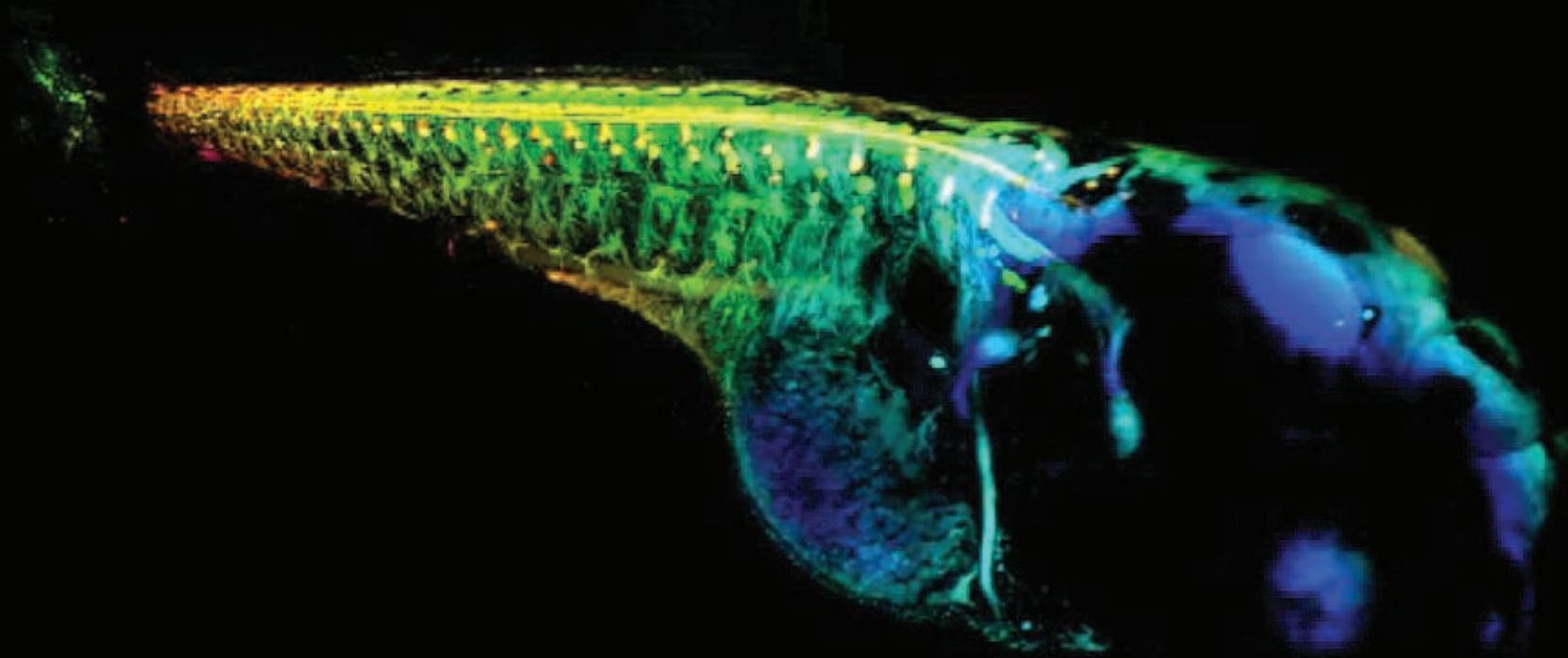
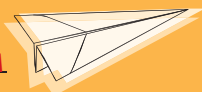


UNIVERSITY OF PITTSBURGH SCHOOL OF MEDICINE | SPRING 2016

PITTMED



WHAT THIS FISH
TELLS US ABOUT YOUR BRAIN



THEY WERE THERE

Perhaps you remember this photo of pediatric neurosurgeon A. Leland Albright from our Winter 2016 story "Where Others Don't Go." Only after publication did we learn who the photographer was: longtime reader—and *Pitt Med* contributor—Jim Judkis.

The photo was taken in 1992. In it, Judkis's son, Will, pictured with Albright, is undergoing a checkup months after having a brain tumor removed by hyperfractionated radiation—a therapy rarely used on

patients as young as Will, but one that Albright recommended for him. To Judkis, the photograph represents a "sweet memory" and "a lot of happiness" following Will's difficult, cancer-ridden toddler years. It's also a great depiction of Albright's surgical hands, which Judkis marveled at. He remembers Albright acting playfully the day the photo was taken—he made a paper airplane for Will and flew it into the examination room. Will, now in his mid-20s and healthy, "normally wouldn't have any inclination to read *Pitt Med* magazine," says his father, "but he said, 'I'm gonna read this' when he saw the photo."



JIM JUDKIS

EDITOR'S NOTE

For 16-plus years, the name Macy Levine, MD '43, has appeared on our masthead. Now the retired internist is retiring from his role with us. We were blessed for all these years to have had his help with our obituaries section. He cared about what happened to his classmates and that their stories were told.

This seems a good time to speak of transitions, with the Match results in this issue. In Pitt Med's editorial world, we've been boasting about our own crop of up-and-comers: Our fall intern, Brady Langmann, is at Esquire this semester; this summer he'll help out at CBS Evening News in New York. Spring intern Jessica Boddy will be at Science. And another from our ranks, Brett Murphy (A&S '13), after interning at CNET, will be a Google News Lab Fellow with Investigative Reporters and Editors—he is graduating from Berkeley's J-school. (We can't help but mention one of his professors was Pitt Med magazine's own Rebecca Skloot, MFA '08, who has just announced that her best-selling The Immortal Life of Henrietta Lacks is being made into a movie in which Oprah Winfrey will star and executive produce.)

Speaking of Berkeley, Robin Mejia, veteran contributor to the magazine, is walking out of there this spring with a PhD in biostatistics in hand. (She is, by the way, relocating to Pittsburgh . . . as is this editor, who has been telecommuting across 2,635 miles for 16 years.) —Erica Lloyd

RECENT MAGAZINE HONORS

Carnegie Science Center
2016 Science Communicator,
Honorable Mention, Robyn K. Coggins

CORRESPONDENCE

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: 412-624-4152
Fax: 412-624-1021
E-mail: medmag@pitt.edu
pittmed.health.pitt.edu

For address corrections, or to change your print/online subscription preferences:

Pitt Med Address Correction

ATTN: Ashley Knoch
M-200K Scaife Hall
University of Pittsburgh
Pittsburgh, PA 15261
Phone: 412-648-9059
E-mail: medalum@medschool.pitt.edu

CARVING OUT TIME

To everything there is a season. But lately, doesn't it seem like you've got way too many things going on in the spring? There's your kids' graduations, grandkids' graduations. Well, your alma mater is right there with you, crunch-timing for every new crop of MDs, turning their tassels with all the pomp and circumstance they deserve.

So this year, **Medical Alumni Weekend is moving to the fall.** We hope you'll find it easier to turn, turn, turn out for a little more relaxed time of year. So save the date!

**Medical Alumni Weekend
September 23–25, 2016**

For information:
Ashley Knoch
412-648-9059
akk57@pitt.edu



PITTMED

UNIVERSITY OF PITTSBURGH SCHOOL OF MEDICINE MAGAZINE, SPRING 2016

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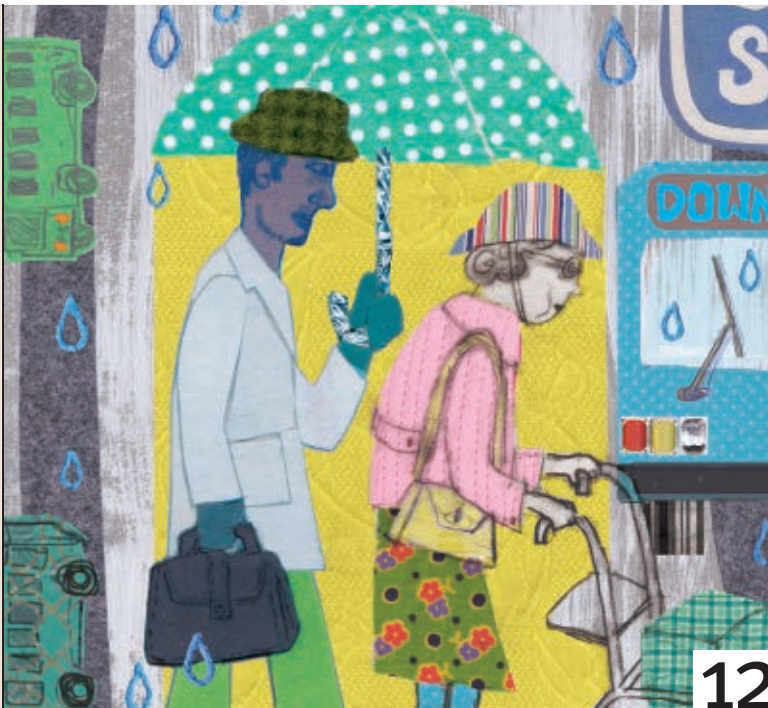
CONTRIBUTORS

[Cover] Our cover model is a 6-day-old zebra fish. This portrait was snagged during a weeklong international microscopy course at Mount Desert Island Biological Laboratory, in Maine, co-led by Pitt cell biologist **SIMON WATKINS**. Watkins created the image with **MICHAEL DAVIS**, of Nikon, and **SANDRA RIEGER**, a Mount Desert faculty member. Watkins notes that some midnight oil was burned on the project; the image is a montaged 3D reconstruction, captured with an "exotic and highly specialized multiphoton microscope," he says. "It's actually part of a movie, in which the obvious parallel between a zebra fish and a star destroyer is highlighted." Yes, he is referring to *Star Wars*. You've gotta see the trailer: bit.ly/darthfish.

JILL NEIMARK's ["Fishing for Clarity"] stories have appeared in *Psychology Today*, *Scientific American*, *Science*, and *Discover*. She enjoys science writing because it allows her to "find out fundamental things about how the world works." While researching her feature, Neimark found Pitt's use of zebra fish to visualize mitochondria "a truly disruptive technology." Neimark also writes adult and children's fiction, including Book of the Month selection *Bloodsong* and Teachers' Choice Award-winning *I Want Your Moo: A Story for Children about Self-Esteem*. Neimark is based in Atlanta.

COVER

Trawling for answers to neurodegeneration with zebra fish. (Cover: Simon Watkins, Michael Davis, Sandra Rieger. © 2016.)



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Doctors Worth Loving

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An eye-opening new program pairs medical students with patients.
The relationship lasts for their entire med school career.

BY ROBYN K. COGGINS

Fishing for Clarity

18

The big catch for understanding neurodegeneration seems to be a tiny organelle, i.e., the mitochondrion—and Pitt scientists are illuminating its missteps. In see-through zebra fish, they can spot what's going wrong in real time, as no one has before.

COVER STORY BY JILL NEIMARK

The No-Nonsense Pathologist

24

In the '60s, Emmanuel Farber's studies in chemical carcinogenesis landed him on the committee that would pen perhaps the most important public health document of the century. The fiery Pitt pathology chair called "Bull!" on Big Tobacco (and a lot more).

BY ELAINE VITONE

Thank You for Not Smoking

30

When Nixon appointee Jesse Steinfeld took office as U.S. surgeon general, ashtrays were scattered throughout his federal office suite. The Pitt A&S graduate cleaned house. He advocated for nonsmokers' rights, warned against the impact of television violence on children, and more.

FOLLOW-UP BY THOMAS H. MAUGH II

PITTMED

PUBLISHER

Arthur S. Levine, MD

EDITOR IN CHIEF

Erica Lloyd

ART DIRECTOR

Elena Gialamas Cerri

SENIOR EDITOR

Elaine Vitone

ASSOCIATE EDITOR

Robyn K. Coggins

CONTRIBUTING EDITOR

Chuck Staresinic

INTERNS

Imaz Athar

Jessica Boddy

PRODUCTION MANAGER

Chuck Dinsmore

CIRCULATION MANAGER

Ashley Knoch

EDITORIAL ADVISORS

Lisa Barsom, PhD '97

Jeremy Berg, PhD

Michelle Broido, PhD

Nancy Davidson, MD

Paula Davis, MA

Joan Harvey, MD

David Kupfer, MD

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Bennett Van Houten, PhD

Simon Watkins, PhD

Marshall Webster, MD, Res '70

UNIVERSITY COMMUNICATIONS

Susan Rogers

Cindy Gill



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I watch the ripples change their size
But never leave the stream
Of warm impermanence and
So the days float through my eyes
But the days still seem the same
—David Bowie, “Changes”

A decade ago, a group of geneticists from around the world embarked on the largest-ever search for the genetic basis of schizophrenia. They found associations in more than a hundred disparate chromosomal areas. Surprisingly, the association that was far and away the most damning to these patients was a locus on chromosome 6 that's home to most of the known genes that govern, of all things, the immune system.

This winter, Aswin Sekar, a bright graduate student in the lab of Harvard geneticist Steven McCarroll, spent a weekend holed away on his couch in Boston, combing through data; he compared patients with schizophrenia against controls in a sample of 64,000 people from 22 countries and found a correlation between risk for schizophrenia and a variant of a gene called *C4*, which lives on chromosome 6. A protein that it encodes was known to mark cellular debris for disposal by the immune system and then discard it. This same protein, it turns out, has evolved in us to serve in another integral cleanup job—in the brain.

Adults have 40 percent fewer brain connections than newborns do. From infancy through adolescence, an elaborate pruning of synaptic connections takes place. The connections that prove most useful stay with us—a classic case of use it or lose it. A mouse model showed that a protein encoded by *C4* is what marks the synapses for pruning. The Sekar data suggest that people with schizophrenia are more likely to have *C4* expressed more often, and that probably results in runaway pruning. Although not yet proven, it has been suggested that the regions of the brain that are excessively pruned may correspond to regions thought to be involved in schizophrenia.

The finding has a certain logic, as families with a history of schizophrenia are often plagued by autoimmune diseases like rheumatoid arthritis, celiac disease, and type 1 diabetes. They also have fewer synaptic connections. Our own David Volk has shown that people with schizophrenia also show evidence of inflammatory responses in the brain.

Skin heals, the liver regenerates. Every part of us responds to injury in one way or another. But the brain and the immune system share a unique commonality: Both respond to new experiences and threats not just by patching themselves back together, but by transforming themselves at the most basic molecular levels. Notably, in addition to *C4*, genes (called *RAGs*) that promote the DNA recombination that underlies new antibody formation are also expressed in the brain and may be engaged in learning and memory.

It has been said that the ability to adapt well is a mark of intelligence; that ability could also be critical to our health.



JOSHUA FRANZOS

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



*Devoted to noteworthy happenings
at the medical school*

Preventing Stillbirth

A stillbirth is a tragedy for any mother. And according to a study in October's *American Journal of Clinical Nutrition*, obese women are at higher risk than their leaner counterparts for such a devastating loss.

Hyagriv Simhan, MD medical director of obstetrical services at Magee-Womens Hospital of UPMC, and colleagues found that hypertension and placental disease seem to cause the most stillbirths among mothers who were obese before conception.

Doctors can advise women to lose weight before they get pregnant. Yet once they conceive, mothers can't undo the risk associated with prepregnancy obesity, even if they shed a few pounds while expecting.

Simhan hopes that will change. Pinpointing the causes and mechanisms of stillbirth could pave the way for effective interventions for future mothers-to-be.

"Prior to and during pregnancy, there should be things that we offer to women to modify their risk," says Simhan, who's also associate professor of obstetrics, gynecology, and reproductive sciences and chief of the Division of Maternal-Fetal Medicine at Pitt. He adds, "What we need is prevention."

—Jennifer Larson

MARTIN BOTVIDSSON/GETTY IMAGES



MICROCEPHALY UNDER SURVEILLANCE

When it comes to combating the international Zika outbreak, the biggest challenge, says Ernesto Marques, an MD/PhD professor of infectious diseases and microbiology at Pitt Public Health, is a lack of information. Marques estimates there are thousands of published scientific papers on Ebola and dengue fever, but only a few hundred on Zika.

"The information is not there. I can't go to PubMed and find answers," he says.

Marques, a member of Pitt's Center for Vaccine Research and a dual Brazilian-American citizen, hopes to add to the body of knowledge with a 12-hospital study planned for this summer in Brazil. The country is currently investigating 4,000 cases of microcephaly—a congenital birth defect causing an abnormally small head, among other effects—linked to pregnant women infected with Zika. Previously, Marques's team found the virus in placentas, amniotic fluid, and infant brains. He is testing the link between microcephaly and Zika—which is usually transmitted by mosquitos (and now we are learning is also transmitted sexually). The study involves 200 babies with microcephaly and 400 healthy babies to test the correlation, as well as look for possible environmental risk factors like pollutants. "It's the very beginning of a long process," Marques says. —Rachel Wilkinson

FOOTNOTE

For Rachel Brick's latest composition, the cellular and molecular pathology graduate student drew inspiration from the Cathedral of Learning, as well as from the medieval soundscapes of the game series *Assassin's Creed*. This winter, she donned a floor-length, hooded cape to film a solo violin music video in the Nationality Rooms, traipsing from Romania to Scotland. The video is still in production, but you can hear Brick's music on SoundCloud—follow IceRequiem.



CAMI MESA

Overheard Randomized Trials and Big Data Get Hitched

Derek Angus, an MD/MPH, has long argued that multicenter megatrials result in the most informed clinical care—especially for complex conditions such as the brain cancer glioblastoma multiforme, pneumonia, or sepsis. Based in part on a blockbuster study he led, a new definition of, and treatment guidelines for, sepsis appeared in the February 23 issue of *JAMA*.

But randomized clinical trials are long and expensive, and they can be discomforting for patients and clinicians. In a 2015 *JAMA* opinion piece, Angus made the case for a new kind of randomized trial that “fuses” with big data. “The big problem with big data is that there’s no randomization in it, and the singular beauty of randomization is that you can gain causal inference,” he says. Marrying them, says Pitt’s Angus (who is a Distinguished Professor, the Mitchell P. Fink Professor, and chair of critical care medicine), “is an idea whose time has come.”

What’s the fusion you’re proposing?

With the rise of big data and electronic health records (EHR), a number of groups have suggested that you could essentially leverage the EHR to create live estimates of the likelihood of getting benefit from a treatment by running, essentially, a large observational cohort study inside the EHR. But we propose going further: using clinical data in the EHR to influence the ongoing trial.

How is this playing out in the clinic?

We’ve received funding from the European Union and the National Health and Medical Research Council of Australia to launch this program in severe pneumonia patients coming to the ICU. We will be testing multiple antibiotic strategies, whether to immunomodulate the patient with corticosteroids, and . . . different ways of providing mechanical ventilatory support—all at the same time. All generate separate weights of evidence and separate probabilities for different subgroups of patients with pneumonia, depending on how bad their oxygenation is and whether they have shock or not. The trial is simultaneously generating 48 separate measures of treatment effects, as opposed to a single normal trial that generates one. And if any particular combination of therapies in any particular patient subgroup is doing better than the others, the next patient who presents will have the odds weighted in his or her favor toward the best performing therapy. So the trial is constantly learning. We are incredibly excited about envisioning a future where clinical care becomes a constant learning tool. —Interview by Robyn K. Coggins

Faculty Snapshots

Pitt has a new place on the editorial board of *Proceedings of the National Academy of Sciences*. Peter Strick, a PhD and University Distinguished Professor, has been appointed to the Systems Neuroscience board of the journal. Strick is the Thomas Detre Professor and chair of neurobiology, scientific director of the University’s Brain Institute, as well as a member of the American Academy of Arts and Sciences and the National Academy of Sciences.

Pitt’s Health Sciences Library System, directed by Barbara Epstein, received two five-year awards, totaling \$8.4 million, from the National Institutes of Health (NIH).

The first renews HSLS’s role as leader of the Middle Atlantic Region of the National Network of Libraries of Medicine (NN/LM). Through this grant, HSLS supports the National Library of Medicine in providing health professionals with access to biomedical information and promoting the availability of reliable health information to the public. The other designates HSLS to serve as the national Web Services Office for the NN/LM.



Strick



Epstein

Ronald Poropatich, an MD and retired colonel from the U.S. Army, has been inducted into the College of Fellows of the American Institute for Medical and Biological Engineering—an honor reserved for the top 2 percent of engineers in this specialty. Poropatich received this honor for his contributions to mobile health and telemedicine in military and civilian settings. In particular, Poropatich was integral to developing and deploying telemedicine for the army beginning in the early ’90s and across several war-torn countries. He also served as the U.S. Army medical informatics consultant. Poropatich is now professor of medicine at Pitt, executive director of the Center for Military Medicine Research, Health Sciences, and senior advisor for telemedicine at UPMC.



Poropatich



Tuan

This May, Rocky Tuan, a PhD, accepts the “Contributions to the Literature” Clemson Award at the 10th World Biomaterials Congress in Montreal. The honor recognizes his extensive list of publications on musculoskeletal biology and tissue regeneration. Tuan is a Distinguished Professor and executive vice chair of orthopaedic surgery, professor of bioengineering and of mechanical engineering and materials science, director of the Center for Military Medicine Research, and associate director of the McGowan Institute for Regenerative Medicine.

—Kristin Bundy

Creative Creations

The 2015 Pitt Innovation Challenge (PInCh), sponsored by the Office of the Provost, the Clinical and Translational Science Institute, and the Innovation Institute, tackled health-related problems in a truly Pittsburgh fashion: by seeking solutions that “bridged” at least two patient life stages. Two top-level grantees, winning \$100,000 each, are affiliated with the School of Medicine.

One winner—also a shoo-in for Most Adorable—is neurosensory environmental adaptive technology (NEATCAP), a hearing-protection device for premature infants. NEATCAP’s team of local inventors is working with Magee-Womens, UPMC Hamot neonatal intensive care unit (NICU) director, Michael Balsan, an MD and associate professor of pediatrics, to evaluate the prototype. This “baby helmet” promises to block high-frequency stressors of the NICU while still allowing voices to reach the baby’s ears, thus reducing infant anxiety and granting parent-child connection at a crucial time for neurosensory development.

ILLUSTRATION TIM GROEN. BASED ON PHOTO COURTESY FRED KIMOCK, NEATCAP.



Another PInCh champ, called Phoenix, is a man-made blood vessel. It was developed by bioengineers advised by Pitt’s Yadong Wang, a PhD. (Wang is the William Kepler Whiteford Professor of Bioengineering; he also holds positions in chemical engineering, mechanical engineering, and surgery.) Phoenix has “the potential to revolutionize vascular access” in dialysis and for many other situations in which resorbable prostheses might aid healing, notes Wang. —Rachel Mennies

For Our Kids

Starting June 1, Terence Dermody, an MD, will be the chair of pediatrics for the University of Pittsburgh School of Medicine, as well as physician-in-chief and scientific director of Children’s Hospital of Pittsburgh of UPMC.

At Vanderbilt University School of Medicine, Dermody, the Dorothy Overall Wells Professor of Pediatrics, directed the Division of Infectious Diseases, the Elizabeth B. Lamb Center for Pediatric Research, and the Medical Scientist Training Program.

Dermody is a virologist with interests in viral pathogenesis and vaccine development. His lab, which he will bring to Pittsburgh, has focused on viral encephalitis in infants (using an experimental model, reovirus) and chikungunya virus. He studies how viruses attach to and enter cells, how cells signal and respond to the presence of viruses, and other critical goings-on at the microscopic level. Yet Dermody is also galvanized by big-picture issues.

Much of what physicians and scientists do, notes Dermody, is look for ways to treat and prevent illness. Considering Pitt’s big data and analytics partnerships with UPMC and Carnegie Mellon University, its pediatric research talent, and community support, he says, “We have the opportunity to ask a different kind of question: What are the correlates of wellness? . . . And what is different about the 18-year-olds who are not ready, either medically or psychologically, to be on their own?”

“What has attracted me most to Pittsburgh is the chance to make a difference in the lives of children in a major American city,” says Dermody. “I think this is important. This is our [pediatricians’] space. These are our kids.” —Erica Lloyd



Dermody

FOOTNOTE

Share the love—and the expertise.

At least eight former Pitt med faculty members have gone on to become deans at other schools across the country in recent history.

Of late, such deanships are held by David Perlmutter (he now oversees the medical school and all health sciences at Washington University in St. Louis), Steven Kanter (who runs the show at the University of Missouri-Kansas City med school), and John Reilly (now leading the med school and health affairs at the University of Colorado).



SPECIAL DELIVERIES

In complicated obstetric crises, a no-risk simulation beforehand can save lives. Pitt ob/gyns used to walk over to WISER (Pitt's Peter M. Winter Institute for Simulation, Education, and Research) to train for these double-trouble situations. But as of September, Magee-Womens Hospital of UPMC has its own specialized satellite location—complete with a simulated mother with a motor in her belly who births a pseudo-baby. (Nurse Karen Stein is shown with the mommy mannequin here.)

The new center, directed by Gabriella Gosman, an MD and associate professor of obstetrics, gynecology, and reproductive sciences, is also equipped with a simulation information management system (SIMS) that analyzes how trainees perform during procedures. SIMS offers hard data to improve skills, from placing an infant IV to treating preeclampsia. —Imaz Athar

Next Generation

Catherine Byrd, a third-year medical student, recently received Career Education and Enhancement for Health Care Research Diversity Program support and also the 2016 In-Training Award from the Society of Critical Care Medicine. Byrd is researching a novel resuscitation therapy for traumatic brain injury and hemorrhagic shock. Her mentor is Patrick Kochanek, an MD professor and vice chair of critical care medicine and director of the Safar Center for Resuscitation Research.

The prevalence of hepatitis C in U.S. prisoners is high. Estimates run from 15 to 34 percent, but testing for the virus is low. As infected prisoners enter back into the general population, hepatitis C is likely to spread further. Tianhua He, a student at Pitt med-affiliated Tsinghua University who has worked with Pitt's Public Health Dynamics Lab, helped create a model showing a way to reduce transmission. As first author of a November *Annals of Internal Medicine* paper, she suggests that universal hepatitis C testing in prisons, for which inmates could opt out, would significantly reduce transmission and associated deaths, resulting in health and economic benefits for the entire nation.

Chris Murawski has published 52 papers in peer-reviewed journals and delivered 61 podium presentations at academic meetings—those have been mostly on foot, ankle, and knee repair. The fact that he's accomplished this volume of study all before his 26th birthday has earned him a *Forbes* "30 Under 30 2016" nod in its health care section. Murawski, a second-year Pitt medical student, has years of experience working with orthopaedic surgery chair, Freddie Fu, an MD; Murawski has his sights set on a career in orthopaedic surgery.

Newly minted PhD Arturo Lopez Pineda won the 2015 Marco Ramoni Distinguished Paper Award for Translational Bioinformatics for his paper discussing the epigenetic regulation of cancer genes—specifically, the discovery of relevant groupings of methylated gene sites that may help differentiate lung cancer subtypes. In December, he successfully defended his dissertation on models of molecular cancer data. "He is truly passionate about using his computational skills to conduct transformative research," says Vanathi Gopalakrishnan, a PhD associate professor of biomedical informatics and Lopez Pineda's research advisor. Lopez Pineda recently accepted a postdoctoral research fellowship in genetics at Stanford University.

—Jessica Boddy



HOUSE-NAMING PARTY

The University of Pittsburgh School of Medicine's advising program just "moved" into six new houses, and the school wants you to help name them.

These groups—"like nonresidential Harry Potter houses," associate dean for student affairs Joan Harvey, an MD, jokes—each contain one advisory dean and roughly 20 students per class year, granting "housemates" access to mentorship, career development, and professional enrichment opportunities. And the houses foster social community through events like meet-ups at Peter's Pub, Arsenal Bowl, or Frick Park. (There was even a House Olympics.)

While Pitt med doesn't yet have a sorting hat for its houses (stay tuned), the school's 2015 orientation instead introduced incoming students to their deans and houses in a spirited scavenger hunt at the Andy Warhol Museum, which culminated in the bestowing of an iconic trophy (see left) upon the winning house, for now known as KMS (named for advisory dean Kathleen McIntyre-Seltman).

As the program anticipates its second year, Harvey is searching for house names—and she wants faculty, staff, students, and alumni to submit ideas. "We're looking to honor special contributors," she says, "with a connection to Pitt med." Honorees should come from the school's legacy rather than its present-day achievers—otherwise the sky's the limit. And because Pitt med is home to trailblazers across gender and race lines, Harvey seeks nominations that reflect the diversity of the people who've shaped the school.

Have a great idea? You can send recommendations to harvey@medschool.pitt.edu through the first half of 2016.

—Rachel Mennies

—Photo illustration by Tim Groen

INVESTIGATIONS

Explorations and revelations taking place in the medical school



Acute infections in the gut can throw the immune system out of whack. Timothy Hand and colleagues are learning ways to reboot the system in mice.

REBOOT AND REBUILD

THE IMMUNE SYSTEM'S RESET BUTTON

BY SHARON TREGASKIS

Public health experts have known since the '60s that kids who are chronically malnourished don't mount the same vigorous immune response to vaccinations as their peers. This limitation is especially troubling in the developing world: Children most in need of protection from an array of infectious diseases get the least benefit from vaccines.

Timothy Hand, a PhD assistant professor of immunology and of pediatrics at the University of Pittsburgh, has devoted his research career to understanding the relationship between the immune system and the microbiome—the rich ecosystem of bacteria, fungi, and viruses that live largely in the gut. His current investigations explore how “immunological scarring” in the wake of a single acute intestinal infection could explain incomplete vaccination. This scarring may also play a role in a host of chronic inflammatory conditions such as ulcerative colitis and Crohn's disease.

Like soldiers in urban warfare, immune cells patrolling the gut must somehow differentiate dangerous pathogens from the thousands of microbial species that aid in our digestion and immune function. Further complicating the job: Though beneficial at certain levels, microbes can wreak havoc if their numbers grow out of control. Says Hand, “Infection in the intestinal tract presents a special problem for the immune system.”

In a 2012 paper published in *Science*,

Hand and Yasmine Belkaid, his mentor at the National Institutes of Health, where he was a research fellow at the time, demonstrated that during an infection—the fog of war—immune cells in the gut don't discriminate; friendly fire is rampant as the immune system blasts beneficial and hazardous microbes alike. But once the infection clears, immune cells that had previously attacked beneficial microbes stand down.

“They're sensitized, and they can be reactivated very easily, but they're ignoring [the beneficial microbes],” Hand says.

“As long as the barrier of the gut is maintained, and as long as the cells have the correct regulatory mechanisms in place, they don't become activated.”

Hand and his NIH colleagues had a hunch that acute infection might throw those regulatory systems out of whack. To find out, they exposed mice to a particularly vicious foodborne pathogen. In a paper published last October in *Cell*, Hand and his coauthors revealed how more than nine months later—nearly 25 years in human terms—the gut tissue and immune function among most of those experimental mice remained altered, though the infection was long gone.

Abscesses had formed in the murine lymph nodes, which were populated with dangerous levels of microbes congregating where they didn't belong. And like a road pockmarked by winter weather, the linings of their guts had been transformed. The once-tidy structure of the fatty tissue sandwiched between

the intestinal lining and lymph nodes had become so cluttered that motility of the cells vital to immune communication and function was drastically impaired.

The team then administered a series of vaccines to the mice and found that they triggered both hypersensitivity to food antigens and relatively weak responses to infectious agents.

Finally, the scientists effectively hit a reset button in their subjects' immune systems—by giving the mice a massive dose of broad-spectrum antibiotics.

“The chronic problems in the mouse model were caused by a broken interaction between the immune system and the lymphatic cells that carry immune cells,” says Hand, who cautions that, in humans, using antibiotics might be overkill.

“We need to think of new ways to fix that relationship,” he says. A systemwide reset might be accomplished instead with comparatively gentle interventions such as probiotics or dietary changes.

In his ongoing work—which includes collaborations with investigators at Children's Hospital of Pittsburgh of UPMC—Hand is investigating the particular host- and pathogen-related factors that can trigger permanent damage.

“I'm very, very interested in the vaccination defect,” he says.

He notes there's a big effort under way to determine what it is that makes a vaccination work or not work. ■

WEATHERING THE STORM

**PNEUMONIA DRUGS
TO TURN THE TIDE
BY NANCY AVERETT**



POBYTOV/GETTY IMAGES

Of the more than 1 million Americans who are hospitalized for pneumonia each year, about 5 percent die. Their demise is often caused by severe inflammation brought on by what experts call a “cytokine storm,” during which the immune system—called to duty by cytokine messenger proteins—overreacts and sends too many white blood cells to fight the infection. The white blood cells release more cytokines, which in turn signal the release of more white blood cells. This positive feedback loop eventually causes excess inflammation and damages healthy tissues and organs.

Treatment presents a delicate dilemma. “You don’t want to shut down inflammation, because inflammation itself is important for healing and normal repair after infection,” says Rama Mallampalli, Pitt MD professor of medicine, chief of the Division of Pulmonary, Allergy, and Critical Care Medicine, and director of the Acute Lung Injury Center of Excellence at the University of Pittsburgh. “You want to temper [inflammation], so it’s more controlled and doesn’t become hyperinflammatory.”

In May 2013, Mallampalli published a *Nature Immunology* paper with Bill Chen, a PhD and Mallampalli’s codirector at the center, Bryan McVerry, Pitt MD assistant professor of medicine and environmental and

occupational health, and Frank Sciruba, the MD director of Pitt’s Emphysema COPD Research Center as well as the Pulmonary Function Exercise Physiology Laboratory. They demonstrated that a particular protein, Fbxo3, which is activated during severe infection and pneumonia, stimulates cytokine secretion from human inflammatory cells. Fbxo3 is “very, very pro-inflammatory,” Mallampalli says. The team has since designed, synthesized, and tested a class of small molecules known as F box inhibitors that could block Fbxo3’s actions. The drug candidate is an attractive alternative to corticosteroids such as prednisone, which are used to treat severe inflammation but are not tolerated well by some patients. In January, Mallampalli, a National Institutes of Health–funded investigator, received \$100,000 in new support for his F box inhibitor work when he was named a Harrington Scholar-Innovator—an award that recognizes physician-scientists who have “the potential to change standard of care.”

“With this and other support, we should be able to move [this research] to first-in-human studies; that’s our goal,” Mallampalli says. “We’ve already done large- and small-animal studies and numerous efficacy studies.”

There’s more news from Mallampalli on the perfect storm that is pneumonia.

In addition to perilous inflammation, the

disease, which strikes between 5 and 10 million Americans a year, also often causes epithelial cell death in the lung, for reasons that are not clear.

In October 2015, Mallampalli, Chen, and Chunbin Zou, an MD/PhD research assistant professor of medicine, published a paper in *Science Translational Medicine* demonstrating that a particular strain of pneumonia-causing bacteria, *Pseudomonas aeruginosa*, activates a protein called Morf4l1, “which acts like a death toxin that kills the lung cells,” Mallampalli says. Normally, another F box protein, Fbxl18, destabilizes Morf4l1 so that it does not build up in epithelial cells; however, the bacteria induce a process that protects them from Fbxl18.

Mallampalli and his colleagues screened thousands of small-molecule drugs for one that would bind to Morf4l1 and block its actions in animal models. They found what they were looking for in argatroban, a drug previously approved by the FDA as an anticoagulant. Their next step: a hard look at previous UPMC patients’ outcomes to see whether those who took argatroban differ from controls when it comes to pneumonia incidence and severity.

P. aeruginosa is antibiotic resistant. If the new use for argatroban proves successful, the drug would become a promising nonantibiotic treatment for bacterial pneumonia—good news indeed. ■



TIM GROEN

TRAUMA'S IMMUNOLOGICAL IMPACT

BY ALLA KATSNELSON

Say you're in a bad car crash: broken bones, head wound, internal bleeding, the whole nine yards. Your blood pressure tanks, depriving the cells in your body of oxygen. It's not just the trauma and the bleeding that are so destructive—it's also their immunological aftermath.

According to the textbook understanding of immunology, microbial pathogens or other infectious invaders are what spur the innate immune system into action. But in the past 15 or 20 years, scientists have realized that noninfectious events—heavy blood loss, tissue damage, a broken arm, or even a planned surgery that piques some parallel danger-sensing system—can also ignite inflammation that *itself* can bang tissues around.

"It's only recently been appreciated that such injuries can activate all the same pathways of the innate immune system that infections can," says Melanie Scott, an MD/PhD research assistant professor of surgery at Pitt. "We're only starting to understand how that works."

Scott is at the forefront of this effort. Shortly after arriving at Pitt in 2003 for a postdoc in the lab of surgery department chair Timothy Billiar, an MD and the George V. Foster Professor of Surgery, she began exploring the mechanism of sterile inflammation—that is, inflammation that occurs without an infection—in mouse models of trauma, severe

blood loss, and tissue oxygen starvation (or hypoxia).

Inflammation—whether sterile or not—is activated when immune cells like macrophages release certain immunoreactive substances. Among them is the inflammasome, a recently discovered cluster of molecules that forms in response to signals from receptors that sense infection or danger. The inflammasome's task is to rouse the enzyme caspase 1, which then cranks up production of molecules called cytokines. But what increasingly perplexed Scott was that the inflammasome activated caspase 1 not just in immune cells, but also in other types of cells—such as liver cells—that don't produce cytokines.

"This was strange," she says, "so we asked, *Well, what are these cells really doing with this inflammatory molecule?*" When it came time to launch her own lab in 2007, Scott stayed on at Pitt, where, three years ago, she snagged an R01 grant to explore this question.

In mice engineered to lack caspase 1 in liver cells, she and her colleagues found that hemorrhagic shock and hypoxia were more damaging than in normal animals, suggesting that caspase 1's activation was protective.

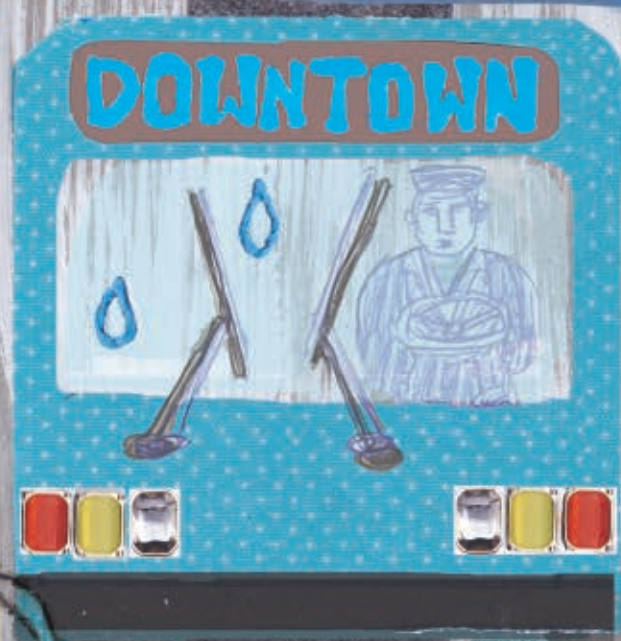
Liver cells—which have high-energy jobs such as making proteins for other parts of the body—are especially rich in mitochondria, the organelles that act as cellular powerpacks. But hypoxia damages mitochondria, causing

them to release what are called reactive oxygen species, which damage cells. In a paper published in the *Journal of Biological Chemistry* in 2013, Scott's lab suggested that activation of the inflammasome and caspase 1 turns on a pathway that chomps up the damaged organelles, essentially recycling them for spare parts. "That protective response is what's removing the production of reactive oxygen species," Scott says.

Her lab is trying to work out the details of how this pathway is regulated. Scott believes that it's DNA from the struggling mitochondria that sound the danger signal activating the inflammasome, and that its activation is graded, depending on the amount of reactive oxygen species the damaged mitochondria produce. That's interesting, she says, because inflammasome activation has generally been thought to be all or nothing.

Ultimately, hammering out the details of inflammasome activation in its many permutations will help scientists understand many disease processes, beyond trauma and hypoxia, says Scott, such as autoimmune diseases and inflammation associated with obesity. Her work also underscores the fact that the effects of revving up or stalling this activation may vary by cell type.

"We're not really there yet," she says, "but the idea is to find some way to regulate these different pathways in a beneficial manner." ■



THE FOUR-YEAR PROGRAM THAT PAIRS STUDENTS
WITH PATIENTS | BY ROBYN K. COGGINS

DOCTORS WORTH LOVING

You've got a crumpled slip of paper in your hand with a name and phone number on it—or maybe you're hovering over the “call” icon on your cell phone. Regardless, you're nervous. You've thought through the best way to arrange a meeting—in a public, neutral place like a coffee shop where you can get to know each other. Now, all you have to do is call this stranger and initiate a relationship—hopefully one that lasts for years to come. Cripes, why did you volunteer for this? What do you even say when he picks up?

Mike Bruno knows the feeling. “There's the anxiety about the unknown, like, *Who is this guy I'm about to go meet? What's he gonna be like? What's he gonna think of me?*”

Bruno dialed, waited. The voice at the other end wasn't what he was expecting.

“He said, ‘Not interested!’ and hung up,” Bruno recalls. Turns out, the stranger thought Bruno, then a first-year medical student at Pitt, was an out-of-state telemarketer.

Why would somebody with a complex illness to manage agree to another obligation—a unique relationship with a medical student? In Pitt med's Longitudinal Alliance Project, participants find compelling reasons. And we can all be thankful that they do.

ILLUSTRATIONS | CATHERINE LAZURE

Deep breaths. Summon courage. Dial again. On the second try, the man gave Bruno enough time to explain himself—that he was a medical student participating in the Longitudinal Alliance Project (LAP) and that he'd been given the man's contact information as part of the program. In effect, the man was Bruno's very first patient.

At the University of Pittsburgh School of Medicine's annual curriculum colloquium in 2012, Arthur S. Levine, an MD, senior vice chancellor for the health sciences, and the John and Gertrude Petersen Dean, proposed a new program to neatly complement the med school's basic science strengths. He suggested pairing students with a moderately complex case, a patient whom they would follow through the course of their education. The only other longitudinal experience, after all, is the scholarly project—the four-year research endeavor Pitt med students undertake. This was like adding another, very different pillar to

it's these students' first shot at a long-term patient relationship.

"You know, in some sense, it's kind of easy and superficial to spend your whole life having one-night stands," Maier offers as an analogy. "But that's not the way to build relationships or a successful community on all sorts of other levels. And I suspect the same is true in medicine."

"In all of our clinical experience, we're standing next to the doctors," Bruno explains. He's an articulate young man with a neat haircut. Today, he's donning a T-shirt from UConn, his alma mater. "But in this program, it flips our roles and lets us sit beside the patient. And it has a whole different tone to it. Because after the visit, we don't just go and talk to the doctor and debrief with the doctor: *So what do you think of this lab value?* Instead, we're debriefing with the patient: *So what do you think about what the doctor said? Did you get everything out of that?* That is really

"kids today aren't seeing the full progression of how things go," or so her elders put it. "They aren't seeing an infection heal. They're only seeing the antibiotics get started, and then [the patients] finish at home." Programs like LAP, she suggests, are "one way to try to bring continuity back."

And LAP brings that up front—before students take real medical histories, before they wield stethoscopes, before they're in clerkships.

Each year of LAP is loosely guided by a theme. Getting to know the patient is the bulk of year one. Getting to know the health care team and its interprofessional interactions makes up year two. Maier arranges for other health professionals to join in on small group discussions that year, starting the tilt toward medicine-as-team-sport thinking. In the third year, the focus is on the different specialties of medicine and how they interact—how a family doctor might refer her patient to a cardiologist, who then refers him to a radiologist for

"In all of our clinical experience, we're standing next to the doctors," Bruno explains. "But in this program, it flips our roles and lets us sit beside the patient. And it has a whole different tone to it."

support the curriculum.

Robin Maier, an MD, assistant professor of family medicine, and director of medical student education in that department, attended that colloquium and thought the program sounded interesting. What impressed her, she says, is that "there's this sense of seeing the medical system from the inside out, from the patient perspective," rather than the usual doctor-side-in way of doing things. After telling the dean as much, she was quickly asked to head the pilot program.

Maier, who's also the clerkship director for family medicine, launched LAP in 2013. Mike Bruno was in the inaugural class of 10—all volunteer students who'd been handed a pamphlet on the program. The brochure promised an experience to "put a human face to your pathophysiology learning, to facilitate communication ... [and] to identify barriers to care and gaps in care."

But the program is even more than that—

what distinguishes this experience—and why I think it's valuable."

There's an obvious benefit to the traditional apprentice-master style of medical education; it lets students see the work life of a physician—the grind, the frustrations, the victories. But, as Lisa Podgurski, an MD clinical assistant professor of medicine specializing in palliative care, and a leader of small group sessions for second-year LAP students, points out, without a long-term view of a patient, students are really only seeing a small part of a person and an illness.

"The average length of stay in a hospital is somewhere around four days. And so you see very discrete snippets of someone's illness course, and it's much more rare to see all of it," she says.

During medical school at Harvard, Podgurski participated in a shorter longitudinal program called the Cambridge Integrated Clerkship. The idea behind it, she says, is that

imaging and then sends the result back to the patient and the primary doctor. Ultimately, as the student grows in his medical knowledge, LAP grows with him. Bruno says that what he gets out of the program "changes all the time," depending on what he's learning elsewhere in the curriculum. It's organic and symbiotic.

In that first year, Podgurski (Res '12) and Maier (Res '04) want students to really understand the day-to-day life of their LAP patients. From the quotidian—How do they get around? What neighborhoods are they in? With whom do they live? Do they work?—to the increasingly intimate—What are their family and home lives like? How does their background and culture affect their everyday lives? What are their struggles? Put another way, these students gradually discover what interpersonal and social factors influence this person's health.

Of course before Bruno, or any of the students, receive a LAP patient's contact informa-



Baby food or medication?
One student was surprised
to learn the reason a LAP
patient decided not to fill
her prescription.



tion, they are given briefings on confidentiality requirements, HIPAA rules, and the like. During LAP orientation and beyond, students are reminded that their role is not to offer medical advice or translation to these patients. Bruno likens the relationship to being ambassadors for the medical community.

Though students are never required to do a home visit, they can if their patient invites them and their faculty mentor gives permission. Students mainly communicate with patients over the phone, through texts and e-mails, and during medical appointments or other in-person meetings.

By the end of that first year, Bruno was expected to understand the biology of his patient's conditions. As a capstone, he and the other students each gave a presentation to the small group on the medical science behind their patients' health concerns and wrote

reflective papers on their experience with the patient and LAP.

Both Maier and Podgurski have formal training in medical education—the former as a fellow of the Society of Teachers of Family Medicine and the latter as a graduate of Pitt's medical education master's program—and both model the role of thoughtful communication in medicine. They were a natural pair to codesign the LAP curriculum.

Maier makes a point of never asking students what specialty they plan to enter, understanding the pressure behind such a question and the assumptions that might come with the answer. In her presence, discussions are considerate in every sense of the word, and revelations are important but always provisional.

For instance, when a LAP patient opted to meet her med student for a meal at a fast food restaurant, Maier and the group thought

about why she might be making that choice—maybe the restaurant is close to home, or maybe she thought the student would feel more comfortable there. The group didn't judge; they wondered.

The learning that goes on in these group sessions, though difficult to quantify, is a huge part of LAP's success, the students say. The sheer breadth of conditions and individual circumstances each student encounters—and therefore shares with the others in his group—range from children with Down syndrome to adults with cancer, from people on dialysis to those newly diagnosed as diabetic. Young, old, pregnant, single, rich, poor. Some have trouble with Pittsburgh transit and miss appointments when the ACCESS buses don't run on snow days. Others are caring for young or sick loved ones and don't have the energy or time to focus on themselves. Some don't have a car

or a grocery store within walking distance of their homes. When, as has happened twice, a patient in the program dies, the students grieve together. When another patient's diabetes comes under control—because of a dental procedure, of all things—they celebrate.

Recruiting that range of patients willing to begin such a relationship with a medical student is a challenge. But LAP has its own matchmaker: Patricia Zahnhausen. A longtime education coordinator for the Department of Family Medicine, she schedules elective courses, recruits sites and physicians for clerkships, and performs other vital

have left the program. The most recent LAP group numbers nearly 60, and Zahnhausen and Maier expect next year's group to be even bigger.

But what about those patients? What's in it for them? Why would someone who already has a complex illness to manage agree to this unique relationship? According to Zahnhausen, some of them love teaching the next generation of doctors; Podgurski has even heard it described as leaving their "legacy." The LAP patients help med students understand the health care system, and they help improve it.

Facebook okay? How about sharing a car ride to an appointment?

"That's why I think these small groups are good to debrief," says Bruno. "What it came down to was, [texting photos] wasn't too much. . . . I think her patient sent it to her more as a practical thing, like 'so you recognize me.' I think it was really a sweet gesture. It was a little jarring at first."

Other times, of course, students share what they're learning about a LAP patient's feelings. Arjun Prabhu, who's also in Maier's small group, is a thoughtful student with an easy smile and a master's in bioethics. He was

"At first, [the volunteers] were patient with the student, figuring out how to have them around. Then there was a period of time where I could tell they're kinda like, *Oh, no, this isn't a good idea.*"

Maier's voice grows more quiet: "And then the student just kept being there! And all of a sudden . . . they love these students."

administrative work to make programs like LAP run.

LAP started with patients from Maier's practice and other family and internal medicine colleagues' patient pools, as well as an outpatient ob/gyn clinic and a pediatric oncology group. Then Zahnhausen approached local dialysis clinics. They've since sought out gastric bypass recipients, orthopaedics and endocrinology patients, those with autoimmune diseases—just about anybody who visits health care providers more than a few times per year. Next year, they want to include patients at the VA Pittsburgh Healthcare System.

Zahnhausen usually meets patients face-to-face and signs them up on the spot. She then follows up with consent forms and matches them with a student of the gender and language background of the patient's choice. Before long, the student makes that scary first call.

The patient recruiting process for each student class takes Zahnhausen two to three intense months. "It's a labor of love," she says. And a job well done: So far, only a half-dozen or so of the nearly 100 patients she's enlisted

It takes a while to get there, though. Maier summarizes the general steps toward intimacy: "At first, [the volunteers] were patient with the student, figuring out how to have them around. Then there was a period of time where I could tell they're kinda like, *Oh, no, this isn't a good idea.*"

Maier's voice grows more quiet: "And then the student just kept being there! And all of a sudden . . . they love these students: *This is my student. They may not be perfect, but this is the one I love.* And they'll complain—*Why is the medical school making them so busy that they can't come to all my appointments?* That's so real," she nearly whispers, awed.

In the small groups, Podgurski says, "We focus a lot on handling emotion, because that's a big part of being sick and having a loved one be sick."

Sometimes it's the students' emotions they are addressing. One patient frequently texted and sent photos of herself to someone in Maier's small group. This started a debate—is it okay to be in frequent texting contact with LAP patients? Students in Podgurski's small group also struggled with the boundaries of engagement—is friending each other on

assigned a girl born with a rare genetic syndrome accompanied by a host of complications, most notably intellectual disability and gastrointestinal issues.

Prabhu had never spent much time with kids, so he was nervous about working with Alice (not her real name), especially because she's nonverbal. "I never really thought about different kinds of kids," he says. "And I had never really interacted with a lot of people with intellectual disabilities." His hesitancy soon abated, however, when he was able to talk to the girl's mother about how it felt for her to parent a child whom she, too, initially felt unprepared for. (Alice wasn't diagnosed until after birth.)

"It completely changed her life," Prabhu says. She had to miss work and eventually chose to quit her job so she could spend more time taking care of Alice. She had trouble relating to fellow parents, she told Prabhu, because they bonded over their kids taking dance classes, struggling in school, making friends. Now in her early teens, Alice just started attending school but still can't participate in some activities with other kids her age.

Prabhu had never considered how tough it might be to parent a kid with medical challenges. “Her mother said she feels she and her husband relate more to people without kids,” Prabhu says—with those friends, the focus isn’t on typical kid activities that Alice doesn’t take part in. Yet as powerful as those difficult moments can be, Prabhu came to realize that Alice’s and her family’s lives don’t revolve around them.

Alice loves horses and car racing. She adores country music—so much so that the family dog is named after her favorite singer. As Prabhu has spent more time with the family at doctor’s visits and through e-mail updates, he’s found himself empathizing with them; feeling anxious, triumphant, or relieved as they do; worrying about the things they worry about—all the while hoping he can live up to what they need. That he might be the kind of doctor they’d love some day.

In his recent rotation in the emergency department, Prabhu was reminded of Alice and her mother.

“*You’re doing a good job*—somebody said that to a patient’s mom yesterday,” he says. “And it reminded me of my longitudinal patient’s mom—she was just kind of thrown into this. She was saying at first she was really overwhelmed, and it would be nice to hear something like that from a provider.”

Alice’s family has taught him other lessons, too, like making sure to sit at the patient’s level and look her in the eye, even if she doesn’t seem to make eye contact. Stand at the side of the hospital bed, not the foot. Focus on how the patient reacts after hearing medical information. Basic stuff, it seems, but little gestures that—especially when established early in a doctor’s career—make a difference.

One surgeon Alice’s family consulted to see whether she might benefit from a procedure on her spine was dismissive of their request for a consult. He kept insisting that Alice didn’t need surgery and didn’t listen to why they were there—which was just to get information.

Witnessing interactions like these, Maier says, gives students a sense of how frustrating even a seemingly simple doctor’s visit can be for patients. “How hard it is to just line up

the medicines. How hard it is to get appointments. How hard it is to deal with the insurance companies. Just sort of the labor involved in caring for a chronic disease,” Maier lists. “It’s giving students real insight into how it is to deal with the medical system ... which is something that makes every kind of physician a more effective physician.” It teaches them what kind of doctor they want to be.

In Bruno and Prabhu’s final LAP year, Maier will ask their small group to think critically about the health care system as a whole. Issues under that umbrella—such as how the Affordable Care Act is affecting insurance premiums or how patients cope with unexpected medical bills—have come up all the way through the program, of course. But as these nearly doctors apply for residencies and steel themselves for the hands-on work of everyday doctoring, they will be looking at a whole new level of responsibility, and a much more challenging environment in which to build relationships.

How will Bruno quickly establish a rapport with a feverish child in the emergency department? What will Prabhu say to the woman who’s refusing a cast on her broken arm because she doesn’t have insurance? How will they apply the lessons from LAP to their practice?

Dean Levine, in fact, has called for an increased emphasis on “social medicine” within the fourth-year curriculum, which fits nicely into the planned themes for LAP. The concept of social medicine has been around since at least the early 1800s, when the so-called father of modern pathology and “Pope of German medicine,” Rudolf Virchow, famously proclaimed that “Medicine is a social science, and politics is nothing else but medicine on a large scale. Medicine as a social science, as the science of human beings, has the obligation to point out problems and to attempt their theoretical solution.”

No one expects the LAP students to run for city council anytime soon, but seeing their patients’ experiences through the lens of social medicine is yet another way to look past the pathophysiology trees and see the forest of societal factors that surround them. How healthy an individual is, the theory argues, becomes a societal concern. In this

view, governments and public institutions should promote health and healthy behaviors in individuals, and we should all recognize that social and economic factors influence not just disease, but medicine as a discipline.

As a whole, America does not tend to see medicine in this way. On top of that, Maier says, “We spend enormously more money” than other developed nations, “and we generally don’t do quite as well in terms of outcomes.

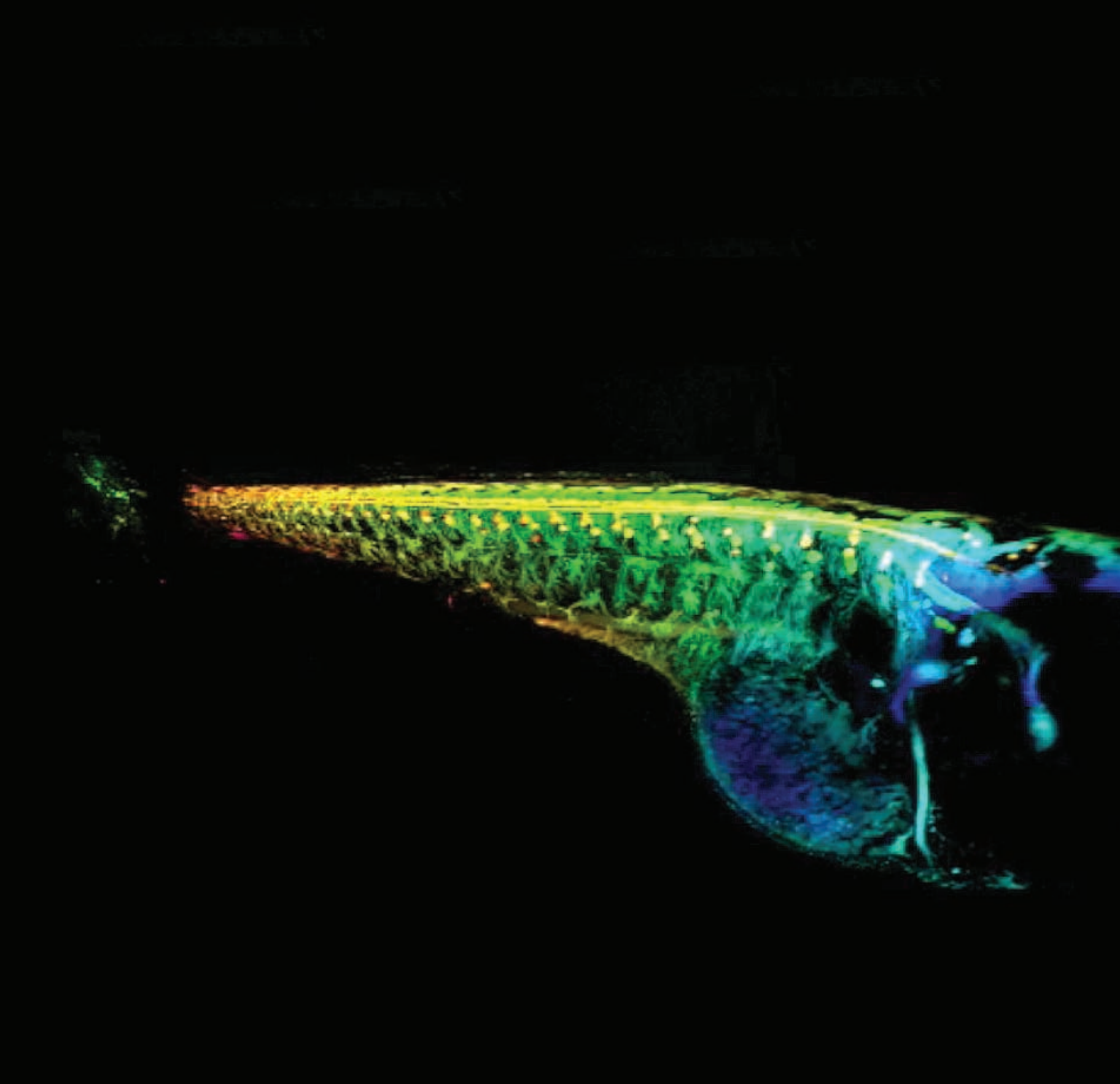
“We do an awful lot of urgent care and in-and-out kind of stuff and, as a result, all sorts of things get lost in the shuffle because there’s not good continuity.” Continuity of care is linked to better health outcomes, and it tends to deepen respect and understanding.

Bruno and Prabhu both call LAP the best thing they did in medical school. Despite that sentiment, Maier and the students think it’s best to build LAP slowly, sticking with students who seek out the experience; these self-selected 92 students value being collaborators in a self-guided program. Bruno’s advice to future LAP students sums it up: “Have fun with it. Remember that this is something for you. You’re not being graded. You don’t have to be in a super analytical position. You get to be a person to this person, sit by this patient’s side.”

Maier and the other third-year LAP students have been negotiating the best way to cap off the program when the time comes. There’s talk of elder students “handing off” their patients to the incoming first-year brigade. They like the sense of continuity and kinship that would provide. But would the magic of the relationship carry over to a new partner? Maier’s not one to dictate, so she probably won’t prescribe an ending to this either.

Will Mike Bruno send his patient a holiday card after he graduates—something to keep the relationship going? His reply is quick: “I think it would be great to stay in touch, but a Christmas card? I don’t think so, only because he’s not that kind of guy.” ■

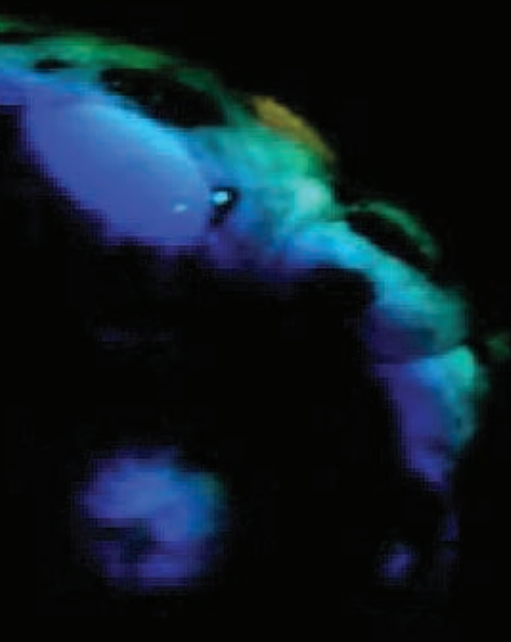
If you know someone who’d like to “adopt” a medical student, contact Patricia Zahnhausen at 412-383-2248 or zahnhausenpe@upmc.edu.



One fish, two fish, red fish, see-through fish. This zebra fish has been bred to be transparent. With this model, Edward Burton, Simon Watkins, and others at Pitt are seeing mitochondria misbehaving in real time. Many labs are now turning their focus to mitochondria; when the organelle is not functioning correctly, it can lead to Parkinson's, Alzheimer's, and Huntington's diseases. Mitochondria also seem to have difficulty doing their job in the presence of other neurological disorders and brain injury.

AS SCIENTISTS TRAWL FOR ANSWERS REGARDING
NEURODEGENERATION, THEIR BIG CATCH IS A
TINY ORGANELLE | BY JILL NEIMARK

FISHING FOR CLARITY



About 2 billion years ago, a couple of bacteria swimming in the primordial soup collided and tried to eat each other. Instead, they merged and formed an unexpected truce that changed life on Earth. Over eons, their descendants slowly evolved—one acquired novel genes and became the home structure, while the other moved in, gave up most of its genes, and slowly morphed into mitochondria, those tiny organelles dedicated to producing energy. With all that extra energy available, life was free to invent a dazzling array of creatures far more complex than bacteria—from hyacinths to hyenas, mushrooms to mice, fruit flies to falcons. Today, mitochondria are scattered through our cells like stars in a night sky. They mostly allow themselves to be regulated by the nuclear genome, and the energy they produce is so critical to cellular function that we now suspect mitochondrial impairment to be centrally involved in many diseases of aging and neurodegeneration.

ZEBRA FISH IMAGE | SIMON WATKINS, MICHAEL DAVIS, AND SANDRA RIEGER

“Mitochondria is where everybody’s research is leading now,” says the University of Pittsburgh’s J. Timothy Greenamyre—MD/PhD vice chair and Love Family Professor of Neurology, chief of the Division of Movement Disorders, and director of both the Pittsburgh Institute for Neurodegenerative Diseases and the American Parkinson Disease Association Advanced Center for Parkinson’s Disease Research at Pitt. “We’re all studying mitochondria, especially for neurodegenerative diseases.” And what Greenamyre and colleagues are uncovering is changing our understanding of diseases like Alzheimer’s, Parkinson’s, and Huntington’s, and paving the way for potential new therapies and drugs based on novel insights into mitochondrial function.

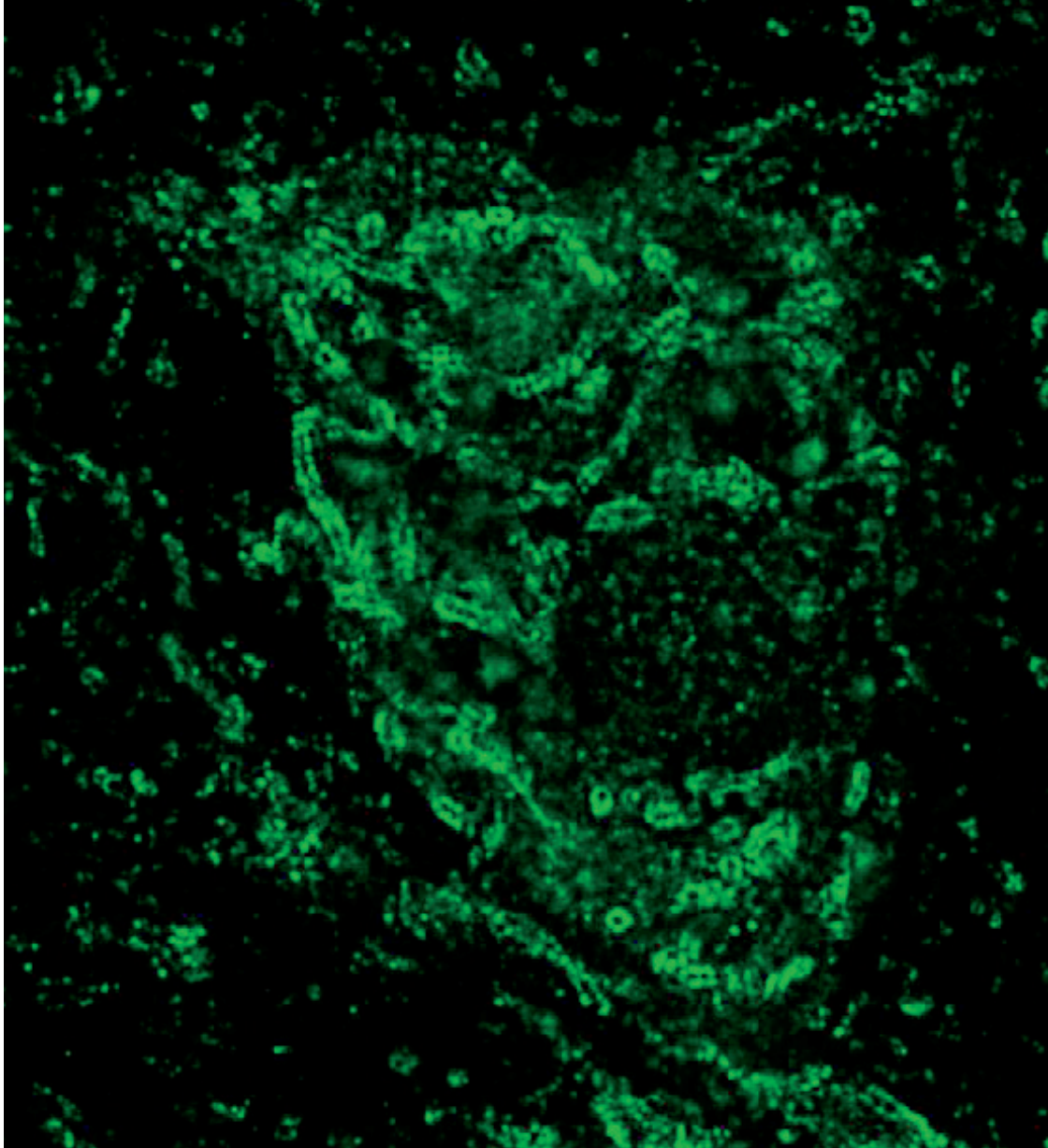
Take Greenamyre’s collaborative work with Edward Burton, an MD/DPhil associate professor of neurology at Pitt. The two recently demonstrated that gene therapy can prevent Parkinson’s symptoms in rats. Their study used a small, harmless virus called AAV2, engineered to safely transport a piece of genetic code into the brains of rats. That genetic code blocks production of a protein, α -synuclein, which builds into damaging clumps in the substantia nigra—a streak of tissue in the midbrain—of people with Parkinson’s disease. The substantia nigra regulates motor function and is studded with long and delicate dopamine-producing neurons; it slowly loses function in Parkinson’s, producing the disease’s abnormal movements, stiffness, and immobility.

In the experiment, gene therapy was delivered to the right side of the rat brain, which controls the left side of the body, and then the rats were given a precise dose of the pesticide

this approach could be translated into clinical trials at UPMC and Pitt. (Other Pitt investigators are already set to begin another gene therapy in Parkinson’s patients, one that enhances a brain enzyme that converts the most common Parkinson’s drug, levodopa, into dopamine.)

This remarkable study builds on the rote-

defective throughout the body. But the very selective neurodegeneration happens only in the substantia nigra of the brain, leading to the actual disease. Rotenone exposure reproduces both those conditions, so it’s an exquisitely accurate model. “There was a very big reaction, a lot of press, a lot of hubbub about that first paper on the rotenone mouse model in



“We will be able to see dynamic biochemical changes in the neurons of a living brain.”

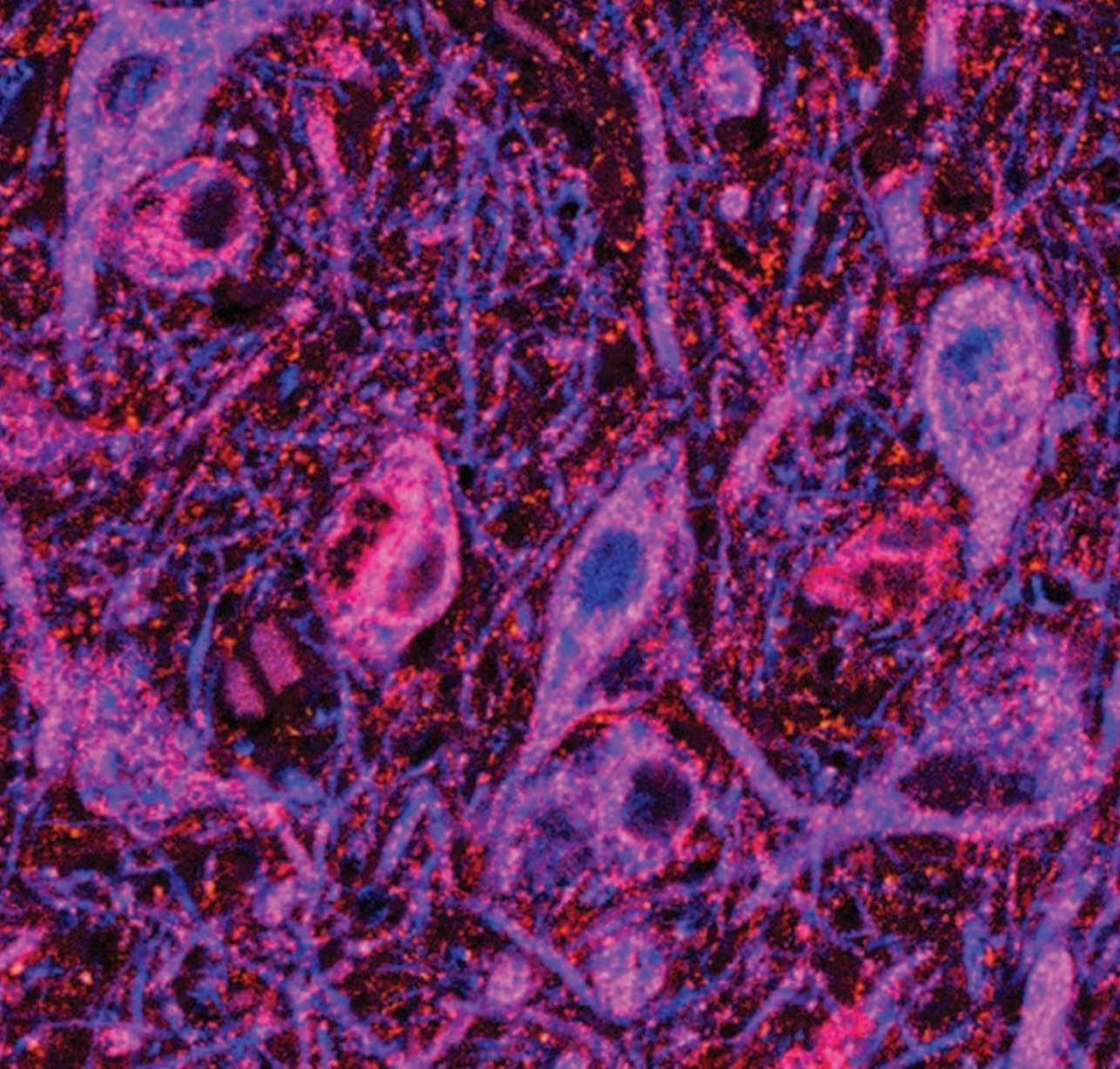
rotenone. Exposure to rotenone can lead to Parkinsonian symptoms. After the rats were injected with the pesticide, motor function on their “treated” left side remained normal, while the untreated side developed symptoms. In contrast, untreated rats, as well as rats given a control virus that contained no gene therapy, developed full-blown Parkinson’s symptoms after rotenone exposure. The findings were published in July 2015 in the *Journal of Clinical Investigation*. Eventually,

none rat model of Parkinson’s that Greenamyre developed 15 years ago.

“Rotenone is unique,” says Greenamyre, “in that it is a pesticide, and pesticide exposure is a known risk factor for Parkinson’s. But it also inhibits a very complex [mitochondrial] enzyme we simply call complex 1 that is impaired in Parkinson’s disease.” In Parkinson’s, complex 1 deficits appear in multiple places—blood, muscle, platelets—suggesting that mitochondrial function is

2000,” says Greenamyre. “It has been cited 2,000 times.”

Building on the gene therapy study, Greenamyre and colleagues have now shown how the dance between the nuclear genome and the mitochondria—the dance first started in that symbiotic union 2 billion years ago—is impaired in Parkinson’s and why α -synuclein may be so crucial. It turns out that mitochondria can’t function without importing proteins made and regulated by the cell’s nucleus, and



THIS PAGE: This image from J. Timothy Greenamyre and his team shows abnormal buildup of a protein, α -synuclein—pictured here in red—littering the landscape of the brain's dopamine-producing neurons (stained blue). It is thought that too much α -synuclein impairs mitochondrial function. As the mitochondria falter, the neurons also falter and eventually die.

OPPOSITE PAGE: When ordinary microscopes visualize mitochondria, they show up as blurred blobs. The new STED (stimulated emission depletion) microscope just installed by Simon Watkins offers super-resolution microscopy. In this image, a slice of a rat's substantia nigra—part of the brain affected in Parkinson's—is shown. The mitochondrial membrane here is stained fluorescent green, showcasing many tubular mitochondria that fill just one dopamine-producing neuron. This extraordinary level of detail allows Ed Burton and his team to gain far greater insight into how mitochondria function in healthy and damaged neurons.

STUTTERS AND STOPS

More than two decades after the cause of Huntington's disease was discovered, there is still no treatment—largely because it had been unclear how the mutant *HTT* gene led to the death of neurons. A recent *Nature Neuroscience* paper uncovers this mechanism.

"It's becoming more and more obvious that mitochondria are a central player in neuronal health," says principal investigator Pitt's Robert Friedlander, an MD, the Walter E. Dandy Professor and chair of neurological surgery, and head of cerebrovascular neurosurgery at UPMC.

Friedlander's group found that mutant huntingtin, the protein transcribed from *HTT*, blocks other proteins from entering mitochondria. Lacking these important proteins, mitochondria gradually begin to function inappropriately. Ultimately, this leads to the activation of the cell death pathway. This process occurs very early in the progression of Huntington's disease, and it is specific to neurons, despite the fact that the Huntington's gene is present in every cell in the body.

"It's a very direct link between the cause of the disease and a relevant disease pathology," says Friedlander.

Understanding the significance of this finding requires a little background about why it isn't feasible to treat Huntington's, a wholly heritable disease, with gene therapy. It isn't a good idea to remove the *HTT* gene entirely, because this manipulation is lethal in mice at the embryonic stage. Targeting the mutation alone is difficult, because its presentation is subtle—just a stutter in the DNA sequence. Friedlander's newly discovered pathway from mutant huntingtin to the demise of neurons opens up new avenues for drug development.

Even more exciting, Huntington's disease shares many of the same mitochondria-mediated cell death pathways with Parkinson's, ALS, and Alzheimer's, so a drug that works to treat one disease may very well work on others, Friedlander notes. —Erin Crowder Hare

that excess α -synuclein impairs that ability—interrupting their *pas de deux*.

“Although mitochondria contain their own genome,” says Greenamyre, “they must import 99 percent of the proteins they need. The mitochondrial import machinery is highly regulated and dependent on the nuclear genome.” In new work, forthcoming in *Science Translational Medicine*, Greenamyre shows that α -synuclein binds to an outer membrane receptor on mitochondria that imports proteins. It is at that receptor’s door that excess α -synuclein begins the vicious cycle. “We’ve seen that gene therapy may help downregulate production of α -synuclein,” says Greenamyre, “but we are also going to try to upregulate the [outer membrane] protein, so that the receptor is more active and can import more proteins. That might be another effective approach.”

Meanwhile, Burton is building on his collaborative work with Greenamyre by turning

system, the spinal cord, the glial cells, the living animal brain, in cell culture; so the fish offers this extraordinary model. It’s almost as easy to [use] as tissue culture, but it’s a living vertebrate animal.”

Burton is now beginning to screen compounds that are already FDA approved, or being used in humans in clinical trials, to see if the drugs can prevent the buildup of α -synuclein in Parkinson’s, as well as the accumulation of toxic tau proteins in Alzheimer’s. (When tau misbehaves, it tangles typically parallel cells in the brain, blocking nutrients and eventually causing cell death.)

“We are screening 1,280 different compounds in the fish. If any of them work, they could be used off-label in humans,” Burton says.

The long-term aim is to develop improved treatments for neurological diseases associated with movement disorders such as Parkinson’s and Huntington’s, as well as “tauopathies”

mitochondria,” Burton explains. “But the investment of time is worth it.”

Burton has already used fluorescent proteins sensitive to chemical changes in dopamine neurons, and plans to use the fish to recreate the Parkinsonian susceptibility of dopamine neurons to mitochondrial inhibitors in the presence of α -synuclein.

“We will be able to see dynamic biochemical changes in the neurons of a living brain. Nobody has done this before. Combined with the rapid screening capacity of zebra fish, there is tremendous potential to understand the basis for cellular susceptibility in diseases like Parkinson’s, and to develop novel therapies.”

To watch mitochondrial dynamics in these brightly lit transgenic fish, Burton has been working with Sarah Berman, an MD/PhD associate professor of neurology. Berman mastered fluorescent tagging work during a postdoc at Johns Hopkins, where

“It’s really cool to see red fluorescent mitochondria moving up and down the neuron. We don’t understand why they’re leaving and then stopping and coming back.”

to, not the rat, but the zebra fish to screen new drugs and to determine more precisely how α -synuclein is altering function. Zebra fish share about 70 percent of their genes with us, reproduce easily and copiously (they produce 50 to 100 embryos a week), and can be administered drugs simply by dosing the water in which they swim. The fish are particularly useful for studying neurodegeneration because the embryos are transparent and have a fully specialized nervous system by five days. The adult fish can be genetically engineered to be transparent, as well. And now, with fluorescent tagging of cell membranes, neurons, and mitochondria, scientists can watch a nervous system in action in real time as it responds to various chemicals.

“The zebra fish facility at Pitt is one of the largest in the world—it can house something like a quarter of a million fish in 11,000 tanks,” says Burton.

“Screening drugs or testing the effects of genetic mutations [is] far faster and more practical in fish than in mice, and much more informative than cell culture. You can’t replicate the blood-brain barrier and the nervous

such as Alzheimer’s and those associated with traumatic brain injury (including in football players). Burton hopes to discover just how and why α -synuclein makes nerve cells vulnerable to mitochondrial inhibitors like rotenone.

“Perhaps α -synuclein enhances production of reactive oxygen species by mitochondria, or inhibits the repair of damaged mitochondria,” he says.

What’s most remarkable is the way Burton has applied genetically encoded fluorescent probes to mitochondrial function. With color-coded fluorescent tagging—cerulean blue, green, cherry, and other colors—he can light up different structures in the see-through fish. The outline of neurons might be green, the mitochondria themselves red. Then, using microscopes so powerful they can capture three-dimensional views of organelles and record the actual movement of mitochondria inside cells, they reveal a once invisible wonderland.

“It takes us about a year to make a [line of] transgenic zebra fish with a green outline to the neuron and a red outline to the

she and her mentor were early adopters of this technique to study mitochondria in brain cells.

“I have always been fascinated by why the dopamine neurons are the ones that die in Parkinson’s disease,” she says. “What is it about these neurons that make them so susceptible? Dopamine itself can cause oxidative stress. Dopamine forms a highly reactive chemical called quinone, so neurons that produce dopamine are under a higher load of oxidative stress.”

At the same time, Berman notes, a lot of evidence points to mitochondrial dysfunction in Parkinson’s disease. There is now evidence, for instance, that two proteins linked to familial forms of Parkinson’s disease, parkin and PINK1, interact in a common pathway to regulate mitochondrial fission and fusion. Parkin might also play a role in keeping mitochondria healthy, by targeting damaged mitochondria for destruction.

All mitochondria divide (a process called fission) throughout their lifetimes—spawning offspring, much like their independent bacterial ancestors. But they also fuse, per-

haps to exchange genes, discard damaged DNA, and replace it with healthy DNA. Berman's work focuses on how dysfunction in these mitochondrial events contributes to neurodegeneration.

"It's really cool to see red fluorescent mitochondria moving up and down the neuron. We don't understand why they're leaving and then stopping and coming back." But she hopes to find out. Already, by using fluorescent tagging on neurons in cell culture, Berman has learned that inhibiting mitochondrial fission is beneficial for neurons exposed to low, chronic doses of rotenone.

"One of the beauties of working with zebra fish," says Berman, "is we will be able to look in detail at the pathology and the triggers of degenerative diseases like Parkinson's." The researchers plan to knock out the *Parkin* gene in zebra fish and see how it affects the mitochondria.

"As a practicing neurologist who treats Parkinson's," says Berman, "I have good symptomatic medicines to help patients manage their motor symptoms for many decades. But why are the cells dying in the first place? We want, as researchers, to find the earliest changes and target our therapy to those systems before [the cells] start dying."

Burton's transgenic fish are generating a bit of a neuro-buzz on campus. Funded by a grant from the National Institute of Environmental Health Sciences, Pitt's Bennett Van Houten is now working with

Burton and coprincipal investigator Patty Opresko, a PhD associate professor of environmental and occupational health, to discover how mitochondria, by generating free radicals, may eventually damage telomeres. Telomeres are the caps at the end of each strand of DNA that protect our chromosomes, and they shorten with age.

"The ability to see into the developing zebra fish brain and actually track living mitochondrial behavior is unprecedented," says Van Houten, a PhD, the Richard M. Cyert Professor of Molecular Oncology, and associate director for basic research at Pitt's Aging Institute. And, he adds, "None of this zebra fish work would be possible without our imaging center."

At Pitt's Center for Biologic Imaging, Simon Watkins collaborates with all of these researchers, offering the skills of his team and the use of a 6,500-square-foot suite that houses about 30 microscopes. (Watkins, a PhD, is a Distinguished Professor and vice chair of cell biology.)

"I pinch myself every day when I interact with Watkins," says Van Houten. "The ability to go over to that facility to use the tools he's assembled is truly extraordinary."

Each image from a microscope may have 80 or 90 moving mitochondria. To quantify the movements, the images are fed into computers and analyzed.

Van Houten thinks that this kind of work will ultimately, well, illuminate mitochondrial dysfunction as part of the pathophysiology of many common neurodegenerative diseases. Burton concurs:

"We've made zebra fish models of Parkinson's disease, progressive supranuclear palsy, dystonia—we can subject them all to this level of analysis. Mitochondria are dynamic, and neurons are constantly shuffling their mitochondria around. We've been looking closely at the axon—the projection from the nerve cell that is communicating with other nerve cells. It's a long, narrow projection, and we see the mitochondria moving down it a bit like cars on the freeway. Some are moving out from the cell; some are moving in. Is the neuron trying to pull some of them back into the cell body to repair them? Nobody's ever seen this in dopamine neurons in the brain before. It's really quite striking. Our zebra fish models will provide the tools we need to understand why this is happening and how it contributes to disease." ■

A BIOMARKER FOR PARKINSON'S DISEASE?

Working in collaboration with J. Timothy Greenamyre's laboratory, Laurie Sanders, a PhD, assistant professor of neurology, and member of the Pittsburgh Institute for Neurodegenerative Diseases, has discovered a potential blood biomarker for Parkinson's disease—both the hereditary and sporadic forms. That biomarker manifests as increased mitochondrial DNA damage. "We have a common phenotype between the two kinds of Parkinson's now. The assay may ultimately help catch Parkinson's in its earliest stages." Sanders hopes to explore the dysfunctional repair pathways that lead to the damage, then find drugs to target them. In the genetic, familial forms of Parkinson's disease, mutations in a gene called *LRRK2* are common. These lead to an increase in kinase activity, and as kinase activity increases, mitochondrial damage increases, as well. "When we use gene editing to return the *LRRK2* gene to its non-mutated wild type state, there is no damage in the neurons," says Sanders. "We are looking at kinase inhibitors, but what is unique about our approach is we are using our biomarker to monitor their effectiveness." —JN

NEUROPROTECTOR

What causes neurons to shrink and dwindle in people with Parkinson's disease? Charleen Chu's laboratory at Pitt has discovered a mechanism that regulates both quality control and growth for neurons. Chu, an MD/PhD, holds the A. Julio Martinez Chair and is a professor of pathology in the School of Medicine.

When mitochondria are damaged, molecules such as PINK₁ accumulate on the surface, alerting the cell to consume the misbehaving organelle. Clearing non-functional mitochondria staves off cell death. Healthy mitochondria import PINK₁, cleave it, and release the shortened protein. Shortened PINK₁ signals the growth of long and elaborate dendrites. These bushy branches allow neurons to stay in touch with their neighbors—and that's critical for health and functionality. So one molecule, whose function is lost in familial Parkinson's disease, facilitates neuroprotection through two distinct avenues. Looking forward, we can imagine the use of this potent messenger in treatments that slow or halt the progression of neurodegenerative diseases brought on by age, toxins, and genetic predisposition. —ECH

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FARBER CALLED “BULL” ON BIG TOBACCO
(AND A LOT MORE) | BY ELAINE VITONE

THE NO-NONSENSE PATHOLOGIST

If you were wandering the sixth floor of Scaife Hall searching for Pitt’s famous pathology chair in the 1960s, you wouldn’t have had to look for long. Emmanuel (Manny) Farber—whose reputation preceded him for his breakthrough studies of chemical carcinogenesis and his instrumental role in taking on the cigarette industry—had the kind of penetrating voice that carried down the corridor. That was especially the case when he was excited—and on the job, he always was.

Every morning at 10:30, Farber—a 5' 7" dynamo who lived his life on fast-forward—would gather the pathology pack around a fresh pot of coffee and a carousel of slides. Mostly liver-cancer researchers like him, the scientists assembled for a uniquely open confab, with faculty, grad students, and postdocs alike encouraged to speak up, and often.

The late Emmanuel Farber’s pathology department was vibrant intellectual territory. Farber was also an influential member of the surgeon general’s advisory committee that penned the 1964 report on smoking and health.



Farber’s liver model helped scientists understand that in cancer, context matters.

CIGARETTE ADVERTISEMENTS FROM THE COLLECTION OF STANFORD RESEARCH
INTO THE IMPACT OF TOBACCO ADVERTISING | PHOTOS COURTESY NAOMI FARBER

But, if you didn't lead with verifiable data—peer-reviewed, published, and replicated to Farber's satisfaction? That, he insisted, was not science, but "BULL ...!"—and he'd let you know, in so many words.

Well, exactly one.

There were, in a sense, two Farbers: One, a departmental uncle, a mensch who was not above wearing a Santa suit (though he was culturally Jewish) at the parties he hosted in his Pittsburgh home, where his wife, Ruth, played the piano. A scientific shepherd who over the course of his career served as president of the American Association for Cancer Research (AACR); editorial board contributor at numerous cancer, liver, pathology, and biochemistry journals; and a member of too many panels and societies to mention. A man who, in the days before strict rules about grant reviewers and applicants steering clear of each other, would simply call an investigator up and say, *Hey, I think there's a better way to go about this*, and step in to try to help.

And then there was the other Farber, the no-nonsense academic who so abhorred superficiality, and so delighted in the sport of scientific sparring, that he rattled his colleagues' and mentees' nerves, often with a devil's advocate shtick that was all too convincing. He might use his favorite one-word retort on you, for example, when discovering that you had an animal model of a disease. He'd scoff, question how a rodent could be useful in the study of complex human pathogenesis. *How does that relate?!* In the meantime, he himself was working on a new rat model of liver cancer.

Farber came to Pitt from Tulane University in 1961 to fill the sizable shoes of Frank Dixon, the Jonas Salk recruit who had built in Pittsburgh one of the premier research-focused pathology programs in the country. (Dixon had left for an appointment as founding chair of experimental pathology for the Scripps Clinic and Research Foundation in La Jolla, Calif.; he then led what would become the Scripps Research Institute.) Pitt pathology at the time, like Dixon, had a big immunology bent—so big, there was room for little else. Farber changed all that, building a full-fledged academic department ingrained in what he called biochemical pathology, the close study of the

chemistry, anatomy, and physiology of cells in the presence of disease.

By the time of his death in August 2014 at age 95, Farber had garnered such honors as the inaugural fellowship of the AACR Academy, bestowed just shy of the 50th anniversary of the 1964 surgeon general's report on smoking and health. He served on the committee that authored the report, which remains one of the most important publications in the history of public health.

Farber, who completed med school and trained in pathology in his native Ontario, Canada, realized early on that his specialty presented a unique window into the mechanisms of disease processes, an exciting, problem-driven mode of medicine. At UC Berkeley he completed a PhD in biochemistry, a move that was almost unheard of for pathologists at the time.

Farber did early work on the biochemistry of cell death and was among the first to observe it as an active process involving the cell's own biochemical/metabolic processes. He also showed that carcinogens can bind to nucleic acids, which then create specific DNA adducts. He demonstrated chemical carcinogenesis as a chain reaction, establishing a disease model that followed a predictable series of sequential steps.

The progression of these steps would later prove to have predictive value, in terms of understanding how aggressive a cancer would be, says Richard Hegele, chair of pathology at the University of Toronto, where Farber was chair emeritus and professor when he died. Such insights proved helpful in determining which therapy would work best for a given case—contributions that "evolved toward precision medicine," Hegele says.

Ezio Laconi, professor of pathology at Italy's University of Cagliari, who was a PhD student in Toronto when he first met Farber, says his former chair's greatest legacy is a fundamental principle of cancer biology that in recent years has been gaining new appreciation. And that principle is: Context matters.

Before a tumor appears, usually there are alterations in tissues, says Laconi, because they've been "suffering for a long time" from stressors like inflammation—conditions that create "optimum soil" for the emergence of cells that progress toward cancer.

In his Pittsburgh lab, Farber launched investigations that would lead to his greatest claim to fame, the Solt-Farber resistant hepatocyte model of carcinogenesis. It begins with the liver, a unique organ that, when healthy, can regenerate to its original size, even if you remove as much as two-thirds of the organ. Farber and his collaborators found that if you do so chemically and using certain toxic agents that are known to halt cellular proliferation, the liver regenerates anyway—but bulks back up with cancer cells instead.

"That was a famous discovery for liver biology," says Pitt's current chair of pathology, George Michalopoulos, an MD/PhD and Maud L. Menten Professor of Experimental Pathology.

"This [liver model] has been studied all over the world," notes Henry Pitot, former director of the McArdle Laboratory for Cancer Research at the University of Wisconsin, Madison, adding that researchers like to use this particular model because it yields precancerous areas within weeks instead of months or years.

For Laconi, this finding, which was published in *Nature* in 1976, had far grander significance, presenting a new paradigm: When a toxin poisons the body continuously over time, robbing a given tissue's cells of their ability to multiply, what's left standing is a very small number of stubborn, embattled survivors—the cockroaches of cell life. Farber believed that, in the great majority of cases, precancerous cells are a response—an adaptation—to toxicity. For adults older than 50, most cancers are "certainly explainable, at least in principle" with this concept, says Laconi, pointing out that most known risk-factor agents are toxic in nature: UV exposure, certain viruses, and of course smoking.

"As Dr. Farber used to say, one of the main features of biological systems is, they react," says Laconi. "They try to adapt to environmental conditions."

"I never thought I would be a pathologist," says Stewart Sell (MD '60), professor of biomedical sciences at University at Albany, SUNY. "Who wants to sit around and look at a microscope all day? But [at Pitt] it wasn't just looking at slides or making a diagnosis. It was thinking about how these things happened. And, how could you set up an experiment that could show how these



UNIV. OF PGH., DEPT. OF PATH. 1964
Farber (center, front row, in glasses and white, polka-dotted tie) came to Pitt in 1961 as chair of pathology. Among his many contributions, his work helped doctors predict how aggressive a cancer might become.

diseases occurred? That stimulus was fantastic.” Sell returned to Pitt as a junior faculty member. At the time, the immunologist wasn’t particularly interested in hepatocarcinogenesis, but the lively discussions reeled him in. “I started a project in liver cancer that led to a continuing interest. We are still funded for this.”

In 1965 Farber secured \$30,000 from the National Institutes of Health to make Pitt the host of a first-ever conference on “biochemical pathology,” held at Seven Springs resort. Forty scientists from seven countries came in June

to present papers, which were published in a seminal book the following year. “One of the potentials of the field,” the press release read, “is the detection of disease-caused changes in cells before the disease becomes clinically evident in the patient.”

With Farber at the helm, Pitt’s crew of academic pathologists had an uncommon abundance of time to devote to their studies, while maintaining close ties to the clinical

pathologists. Many in the department at the time would rise to prominence in the field: Nobuyuki Ito (Fel ’64) became dean of Nagoya City University Medical School in Japan; Bob Kisilevsky (PhD ’69) is professor emeritus of pathology and molecular medicine at Queen’s University in Ontario; Mike Lieberman (MD ’67, Res ’70, PhD ’72) was pathology chair at Baylor and founding director of the Houston Methodist Research Institute; Benito Lombardi and Hisashi Shinozuka founded the carcinogenesis research section of Pitt’s Division of Experimental Pathology; Frank Sherman (MD ’38) directed pathology at Children’s Hospital of Pittsburgh of UPMC; Herschel Sidransky chaired pathology at George Washington University; and Robert E. Lee (MD ’56) served as pathology professor at Pitt.

In high school and college, Joe Locker (A&S ’67) worked next door to Farber in the lab of Joseph Leighton (who would, by the way, go on to chair pathology at Medical College of Pennsylvania, which was later absorbed by Drexel University). Locker is now a pathology professor at Pitt. “Manny took an active interest in my scientific devel-

BURNING ISSUE

In 2014, Acting United States Surgeon General Boris D. Lushniak released *The Health Consequences of Smoking—50 Years of Progress*. Data on smoking’s effects are detailed in the new document, the contributing authors of which include Nancy Davidson, University of Pittsburgh Cancer Institute director, president of the American Association for Cancer Research, and Pitt’s Hillman Professor of Oncology; Steven Shapiro, chief medical and scientific officer for UPMC and Distinguished Professor of Medicine at Pitt; and Hilary Tindle, former Pitt assistant professor of medicine, epidemiology, and clinical and translational science (now at Vanderbilt). A few highlights:

- Smoking is still the biggest cause of preventable death and disease in the United States.
- Smoking rates among adults and teens are half of what they were in 1964, and today’s smokers don’t smoke as many cigarettes. However, because of changes in the composition of cigarettes, smokers are at an even higher risk for lung cancer now than 50 years ago.
- Adding filters to cigarettes has done more harm than good. Because they cut irritation, filters encourage deeper inhalation. And some of the 69 known carcinogens in this toxic smoke are at even higher levels in today’s cigarettes.
- Women are now in just as much danger of dying from smoking-related diseases as men, for the first time in history.
- In the last 50 years, more than 100,000 infants have died of SIDS, conditions associated with premature birth and low birth weight, and other obstetric complications resulting from parental smoking.
- The economic cost of smoking is approaching \$300 billion annually—and climbing.
- We now know that smoking is linked to diseases in almost every organ in the body. —EV

NICO-WEEN

Nicotine withdrawal isn’t pretty: irritability, tanking mood. And the so-called “light” cigarettes on the market give smokers no leg up in cutting down. Studies show that these products, which differ from their counterparts only in their ventilation systems, just train smokers to inhale more deeply and more often.

But a six-week study published in the *New England Journal of Medicine* in October showed that if you instead reduce the amount of nicotine in cigarettes, smokers don’t experience the usual fallout. Those who were given smokes with less than 15 percent of the usual dose actually lit up 23 to 33 percent less, and with “minimal” signs of withdrawal. A month later, these smokers were twice as likely to have tried to quit again, compared to controls who smoked cigarettes with typical amounts of nicotine.

The preliminary study made a splash in the national media, and since then, several long-term follow-up trials have continued to build the case for FDA regulations on nicotine levels. If enacted, such legislation could have an “enormous” impact on public health, says lead author Eric Donny, a PhD professor of psychology with a secondary appointment in psychiatry at Pitt. “One model predicted that the prevalence of smoking in the U.S. would fall to under 5 percent.” —EV

opment,” Locker says, “and we had a lot of scientific contact over the next 40 years.”

Throughout Farber’s career, he reached out to chemists, physicists, microbiologists, mathematicians, and others. Multidisciplinary brain trusts are commonplace in pathology departments today, but at the time, people thought the idea was “crazy,” recalls Sarma Dittakavi, who first met Farber as a postdoc at Pitt in 1965, and was then recruited by him, twice—first when Farber left Pitt to direct Fels Institute for Cancer Research & Molecular Biology at Philadelphia’s Temple University in 1970, then when Farber returned to his alma mater, University of Toronto, as pathology chair in 1975.

As a trainee, Mike Lieberman fell for Farber’s enthusiasm hook, line, and sinker. Presbyterian Hospital’s pathology chief had told the up-and-comer that what he really needed to satisfy his natural curiosity was a research project—so he should go talk to Farber. Within 30 minutes, Farber convinced him to do a new combined residency/PhD program he had started, one of the first of its kind in the country. “I never regretted it,” Lieberman says.

Fun Farber fact: Previously, he had also founded a PhD program at Tulane, its inaugural enrollee being Pitot, who went on to mentor Pitt’s own Michalopoulos. “He gave me great leeway,” recalls Pitot—so he paid the favor forward. “I gave [Michalopoulos] the bit, and said, ‘Go,’ and he’s become an expert in the field.”

Michalopoulos met Farber as a resident in Wisconsin. Farber “was always very helpful,” he says of his scientific grandfather. Once, Michalopoulos wrote a grant that included a salary for a technician—which Farber advised him to nix. “And he was right. We were forced to dig in and get the results [ourselves]. If they were coming to us served on a platter, we probably would have missed them.”

On the front page of the April 26, 1961 *Pitt News*, the student newspaper ran a story about the appointment of Emmanuel Farber as pathology chair. On the back of that same issue was a half-page ad for Tareyton cigarettes, bragging that their dual filter was “definitely” proven “to make the taste of a cigarette mild and smooth.”

This was the tobacco industry’s new MO:

outwardly denying the fact that their product was anything less than healthy; internally circulating memos about the urgent need to develop “a medically acceptable cigarette,” pronto; and promoting the hell out of their new filtered cigarettes, which they hoped would sidestep the problem altogether—of course, to no avail.

In Philip Morris’s pocket were experts from premier universities who would attack any smoking-related science of substance. Cigarette producers sent pro-tobacco broadsides to 200,000 clinicians and ran ads featuring lab-coated docs lighting up. In the middle was the public, confused and swept up in misinformation.

The stakes could not have been higher. It was time to call “BULL!” on Big Tobacco.

On November 9, 1962, Surgeon General Luther Terry and his deputies convened for the first time with 10 scholars (selected from an original list of 200 names put forward by private health and government officials). The committee’s charge: to vet the entirety of the relevant scientific literature to date—some 7,000 articles. Among the 10, Farber was the “most original thinker,” writes Richard Kluger, author of the 1996 book *Ashes to Ashes*. (He also quotes the committee’s scientific coordinator, Peter Van Vechten Hamill, who called Farber “a volatile little guy with a highly superior IQ.”)

In the modern-styled National Library of Medicine in Bethesda, Md., the committee convened nine sessions of two to four days each over the course of 13 months. They usually got together in the mezzanine, or in the third subbasement, where as many as 30 staffers at a time (each with government clearance) typed and copied and clamored around the clock. Armed guards secured the building.

In analyzing 36 population studies, the committee and their armies of consultants found that smokers died of lung cancer at a rate 10.8 times higher than nonsmokers. And that the more people smoked—and, the longer they kept at it—the greater the risk of lung cancer. And that this was the case no matter who you were, where you were from, what your socioeconomic standing was, or what the air quality was like in your town.

Before committing what became their famous tome to paper, the committee had

one lingering issue to settle: the American Cancer Society–funded study, which was integral to their case because it combined epidemiological and histological evidence (including samples from both humans and experimental animals) so beautifully . . . perhaps too beautifully. The study was troublingly perfect.

Farber wanted to see the specimens for himself. So off to New Jersey he went.

For two days, Farber led the effort to scrutinize the slides—the last day running from 4:30 a.m. to 10 p.m.—until he was satisfied. Though there weren’t fully formed tumors (the animals often died first from the poison of the smoke), the start of cancer was there, in the form of cellular changes he was familiar with. (Throughout his career, he was always a strong proponent of the importance of dynamic, whole-organism studies.) And, to everyone’s relief, the samples, in Farber’s fastidious assessment, were carefully and honestly come by.

Months later, the U.S. government published the report in a secure, fenced facility, and Terry released the document to the public. To date it has still done more to prevent smoking-related disease than any other preventive measure.

But if you ask Farber’s friends and family, he never bragged about it. “He thought it immodest to talk about himself,” says his daughter, Naomi Farber.

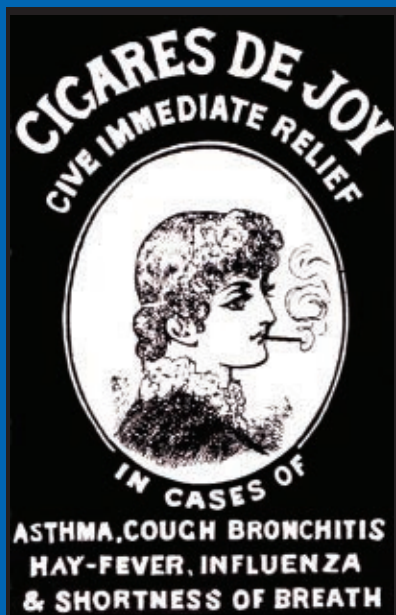
You’d hear it in the hall, recalls Lori Cutler of the 11 years she spent at the IBM Selectric typewriter outside Farber’s office at the University of Toronto. *ONCOGENES?! WHAT ONCOGENES?!*

“He’d be yelling,” she says. “I’d be on the phone, and [the person on the line] would say, ‘Who’s that?’ And I would say, ‘Oh, that’s my boss.’” Cutler pauses, cutting up. “The secretary beside me would say, ‘Here comes Dr. Farber with his BULL ...!’”

Farber enjoyed arguing for the sake of arguing, it’s true. But he was also known to fundamentally disagree with colleagues.

He disagreed with Pitot about how cancer arose in the liver.

He disagreed with Lombardi about the significance of what are called oval cells, which Sell eventually showed to be liver cancer stem cells. Ironically, Farber, who’d actually discovered the existence of oval cells and gave



them their name, was sure they were ductal cells and nothing more. “It was kind of sad for me,” says Sell. “He could have had much more credit, if you will, for this whole idea.”

And, from the 1970s on, Farber disagreed with seemingly everyone when it came to oncogenes—the genes that can act like accelerator pedals for cancer. “BULL!” etc. “What’s the evolutionary advantage of that?!”

As the initial theories about the genetic origins of cancer were cropping up, Farber was unconvinced. He said: You can’t explain tumor formation with a single event. “And in my opinion, that was correct,” says Laconi. “Those simplified approaches are not getting

us very far ... particularly, in our ability to cure cancer. There are a few examples where genetic approaches have given some results, but overall we’re nowhere close to what we were hoping for when Richard Nixon declared war on cancer in 1971.”

As cancer research waded deeper into oncogenes, Farber couldn’t abide it. But he continued to grow and thrive nonetheless.

“My dad had this philosophy,” says Naomi Farber. “Do something, give it your best, transform it, and then move on.”

After a decade as pathology chair in Toronto, in which he grew the graduate program from a handful of people to more

than 150 students, he stepped down to focus on his research and his teaching. In his leadership roles in his department, as well as the broader pathology community, he fostered the development of subspecialties in the field: experimental pathology, biochemical pathology, and toxicologic pathology.

And he brought undergraduates into the fascinating (albeit often grim) world of pathology. He designed a “Principles of Pathobiology” course, a problem-oriented way of teaching life sciences—and it was a runaway hit, growing quickly from 40 to 140 students per semester. The class started in 1978 and is still going strong in Toronto.

In examining slides and sometimes even whole organs, the students found context for the content they were learning and came to appreciate the features of normal versus diseased specimens side by side: controls versus the lungs of a miner or the liver of an alcoholic. And invariably, several students quit smoking by term’s end, notes Dittakavi, who cotaught the class with Farber for many years.

Cutler came into the lecture hall to help set up for the class a few times and stayed to be awed by the boss who was like a father to her. When he got stirred up, the tempo, pitch, and volume of his voice would uptick. “His eyes would light up when he would see all these students in the room eager to take the course.”

“His enthusiasm was contagious, especially for young people,” says Laconi. “He was, in Italian we say, a *faro*, a lighthouse. He illuminated my path to research.” ■

SMOKE AND MIRRORS

In 2005, the University of Pittsburgh’s Brian Primack had just wrapped up a public health class on cigarette smoking; and a student came up to him, saying, “I don’t know if you know this, but hookah [or water pipe smoking] is what we all do now.” At that time, Primack says, hookah use was flying under the radar, and e-cigarettes had not yet entered the market in the United States.

Motivated by that after-class discussion, Primack, MD/PhD professor of medicine, pediatrics, and clinical and translational science, began to study the prevalence of hookah smoking—and later e-cigarette use—among middle school, high school, and college students. What he found is that young people believe vaping and hookahs are more socially acceptable than smoking cigarettes. They also see them as less harmful and less addictive—Primack has found otherwise. (Note the Royal College of Physicians is now recommending that cigarette smokers switch to vaping; that stance is not shared by FDA officials who will begin regulating *all* tobacco products this August.)

Data published by Primack in *Public Health Reports* and *JAMA Pediatrics* showed that water pipes are more toxic than cigarettes, and vaping is a potential new gateway to smoking, even for young people who said they never intended to smoke traditional cigarettes.

One allure for the young set is that vaping, as well as hookah tobacco, can have a fruity or candy-like flavor. And overall there are few negative social implications or media influences.

Primack is working to change that. In his roles as Pitt’s assistant vice chancellor for research on health and society and director of the Center for Research on Media, Technology, and Health, he’s reaching out to empower youth—teaching them to analyze how the tobacco industry can manipulate people through advertising, educating them on the risks of these devices, and hopefully extinguishing the temptation to experiment altogether.

In the meantime, he notes, as more adults heed smoking warnings and put their butts out for good, more young people could be getting hooked. —Kristin Bundy

JESSE STEINFELD PROTECTED THE PUBLIC

BY THOMAS H. MAUGH II

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(AND MINOR ADAPTATIONS)

THANK YOU FOR NOT SMOKING

Three U.S. surgeons general have played the biggest roles in alerting the public to the dangers of tobacco.

In 1964, Luther Terry, an MD, issued the first Surgeon General's Report on Smoking and Health, irrefutably linking smoking with lung disease and other illnesses. The report eventually led to a sharp drop in smoking and to the first warning labels on cigarette packages.

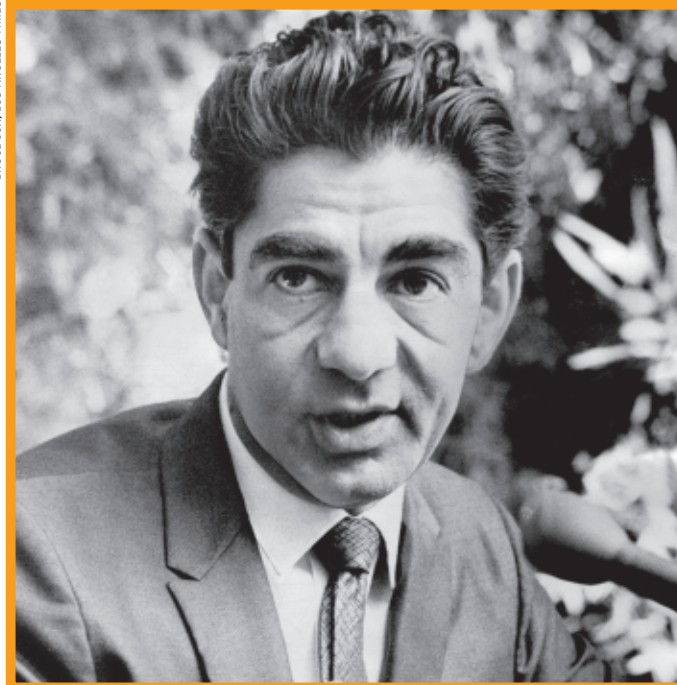
Seven years later, Jesse L. Steinfeld, an MD and graduate of the University of Pittsburgh College of Arts and Sciences, issued another report that focused on the dangers of secondhand smoke. He proposed what he called the Non-Smoker's Bill of Rights, saying that the country must free nonsmokers from the hazards and annoyance of other people's addictions. He strengthened the warning on packages and issued the first ban on smoking in certain government buildings.

In the 1980s, C. Everett Koop, an MD, accelerated the war against tobacco, producing the first ban on smoking in airplanes. (Steinfeld had advocated ardently for this, as well.)

The tobacco industry lobbied vigorously for Steinfeld's removal, and he became the first surgeon general ever forced out by the president.

Steinfeld died in 2014 in Pomona, Calif., from the aftereffects of a stroke. He was 87.

BRUCE COX, LOS ANGELES TIMES



Pitt Arts and Sciences grad Jesse Steinfeld was surgeon general from 1969 to 1973 under President Nixon.

He “was at the leading edge of the social changes we are all benefitting from today,” said UC San Francisco tobacco expert Stanton A. Glantz. “He started people thinking about the issue [of nonsmokers’ rights] differently. Even getting partial smoking restrictions was a major accomplishment at the time.”

Terry’s report and other activities during the 1960s led Republicans—and some Democrats—to argue that surgeons general were intruding inappropriately into private life. They viewed Richard Nixon’s election to the White House in 1968 as an opportunity to defang the position.

That effort had already begun in 1968 with a reorganization of the Department of Health, Education, and Welfare (HEW) that removed a large part of the organization from the surgeon general’s purview.

Steinfeld taught at the USC School of Medicine during the 1960s and lived in Orange County, where he met Nixon campaign organizer Bob Finch. In 1968, he moved to the National Cancer Institute and became deputy director the following year. In 1969, he planned to return to USC, his wife and family having already packed and left for the coast.

But Finch, by then Nixon’s HEW secretary, promised to appoint him surgeon general if he would stay in the capital. Nixon and his aides really didn’t know Steinfeld but thought he was a personable man who could be a good spokesman for their conservative social views. That proved to be a mistake.

When Steinfeld took office in December 1969, he noticed at least 13 ashtrays scattered around the suite. He immediately had them all removed and posted signs saying “Thank you for not smoking.” He also refused to meet with tobacco industry lobbyists.

Although much of the office’s bureaucratic power had been stripped, Steinfeld used it as a bully pulpit to promote what he considered good health policies. A new surgeon general’s report, released in 1972, was already in preparation, but he adopted it and made it his own. That report’s central point was that there is “no disagreement” that cigarette smoking is lethal. The report was the first to discuss the health issues of secondhand smoke.

Steinfeld called for a ban on smoking in virtually all public places, including restaurants, theaters, planes, and trains. It took several years for that to begin to be accomplished, however.

He also changed the warning labels on cigarette packages. After Terry’s report, the labels bore a warning that tobacco use “may” be connected to health problems. Steinfeld successfully

changed the labels so that they read, “The surgeon general has determined that cigarette smoking is dangerous to your health.” The warning was also made larger, and tobacco advertising on television and radio was banned.

In fairness, some have argued that tobacco companies favored the warnings because they feared that each of the states would impose their own requirements, and they didn’t want to deal with 50 different labels. They also hoped the warning would indemnify them against lawsuits, but Steinfeld and Congress made clear that was not the case.

Shortly after Nixon declared his famous “War on Drugs,” Steinfeld told a Los Angeles convention that the real No. 1 problem was smoking, lacing his speech with statistics about the epidemic of lung cancer and other smoking-related diseases.

He took on other issues, as well. He argued successfully for the government to take a larger role in promoting the fluoridation of water, banning the pesticide DDT, and banning cyclamate, an artificial sweetener thought to cause cancer.

He also argued that violence on television had a disturbing effect on the social development of children and called for networks to impose some type of self-censorship or to, at least, label programs that contain violence to alert parents. His superiors ordered him not to testify before Congress on the issue, but he was subpoenaed and decided to testify without clearing his testimony first. That further frayed his relationship with the administration.

Nixon and HEW came under tremendous pressure from the tobacco industry to get rid of Steinfeld. When Nixon was reelected in 1972, he asked all members of his administration to submit letters of resignation. (This is common practice for presidents, who then determine whether to ask officials to continue on.) After he had been forced to rewrite it twice to weaken it (and take out requests for continued funding of cancer research, his wife, Gen Steinfeld, told *Pitt Med*), Steinfeld’s letter was accepted. The office of the surgeon general then remained vacant until Jimmy Carter appointed Julius Richmond, an MD, in 1977.

The only other surgeon general forced out of office was Joycelyn Elders, an MD, who was fired in 1994 by Bill Clinton after she made comments during the AIDS epidemic that were interpreted as meaning that children should be instructed in how to masturbate.

Jesse Leonard Steinfeld was born Jan. 6,

1927, in West Aliquippa, Pa., also the home of musician Henry Mancini. Steinfeld rode the school bus with Mancini and fondly recalled standing outside the Mancini house while Mrs. Mancini yelled, “Henry, sit down at that piano and practice!”

Teenage boys in West Aliquippa were routinely placed in the vocational track with the prospect of working in the mills or other local industry, but Steinfeld persuaded his counselor to place him on the academic track. He graduated from high school at 16, and 19 months later, in 1945, received his bachelor’s degree from the University of Pittsburgh. He received his medical degree in 1949 from what is now Case Western Reserve University. (He’d had his heart set on Pitt med, but learned of his acceptance here after already enrolling at Case Western, notes Gen Steinfeld.)

He did his internship at what is now Cedars-Sinai Medical Center in Los Angeles and had residencies at the VA Hospital in Long Beach and UC San Francisco. His residency was interrupted so he could serve as a physician on a Coast Guard cutter in the North Atlantic during the Korean War.

After being forced out of his job as surgeon general, Steinfeld spent a year at the Mayo Clinic and two years at UC Irvine. From 1976 to 1983, he served as dean at the School of Medicine at the Medical College of Virginia. In 1983, he became president of the Medical College of Georgia.

At Georgia, he created a master plan for the future of the school and new facilities. “He was truly a visionary leader whose time here, unfortunately, was short,” said his successor, Francis J. Tedesco, an MD. “He laid the groundwork for future development.”

Steinfeld retired in 1987 yet remained a passionate advocate for nonsmokers’ rights. He testified in several trials, including one case filed by flight attendants against the major airlines. He and Terry also petitioned the Food and Drug Administration to regulate tobacco as a drug.

According to his daughter Susan, “He was a voracious reader, loved classical music, a good joke, and home cooking . . . he was immensely proud to have accomplished everything he did as the son of Jewish immigrants.” ■

Editor’s Note: With a \$100,000 gift, Gen Steinfeld created the Dr. Jesse Steinfeld Endowed Scholarship at Pitt in March 2015; the fund will support MD student(s) in the School of Medicine.

When the PATIENTS Become the DOCTORS

BY EM DEMARCO



XENIA CATALINA FERNANDEZ

AGE 26, OF PAWTUCKET, R.I.; CLASS OF 2018; PLANS TO GO INTO PEDIATRICS

DIAGNOSIS DATE:
FEB. 11, 2004, AGE 13, ACUTE LYMPHOCYTIC LEUKEMIA (ALL)

TREATMENT SUMMARY:
ABOUT 2-1/2 YEARS TOTAL. FIRST MONTH INDUCTION, THEN CONSOLIDATION, THEN MAINTENANCE; FINISHED MAY 2006.



MATTHEW KOCHER

AGE 22, OF OAKDALE, PA.; CLASS OF 2019; PLANS TO GO INTO PEDIATRICS

DIAGNOSIS DATE:
MARCH 1, 2005, AGE 11, ACUTE MYELOID LEUKEMIA (AML)

TREATMENT SUMMARY:
THREE HEAVY ROUNDS OF CHEMO, THEN A BONE MARROW TRANSPLANT; BEGAN IN MARCH AND FINISHED AUGUST 2005.



XENIA AND MATTHEW SHARED MEMORIES OF THINGS THAT HELPED THEM GET THROUGH TREATMENT -- INCLUDING SUPPORT FROM FAMILY, HOURS OF TV, PLAYING VIDEO GAMES WITH FRIENDS IN THE HOSPITAL ...

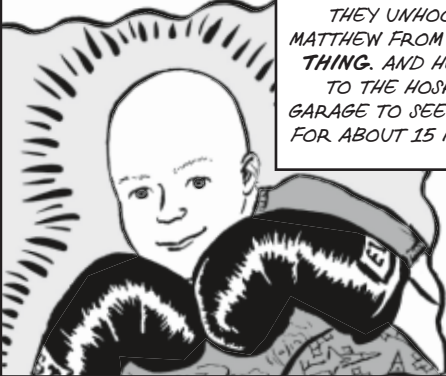
MATTHEW'S FAMILY KNEW HE LIKED **GETTING MAIL** -- IN THE HOSPITAL, HE RECEIVED 25 CARDS A DAY FROM FAMILY, FRIENDS, AND COMPLETE STRANGERS FROM ALL AROUND THE WORLD.

I STILL HAVE THEM. THEY'RE IN A **BIN** UNDER MY BED.


"MY MOM WAS PRETTY MUCH MY ROCK," XENIA SAYS. AT ONE POINT, XENIA WAS CRAVING **RAVIOLI** MORNING, NOON, AND NIGHT FOR ALMOST AN ENTIRE MONTH. SO HER MOM KEPT THE FREEZER STOCKED WITH IT.

I DIDN'T EAT [RAVIOLI] FOR **THREE YEARS**, I WAS SO TIRED OF IT!

"ONE OF THE **DARKEST** POINTS ... I TOLD THE DOCTORS ALL I WANTED TO DO WAS SEE MY **BEST FRIEND**. AND THEY'RE LIKE, 'BRING HIM IN!' I SAID, 'BUT YOU DON'T UNDERSTAND -- IT'S A FOUR-LEGGED ANIMAL.'"



A FEW DAYS LATER, THEY UNHOOKED MATTHEW FROM **EVERYTHING**. AND HE WENT TO THE HOSPITAL GARAGE TO SEE HIS DOG FOR ABOUT 15 MINUTES.



"TEN DAYS LATER, I WAS HOME. IT WAS A **TURNING POINT** FOR ME."

MATTHEW, DURING TREATMENT. A FAMILY FRIEND AND CANCER SURVIVOR GAVE HIM THESE BOXING GLOVES.

AS PATIENTS, WHAT **SURPRISED** YOU?

"I HAD **NO CLUE** WHAT I WAS GETTING INTO ... [THE CLINIC] WAS SUPER **COLORFUL** ... IT WAS NICE BECAUSE, YEAH, YOU'RE **SICK**, BUT YOU'RE **STILL A KID**, AND THEY STILL WANT YOU TO HAVE FUN."



"EVERY TIME I WALKED IN ... I WOULD SEE THE RECEPTIONIST [AND SAY], 'I'M **HERE!**'"

XENIA, DURING TREATMENT. ONE OF HER DOCTORS CALLED HER **BROOKLYN**, BECAUSE SHE OFTEN WORE THIS SHIRT TO CLINIC.

SO, IT SOUNDS LIKE HUMOR WAS A **COPIING MECHANISM**?



YES!

ONE TIME ... I BELIEVE HE WAS THE **HEAD** OF THE ONCOLOGY DEPARTMENT ... THE RESIDENTS ALL KNEW I WAS GOING TO PULL A **PRANK**.




YOU PRANKED THE **ATTENDING**? THAT IS EPIC!




I LAID IN BED AND WENT, "OH, I'VE GOT THIS **PAIN** IN MY BELLY!"




"I HAD A **FART MACHINE** UNDER ME -- [THE ATTENDING] PRESSED DOWN ON MY **STOMACH**."



"MY DAD HAD THE **BUTTON**, SO HE PRESSED IT AND IT WENT OFF."



"[THE ATTENDING] **JERKED BACK** ... ALL THE RESIDENTS WERE **BUSTING UP LAUGHING!**"



WHEN DID YOU DECIDE TO BECOME **DOCTORS**?

IN HIGH SCHOOL, HE SHADOWED A RESEARCHER AT **HILLMAN CANCER CENTER**. BUT MATTHEW DECIDED WORKING AT A RESEARCH BENCH WASN'T FOR HIM.

AT FIRST, I WANTED **NOTHING** TO DO WITH MEDICINE.

BECAUSE OF WHAT YOU'D GONE THROUGH?

YEAH.



"I WANTED TO ACTUALLY **BE THERE** AT THE BED, SEEING THE PATIENTS, TELLING THEM IT'S GOING TO BE **OKAY**."

XENIA SAYS SHE HAD TO UNDERSTAND HER TREATMENT BECAUSE **ENGLISH** WASN'T HER **MOM'S FIRST LANGUAGE**. HER DOCTORS TOLD HER SHE SHOULD CONSIDER A MEDICAL CAREER, SHE SAYS. BUT THAT WASN'T ON HER MIND UNTIL LATER.

[**ZACHARY**] WAS PRETTY MUCH MY **CLINIC LITTLE BROTHER**. HE WAS 8 OR 9 WHEN WE MET. WE WERE REALLY GOOD FRIENDS. WE WENT THROUGH TREATMENT AROUND THE SAME TIME.



THEN MY MOM GETS THE **CALL** ... **ZACHARY PASSED AWAY**.

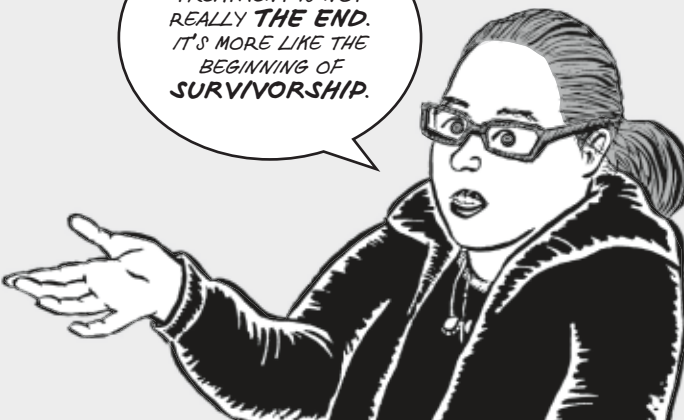
IT **JOLTED** ME AWAKE. ... I WAS ABOUT 16. I JUST DECIDED, I **NEED** TO GO INTO MEDICINE.



ANY **FINAL THOUGHTS** YOU WANT TO SHARE WITH READERS?

WE GET THE DIAGNOSIS, WE GET TREATED, AND -- IF WE END UP BEING IN THE **LUCKY** GROUP -- WE **SURVIVE**. BUT IT'S NOT LIKE THAT'S THE END. ... WE HAVE TO KEEP A LOOKOUT FOR OUR **HEALTH**.

THE END OF TREATMENT IS NOT REALLY **THE END**. IT'S MORE LIKE THE **BEGINNING OF SURVIVORSHIP**.



MATCH RESULTS

CLASS OF 2016

ANESTHESIOLOGY

Bintrim, Daniel
UPMC/University of Pittsburgh, Pa.
Dewasurendra, Anusari
UPMC/University of Pittsburgh, Pa.
Lee, Andy
University of Washington Affiliated Hospitals
Lehman, David
Emory University, Ga.
McDermott, Sean
UPMC/University of Pittsburgh, Pa.

DERMATOLOGY

Au, Jeremiah
University of Illinois Chicago Medical Center
Engeln, Kathleen
Michael E. DeBakey VA Medical Center,
Harris Health System, Texas Children's/
Baylor College of Medicine
Eseonu, Amarachi
Johns Hopkins Hospital, Md.

EMERGENCY MEDICINE

Covell, Benjamin
Carolinas Medical Center, N.C.
Daley, Michael
John H. Stroger, Jr. Hospital of Cook County, Ill.
Eng, Michael
University of Wisconsin Hospital and Clinics
Filip, Ari
UAMS Medical Center/
University of Arkansas for Medical Sciences
Hsu, Diane
Los Angeles County-Harbor-UCLA Medical Center,
Calif.
Huh, Alexander
UPMC/University of Pittsburgh, Pa.
Jennings, Ryan
UPMC/University of Pittsburgh, Pa.
Kim, James
University of Arizona-Tucson Campus Hospital
Manchester, Leah
Yale-New Haven Medical Center, Conn.
Scanlon, Matthew
University of Cincinnati Medical Center, Ohio
Wasserman, Deena
Temple University Hospital, Pa.
Ye, Jinny
Duke University Hospital, N.C.

FAMILY MEDICINE

Aninwene, Amanda
Oregon Health & Science University Hospital
Kelly, John
Memorial Hospital of South Bend, Ind.
Laskow, Bari
Swedish Medical Center, Wash.
Rapakko, Salla
Sutter Health, Calif.
Santizo-Deleon, Elsy
York Hospital, Pa.

FAMILY MEDICINE AND PSYCHIATRY

Lin, Liu yi (Laura)
UPMC/University of Pittsburgh, Pa.

INTERNAL MEDICINE

Abraham, Neethu
UPMC/University of Pittsburgh, Pa.
Ahn, Brian
UPMC/University of Pittsburgh, Pa.
Ahn, Michelle
UPMC/University of Pittsburgh, Pa.
Black, John
UPMC/University of Pittsburgh, Pa.
Brase, Amanda
University of Iowa Hospitals and Clinics
Choi, Myung Sun
Oregon Health & Science University Hospital
Cui, Liang Richard
Christiana Care Health System, Del./
Thomas Jefferson University
Frank, Rachel
Massachusetts General Hospital/Harvard University
Han, Katrina
UPMC/University of Pittsburgh, Pa.
Hu, Jennifer
Beth Israel Deaconess Medical Center/
Harvard University, Mass.
Kirakossian, David
Kaiser Permanente Santa Clara Medical Center/
Stanford University, Calif.
Lesky, Daniel
Emory University, Ga.
Lo, Kelly
California Pacific Medical Center,
San Francisco
Minkoff, David
Emory University, Ga.
Mohanty, Aditya
John T. Mather Memorial Hospital/
Stony Brook Medicine, N.Y.
Mukherjee, Abhigyan
Robert Wood Johnson University Hospital/
Rutgers University, N.J.
Nieves, Ricardo
UPMC/University of Pittsburgh, Pa.
Ross, Mitchell
Beth Israel Deaconess Medical Center/
Harvard University, Mass.
Scanlan, Bethany
Vanderbilt University Medical Center, Tenn.
Shafir, Adi
UPMC/University of Pittsburgh, Pa.
Shah, Niyati
UPMC/University of Pittsburgh, Pa.
Tao, Sunny
UPMC/University of Pittsburgh, Pa.
Wayne, Max
University of Michigan Hospitals
and Health Centers
Woo, Jean
Allegheny Health Network, Pa.
Xie, Maylene
UPMC/University of Pittsburgh, Pa.
Zou, Richard
UPMC/University of Pittsburgh, Pa.

INTERNAL MEDICINE— GLOBAL HEALTH

Oluwole, Olubusola
UPMC/University of Pittsburgh, Pa.

INTERNAL MEDICINE—PEDIATRICS

Moghul, Ayesha
Geisinger Health System, Pa.
Rizvi, Afshan
Texas Children's, Harris Health/Baylor College of Medicine
Rosenbaum, Lucy
Ohio State University Hospital,
Nationwide Children's Hospital
Toocheck, Corey
Ohio State University Hospital,
Nationwide Children's Hospital

INTERNAL MEDICINE— WOMEN'S HEALTH

Patel, Neeti
UPMC/University of Pittsburgh, Pa.
Wang, Yanting
UPMC/University of Pittsburgh, Pa.

MAXILLOFACIAL SURGERY

Chambers, Michael
UPMC/University of Pittsburgh, Pa.
Shah, Gaurav
UPMC/University of Pittsburgh, Pa.

NEUROLOGY—PEDIATRIC

Chitrapu, Anjani
Cincinnati Children's Hospital Medical Center/University of
Cincinnati, Ohio

OBSTETRICS/GYNECOLOGY

Jean, Katie
UPMC/University of Pittsburgh, Pa.
Salomon, Morgan
University of Toledo, Ohio
Sears, Sarah
MetroHealth Medical Center/
Case Western Reserve University, Ohio
Whitney, Janelle
Tufts Medical Center, Mass.

OPHTHALMOLOGY

Burrow, Michael
University of Utah Medical Center
Kuhn, Julia
UPMC/University of Pittsburgh, Pa.
Michelson, Sarah
University of Michigan Hospitals and Health Centers
Mortensen, Peter
UPMC/University of Pittsburgh, Pa.

ORTHOPAEDIC SURGERY

Boakye, Lorraine
UPMC/University of Pittsburgh, Pa.
Dombrowski, Malcolm
UPMC/University of Pittsburgh, Pa.
Morales, Alejandro
UPMC/University of Pittsburgh, Pa.

OTOLARYNGOLOGY

Ettyreddy, Abhinav
Barnes-Jewish Hospital/
Washington University in St. Louis, Mo.
Fingersh, Andrey
University of California, San Diego Medical Center
Heft-Neal, Molly
University of Michigan Hospitals and Health Centers
Kim, Jee-Hong
LAC+USC Medical Center/
University of Southern California
Lee, Jake
Barnes-Jewish Hospital/
Washington University in St. Louis, Mo.
Newsome, Hillary
Medical College of Wisconsin Affiliated Hospitals



LEFT: Malcolm Dombrowski and Lorraine Boakye show off their matches—both are training at UPMC for orthopaedic surgery (and 36 of their classmates will stick around UPMC with them). **RIGHT:** Match Day played out a little differently this year. Rather than each name being called out one by one by an exuberant one, the students opened their envelopes together (more or less).

PATHOLOGY

Birkness, Jacqueline
Johns Hopkins Hospital, Md.
Farrell, Daniel
University of California, Irvine Medical Center

PEDIATRICS

Barrington, Elizabeth
Bristol-Myers Squibb Children's Hospital/
Rutgers University, N.J.
Bohnhoff, James
UPMC/University of Pittsburgh, Pa.
Boiko, Julie
San Francisco General Hospital,
SF Kaiser Permanente Medical Center/
University of California, San Francisco
Cody, Ellen
Children's Hospital Colorado/University of Colorado
Cummings, Erin
Children's Hospital of Pittsburgh of UPMC/
University of Pittsburgh, Pa.
Howard, Amari
Nemours/Alfred I. duPont Hospital for Children, Del./
Thomas Jefferson University, Pa.
Keerthy, Divya
Jackson Memorial Hospital/Jackson Health System/
University of Miami, Fla.
Negrin, Isabela
West Virginia University Children's Hospital
Newlon, Claire
Hershey Medical Center/
Pennsylvania State University
Nyman, Katherine
Children's National Medical Center/
George Washington University, D.C.
Okafor, Debra
Yale-New Haven Children's Hospital, Conn.
Perry, Michelle
Children's Hospital of Pittsburgh of UPMC/
University of Pittsburgh, Pa.
Pompa, Anthony
Children's Hospital of Pittsburgh of UPMC/
University of Pittsburgh, Pa.
Quidley-Martin, Maria
Children's Hospital of Philadelphia/
University of Pennsylvania
Roy, Nikita
Cohen Children's Medical Center/
Hofstra University, N.Y.
Wang, Kaylie
University Hospitals Case Medical Center,
Rainbow Babies and Children's Hospital/
Case Western Reserve University, Ohio

White, Whitney
NYU Langone Medical Center, Bellevue Hospital/
New York University

PEDIATRICS — MEDICAL GENETICS

Forsyth, Raelynn
Johns Hopkins Hospital, Md.

PHYSICAL MEDICINE & REHABILITATION

Baidoo, Kevin
Rush University Medical Center, Ill.
Markos, Steven
JFK Medical Center Program/
Rutgers University, N.J.
Wang, Steven
Montefiore Medical Center/
Albert Einstein College of Medicine, N.Y.

PSYCHIATRY

Cheng, Carol
UPMC/University of Pittsburgh, Pa.
Suter, Daniel
Mount Sinai Hospital/Icahn School of Medicine, N.Y.

RADIATION ONCOLOGY

Chapman, Bhavana
MD Anderson Cancer Center/University of Texas
Holt, Douglas
VA Medical Center, Denver Health Medical Center,
Children's Hospital Denver/University of Colorado
Rashid, Arif
Hahnemann University Hospital/
Drexel College of Medicine, Pa.
Xu, Karen
Emory University, Ga.

RADIOLOGY — DIAGNOSTIC

Khalaf, Alexander
Stanford Hospital and Clinics, Calif.
Kilbridge, Matthew
UPMC/University of Pittsburgh, Pa.
Vu, Nicholas
UPMC/University of Pittsburgh, Pa.
Wolf, Joel
Jacobi Medical Center/
Albert Einstein College of Medicine, N.Y.

SURGERY — GENERAL

Aveson, Victoria
NewYork Presbyterian-Weill Cornell Medical Center
DeLahunta, Daniel
Loyola University Medical Center, Ill.

Etchill, Eric
Johns Hopkins Hospital, Md.
Hernandez, Sergio
University of South Florida
Hunter, Oriana
Lehigh Valley Health Network, Pa./
University of South Florida
Sadowsky, David
Montefiore Medical Center/
Albert Einstein College of Medicine, N.Y.
Teng, Cindy
UPMC/University of Pittsburgh, Pa.
Welborn, Seth
University of Louisville Hospital, VAMC,
Jewish Hospital, Ky.
White, Allana
University of Colorado Hospital
Zolin, Samuel
Cleveland Clinic/
Case Western Reserve University, Ohio

SURGERY — NEUROLOGICAL

Choi, Phillip
University of Texas Health Science Center at Houston
Zhang, Zel
UPMC/University of Pittsburgh, Pa.

SURGERY — PRELIMINARY

Kano, Daiji
NewYork-Presbyterian Hospital, Queens—Weill Cornell
Medical Center
Villanueva, Hugo Jose
Conemaugh Memorial Medical Center, Pa.
Zhang, Dongning
UPMC Mercy/University of Pittsburgh, Pa.

SURGERY — THORACIC

D'Angelo, Alex
NewYork-Presbyterian Hospital/
Columbia University Medical Center

SURGERY — VASCULAR

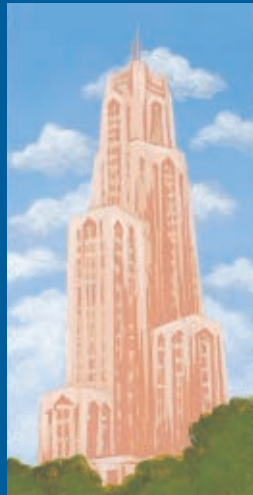
Kim, Joyce
West Jefferson Medical Center, Baton Rouge General
Medical Center/Louisiana State University

TRANSITIONAL MEDICINE

Dhaliwal, Amardeep
Crittendon Hospital Medical Center, John D. Dingell VA
Medical Center/Wayne State University, Mich.

UROLOGY

Kang, Audrey
University of Chicago Medical Center, Ill.



CLASS NOTES

'60s

A father-son duo took center stage at Saint Vincent College's December commencement ceremony. **Thomas Gessner** (MD '68) received the honorary Doctor of Science degree from his undergraduate alma mater in Latrobe, Pa. Gessner's son, Christopher Gessner, president of Children's Hospital of Pittsburgh of UPMC and Western Psychiatric Institute and Clinic, served as the event's principal speaker. Thomas is an emeritus staff member at Excelsior Hospital, where he has held positions as medical director and pediatrician. During his clinical career, he served on the faculties at Pitt, West Virginia University, and Thomas Jefferson University. Thomas also is president of the Latrobe Area Hospital Charitable Foundation Board, a member of Saint Vincent's board of directors, and a member of the advisory council for Saint Vincent's Herbert W. Boyer School of Natural Sciences, Mathematics, and Computing.



Thomas and Christopher Gessner

'70s

Psychiatrist **Bryan Stevens**'s (MD '71) ability to read faces inspired him to find "hidden elements" in what would become a serious hobby—collecting Mexican folk dance masks. "I approached them as if they were patients," Stevens says of the hundreds of dance masks he has studied. For instance, he learned that some of the masks displayed otherwise disguised feelings of mistreatment by conquerors. Stevens was introduced to Mexican masks on a trip to

Santa Fe, N.M., in 1987. Nearly 30 years later, he is still taken with how "abstract and elegant" they are. After retiring from psychiatry six years ago, Stevens wrote a book, *Mexican Masks and Puppets: Master Carvers of the Sierra de Puebla*, and began sharing his anthropological findings at community lectures. He also blogs at mexicandancemasks.com.



Mexican dance masks have fascinated Stevens for decades.

'80s

Ask **Steven Zimmet** (Family Medicine Resident '81) about his career in medicine, and he'll tell you: "It's been an interesting trip." After practicing family medicine for a few years, Zimmet shifted his focus to dermatology and venous disease. "Until recently the disease process was basically ignored," says Zimmet. "Some people refer to venous disease as 'the Cinderella of medicine.' It's been a great time to be in the field because there has been so much technological evolution." Zimmet was one of the first doctors to use ultrasound to diagnose and treat venous insufficiency and to perform endovenous laser ablations—a now-standard treatment for varicose veins. Among his distinctions, Zimmet serves as president of the American Board of Venous & Lymphatic Medicine and as editor of *Phlebology: The Journal of Venous Disease*.

During her 31 years at Pitt, **Halina Zyczynski** (Obstetrics and Gynecology Resident '89) has garnered an abundance of titles: professor of obstetrics, gynecology, and reproductive sciences; founding director of the Division of Urogynecology and Pelvic Reconstructive Surgery; and medical director of the Center for Continence and Pelvic Floor Disorders. After years of working as a generalist in ob/gyn,



Zyczynski

Zyczynski recognized the need for better treatments for pelvic floor disorders, which affect upward of one in four women. "It didn't seem like a great achievement to help women live longer if we weren't going to simultaneously commit to improving the quality of their lives," she says. Since 2000, Zyczynski has continuously received NIH funding for her clinical research; in August, she published findings in *Obstetrics & Gynecology* showing that stress incontinence surgery helps alleviate most women's overactive bladder symptoms. "I love my patients, and that's where this all started."

'90s

Jennifer Momen (Pediatrics Resident '94) has been appointed medical director of the School of Physician Assistant Studies at Alderson Broaddus University in Philippi, W.Va., where she teaches pediatrics and physical diagnosis, among other courses. Momen is also a student; she's pursuing her master of public health at West Virginia University. Her thesis plays off her enthusiasm for preventive medicine and concerns pediatric oral health: she's exploring the association between early dental visits and dental outcomes in childhood.

Srinivasan Beddhu (Nephrology Fellow '99), a professor of medicine at the University of Utah, and colleagues found that adding short, light-intensity activities to one's everyday routines is strongly associated with a reduced risk of early death. These results, which were published in the *Clinical Journal of the American Society of Nephrology* in July 2015, showed that walking or cleaning for just 2 minutes per hour could make a difference: "When we take 2-minute walks many times, the energy expended adds up, strengthening the heart and muscles and improving general health," says Beddhu, whose research interests include obesity and cardiovascular disease. He notes that Pitt med taught him the importance of building a strong research team—and, in fact, he's collaborating on studies related to diabetic kidney disease with Pitt's **Linda Fried** (Nephrology Fellow '96), a professor of medicine.

'00s

Randy Bruno (Neurobiology PhD '02) once aspired to be a computer scientist studying artificial intelligence, but he switched to neuroscience so that he could try to understand the human brain first. After receiving his Pitt PhD, he conducted postdoctoral research on neural connectivity underlying sensory perception with Nobel Prize winner Bert Sakmann at the Max Planck Institute for Medical Research in Heidelberg, Germany. Now an associate professor of neuroscience at Columbia University, Bruno studies how the neocortex mediates sensation and perception. His latest work shows that sensory signals from our environment are copied to both the upper and lower layers of the neocortex. Surprisingly, these two halves do not always communicate with each other about incoming sensory signals. Bruno has published these studies in *Nature Neuroscience*, *Neuron*, and *Science*. His laboratory is now investigating when the upper and lower halves of the cortex interact and how their interactions contribute to normal behavior. Bruno says this information may be important in identifying treatments for human neurological and psychiatric disorders.

Constantinos G. Hadjipanayis (Molecular Genetics PhD '05, Neurosurgery Resident '06) was appointed professor and chair of the Department of Neurosurgery at Mount Sinai Beth Israel in New York, N.Y., last fall. Hadjipanayis got his doctorate in molecular genetics and biochemistry while still a neurosurgery resident and intern at Pitt. Director of neurosurgical oncology at Beth Israel and an NIH-funded scientist, Hadjipanayis is particularly interested in novel treatment options for glioblastoma (a malignant tumor affecting the brain and/or spine). Hadjipanayis says he wants "to provide better ways to visualize and therapeutically target brain tumors so patients can beat this terrible form of cancer." He notes that he was the first doctor in North America to use fluorescence-guided surgery for gliomas, a technique that vibrantly lights up often-undetectable malignant brain tumors at the margins.

'10s In June, **Jennifer Corbelli** (Internal Medicine Resident '10, Women's Health Fellow '13) will begin as program director for the internal medicine residency at UPMC Montefiore/Presbyterian. An assistant professor of medicine, Corbelli finds fulfillment in medical education—the subject in which she received her master's degree in 2013. In addition to teaching lecture-based courses like population health and medical interviewing, she takes pride in clinical teaching. She finds the best part to be "getting medical students to realize they aren't extraneous and do have something very important to offer, and helping the residents progress to become autonomous, independent doctors." The internal medicine residents at UPMC chose Corbelli to receive the Outstanding Teaching Attending Award last year. Corbelli also volunteers at the Birmingham Free Clinic in Pittsburgh's South Side and at the Women's Center and Shelter of Greater Pittsburgh.

—Imaz Athar, Jessica Boddy, Keith Gillogly, and Susan Wiedel

PRANAV SHETTY

EBOLA AND OPTIMISM

Perhaps Pranav Shetty's (MD '07) most formative experience at Pitt med was his disaster-relief work overseas. He's now global emergency health coordinator for International Medical Corps, a nonprofit organization that provides health and emergency services. During the Ebola outbreak of 2014, he traveled to West Africa to train responders and establish two treatment units in Liberia.

His work earned him an invitation from President Barack Obama to attend the 2015 State of the Union address, where Shetty represented military and civilian health care workers deployed to West Africa to combat Ebola. In regard to the outbreak, Shetty has maintained guarded optimism. "We're miles ahead of where we used to be, but it's still not over," he says, noting that new Ebola cases have appeared even after countries have received the all clear. "A threat anywhere is a threat everywhere."

Shetty in Liberia

COURTESY INTERNATIONAL MEDICAL CORPS/STUART J. SIA



MAA SAYS, MEET THE HENCH AWARD WINNER

When **Eric Klein** (MD '81) was a urology resident at Cleveland Clinic, radical surgery was the main option for many patients with prostate cancer, which was then a much deadlier disease. Because half of newly diagnosed cases were metastatic, there were no good medical alternatives to castration.

Some 30 years later, Klein, chair of the Glickman Urological & Kidney Institute and a staff member in the Taussig Cancer Institute at Cleveland Clinic, has seen a sea change in the field. Patients come to him with elevated levels of PSA, an early marker for prostate cancer (as well as a number of benign conditions). Those who require treatment for prostate cancer are far fewer—and their cancers are usually curable. Many more turn out to have low-grade, nonlethal cancers, so the majority of the time, "the main goal is to prevent people from being over-treated. . . . It's really been an interesting evolution."

In the intervening years, the field has learned that not every PSA-detected cancer needs surgery, radiation, or other treatment, all of which come with side effects that can mean quality of life takes a hit. The trick, of course, is deciphering what separates those who need treatment from those who are better off with watchful waiting. Klein—who was honored with Pitt's Philip S. Hench Distinguished Alumnus Award in August 2015—has been at the forefront of this effort throughout his career as a physician-scientist.

More than 20 years ago, he started a database that linked prostate-tumor biopsies with patients' outcomes, a powerful tool that's made Cleveland Clinic an important ally in broadening our understanding of the biology of prostate cancer. His group has been involved in developing or validating three of the four genomic tests for prostate cancer that have entered the market in recent years. Now, they're investigating how genomics can inform precision medicine across all stages of prostate cancer: how best to use imaging studies, when treatment is necessary, which treatments are best for which patients. It's a far cry from his training days, he says. "That's been very satisfying."

To nominate candidates for the Hench award, contact **Jen Gabler** at jag188@pitt.edu.

—Elaine Vitone



Klein

Shetty was born in India, but when he was 1, his family moved to Trinidad and eventually to Pittsburgh. His relief efforts have also brought him to Haiti, Libya, South Sudan, Jordan, Iraq, the Philippines, Europe, and Yemen.

He completed a residency in emergency medicine at Harbor-UCLA Medical Center and a fellowship in global health and international emergency medicine at the University of Maryland, where he also received his Master of Public Health degree.

During his emergency medicine instruction at Pitt, Shetty says he learned an important truism that he's applied to his Ebola response efforts and elsewhere: Don't try to learn everything about the patient before trying to help. "You don't have to have everything figured out before you could save somebody's life," he says. "Don't let lack of knowledge become lack of action." —KG

JEANNE COOPER

JUNE 29, 1921–NOV. 14, 2015



Jeanne Cooper (Res '56) knew something was wrong. Her sister-in-law had recently undergone a hysterectomy and was in pain, but the surgeon who had performed the procedure thought she was fine. Cooper, an MD, wasn't convinced, so she ran tests. It turned out her sister-in-law's bowel was leaking, which could have led to life-threatening infections. The surprised surgeon hesitated about what to do next. According to Cooper's daughter, Toni Ault, a poised Cooper said, "Look, I booked an OR. I'll meet you upstairs in an hour." In the end, Cooper's sister-in-law survived and lived a long life.

Cooper's father died when she was an infant, and she grew up during the Depression. But, says Ault, the challenges her mother faced made her empathetic and inclusive.

Cooper "had high self-esteem, high confidence, and ability and wisdom," recalls Robert Hartsock (MD '57), who served on Pitt's pathology faculty with Cooper.

Cooper knew she wanted to be a doctor at a young age. She and her brother, William M. Cooper (Res '44, '48), played doctor–doctor as kids, not doctor–nurse. Cooper received her medical degree from Hahnemann Medical College in Philadelphia in 1947. After completing her Pitt residency at the VA Hospital and Presbyterian Hospital, she became a staff

pathologist at Mercy Hospital in Pittsburgh and later the department's chair and laboratory director.

Cooper

cal professor of pathology at Pitt. Although some instructors were domineering, a "self-assured" Cooper would teach by example and understanding, says Hartsock. She was awarded the Pathology Teaching Award in 1988. Although Cooper was demanding of her coworkers, she developed camaraderie with them, even giving dating advice at times.

"If we all tried to emulate her, maybe we'd all be a little better," Ault says. "She treated everyone with dignity and respect."

—Imaz Athar

NIEL WALD

OCT. 1, 1925–NOV. 28, 2015

Growing up in a Manhattan high rise, Niel Wald didn't have many opportunities to connect with nature. As an adult, he took his children fishing and sailing. He didn't reel in many big catches, says his son, David: "He just loved being out there. He liked to be in control but respected nature." That respect informed Wald's career, which he devoted to caring for people affected by one of the most powerful natural forces: radiation.

Wald, a specialist in radiation health, traveled to Nagasaki and Hiroshima, and to Chernobyl and Three Mile Island, where he treated patients and assembled what's considered the most important compilation of data on human exposure to radiation. He also developed a more efficient way of assessing it: a computerized method that automatically detects chromosomal aberrations in patient samples. Wald's colleagues note that he put nuclear concepts into perspective for patients simply by approaching the matter with a calm demeanor and positive outlook—both kept strong by his trust in science.



Wald

When he was about 10 years old, Wald decided to pursue a medical career after receiving a book about science from his uncle, a physician. Wald received his MD from New York University in 1948. After serving as a flight surgeon and radiobiologist in the U.S. Air Force, he was hired as an associate research professor of radiation health in Pitt's Graduate School of Public Health and as an assistant professor of medicine at Pitt's School of Medicine in 1958.

Wald retired from Pitt in 2004 and was named professor emeritus. Soon after, he began writing an autobiography that, although unfinished, contains vivid stories of his early career—the most unusual, perhaps, is that of his affection for a rhesus lab monkey he nicknamed Mo.

"When he had a question," says his son, "he stayed at it until it was solved. Science was his religion." —Jessica Boddy

IN MEMORIAM

'40s

WILLIAM W. SCHILDECKER
MD '43
JAN. 20, 2016

ROBERT S. VANDERVORT
MD '46
JAN. 7, 2015

STANLEY F. KACZOR
MD '49
JAN. 25, 2016

'50s

JAMES S. BATES
MD '53
JAN. 27, 2016

DAVID M. SIMPSON
MD '53
JAN. 20, 2016

WILLIAM VICTOR LYDEN
MD '55
NOV. 15, 2015

WILLIAM J. CRAWFORD II
MD '56
MARCH 3, 2016

JOSEPH T. ANZALONE
MD '57
FEB. 2, 2016

'60s

ROBERT J. REED III
RES '60, '62
JAN. 31, 2016

KARL HARRIS MORGAN
MD '61
APRIL 6, 2015

GEORGE M. FITTING JR.
MD '64
MARCH 4, 2016

ROBERT F. GREENE
FEL '64
MARCH 8, 2016

RONALD CHARLES LENTHALL
MD '66
JAN. 30, 2016

PAUL H. ZANETTI
RES '66, '68, '72
MARCH 11, 2016

'70s

INDRAVADAN N. PANDIT
RES '70, FEL '71
JAN. 20, 2016

'80s

MICHAEL SCHUSTER
RES '86
DEC. 14, 2015

'90s

MARK A. STOREY
RES '90, '93
FEB. 3, 2016

'00s

JOHN A. KNAPP JR.
RES '07
FEB. 9, 2016

FACULTY

RAYMOND B. KARASIC
RES '80
JAN. 19, 2016

GREGORY HOYSON
MD '82
DEC. 27, 2015

JOSEPH M. KETTERING
MD '90, RES '91
JAN. 10, 2016

LINDA VAN MARTER BIG LEAPS FOR LITTLE LUNGS

BY SARAH C. BALDWIN

One might assume that Linda Van Marter (MD '80) was destined for a life in medicine. Born in Magee-Womens Hospital while her father, Neal (MD '54), was in his first year of medical school at Pitt, she grew up in Erie, Pa., in the top two stories of a three-story house: The first floor was where her father, by then a family practitioner, had his office. She remembers observing him with patients there and even rounding with him at the hospital. But it didn't occur to her that she might follow in his footsteps.

"I didn't realize then that girls could be doctors," says Van Marter. "Boys became lawyers and doctors, and girls—if they didn't become homemakers—became teachers and nurses."

Because her father had referred patients to Massachusetts General Hospital (MGH), she was aware of the nursing school there, so she headed to Boston. "It was at MGH that I encountered women physicians—including a former nurse—who inspired me to go to medical school," she recalls. She then enrolled at Pitt as an undergrad and stayed on through medical school, supporting herself by working as a cardiovascular weekend charge nurse at UPMC Shadyside Hospital. Then it was back to Bean Town for her internship and residency at Boston Children's Hospital, followed by a neonatal-perinatal medicine fellowship at Harvard (where she picked up an MPH along the way). In 1986, she joined the faculty of Harvard's Division of Newborn Medicine in the Department of Pediatrics, where she was the first to pursue a research career in neonatal epidemiology. Since 1988, she has practiced exclusively at Brigham and Women's Hospital, which contains Harvard's largest perinatal-neonatal service, accommodating some 9,000 births per year, many of which are designated high-risk.

Neonatology was a relatively new field then, Van Marter says, "but I was fascinated by

the medicine, the clinical challenges, the research opportunities, the intensity." That fascination has not ebbed in 30 years, and she continues to serve as associate professor of pediatrics at Harvard and vice chair of pediatric newborn medicine. Her research has focused on the epidemiology of neonatal cardiopulmonary disorders, including persistent pulmonary hypertension of the newborn (PPHN), which generally affects otherwise normal full-term infants, and chronic lung disease of prematurity (also called bronchopulmonary dysplasia). Van Marter was among those who identified the association between PPHN and factors such as maternal intake of nonsteroidal anti-inflammatories and antidepressant and antianxiety drug exposure during pregnancy (specifically, SSRIs). She was also in a group that evaluated treatment of PPHN babies with inhaled nitric oxide versus heart-lung bypass—two therapies that have dramatically reduced mortality.

"It was very, very hard early on," she says. "When I was training, 30 to 50 percent of full-term babies with PPHN died. To be able to save them now is wonderful."

But, she says, "We still have a lot of work to do in the chronic lung disease of prematurity. We now know that extremely preterm babies suffer from structural as well as biochemical lung immaturity and are at increased risk of long-term lung problems. My research focuses on the intersection of the biological

immaturity of these babies and the impact of specific care practices on the likelihood of an infant developing chronic lung disease. I strive to discover new treatments that will enhance survival and lifelong health of ill or immature infants."

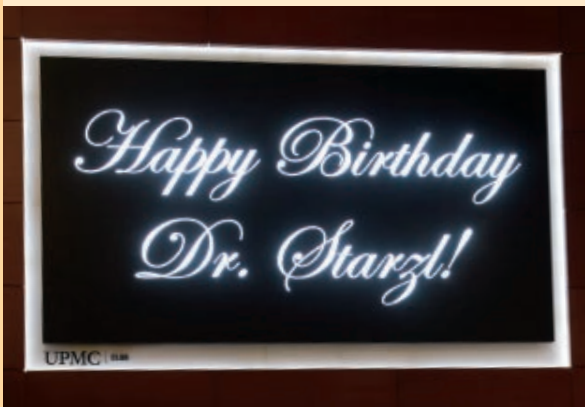
Van Marter considers herself "an intensivist at heart," relishing the challenges of complex medicine, the procedural aspects, the hands-on work. But she also loves the "softer side"—counseling families, supporting them as they're reunited with a baby who is hospitalized. She often develops a relationship with the family and has continued to follow some of her patients for decades.

Even more than loving the research and practice and teaching and learning, she says, "I love seeing healthy babies go home to their families and grow, thrive, and become happy children and productive adults." ■

COURTESY KATHERINE C. COHEN/BOSTON CHILDREN'S HOSPITAL



Van Marter's clinical research helped identify risk factors for persistent pulmonary hypertension of the newborn.



A Starzl soiree to remember. RIGHT: The guest of honor and his wife, Joy Starzl, put their best Facebook forward.



STARZL-STUDDED EVENT

In March, Heinz Field hosted a fête fit for a father of organ transplantation as Thomas Starzl celebrated his big 9-0. Pitt's Arthur S. Levine (the John and Gertrude Petersen Dean of the School of Medicine and senior vice chancellor for the health sciences) and Abhinav Humar (chief of transplantation) presided over the festivities. Among the attendees for the bash were Jake Wheatley, Pennsylvania state representative; Rich Fitzgerald, chief executive of Allegheny County; Mark Nordenberg, Pitt chancellor emeritus; and a whole flock of family and friends. More than 200 fellows came from all over the world, including Argentina, Belgium, Brazil, France, India, Italy, Japan, Sweden, and Taiwan, to attend.

—Elaine Vitone
—Photography by Joe Appel

CALENDAR

FOR ALUMNI & FRIENDS

Unless otherwise noted, for information:
Ashley Knoch at 412-648-9059 or
akk57@pitt.edu

CLASS OF 2016 LUNCHEON

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

SCOPE AND SCALPEL: STARZL WARS

MAY 20, 7 p.m.
MAY 22, 2 p.m.
Central Catholic High School
McGonigle Theater
For information:
scopeandscalpelsociety@gmail.com
For tickets: scopeandscalpel.org/tickets

RECEPTION FOR RYAN MCGARRY (MD '09) COMMENCEMENT SPEAKER

MAY 21, 6–8 p.m.
Andy Warhol Museum

CLASS OF 2016 GRADUATION CEREMONY

MAY 23, 4 p.m.
Soldiers & Sailors Memorial Hall & Museum
For information:
Rhonda Matthews at 412-648-9674 or
rmatthews@medschool.pitt.edu

WHITE COAT CEREMONY

AUGUST 14, 3 p.m.
Scaife Hall, Auditoriums 5 & 6
Reception immediately following in the
Petersen Events Center Lobby

ORIENTATION LUNCHEON FOR THE INCOMING CLASS

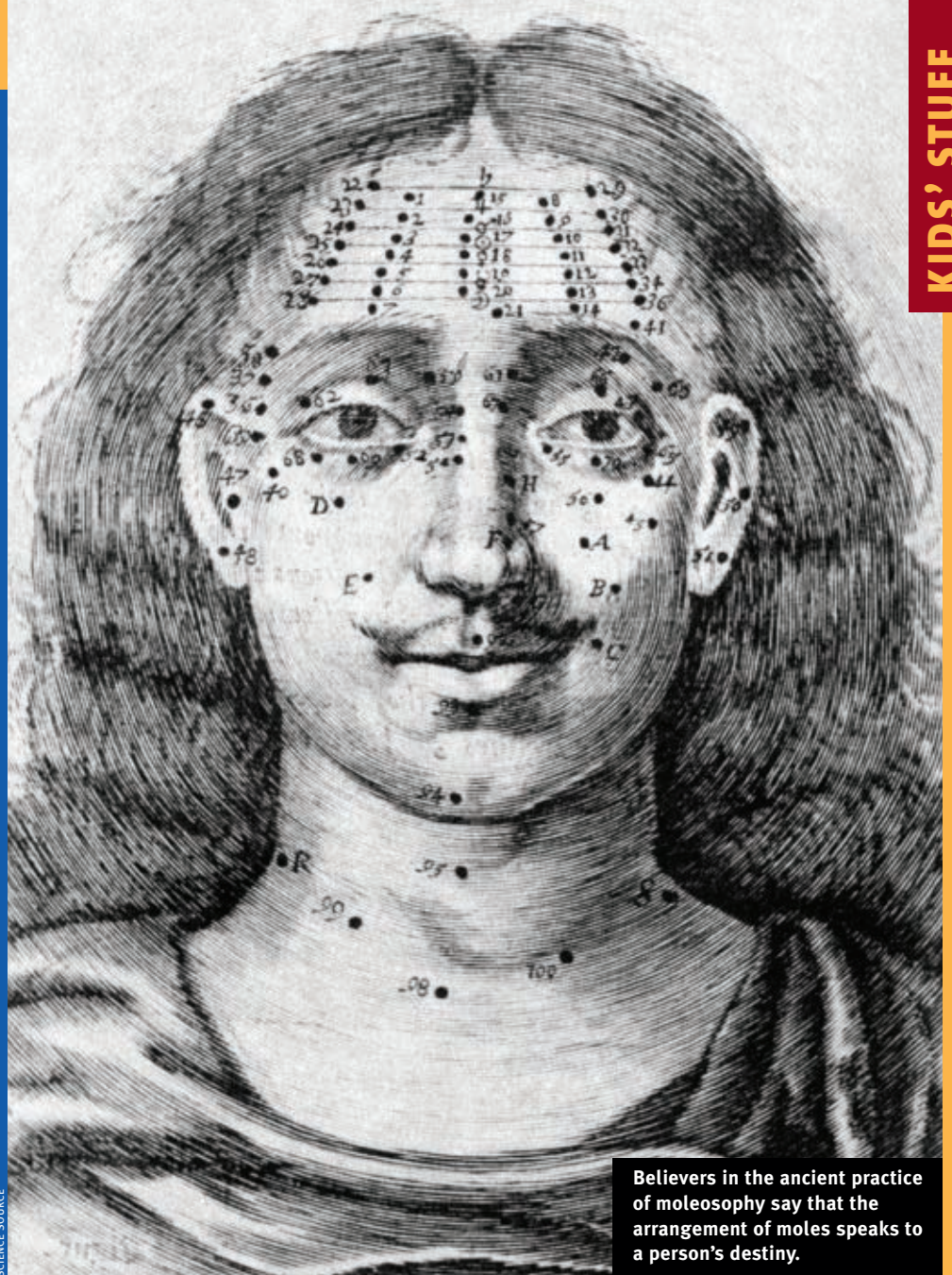
AUGUST 19, 11:30 a.m.
University Club, Ballroom B

MEDICAL ALUMNI ASSOCIATION REUNION WEEKEND

SEPTEMBER 23–25
Reunion Classes:
1956, 1961, 1966, 1971, 1976
1981, 1986, 1991, 1996, 2001, 2006

To find out what else is happening at
the medical school, visit health.pitt.edu
and maa.pitt.edu.

SCIENCE SOURCE



Believers in the ancient practice of moleosophy say that the arrangement of moles speaks to a person's destiny.



FOR REAL! TWEEN SCIENCE

Holy moley, what's that spot? Angel's kiss, port-wine stain, stork bite—all silly names for common marks on your skin. If you were born with a dot or a splotch, that's called a birthmark.

Every person is born with the same number of pigment cells, or the cells that give our skin its color. But sometimes those cells don't spread out evenly; they clump up and form "birth moles" early in life.

You can also develop spots as you grow. These specks are called "acquired moles," and your genes play a big role in whether you'll get them. If your parents have moles, and if you spend a lot of time in the sun, you're much more likely to develop a few dots.

Finally, there are marks with a red hue, called hemangiomas (pronounced like he-man-gee-OH-muhs, sounds like a kind of superhero), which are caused by blood vessels grouping together near the surface of the skin.

So enjoy, and maybe even connect, your tiny constellations. Nobody else has the same ones as you! —Robyn K. Coggins

Thanks to Pitt pediatric dermatologist Douglas Kress for his help explaining these beautiful blemishes.

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MAKING TRACKS

We've got a good thing going here: 16 years of award-winning stories. And now, you can take *Pitt Med* on the go—in your car, on your morning jog, and anywhere you might wander.

To get more mileage out of our trunkful of tales, we've launched a new Read Aloud feature for Pitt Medcast, a podcast series from these editorial offices. Our first foray: "Let's Talk About Sex," a journey through biology that isn't binary, and the challenges it brings. And up ahead: "When Fred Met Margaret," a trek through Mister Rogers' neighborhood that signposts the indelible influence of Pitt's own Margaret McFarland. We hope you'll tune in as we take this show on the road.

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