the Ravitch Society—trainees from his 45-year teaching tenure at Johns Hopkins, Columbia University, the University of Chicago, and the University of Pittsburgh, where he arrived in 1969 and remained until his death in 1989—met annually in conjunction with the American College of Surgeons. Three generations of surgeons from all over the world would laugh over drinks, sharing stories and filling in one another's punch lines. If Ravitch wasn't presenting at some other conference that weekend (he continued teaching and lecturing until his death at age 78), he'd make an appearance, too.

The society wasn't just about merrymaking in the hotel bar though. A few months before Ravitch died of prostate and colon cancer, Hopkins named its first Mark M. Ravitch Chair of Surgery, funded by the society. Pitt endowed its chair at about the same time, too.

After his death, several Ravitch Society members, including the late Henry Bahnson, cardiothoracic surgeon and chair of Pitt's Department of Surgery from 1963 to 1987, were interviewed in a 30-minute video celebrating Ravitch's life and career. "I can remember distinctly," said Bahnson in the video, of his training under Ravitch at Hopkins, "Mark would come into the operating room, and I don't know if he'd do it intentionally or not, but he would stand up on a little stool, and he would stand up close, and the tips of his soles would dig into my calves."

Ravitch fans, friends, family, and surgical progeny also took part in the May 1990 "*Festschrift*" issue of *Surgical Rounds*, a journal for which Ravitch had edited and penned a column titled "Thoughts from a Surgical Curmudgeon."

In talking to those in the halls of Pitt who knew him, and sifting through the letters, eulogy transcripts, and essays written in his honor—not to mention the tomes of his own writing—one has to wonder what Ravitch would have to say about how his memory has endured.

Well, besides the obvious: Festschrifts *are not posthumous. The word they were looking for was* Gedenkschrift.

Ravitch was born in 1910 in New York City, the only child of Russian intellectuals, and grew up in the Bronx, near Crotona Park. He graduated from high school at 15. After receiving his bachelor's degree in zoology from the University of Oklahoma in 1930, he applied to Harvard Medical School but was rejected—a lucky break, as he later saw it, since it brought him to Hopkins, where he completed his MD, surgical internship, and pediatric residency, then remained to conduct research in surgery.

Ravitch trained under the renowned Alfred Blalock in the days when being a resident meant you essentially lived in the hospital. (Marriage was forbidden. Ravitch and his wife, Irene, married anyway, in secret, during his second year. They had three children: Nancy "Bunny" Ravitch Schwentker in 1941, Michael Mark Ravitch in 1943, and Mary Robin "Binnie" Ravitch in 1946.) Ravitch served three years on the European front during World War II. Once, during the Battle of the Bulge, he operated for 72 hours straight. In 1946, he returned to Baltimore as the first director of Hopkins' blood bank.

I truly believe,* wrote John Landor, *that Dr. Mark Ravitch always looked upon adults simply as grown children!

Two years later, Ravitch published a paper that proved to a skeptical American surgical community once and for all that a nonoperative approach to reducing hydrostatic pressure in infants and children with intussusception saved lives. He would eventually become the first to elucidate this once-mysterious ailment with comprehensive basic and clinical science.

In 1949, he developed a technique for correcting pectus excavatum, a congenital deformity that twists the sternum inward, creating a "funnel chest." His method, which involved disconnecting the ribs to allow the sternum to reshape, was standard care for decades.







LEFT: Nikolai (Mykola) Amosov, the Lenin Prize–winning surgeon who first demonstrated surgical stapling for Ravitch, in a snapshot taken by Ravitch in 1958. MIDDLE: (Clockwise from the left) Mark Ravitch, Louise and Hank Bahnson, Peggy Hanlon, and Irene Ravitch. ABOVE: Major Mark Ravitch, who served in the Battle of the Bulge.

Throughout his career, Ravitch remained the world authority on chest-wall deformities.

In the ensuing decades, spent in New York, Baltimore, Chicago, and Pittsburgh, Ravitch would innovate procedures for a number of surgical challenges. "He was probably one of the most prominent surgeons of the 20th century," says Marshall Webster (Res '70), now senior vice president of UPMC after serving as executive vice president of UPMC, president of its Physician Services Division, and Mark M. Ravitch Professor of Surgery at Pitt.

After Ravitch left Hopkins, he practiced general surgery, but, as John Landor, then-professor of surgery at SUNY Health Science Center at Brooklyn, noted in his *Surgical Rounds* tribute, Ravitch's first and most enduring love was pediatrics. *Were it not for the siren call of the intriguing possibility of applying stapling technology in general surgery …,* he wrote, *he might have ended his illustrious career solely recognized as a pediatric surgeon.*

At the start of Ravitch's career, children were still treated as small adults. He advocated for establishing pediatric surgery as a distinct specialty and is still considered a founding father of it. Among his many awards and accolades was the William E. Ladd Medal of the American Academy of Pediatrics—the highest honor for contributions to the field of pediatric surgery.

I truly believe, wrote Landor, *that Dr. Mark Ravitch always looked upon adults simply as grown children!*

In September 1958, Ravitch and his colleague, Duke University's Ivan Brown, walked into the thoracic surgery institute in then-Soviet Kiev. Ravitch, of course, acted as interpreter (his Russian was "badly accented and ungrammatical," by his own estimation—he spoke "like an Armenian," his Russian-born father teased). In the large office, behind an enormous desk, the Americans found the surgeon-in-chief, Nikolai (Mykola) Amosov, a man of slight build, his teeth capped in stainless steel.

Ravitch probably wasn't expecting much to come of this meeting. As representatives of the National Research Council, his group had been sent to meet with experts at the blood-transfusion institute, but it was now clear that that was out of the question. In the medical facilities that did honor the group's requests to visit in this Iron Curtain era, everyone was quick with offers of food and vodka, but when Ravitch asked if they could visit the wards, the answer was, without fail, *Nyet.*

To Ravitch's delight, Amosov leveled with him, speaking freely of his mortality and complication rates. Ravitch asked if his group could attend rounds. Amosov did his best to comply, but an administrator intervened. *Ward 1 is too untidy. . . . Ward 2's visiting hours are over. . . . Nyet. Nyet. Nyet.*

Clenching his teeth, Amosov said, "Bring

Semenov, Ivanov, Salydkin here at once, with their x-rays and their charts." And, straight away, the three patients were sent shuffling into the office in their robes and slippers, their charts and x-ray folders in hand.

What these cases revealed startled Ravitch: 3- and 4-inch double lines of thin white "B"s—metal staples—in the chest x-rays. Amosov said his institute had used them in some 200 lung resections. The following day, in Amosov's operating room, Ravitch marveled at the instruments' "extraordinary simplicity and efficiency."

Ravitch tried to find a government office where he could request a stapler to take home, but none of his calls panned out. *I suppose it was not unlike what might have happened if one had been at Fort Bragg in 1939 and seen a bazooka and said, "That looked like a dandy little weapon, and how did one purchase one?"* he later wrote. Ravitch gave up and went sightseeing.

A few nights later, he and his colleague were dining in a Leningrad café when a young couple asked if they could share the Americans' table; all the others were taken. Ravitch got to chatting with the locals and mentioned the staplers, which the young man said he was familiar with. In fact, they're made at a factory just outside the city, he said.

Upon hearing this, Ravitch thought of something curious that he had seen in Nevsky Prospect: a storefront sign with rounded gold letters on a black background that read, "Surgical Instruments and Apparatus."

Ravitch had puzzled at this. A business-district store selling the tools of an industry that was entirely government run? It made no sense. But he and Brown visited the store the next day and found it was true.

The only stapler they had in stock that day was a bronchial stapler.

"Is it for sale?" he asked the clerks.

"Yes."

"Is it for sale for cash?"

"Of course."

"How much?"

"440 rubles."

"Could we buy it right now?"

"Naturally."

"We are foreigners," Ravitch said, though he knew that was plain enough.

"What of it?"

Ravitch and his companion each left the store that day the proud owner of a 33-centimeter-long, 640-gram bronchial stapler in a black-velvet-lined birchwood box.

A few days after his return to Baltimore, Ravitch presented the stapler in the auditorium during grand rounds, demonstrating on an autopsied human lung. With one stroke of the instrument, he closed the bronchus—an operation that normally would require a dozen silk stitches, each individually sewn, tied, and cut. When Ravitch finished, a distinguished thoracic surgeon in the audience spoke up: *Well, that's great, but it looks awfully big and heavy. Besides, I love to sew.*

Ravitch would hear these same complaints for the next decade. And he understood why. *Surgeons are craftsmen,* he wrote. *They are proud of their art and reluctant to believe that an automatic instrument can do things as well as they can, let alone better.*

But Ravitch was convinced. In the July 1959 issue of *Surgery*, he predicted: *There seems to be reason to believe that some of these instruments and their derivatives will find a permanent place in surgery.*

The surgical stapler was invented in Hungary in 1908 (See Last Call, p. 40). But it was the Soviets who first saw its potential to change surgery on a grander scale.

During World War II, the Soviets endeavored to advance the technology, hoping to standardize surgery and better arm surgeons with a range of experience and skill levels to cover vast swaths of territory. The Scientific Research Institute for Experimental Surgical Apparatus and Instruments in Moscow—a monster effort of some 204 engineers, designers, draftsmen, machinists, lab techs, surgeons, and microbiologists—created scores of specialized instruments. There were staplers for bone, blood vessels, and even corneal grafts.

When Ravitch returned to Baltimore, he immediately began a series of animal experiments with colleagues Felicien Steichen, a mentee whom he later recruited as a Pitt professor of surgery and an associate chief of surgery at Montefiore in the 1970s, and Peter H. Weil, then chief resident at Lincoln Hospital in New York. They feared that the pressure from the instruments' closing jaws would damage the tissue, cause the seams to bleed, and allow newly sealed organs to leak. But none of this was the case. As they operated on the bronchus, as well as the lungs, the closures were "perfectly secure," the healing "beautiful." And then, some years later, they tried a more all-purpose Soviet stapler, called the UKL, to close portions of the intestines. *We were absolutely delighted with it,* he wrote.

Ravitch presented on the lecture circuit. Word about the staplers was getting around America. Newspapers covered his talks regularly. The February 1960 issue of *Popular Mechanics* ran a photo of a young beauty in a nursing cap holding a Russian stapler. The caption bragged, *It can even stitch sections of the heart.*

Several manufacturers approached Ravitch but backed out for various reasons (only to regret it later). In the end, it was United States Surgical Corporation, founded by Leon Hirsch, that finally took the plunge. Hirsch and Ravitch met through a patent broker and spent the next three years working together on a line of staplers. Once launched in 1967, these products grew company revenues from $350,000 to more than $1 billion in 1998, when United States Surgical was sold to Tyco International.

Ravitch, citing the inherent conflict of interest, did all of his consulting on product design free of charge.

Ravitch noted that, because each of the Russian staplers was handmade, the parts were not interchangeable. Each staple was loaded by hand into a tiny cartridge (a concern Amosov had dismissed—*Just leave it to young nurses with good eyesight*, he said). United States Surgical's staplers were manufactured to accommodate staple cartridges that were preloaded, fully interchangeable, and color-coded for various staple sizes.

Thoracic surgeons, eager to improve the safety of air-leak-prone bronchial closures, were the first to come around. The gastrointestinal surgeons followed when they realized how much easier it made their most challenging resections—the extreme high and low ends of the gastrointestinal tract.

With today's GIA (gastrointestinal anastomosis) stapler, you load it and fire it, which seals then cuts the ends of the intestine portion you're removing, says Peitzman. "The scrub tech reloads it, which takes 30 seconds. You fire it and resect the other end. You can do an anastomosis in literally a couple of minutes. By hand, the operating time is 10 times longer."

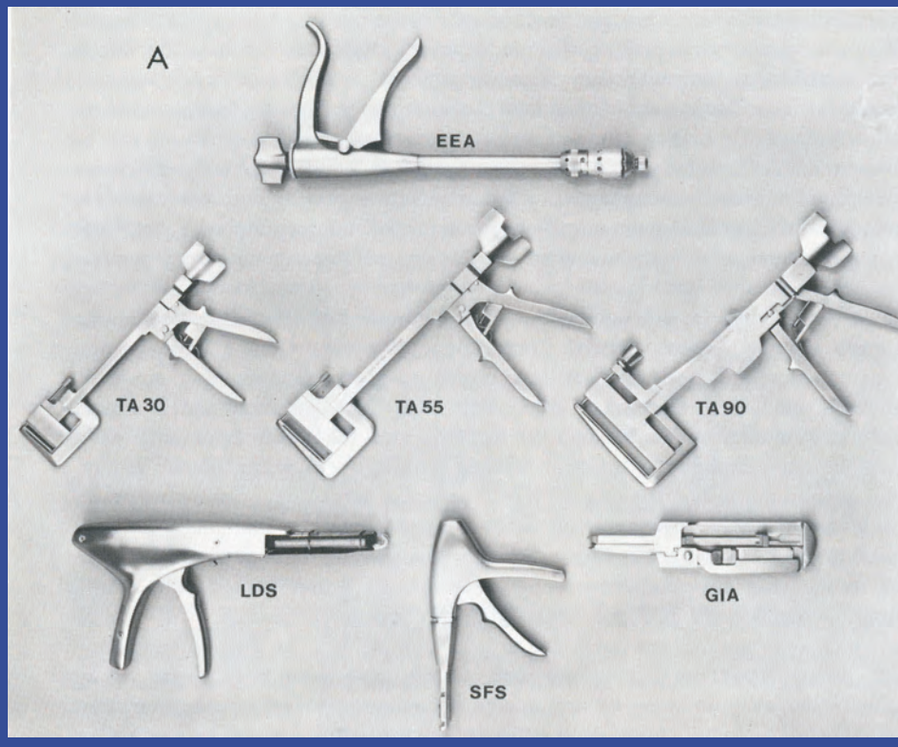
Stapling made possible several entirely new operations. Previously, a patient undergoing rectum resection would spend the rest of her days wearing a bag—staplers make it possible to restore function.

"Almost nobody today would sew the major arteries or veins of the lungs," says Jean-Michel Loubeau (Res '77). "We use staplers to do that now."

Smaller, private hospitals were the first to use staplers. Larger centers and universities came

FELICIEN M. STEICHEN AND MARK M. RAVITCH, *STAPLING IN SURGERY*, 1984





LEFT: The first stapling instrument Ravitch brought home from the Soviet Union, a bronchial stapler. RIGHT: The original line of American surgical staplers, each loaded with disposable, presterilized, preloaded, and interchangeable staple cartridges.

last, influenced by "pressure from below." One of the last barriers was that surgeons quickly became so sold on the technique that they didn't want to bother with prospective clinical trials. (Eventually, and repeatedly, studies would show that stapling and sewing are equivalent in terms of safety.)

At Pitt, Ravitch and Steichen developed a stapling course, which was attended by hundreds of surgeons from all over the world. "They were absolutely great instructors," says Loubeau. "Both Dr. Ravitch and Dr. Steichen had the training that allowed them to do all kinds of operations."

As it turns out, there is still plenty of skill involved in stapling. In fact, entirely new, specialized skills abound, thanks to this instrument once feared as a mechanical replacement to the surgical artist's hand: Staplers opened the door to minimally invasive surgery—starting in the '90s, they were miniaturized for this purpose. Now, even a liver resection can be performed laparoscopically.

In 10th century Arabia, wounds were closed by holding a large ant at the edges until it bit and then decapitating the critter. Through the ages, others used catgut, sheep intestine, and tendons of foxes, squirrels, opossums, moose, caribou, whales, reindeer, rats, rabbits, and kangaroos.

This is a Ravitch aside if there ever was one. He loved history. When the American Surgical Association asked him to write its organizational history in the early 1980s, they figured on a 300 or 400 pager. What they got was two volumes—750 pages each. Much of his material came from his personal library. His family donated his collection, which dated back to 1496, to Falk Library a few years after he died. (You'll find it on the second floor, in the Ravitch Room.) The Ravitches also donated to the National Library of Medicine some 200 boxes from his offices.

During Ravitch's tenure, walking into those rooms in Montefiore (where internal medicine is now) was like walking into the Taj Mahal, says Ferson.

"Flip the lights on, and there were treasures. Pictures of every major general surgeon in the country. Artifacts from his travels around the world."

"He saved everything and knew exactly where everything was," says Theresa Ratti, his assistant of eight years, starting just as *A Century of Surgery* was under way. It was the most interesting job she's ever had, she adds.

"He often said the doctor who got the eponym was never the first person to have described it and could give you lots of examples," says Webster.

Ravitch's office was also a site of surgeon hazing. He used to fill the room with the smoke of cheap cigars, bought at Thrift Drug, even though he knew it bothered guests, Ratti says with a laugh.

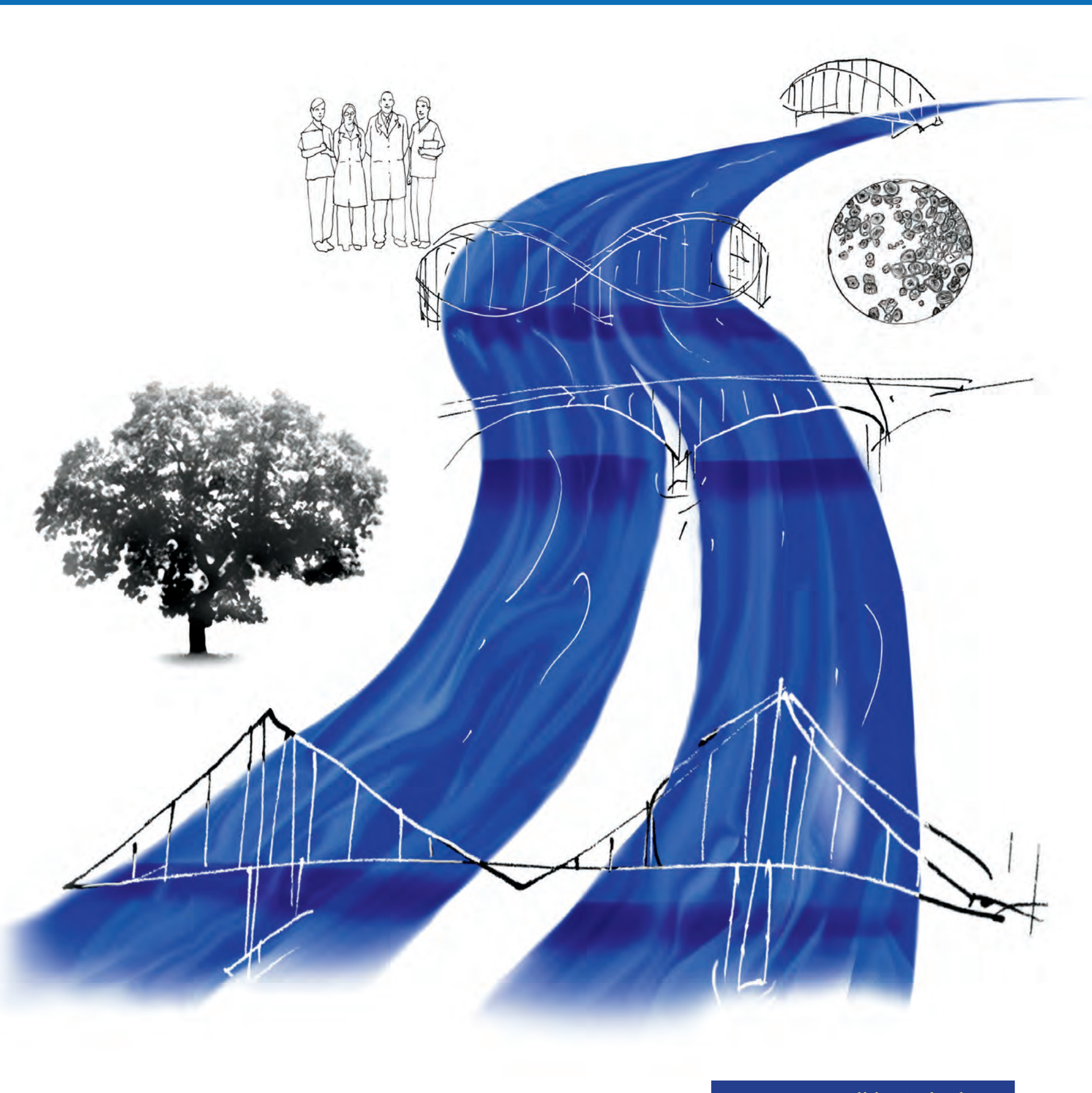
But after the trial by smoke, to know Ravitch was, by many accounts, to find yourself in a special kind of paternal care.

"When I saw that Dr. Peitzman got the Ravitch chair, I was so glad. Dr. Ravitch always really liked Dr. Peitzman and knew he was a solid guy, a solid surgeon."

And when she saw Peitzman in the hall, she told him so—a compliment that still awes and humbles him years later.

"[Ravitch] was the conscience of the residency program," says Ferson.

"We'd be doing an operation, and we'd say, *Okay, what's Dr. Ravitch gonna say about this?* … When you're involved in the milieu of a difficult case, it's unclear what's the right thing to do. But if I step back and pretend I'm in his chair, it's a lot easier. We've all learned to ask those questions: What's the core problem? What's the fundamental issue? Is this a wise thing to do? Sure, you could do it, but is it intelligent?" ■



Rising tides within **politics, technology, and science** are altering health care in this nation. Pittsburgh is ready to make the most of this moment.

THE NEXT BIG THING FOR MEDICINE

BY ARTHUR S. LEVINE WITH ERICA LLOYD

A CONFLUENCE AT THREE RIVERS

As the 19th century gave way to the 20th, medical schools had taken the place of the traditional physician apprenticeship, so Americans who were ill and injured were at the mercy of the graduates of these schools. And the country had more than its share of shoddy, ill-prepared practitioners.

In 1908, Carnegie Foundation for the Advancement of Teaching President Henry Pritchett summoned the help of the well-regarded educator and Carnegie scholar Abraham Flexner to survey the state of medical education in the United States and Canada and offer his suggestions for improvement. After visiting 155 medical colleges in the course of 18 months, Flexner recommended that all but 31 be closed or undergo serious reform. Of those he suggested be closed, he wrote this in his landmark *Medical Education in the United States and Canada*:

These enterprises—for the most part they could be called schools or institutions only by courtesy—were frequently set up regardless of opportunity or need … [Students were exposed to lab work and clinical education in only a handful of the better schools.] Little or no investment was therefore involved. A hall could be cheaply rented and rude benches were inexpensive.

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Janitorial service was unknown. Occasional dissections in time provided a skeleton—in whole or in part—and a box of old bones. Other equipment there was practically none. The teaching was, except for a little anatomy, wholly didactic. The schools were essentially private ventures, money making in spirit and object. A school that began in October would graduate a class that next spring; it mattered not that the course of study was [supposed to take] two or three years.

Not surprisingly, admissions standards were lacking at many of these schools: *No applicant who could sign his note or pay his fees was turned down,* noted the clear-eyed Flexner. And, *Many had "graduated" from nonexistent high schools.* Favoring the scientific and clinical example he knew from the German model (also used by Johns Hopkins School of Medicine), Flexner suggested the schools would be stronger as departments of universities.

Flexner's initial impressions of the University of Pittsburgh School of Medicine were tepid. But by 1910, he found a committed dean and physician in Thomas Shaw Arbuthnot. The new dean had high aspirations and within his first year had improved the facilities, hired "increasingly distinguished" and some full-time faculty, and raised admissions standards (a high school diploma was now required!)—and he was clearly just getting started. (Soon, two years of college would be required.) *Under the management of the University, this School of Medicine proposes to do what is necessary for the development of a Medical School of the First Rank,* noted Flexner.

Beyond Pittsburgh, reform was already in the air as Flexner began his study. Yet his famed report was a tipping point that altered the course of medicine, helping bring about the rigorous standards and preparation we associate with modern North American schools and the profession.

Medicine's next tipping point is now upon us. And Pittsburgh is poised to make the most of this moment.

To use a metaphor Pittsburghers know well, imagine a confluence of rivers. Three, to be exact. A trio of rising forces promises to alter health care in this nation: the push for reform (by that I mean improving quality and lowering cost); informatics (the ability to store and analyze huge troves of data); and an increasingly sophisticated understanding of biology (particularly at the cellular and molecular levels) that is giving us the ability to personalize medicine.

Without delving too deeply into the issue here, especially its politics, I'll quickly address why medicine costs so much in this country. Physicians, typically highly trained and well intentioned, are using every resource at their disposal to try to help their patients. As Steve Shapiro, an MD who came to Pittsburgh to chair our Department of Medicine and is now UPMC's chief medical and scientific officer, put it in an online interview, "The culture of the United States is just to do more—more medicine, more treatment. Doctors like doing more, and patients like us to do more."

But too few of those treatments are based on good evidence, and too much is done to avoid litigation. And, to be frank, the financial incentives for testing and treatment are strong and, often, misaligned with proper care. This vice is inherent in the system.

Our clinical partner, UPMC, has another model. It is one of the nation's two biggest payer-provider systems (the largest that is closely aligned with a research university), meaning it has its own insurance plan. Because it partially finances the cost of the care it provides, it is not marred by a perverse incentive to do unnecessary testing or care. It's notable that UPMC's insurance arm came about in the 1990s, not only because its board recognized the opportunity it would provide to affect the future delivery and analysis of care, but also because certain faculty members at Western Psychiatric Institute and Clinic advocated that UPMC enter the insurance business to protect the chronically mentally ill from the possible negative impact of managed care programs. Since then, UPMC's insurance arm has grown to service more than two million members.

At the same time, UPMC has readjusted its physician-compensation system to reward quality and safety. (See pp. 29–31.)

To get back to how medicine can miss the mark, consider how we treat metastatic cancer in adults. With the exception of testicular cancer and choriocarcinoma (a rare tumor of placental origin), chemotherapy isn't likely to cure cancer at that runaway stage. (I'm speaking of adults, not children here; both childhood cancers and children tend to respond better to chemotherapies.) What happens instead is heartbreaking: Adults with metastatic cancer are offered highly toxic, intensive chemotherapy cocktails. A small number of patients will have a remission, usually not a very durable one. Most will simply get sick from the drugs and end up spending their last days in the ICU.

This is just one example of how modern medicine is off kilter. I could cite examples for many diseases. So how do we become more effective? What physicians and other scientists intend to do at Pitt—and there are similar efforts at other academic medical centers—is to personalize care. That is, we want to give precisely the right treatment, at the right time, to the right patient. For a handful of drugs, this is already common practice. For instance, in 2008 the American Medical Association reported that 21 percent of patients who receive the anticoagulant Warfarin (a common treatment for pulmonary embolism and thrombosis) experience bleeding events. It is now recommended that physicians test to see whether a patient has certain genomic variations to determine optimal dosing—although the impact of these tests is still under investigation.

In the case of metastatic cancers, if we could identify the genes or other molecular mechanisms that make people responsive to chemotherapy agents as opposed to resistant to them, we would save a great deal of money. And, more profoundly, we would avoid compromising the remaining quality of life that people have.

"We are able to ask questions we've never been able to ask before. Never."

As of this January, Jeremy Berg—former director of the National Institute of General Medical Sciences and a thought leader in biomedicine—heads our new Institute for Personalized Medicine. The PhD, who has been a member of our faculty since 2011, also serves as Pitt's associate senior vice chancellor for science strategy and planning and as a professor of computational and systems biology. Jeremy takes the reins as the cost of sequencing a genome (the entirety of an organism's genetic material) has trended down to almost $1,000. We expect that sequencing genomes of patients (likewise viruses, bacteria, and tumors) will be

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Abraham Flexner, whose famed 1910 report was the first tipping point for medicine in this country.

routine in the near future.

Yet identifying a genetic variation is often not enough to fix what ails a patient. "Just in this last decade, we are learning how complex biology is," says Jeremy.

"This is an exciting and also a frustrating time. We are going to be able to measure genomics and other [molecular events] without being able to tell you what they mean," he says.

We still need to understand the disease process, Jeremy explains. "There are many, many different genes contributing to variations throughout the population." He likens human ills to a car that won't start: There could be many reasons—a faulty alternator, an empty gas tank, and so on.

He adds, "We know from previous studies that if you understand what role the gene plays, you can understand the disease process more deeply. It can also provide insight into what role environment plays in disease."

Since taking on his responsibilities at the new institute this January, Jeremy has been knocking on doors to visit with the many teams throughout the medical school that are already on their way to personalizing care in their respective fields. For example, Naftali Kaminski, PhD professor of medicine and director of UPMC's Dorothy P. & Richard P. Simmons Center for Interstitial Lung Disease and our Lung, Blood, and Vascular Center for Genomic Medicine, expects that genomic markers for idiopathic pulmonary fibrosis (most found by his lab), which indicate that the disease will progress more slowly in some patients, will soon guide treatment decisions.

Like Jeremy, another member of our faculty, PhD professor of pharmacology Adrian Lee, has taken on new responsibilities. I'm convinced that Adrian's new role couldn't be found at another academic medical center—at least not on the scale he's operating within.

In addition to pursuing his work as director of UPCI's Women's Cancer Research Center, Adrian is leading the research arm of a massive project that will figure out how to use patient data to foster personalized medicine. UPMC announced in the fall that it is investing $100 million throughout the next five years in a data warehousing, integration, and analysis project that will bring together clinical, financial, administrative, genomic, and other information. This is a tall order.

"UPMC's analytics initiative is one of the most ambitious and comprehensive efforts of its kind in health care," Neil de Crescenzo, senior vice president and general manager for Oracle Health Sciences, notes in a November 2012 news release. (UPMC is partnering with Oracle, as well as IBM, Informatica, and dbMotion in this effort.) "Given the size, scope, and influence of this leading academic medical center, the discoveries made here are likely to transform the practice of medicine far beyond the walls of UPMC."

"When a patient walks in the door, we want to be ready to say, 'You have mutation X, here is therapy Y,'" says Adrian.

To accomplish this goal, we need to link some crucial patient information—genotype and phenotype. Genotype is what we call the specific molecular signature that reveals peculiarities of a patient's genome, or inheritable characteristics. A phenotype is the broader description of a person that ends up in clinical records (like diseases endured, medications taken, weight, and family history). This information, of course, may already exist for some patients and research participants. The difficulty lies in getting medical center and research data systems to talk to one other. Adrian and his partners at Pitt and UPMC are charged with making that happen.

It's messy work.

And without an institutional foundation in place to facilitate the process, physicians and researchers who hope to merge clinical and research data for their studies have the odds stacked against them. Think silos of data. Data sets that don't match up. Absent fields. Data that never made it into the digital realm. "Data graveyards."

"Most researchers would just give up," says Adrian.

Some Pitt researchers—in head and neck cancer and melanoma, for instance—have moved such projects forward succesfully. But there's nothing in place systemwide to make the task less arduous. That has meant going back to patient charts and pathology reports to manually extract data, again and again.

"I think that's a major reason we haven't moved [a lot of promising research] into the clinic," says Adrian. But with Oracle, Pitt's team (of mathematicians, biostaticians, programmers, informatics and IT experts, genomics whizzes, researchers, oncologists and other physicians) is doing the groundwork to make the linking of genotype and phenotype *routine* for scientists at the University.

"To share data and put it in a 'warehouse' is a fundamental change in practice," both logistically and philosophically for scientists, says Adrian. "We're laying the foundation for a house—for a mansion. Hopefully we won't go into foreclosure," he says with a chuckle.

"We are in a time of massive data," Adrian says, adding that UPMC now has 3 petabytes of patient data. Not familiar with a petabyte? A petabyte is equal to 1 quadrillion bytes.

"When you go to your doctor, the physician considers a couple of variables on you," says Adrian. "The human brain can only handle four or five variables at once. But we need to take into account hundreds of variables on you."

The time is ripe for a big data convergence at UPMC and Pitt. Adrian and his colleagues at the cancer center were working toward this independently when they learned that Steve Shapiro and other UPMC leaders had the same goals. "It's snowballed since," Adrian says. In designing the new model, the institutions have pulled together professionals from various disciplines to get their feedback. And Adrian's IT team now meets with UPMC IT representatives every week.

Adrian's counterpart at UPMC, Lisa Khorey (vice president for enterprise systems

$5,495–$10,000: **Cost of sequencing a human genome in 2012. The $1,000 price point, long awaited by the science community, is within reach, experts say. Another hurdle: paying for the analytics to make sense of the information.**

2 PEOPLE, MILLIONS OF DIFFERENCES: **Any two people have millions of differences in their genomes, which are made up of three billion base pairs. Yet, we probably share more than 99 percent of the same genetic material.**

and data management at the medical center), reports that UPMC has been "methodically studying best practices" in health analytics and data management for years with the braintrust down the street at Carnegie Mellon Software Engineering Institute.

"We're now ready to turn what we've learned into action," she says.

On a recent chilly Friday in February here, Adrian and his team got a peek at what the future of medical research in Pittsburgh will look like. Their partners from Oracle had been camped out at Pitt for days preparing the team for a trial run on a prototype that would merge clinical and genomic data.

Their first "use-case"? Breast cancer, which is Adrian's area of expertise.

The system was able to integrate UPMC clinical data from 140 breast cancer patients with molecular findings from The Cancer Genome Atlas. (An impressive portion of the samples for this NIH project has been gleaned from Pitt's excellent tissue bank.)

"We have the first product from Oracle that allows us to do exactly what we said we'd do—integrate clinical and molecular data," says Adrian. "We are able to ask questions we've never been able to ask before. Never."

He notes that this "very small, discrete" use-case, and others that will follow, is designed to work out the glitches involved in integrating key data systems. Yet it's already paying off in terms of what appear to be useful findings (though the work is very preliminary at this point).

"Now we can say—[for] these 140 patients—'Show me genomic differences in women who are postmenopausal versus those who are premenopausal,' for example," says Adrian. "We saw striking differences. We hope these will lead to new treatment strategies."

In February the system focused on changes in DNA copy number and gene expression. Next fall, it will look at point mutations (like missing or additional nucleotides) and structural variants (e.g., chromosomal segments that have moved to new positions) within the 140 tissue samples. "We will never be finished" using the tool, says Adrian. That said, his team will soon move on to similar use-cases for 10 other cancers, as well as other conditions, including diabetes and acute renal failure.

In the rounds that follow, the product is likely to become more robust. "It's like Netflix," Adrian offers. "The system doesn't know much about you when you first sign up, but after ordering tens or hundreds of movies, then it's able to more precisely suggest DVDs you would like." This is how machines learn. They get smarter as we add more data and ask more questions.

The big data world we're entering is not without complications. Earlier this year, Yaniv Erlich from MIT's Whitehead Institute for Biomedical Research reported that his team was able to identify about 50 "anonymous" research subjects by comparing their genomic data to data available on genealogy sites and in other public records. This experiment was conducted to illuminate potential gaps in privacy so they could be addressed. UPMC and Pitt are taking such issues very seriously.

Fortunately, we have a very strong group of ethicists at Pitt who will be working with us as we move forward. For instance, Lisa Parker, associate professor of human genetics in the Graduate School of Public Health and a Center for Bioethics and Health Law faculty member, is an expert on informed consent and confidentiality issues in medical research.

"What 'genetic privacy' can mean is complicated," she says. "We leave behind our DNA on every restaurant water glass. [Still, most people don't] have the scientific resources to analyze DNA and connect genetic information to a name on a credit card slip. What is most important is not possession of genetic material or even genetic information, but how genetic information is used. We need regulations and penalties regarding misuse of information." A federal act (GINA) prohibits health insurers from discriminating on the basis of genetic information; other protections are patchwork at this point.

Lisa also notes that Pitt and UPMC won't presume patient consent: "We want to ask people to participate after we explain the importance of their contribution and the measures we have in place to protect their privacy."

Big data is going to be key to moving personalized medicine forward. Think about how many genomes or partial genomes would be needed to find patterns that will lead to personalized outcomes for patients: "Any given two people have literally millions of differences in their genomes," says Jeremy. "We are very, very similar to each other, but if there are three billion DNA base pairs [in the human genome], and if we are 1 percent different—that's probably a little high—but, 1 percent of three billion is 30 million. So that's lots of differences from one person to another. To try to get enough information to get patterns out of that, you need lots of samples, perhaps a thousand."

In addition to casting a wide net for patient samples, Pitt researchers will be diving deeply into molecular goings-on.

The University is exploring partnerships with other organizations to bring deep sequencing ("deep" because it allows us to detect rare mutations and other molecular anomalies after sequencing an individual genome perhaps hundreds of times) and other new technologies into our portfolio. And our own researchers are helping to uncover the many mysterious compensatory and regulatory machinations at work that were previously tossed aside as "junk DNA."

"What Pitt and UPMC bring to the table is really first-rate basic and clinical science, as well as the patient population," Jeremy notes. UPMC's network now includes 20 hospitals and 400 outpatient sites.

He reminds that correlation is not causation: "There's an idea that you take all the data, put it in a bag, and shake it up, and you'll find out what you need. That didn't work in finance or other fields. Mechanisms really matter. Weather prediction, for example, has gotten better because it's based on solid principles of physics."

That's where strong science enters in. We need to understand the organ and build on that, he says: "One of the most important things in scientific discovery is knowing when you should be surprised. If you are just looking at correlations, that's not a basis for being surprised. It's unlikely to lead you anywhere productive."

What I keep hearing from my colleagues here is we have an extraordinary opportunity in Pittsburgh. Consider the research strength of this University (which shot up to number five in terms of National Institutes of Health research funding a few years ago), UPMC as the largest payer/provider linked to a research university, the technology powerhouse Carnegie Mellon University in the same neighborhood, corporate technology partners like Oracle and IBM. And the secret ingredient: Pittsburghers.

Pittsburghers love their town and are more likely to stick around

than are folks who live in other biomedical meccas—like Boston.

"In the early days of genetic research, places with stable populations, like Salt Lake City, were the powerhouses," reminds Jeremy. That stability, he notes, will be "good for a research tool and good for Western Pennsylvania." And because this stable patient population is so large, we are in an excellent position to make advances in understanding and treating both common and rare diseases that arise within it.

The Salk vaccine could have been called the Pittsburgh, or Pitt, vaccine, Jonas Salk's son, Peter Salk, has said. And according to some, Dr. Salk would have wanted it that way. In the '50s, Pittsburgh scientists, practitioners, and community members (including thousands of children) literally rolled up their sleeves to make history.

This is another Pittsburgh moment. ■

Arthur S. Levine is dean of the School of Medicine and senior vice chancellor for the health sciences. Erica Lloyd is editor-in-chief of this magazine. Michael Fitzgerald and Elaine Vitone contributed to this report.

IN A MAELSTROM

AT HEALTH CARE'S STORMY FRONT, AN OPPORTUNITY TO RETHINK HOW MEDICINE IS DELIVERED

BY MICHAEL FITZGERALD

Diane Holder might forgive you if you accidentally called her Diane Hold-on. Much of her job involves handling the accelerating pace of change coming with health care reform. As president of UPMC Health Plan and its Insurance Services Division and executive vice president of UPMC, Holder is effectively dealing with a maelstrom.

Money drives the maelstrom. Health care sucks up money at a far higher rate here than in other developed nations. Yet compared to the citizens of those nations, the health of Americans is mediocre.

To try to slow down the storm, the U.S. government, which this year will pay for more than half of the medical care doled out to Americans, is beginning to integrate "value-based payments" to hospitals. Instead of paying by volume—number of patients, tests, and procedures—quality of care will dictate payments. In another effort to economize, we will see more care delivered by highly trained nurses and physician assistants working with doctors.

Meanwhile, technology is giving patients access to and control over their entire medical histories. It also allows medical professionals to make virtual house calls. Such trends increase the potential for competition, which should reduce costs.

"We're seeing a lot of changes," Holder says. UPMC is not just waiting to get buffeted by this storm. It has begun shifting away from the pay-for-service model, adopting "shared savings," in which UPMC's Health Plan splits cost savings if quality-of-care targets (such as whether patients get better or stay healthy) are met. In 2012, it also boosted its roster of advanced-practice providers like physician assistants by 16 percent.

With UPMC's partner the University of Pittsburgh, a storied medical research institution, "we have the opportunity to do things differently," says Holder (who is also an assistant professor of psychiatry). UPMC is becoming well positioned to, for example, combine research findings with a database of care information to help suggest more individualized treatments for patients, depending on their unique genetic characteristics. (See Arthur Levine's article, p. 24, for more on how this is unfolding.) Such combinations should reduce inefficiencies and improve outcomes at the same time.

The Health Plan even does its own research: The nonprofit UPMC Center for High-Value Health Care, established in 2011, examines ways to improve service and payment policies for different types of patients and providers.

UPMC has been investigating ways to reduce the incidence of chronic conditions, the source of some 70 to 75 percent of all health care spending in the United States.

For instance, UPMC changed its threshold for paying for nutritional and support services for overweight children. Where once those services were not paid for until the child was officially obese, now UPMC's Health Plan kicks in at a threshold below obesity, which should help reduce the long-term costs associated with the condition.

In another experiment aimed at a chronic condition, UPMC focused on reducing the percentage of smokers on its own staff, which stood at 19 percent, about the same as the national average. UPMC found that patients who combined smoking-cessation coaching with medication to combat cravings were more likely to quit smoking than patients who'd just picked one method. So the health plan waived co-pays for the medication for patients who also worked with a coach. The number of smokers on staff fell by 9 percent.

Solid science may show us the way out of this maelstrom. ■

CHRONIC CHALLENGES

70–75% of every health care dollar is spent on someone with a chronic condition.

35.7%: adult Americans who are obese.
16.9%: Americans 2–19 who are obese.

20%: adult Americans who smoke.

33%: Americans with high blood pressure.
54% of these do not have their condition under control.

8.3%: Americans with diabetes.
0.26%: Americans under 20 with diabetes.

THE PITTSBURGH MODEL

FOR TRANSFORMING HEALTH CARE

Health care reform. Three words that promise systemic, wholesale change in the way Americans receive health care.

"People question whether health care reform is going to happen or not," says Steven Shapiro, the MD executive vice president and chief medical and scientific officer at UPMC, as well as president of its Physician Services Division and a professor of medicine in the School of Medicine. "It has to. Our country simply can't afford to spend 17 or 18 percent of GDP on health care."

And the UPMC/Pitt medical community is not waiting around to see what politicians might imagine; it has a vision for the future of medicine. That vision is built upon what could be called the Pittsburgh Model, which integrates the medical center's care providers and payment system with the University's impressive research power in a way that perhaps no other academic medical center in this country is attempting. "Transform" is a more apt word for what is happening here than "reform."

The big idea? Smarter care that will lead to fewer unnecessary tests, more precise treatments, and healthier Pittsburghers.

Here's how the future is unfolding.

—Compiled by Michael Fitzgerald and Erica Lloyd

SOURCES: CDC, UPMC, UNIVERSITY OF PITTSBURGH.

200 DIFFERENT DATA SOURCES in different systems across UPMC operations—previously "silos" of information—are being accessed and integrated with data sources from Pitt researchers.

"We're starting to build these pathways so we can do the appropriate care, not unnecessary care." *—Michael Becich, chair of Pitt's Department of Biomedical Informatics*

3 PETABYTES: estimated volume of current UPMC patient data.

$100 MILLION, 5 YEARS: investment in melding those sources into a new data warehouse, with help from IBM, Oracle, Informatica, and dbMotion (partly owned by UPMC).

1ST QUARTER, 2013: when the first version of the new data warehouse goes into service.



AN EXPANDED CARE TEAM makes sense on a number of fronts, studies show. You probably don't need an MD to treat poison ivy, for instance. "Intraprofessionalism" is now part of the med students' curriculum at Pitt.

"All sorts of market forces are pushing us toward team delivery of care."

—Benjamin Reynolds, director of the UPMC Office of Advanced Practice Providers

1,400: advanced-practice providers (nurse practitioners, nurse midwives, certified registered nurse anesthetists, and physician assistants) practicing at UPMC in collaboration with or under the supervision of a physician.



16%: increase in UPMC advanced-practice providers from 2012 to 2013.

500: new advanced practice providers UPMC expects to hire within the next four years.

REMOTE CONTROLS

Virtual house calls and telemedicine allow expertise to reach patients from a distance.

3,714: patients served through UPMC telemedicine from 2007 to March of this year at clinics and in-home programs. And Children's Hospital of Pittsburgh of UPMC faculty will soon bring remote pediatric emergency care to four rural hospitals.

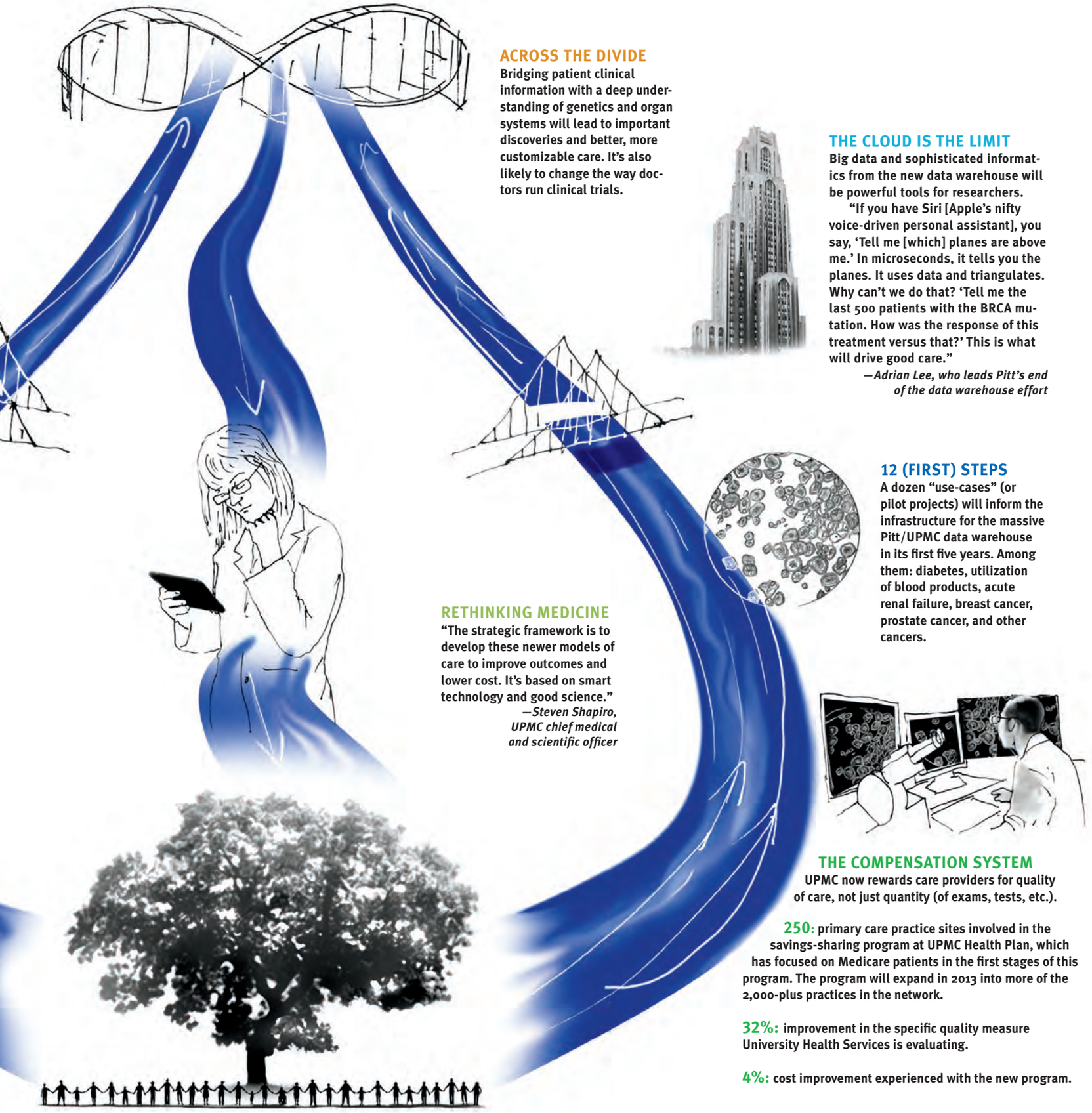
"For the average worker with employer-based health insurance, growth in premiums and cost sharing has largely erased wage gains over the past decade."

—The Commonwealth Fund, May 2012

$7,960: what the U.S. spent per person on health care in 2009.
$3,960: what the median spending was for health care in 2009 in 13 other industrialized nations, ranging from $2,828 in Japan to $5,352 in Norway.

5%: reduction in revenues for most U.S. medical centers in 2012 because of unofficial health care reform by insurers.

$1,080: average MRI scan cost in United States in 2011.
$599: cost in Germany in 2011.



ACROSS THE DIVIDE

Bridging patient clinical information with a deep understanding of genetics and organ systems will lead to important discoveries and better, more customizable care. It's also likely to change the way doctors run clinical trials.

THE CLOUD IS THE LIMIT

Big data and sophisticated informatics from the new data warehouse will be powerful tools for researchers.

"If you have Siri [Apple's nifty voice-driven personal assistant], you say, 'Tell me [which] planes are above me.' In microseconds, it tells you the planes. It uses data and triangulates. Why can't we do that? 'Tell me the last 500 patients with the BRCA mutation. How was the response of this treatment versus that?' This is what will drive good care."

—Adrian Lee, who leads Pitt's end of the data warehouse effort

12 (FIRST) STEPS

A dozen "use-cases" (or pilot projects) will inform the infrastructure for the massive Pitt/UPMC data warehouse in its first five years. Among them: diabetes, utilization of blood products, acute renal failure, breast cancer, prostate cancer, and other cancers.

RETHINKING MEDICINE

"The strategic framework is to develop these newer models of care to improve outcomes and lower cost. It's based on smart technology and good science."

—Steven Shapiro, UPMC chief medical and scientific officer

THE COMPENSATION SYSTEM

UPMC now rewards care providers for quality of care, not just quantity (of exams, tests, etc.).

250: primary care practice sites involved in the savings-sharing program at UPMC Health Plan, which has focused on Medicare patients in the first stages of this program. The program will expand in 2013 into more of the 2,000-plus practices in the network.

32%: improvement in the specific quality measure University Health Services is evaluating.

4%: cost improvement experienced with the new program.

WHERE THE HEART IS The relatively stable and diverse population in Pittsburgh is "good for a research tool and good for Western Pennsylvania."

—Jeremy Berg, who directs the new Pitt–UPMC Institute for Personalized Medicine

1,000: approximate number of patients at UPMC whose genomic data has been gathered for various research efforts (631 for NIH's The Cancer Genome Atlas).

10,000–100,000: guesstimate of number of patients whose genetic data UPMC will have in five years (to be gathered with their consent). That data will feed back into research efforts to improve and personalize care.

55,000: employees at UPMC.
5,500: physicians affiliated with UPMC.
20: hospitals within UPMC.
400: outpatient sites.
234,000: patient admissions in 2012.
4.8 MILLION: outpatient visits in 2012.

NUMBER 5: In the last decade, Pitt (and its affiliates) rose to fifth among institutions receiving NIH funding. The University is now a powerhouse in both basic and clinic sciences. It has been one of the top 10 NIH-funded entities since 1998.

People and programs that keep the school healthy and vibrant



OUT OF THE STARTING GATES

LEVINS ENDOW FUND

BY EM MAIER

Sally Levin is all too familiar with cancer. Orphaned at age 5, when cancer took the lives of her parents, she was reared by an aunt and uncle in Connellsville, Pa., went away to college, then married Leonard Levin, eventually helping him run his family's furniture company in nearby Mount Pleasant.

At age 50, she was diagnosed with lymphoma, the first of what would be four bouts with cancer. In 1989, the disease struck again, this time with Leonard dying of lung cancer. By then, her oldest son, Howard, was running the business, and Sally resolved to start a new life in Pittsburgh. Once here, she threw herself into the cultural life of the community, becoming a patron of the arts and benefactor of a number of institutions, including the City Theatre Company and the Pittsburgh Cultural Trust. She also served as one of the original University of Pittsburgh Cancer Institute (UPCI) Council members and helped start a day center for clients of Jewish Residential Services with mental illness.

Her children—Robert (who now runs Levin Furniture in the wake of Howard's death), Ann, Janet, and Rachel—have established a fund to celebrate Sally's accomplishments. It recognizes her involvement with UPCI and pays tribute to her personal history. Established through a $500,000 commitment, the Sally M. Levin Endowed Fund for Innovative Cancer Research will provide seed money for research led by investigators with original ideas.

"Charitable giving can help support esoteric research, the areas of science and types of disease that don't get as much exposure," says Sally Levin. "People know about breast cancer, about prostate cancer. But there are many other devastating forms of the disease. Ultimately, everyone wants to find a cure—we've been looking for that for years. But it's also important to focus on finding out the causes of cancer—and how to prevent it."

The fund will be especially helpful to young investigators. Research is costly, and there is a pressing need for funding that encourages innovative research, rather than helping projects that are seen as "safe bets." The idea is that the preliminary studies supported by the Levin fund will help investigators secure additional funding, such as federal grants. As Nancy Davidson—director of UPCI and UPMC CancerCenter who is also the Hillman Professor of Oncology—puts it, it will help researchers "get out of the starting gate."

"We feel, as citizens of the city of Pittsburgh, a special commitment to strengthening institutions that have a special role in the city. And certainly the University of Pittsburgh Cancer Institute is a jewel, and one that needs to be supported by the community," notes Robert Levin. "We're really thrilled to be doing that." ■

TO SUPPORT THE LEVIN FUND, CONTACT:
Eleanor Flannery at 412-623-4700 or flanneryel@upmc.edu.



COURTESY LEVIN FAMILY

Sally Levin's own dramatic family history was shaped by cancer.

BOOSTER SHOTS

Pittsburgh Steelers safety Ryan Clark lost his spleen, his gallbladder, and 35 pounds after playing in Denver this past season. Clark carries the sickle cell trait, and the high altitude activated the inherited blood disorder, ravaging his body.

This winter, Clark launched **Ryan Clark's Cure League** (in partnership with UPMC, the University of Pittsburgh's Vascular Medicine Institute, and the Pittsburgh- and Chicago-based Institute for Transfusion Medicine) to raise awareness, donations, and other support to help Pitt researchers develop better care and search for a cure for sickle cell disease.

Steeler defensive end **Brett Keisel** got cut—not from the team, but to advance medicine. Keisel, known for his voluminous facial hair, sheared "Da Beard" in February. This act of grooming, performed in public for the third consecutive year at a Pittsburgh-area tavern, raised money in support of the Division of Hematology/Oncology at Children's Hospital of Pittsburgh of UPMC. The 2012 deforestation netted nearly $40,000 in donations.

—Joe Miksch

FOR MORE INFORMATION ON GIVING TO CHILDREN'S: **www.givetochildrens.org**
TO SUPPORT THE CURE LEAGUE:
www.CureLeague.org



PHOTOS BY JOSH FRANZOS. BROWN BAG ILLUSTRATION BY HARRIET RUSSELL

POWER LUNCH

BREAKING BREAD WITH DEAN LEVINE

BY CHUCK STARESINIC

REPRINTED WITH PERMISSION FROM* NEXT, *THE SCHOOL'S 2012 ANNUAL REPORT.

Aspiring Pitt med students will be glad to know that there is such a thing as a free lunch—at least on occasion. Once a month at the School of Medicine, a dozen med students receive an invitation to have lunch with the dean. This has been going on for well over a decade, since shortly after Arthur S. Levine, an MD, became dean of the University of Pittsburgh School of Medicine and senior vice chancellor for the health sciences. From the beginning of his tenure at Pitt, he was determined to put students at the center of what he does. It's just before noon on a spring day, and a dozen third-year med students are milling about near the glass double doors in the lobby when they are greeted by their host.

"Hi, I'm Art. I'm your dean," he says, as he shakes hands all around. Conversation continues as the group drifts down the hall and settles around



SIMPLY FRESH DESIGNS

a long conference table. Associate Dean for Student Affairs Joan Harvey has also joined the group. Bags crinkle and soft-drink containers pop as the dean explains why he invited them.

"The truth is, there are a lot of demands on my time, and you aren't going to see me all of the time," admits Levine. "But it's important to me that you know that you can come to me with concerns you may have. In my office, students come first.

"I pay attention to every word students say to me, and we try to make changes as quickly as possible as a consequence," Levine says. (Harvey nods in agreement.) "So I want you to speak freely and to tell me what's good and what's bad."

Despite the invitation, nobody wants to begin with a criticism, so there's a good bit of heartfelt praise from students at the outset.

"I came here because of the feeling I got from people in the School of Medicine—from the admissions office staff to the faculty interviewers," says one student.

"It trickles down, too. Despite the competitive nature of medical school, there's a level of generosity and civility among the students that you don't find everywhere."

"I fought hard to get in here. It was my top choice. You hear that med school is cutthroat, but I don't see it."



"I'm on a national committee at AMSA [American Medical Student Association], and I hear stories from students at other schools. I tell them, 'We don't have that at Pitt.'"

"Do you miss California?" Levine asks Lisa Tseng, who did her undergraduate work at Berkeley.

"Yes," she replies without hesitation and with a laugh.

"You should know that it's 55 degrees and raining in Berkeley today," he tells her with a smile. "There's not a cloud in the sky, and it's almost 80 in Pittsburgh."

"I knew nothing about Pittsburgh before I came here," offers another out-of-state student. "I thought the streets were awash in kielbasa."

"Would that they were," replies the dean.

The scholarly project is a major topic of today's discussion.

A student describes a clinical research project she has implemented with a pediatrician, saying, "I have a sense of how it works now—how a research project begins with a clinical question and then is created from the ground up."

"You're all too happy," quips Levine. "I want to hear about things I can fix."

"Okay, here goes," a student ventures. "Can we get some windows in the library?" (Perhaps not; it's in the basement.)

Another student raises a scholarly project concern. His project is less traditional, and he's having trouble incorporating an exploration of health disparities into it. Lynn Egwuatu echoes his concerns, pointing out that there is a wealth of resources for students interested in laboratory science, but it's more difficult to incorporate community work into a scholarly project.

"That's a good point," says Levine.

"Joan, let's bring this up with [Associate Dean for Medical Student Research] David Hackam."

When Meghan Wilson's turn comes, she says, "Being such a nontraditional student, I get a different perspective."

She just finished a neuroscience PhD and is in the third year of the MD program. "When you interview, of course, they say they'll support you.

"But Pitt has really come through for me. Not just once—throughout. If you have a problem, you can approach the administration."

"Meghan and I go back a long time," says the dean.

Paralyzed in a high school skiing accident, Wilson was not accepted into medical school on her first try, despite a soaring GPA, a neuroscience degree, and very high MCAT scores. She began writing to medical schools to explain her situation and her interest in a dual-degree program that would allow her to help translate basic research findings into better care for patients. One of those letters came to Levine; his was the only response she received. Following that introduction, Wilson found a coveted spot in Pitt's NIH-funded Medical Scientist Training Program, a combined MD/PhD program that was exactly what she was looking for.

"I thought it would be good for the school," Levine says. "But more importantly, I thought it would be wonderful for Meghan to grow as any independent person is able to do. I wanted Meghan to achieve her potential." ■



CLASS NOTES

'60s

"I can't tell you enough how Pitt made me. They even taught me how to play squash!" says **Jim Liedtke** (MD '64, Internal Medicine Resident '66). After his training, Liedtke served for two years at Wright-Patterson Air Force Base in Ohio, then completed a cardiology fellowship at Harvard before beginning a career in academic medicine. He was on the faculty at Pennsylvania State University at Hershey from 1971 to 1983, then headed cardiology at the University of Wisconsin until his retirement in 1997. "I had some bright young faculty, and it was a big thrill to see them launch their careers," he says. For the past 15 years, Liedtke has focused on wood sculpture—his work, which is influenced by ethnic art, nature, and Renaissance sculpture, has been shown in galleries and juried exhibitions across the country. His next show is at Elmhurst Art Museum (near Chicago) March 1–April 26.

'70s

Diane Sixsmith (MD '73), who was one of only four women in her Pitt med class, never experienced sexism in medical school, or even when she began her career in New York. She did, however, feel like a "second-class-citizen" for practicing emergency medicine—which wasn't even recognized as a specialty in the United States until 1979. "Most physicians talked to you like you were an idiot," she says. Everything changed in the '90s, though—thanks to, of all things, NBC's *ER*. "We were suddenly superstars and had this glamorous job." Sixsmith, clinical assistant professor of medicine at Weill Cornell Medical College and chair of emergency medicine at New York Hospital Queens, now practices in one of the most ethnically diverse areas in the world, where she runs a competitive residency program. That wasn't always the case, either. A generation ago, everyone wanted to work in Manhattan, rather than the outer boroughs; but now, she's flush with applications from young bilingual MDs looking to come home to Queens. Working in a hospital of some 100 languages is especially rewarding for Sixsmith, "a White, English-Irish-German girl from Pittsburgh," she says. "It's a wonderful experience."

'80s

Since **Christopher Harner's** (Orthopaedics Resident '86) residency days, Pitt's Orthopaedics and Sports Medicine program has exploded, he says. And he's not just talking about its current digs, the 35,000-square-foot teaching and research space at the UPMC Sports Performance Complex on the South Side. "**Freddie Fu** (MD '77, Orthopaedics Resident '82) and I run one of the top programs in the country. We have five fellows per year … and we also have a very large number of visiting fellows from around the world." Recently, Harner was named president of the American Orthopaedic Society for Sports Medicine (a position previously held by Fu). And in September, Harner was also appointed head team physician for the Pittsburgh Penguins. Soon after, he was joined by fellow Pitt orthopaedic surgery faculty members **Tanya Hagen** (Internal Medicine Resident '01, Sports Medicine Fellow '02) and **Dharmesh Vyas** (Sports Medicine Fellow '10), associate and assistant team physicians, respectively.

'90s

Sure, **Michael Bentz** (Microvascular Research Fellow '90, Plastic Surgery Resident '92) is excited about his own work. In the clinic, he focuses on plastic and reconstructive surgery for infants and children, and in his research, he studies gynecologic oncology reconstruction and intra- and extrathoracic reconstruction, as well as educational outcomes. But, as chair of plastic surgery at the University of Wisconsin, he feels the most important products of his academic efforts are his residents. He calls it the "multiplier effect." "Each well-trained resident goes out and treats many more people, and writes more papers, and does more research, and educates future generations. The impact of being a surgical educator really multiplies what I can do as an individual."



Bentz (center) and family standing in front of a glacier while on an Alaskan vacation in 2012.



Metro

There are 72 residents and 175 faculty members in the University of Pittsburgh's anesthesiology residency program. As director, **David Metro** (MD '94, Anesthesiology Resident '98) plays matchmaker. The secret to his success: seeing the program through the eyes of the resident and making sure the mentor/mentee relationship is successful and productive, he says. However, there is no law against switching mentors—or even having multiple mentors. "Sometimes, residents start off in one direction and then go in a different direction. And if that relationship isn't working [any more], you have to be willing to change and not see it as a defeat." According to his chair, John Williams, the matchmaker extraordinaire (who meshes 247 personalities) has made Pitt's anesthesiology program one of the country's best.

Throughout med school and his training, **Thomas Nickolas** (MD '98) had an interest in chronic kidney disease and the factors that cause its progression and further complicate it. For the past seven years, the assistant professor of clinical medicine at Columbia has been working with high-resolution peripheral quantitative computed tomography (HRPQCT), a new CT technology, to understand the effects of chronic kidney disease and kidney transplantation on the bones. Patients with chronic kidney disease, including those who have had kidney transplants, have a high risk of developing osteoporosis and, subsequently, fractures. "Ultimately, my goal would be to develop and study treatments that could prevent fracture in these two patient groups," he says.

'00s

After graduating from Pitt med, **Adrian Maung** (MD '00) completed his general surgery residency at Massachusetts General Hospital, then his trauma and critical care fellowship at the University of Maryland, before settling in at Yale University as an assistant professor in the trauma department. He had graduated from MIT with a mechanical engineering degree but decided he'd rather work with people. "Trauma surgery is a neat field," he says. "What is most rewarding about it is that you can see someone who is potentially very sick, think on your feet, make a diagnosis, and intervene, and many times you see improvement right away."

Having trained with Pitt's Bob Arnold, **Elizabeth Weinstein** (MD '02, Internal Medicine Resident '05, Chief

Resident '06, Hospice & Palliative Medicine Fellow '07) started her career thinking that everyone in cancer medicine appreciated how pain management and other services provided by palliative care specialists can improve quality of life. When she left Pitt, she learned that's not the case. But now, as medical director of supportive oncology at Case Western Reserve University's Seidman Cancer Center, she's spreading the gospel. "I've only been here a year and a half, and [palliative care training] is already a requirement for internal medicine residents."

"The brain is like an egg yolk inside of an egg shell," says **Summer Ott** (Neuropsychology Fellow '07). And when a concussion occurs, that delicate organ experiences drastic chemical and metabolic changes. To protect athletes from these damaging effects, Ott, along with a multidisciplinary team of athletic trainers, brain injury specialists, and physical medicine and rehabilitation specialists, helped pass Texas Senate Bill 2038, which established return-to-play guidelines. Their goal is to educate players, athletic trainers, coaches, and parents about how to manage concussion and spot the warning signs of its delayed effects. Through community-outreach programs in Texas schools, she hopes to raise awareness and help players understand the risks of returning to their sport too soon.

—Katie Martin and Elaine Vitone

MARK ALTER

THE STORY BEHIND THE STORY



Alter

At first blush, it may not seem like history and science have much in common. While the former is fixated on the past, the latter is focused on the breakthroughs of the future. But Mark Alter (PhD '98, MD '99), who holds an undergraduate degree in history from Colgate University, has found a way to marry the seemingly disparate disciplines.

"They are both hypothesis-driven fields, and I enjoy the research processes with each of them," says Alter. "In fact, there are many similarities between history and my current interest in psychology. In one field, you want to know why people did what they did, and in the other, you want to know why people do what they do."

That desire to go behind the scenes has been a constant for Alter. After completing his studies at the University of Pittsburgh, he went on to Brown University's combined residency program in pediatrics, psychiatry, and child and adolescent psychiatry. From there, he began conducting neuroscience research as a child-psychiatry fellow at Columbia University. And today, he is a faculty member in the Center for Neurobiology and Behavior at the University of Pennsylvania.

Alter's research focuses on the transcriptome, the entire collection of RNA molecules in a given cell. RNA plays an important role in putting genetic instructions into action, and, for reasons that have eluded scientists, that activity happens to a greater degree in some cells than others.

Curious to uncover the backstory of this disparity, Alter got to work.

His studies have demonstrated that transcriptome plasticity, the ability to change the amount of gene activity in a cell, is influenced by such factors as age and pharmacological agents. He hopes his work could ultimately lead to new therapeutic interventions in situations where abnormal gene-activity regulation is causing disease or problems with neurodevelopment, such as autism. *—Dana Yates*

MAA SAYS, "COME HOME"

As the new president of the Medical Alumni Association Executive Board, Brian Klatt (MD '97, Res '02) hopes to mold the MAA into a lean, mean, scholarship-fundraising machine. He's talking big galas, big-name headliners, big bucks.

But to do that, he's going to need the help of his fellow alums. Big time.

"We want to expand our executive board," he says. "We want representation from outside this institution—both locally and nationally." Or even globally, says Pat Carver, executive director of alumni relations for the University of Pittsburgh Health Sciences and newly appointed director of the MAA. "We can Skype them in or set up a phone connection." Klatt adds, "It would be nice if each class had a member sit on our board."

Klatt and Carver explain that in November, school officials restructured the 83-year-old organization to put the resources of the health sciences foundation behind it. The hope is that these resources will help the MAA to build on the successes of Susan Dunmire (MD '85), associate professor of emergency medicine, who directed the organization for the past eight years. She, Klatt, Carver, and others at the MAA are focused on supporting the students. "That's why the MAA is here," says Klatt. "The funds are solely to support the students."



Klatt

To draw alumni, MAA 2.0 will be creating more opportunities to get together—for homecoming, for medical alumni receptions, for new award programs, for the heck of it if you happen to be in Pittsburgh and hankering for a bit of coffee and conversation. The MAA office at M-200 Scaife Hall has long been a hive for students, where they're typically greeted with a smile and a cup of joe. A recent renovation makes it more comfy. "It's beautiful," says Carver. "We've got coffee plumbed in like Starbucks and new sofas. I would really like people to come, both students and alumni," says Carver.

"When you come back into town," says Klatt, "you should say, 'Is there a tailgate for the MAA? Are there going to be people I know at the game?' You should come to town thinking about the medical school. It should be fun. And," he repeats, for the zillionth time, "we should be raising a lot of money for scholarships!"

To volunteer for the board, or suggest others MAA might holler home, contact Klatt at klattbrian@hotmail.com or Carver at cpat@pitt.edu. Visit MAA at www.maa.pitt.edu. *—EV*

THOMAS E. ALLEN

JULY 2, 1919—JAN. 26, 2013

Thomas E. Allen (MD '43) was a fierce supporter and advocate for women's reproductive rights until his death in January at 93. Even before Roe v. Wade, "The Doctor of Choice" was working to establish a clinic at what is now Magee-Womens Hospital of UPMC for women who were looking for a safe place to end their pregnancies. And after abortion was legalized in 1973, Allen helped lead the charge to secure a $50,000 grant to open the Women's Health Services clinic in Pittsburgh.



Allen

Kim Evert, CEO of Planned Parenthood of Western Pennsylvania, remembers Allen as a caring physician who took the time to ensure he met every single one of the patient's needs to the best of his ability. Even after he stopped practicing, Allen remained dedicated to Planned Parenthood. "He worked for us from 2001 all the way until 2011. In his later years he still performed informed consent services for clients in Pennsylvania," she says. "He was just a wonderful person to work with. He really took an interest in [patients and staff] and got to know people individually."

Allen was also a major supporter of art and music in Pittsburgh. He chaired the board of the American Wind Symphony Orchestra for 40 years and was personally responsible for keeping the Three Rivers Piano Competition afloat financially. *—Katie Martin*

JAMES J. CORRIGAN JR.

AUG. 28, 1935—DEC. 19, 2012



Corrigan

Throughout more than 40 years in academic medicine, pediatric hematologist and oncologist James Corrigan (MD '61) never stopped teaching. After retiring from his post as dean of Tulane University School of Medicine in 2000, where he had overseen significant growth in the school and made strides in modernizing its curriculum, he became vice president of the Tulane University Health Science Center, a position he held until 2002. Corrigan resumed teaching at the University of Arizona at Tucson in 2004. He had been a founding member of the pediatrics faculty early in his career at UA, retiring in 2011. Corrigan died in December at the age of 77.

His love of educating clinicians left its mark on both institutions. Among his many honors were Pitt's Philip S. Hench Award in 1997 and a Special Merit Award for Outstanding Education, bestowed by the University of Arizona a month before he died.

"He was a master teacher who had his heart and soul in pediatrics. He was a role model for the students," says Fayez Ghishan, professor and head of pediatrics at UA. "Many went into pediatrics because of him."

His method of teaching, dubbed "Corrigan Rounds," was a mainstay.

Alan Bedrick, former mentee of Corrigan and current professor and chief of neonatology and developmental biology at UA, recalls his style of patient assessment: "There were usually four or five residents in a room, and we would present a patient's case to Dr. Corrigan, and he'd say, 'Well, I can think of maybe 20 different diagnoses already,' and the rest of us, we couldn't get past maybe three or four of them. He saw a million possibilities. He was just the consummate teacher." *—KM*

BRUCE W. DIXON

NOV. 3, 1938—FEB. 20, 2013

Bruce Dixon (BS '61, MD '65, Internal Medicine Resident '67) couldn't go anywhere without seeing someone he knew, recalls Marc Cherna, Allegheny County Director of Human Services. "If you went with Bruce to walk through the jail, every inmate would say, 'Hey, Doc.' And he'd start lecturing them. 'Does your grandmother know you're in here?'"



Dixon

Dixon, former associate professor in Pitt's School of Medicine and Graduate School of Public Health, former head of Allegheny County's STD clinic and program, and the longest-serving director of the Allegheny County Health Department, died in February while undergoing surgery. He was 74.

Francis Solano (Res '83), clinical professor of medicine at Pitt and president of Community Medicine at UPMC, was chief resident in 1984, the year Dixon ran his last biweekly rounds. He recalls how the beloved recipient of the Distinguished Teaching Award led residents through his analytical process, accurately diagnosing every case presented to him using nothing more than the patient's history and a physical exam.

"He could calculate how bad the valve was diseased based on just feeling a pulse and listening to a heart murmur," says Solano.

For the last two decades, Dixon led all air quality, environmental quality, and human health programs for Allegheny County. He organized nationally lauded programs to address health disparities, among many other public health concerns, and, in his own quiet way, fought these inequities on the ground, as well.

"I'd be out with him for dinner, and he'd get a phone call," says Cherna. "We'd go to someone's house in a distressed neighborhood, someone who was dying of AIDS, and he'd go in with his little black bag and be greeted like family. He took these calls 24/7 and never charged a dime, and nobody ever knew." *—Elaine Vitone*

IN MEMORIAM

'30s

JOSEPH NOVAK
MD '38
JAN. 22, 2013

'40s

EDWARD FALK
MD '43
FEB. 2, 2013

ROBERT LLOYD BELL
MD '47
AUG. 17, 2011

'50s

ALFRED A. PERFETT
MD '55, RES '64
JAN. 9, 2013

JOHN GRANT SHIVELY
MD '59, RES '62, FEL '64
DEC. 7, 2012

'70s

JOEL ALCOFF
MD '76
JAN. 17, 2013

FACULTY

GIBSON PACKER BUCHANAN
FEB. 2, 2013

LEONARD NAPOLITANO
JAN. 7, 2013

GERRY DOUGLAS
AHEAD OF THE PACK

BY SHARON TREGASKIS



COURTESY ARTURO LOPEZ PINEDA

In 2011, Douglas (second from right) launched the inaugural Summer Internship in Global Health Informatics, taking a team of graduate students to Lilongwe, Malawi, where they worked with Baobab Health employees on maternal and child health projects at a local hospital.

Guests no longer comment on the mounds of boxes, crammed with medical equipment, in Gerry Douglas' (PhD '09) front room. Soon after the Pitt assistant professor of bioinformatics and his wife, Thuy Bui, an MD and associate professor of medicine and medical director for Pitt's Program for Health Care to Underserved Populations, first called their Highland Park residence home, friends and family dubbed the side of the great room across from the fireplace "the warehouse."

Between a rarely played upright piano and an oft-ignored treadmill, Douglas has assembled all of the trappings of a mail-order depot: a digital scale (accurate to one one-hundredth of a pound), a collection of battered luggage from which he's removed every extraneous accoutrement, and, always, more boxes. Throughout the winter, he repacked 3,000 pounds of equipment destined for Baobab Health, a nongovernmental organization he founded with Bui in 2000 to provide data collection and management tools to the Malawian Ministry of Health.

"He's a packing machine, with skills ordinary humans don't possess," says Mary Herbert, clinic director for the Program for Health Care to Underserved Populations. "He's flat-out gifted at packing a crate to go overseas. He will get it within an ounce of the maximum allowed."

Back when he was flying more and using cargo less, he says, he knew the Pittsburgh airport check-in agents by name. They developed a routine. "They would weigh the first, and it would be 50.0 pounds; then the second, and it would be 50.0," he says. The agent would ask if the others were the same, and take him at his word. "On occasions when the airport scale showed more than 50 pounds," he says, "I'd smile and say, 'Better get that scale checked.'"

Douglas deploys the same meticulous attention to detail in all he does, whether designing a touchscreen-based electronic medical record for Baobab or managing the spreadsheet of guest arrivals and departures at the couple's home in the landlocked republic in southeastern Africa. "It's not just for myself and my family when we're there, but to facilitate experiential learning opportunities for Pitt medical students, residents, and faculty," he says. "The house is always full."

In Malawi, intermittent power, low literacy rates, a shortage of health care providers, and high patient volume have traditionally hampered data collection to inform patient care and national policy. Working within those constraints, Douglas designed a touch-screen electronic medical record system that has enrolled 1.6 million patients at 25 sites, where it's used to track lab and radiological results, as well as HIV treatment.

More recently, as director of Pitt's nascent Center for Health Informatics for the Underserved, Douglas has begun mining a decade's experience of process improvement through his work with Baobab. He wants to enhance access to health care for poor Americans. "I want to create a high-level approach to thinking about the lessons we've learned in Malawi and how we can distill its essence into a set of principles," he says. "What is the 'implementation science' of working in informatics in a low-resource setting?"

After myriad dinner table conversations with Bui, Herbert, and their colleagues, Douglas proposed a pilot project at the Birmingham Free Clinic, on Pittsburgh's South Side. "Why can't we apply the successes we've had in developing countries," he muses, "if [clinics in rural and other underserved areas] in the U.S. are experiencing the same problems?"

The vast majority of Birmingham Clinic patients are homeless and afflicted with a constellation of chronic diseases, including diabetes, hypertension, and asthma, says Herbert. "Most are on multiple medications. And our pharmacists hand-label and hand-dispense them," says Herbert. "We move 5,000 prescriptions every year with 10 regular pharmacists. How can we make that process more efficient to improve safety and handle more patients?"

Douglas proposed an elegant little labeling machine he'd successfully adapted for Baobab, complete with bar codes. "Sometimes we work with people who want to create and design things, and you get the sense that they don't really care or understand what you do," says Lauren Jonkman (PharmD '06, MPH '12), who works with students at the Birmingham Free Clinic. "With Gerry, it's really clear that he wants it to be something we'll use, that will actually solve problems."

Jonkman's observation drives to the core of bioinformatics, says Douglas. "It's not about computers, technology—it's about understanding people's problems and building technology to support them. We're trying to make people's jobs easier by helping them do things faster, with fewer mistakes." ■





FASTEN-ATING

Pitt's Mark Ravitch brought the Russian surgical stapler to America in 1958 (see p. 18). But the Russians weren't the first to use staples to suture human tissue. That honor goes to a Hungarian.

In 1907, Budapest-based Hümér Hültl—one of the most famous surgeons of his time—enlisted Victor Fischer, an engineer and fifth-generation designer of surgical instruments, to create "a mechanical stitching device which would shorten the duration of an operation as much as possible ... in the simplest and most reliable way." Fischer completed two models, a 17-centimeter one for suturing the stomach and an 11-centimeter one for the duodenum. Hültl made a splash in the literature, but only 50 of the staplers (top photo) were ever sold. These crank-powered apparatuses could only be refilled by the manufacturer. Each one weighed nearly 8 pounds.

In 1920, Aladár von Petz made a lighter, simpler device—just seven moving parts, down from 12 (see bottom photo). The 32-year-old's namesake clamp placed two rows of staples made of "German silver," a copper, zinc, and nickel alloy.

In 1921, Hültl attended the Congress of the Hungarian Surgical Society. He'd heard that von Petz, 20 years his junior, would be demonstrating his stapler, and Hültl came prepared to defend his own model. But after hearing the nervous young von Petz speak, he sat down beside him, picked up the prototype, and tested it on his leather spectacle case. Surveying the output, Hültl said, simply, "This is better," congratulated von Petz, and left the room.

Once in production, the von Petz clamp was an international success. The Germans made him a verb. To *petzen* is "to use the gastric stapler." —*Elaine Vitone*

PHOTOS BY ESZTER BLAHÁK. COURTESY SEMMELWEIS MUSEUM OF THE HISTORY OF MEDICINE, BUDAPEST.

CALENDAR

FOR ALUMNI & FRIENDS

MEDICAL ALUMNI WEEKEND 2013
MAY 16–19

SENIOR CLASS LUNCHEON (ALUMNI WELCOME)
MAY 17, 11 a.m.
Connolly Ballroom, Alumni Hall

OPENING COCKTAIL RECEPTION
MAY 17, 5:30 p.m.
Ballroom, Pittsburgh Athletic Association

NIGHT AT THE SYMPHONY
MAY 17, 8 p.m. Curtain
Heinz Hall

CHAMPAGNE BREAKFAST
MAY 18, 9 a.m.
11th Floor, Scaife Hall

TOUR OF BIOMEDICAL SCIENCE TOWER 3
MAY 18, 11 a.m.
(Following Champagne Breakfast)

REUNION DINNER GALA
MAY 18, 6 p.m.
LeMont Restaurant

CLASS OF 2013 COMMENCEMENT
MAY 19, 10 a.m.
Carnegie Music Hall

SCOPE AND SCALPEL PRODUCTION
MAY 17, 7:30 p.m., and
MAY 19, 2 p.m.
McGonigle Theater
Central Catholic High School, Pittsburgh
www.scopeandscalpel.org

UPCOMING HEALTH SCIENCES ALUMNI RECEPTIONS
MAY 23, Houston
DATE TBA, Los Angeles

Unless otherwise noted, for more information: Pat Carver 412-648-9059, cpat@pitt.edu. To find out what else is happening at the medical school, go to health.pitt.edu and maa.pitt.edu.

NEW!



GETTY IMAGES

Our ears, especially men's, grow bigger as we age. (For other reasons, the Buddha, shown young here, is typically represented with long ears.)



FOR REAL! TWEEN SCIENCE.

Do his ears hang low? Are your grandfather's ears bigger than your dad's? European scientists noticed that older people's ears seem bigger than those of younger adults. To confirm their suspicions, they measured ears on people of all ages. It turns out that human ears actually keep growing throughout our lifetimes! But why would ears continue to grow when the rest of the body stops? The answer lies in the difference between long bones (like arm and leg bones) and the cartilage that shapes and supports our ears. Long bones have growth plates at each end that add bone in response to hormones our bodies make in large quantities when we are young and growing fast. These plates stop adding bone after puberty, when hormone production slows and we've reached our full height. Ear cartilage lacks growth plates, and it continues to grow—and so do our ears, even when we're old. *—Jenifer Lienau Thompson*

Thanks to Pitt profs Steven Handler, Ernest Manders, and Tahsin Oguz Acarturk for giving us an earful about ears.
For more kid-friendly explorations, visit How Science Works at **www.howscienceworks.pitt.edu**

UNIVERSITY OF PITTSBURGH
SCHOOL OF MEDICINE
SUITE 401 SCAIFE HALL
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ALL TOGETHER NOW

Peaches and Herb reunited because it felt so good, because they understood. You, Pitt med graduate, can reunite for these or other reasons from May 16 to 19 at the Medical Alumni Association's Alumni Reunion Weekend. Come see the newest gaggle of grads off into the world of doctoring at the Senior Class Luncheon. Take in the tip-top tones of the Pittsburgh Symphony Orchestra. Dine on fine food and drink in the view from Mt. Washington's LeMont restaurant. And espy the latest installment of the proud tradition that is Scope and Scalpel. (We're told that the choreography has advanced quite a bit from the rehearsal pictured above.) For more information visit www.maa.pitt.edu.

REUNION CLASSES:
2003 10th Reunion
1998 15th Reunion
1993 20th Reunion
1988 25th Reunion
1983 30th Reunion
1978 35th Reunion
1973 40th Reunion
1968 45th Reunion
1963 50th Reunion
1958 55th Reunion