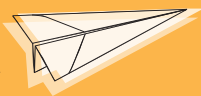




UNIVERSITY OF PITTSBURGH SCHOOL OF MEDICINE | WINTER 2018/19

PITTMED

ON BALANCE SYMMETRY SURROUNDS US. BUT WHY?



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JON KUNITSKY ["Something Was Missing," "God Willing," and others] was this magazine's fall intern. A junior who majors in English literature and communications, he covers culture for *The Pitt News*; and last summer, he interned for *Table* magazine. He says that working at *Pitt Med* has taught him how to frame narratives, even for short pieces, and how to decide what material is most relevant to the story. A native of Roslyn, Pa., Kunitzky aspires to move to New York after graduating and to work for a national magazine.

PITTMED

UNIVERSITY OF PITTSBURGH SCHOOL OF MEDICINE MAGAZINE, WINTER 2018/19 (DEC/JAN/FEB)

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Start noticing it, and you'll see symmetry everywhere. It turns out, that order is important to our development. (Cover: Serengeti130/Getty © 2018.)



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BY CARA MASSET

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I *imagine one of the reasons people cling to their hates so stubbornly is because they sense, once hate is gone, they will be forced to deal with pain.* —James Baldwin

Like all of you, I continue to struggle to make sense of the terrible events that transpired in our city on the morning of October 27. I am deeply saddened that such violence and hate should erupt in a house of worship in Squirrel Hill, a welcoming and peaceful neighborhood that many of us have called home.

You probably already know that among the 11 massacred that day were three members of the Pitt health sciences community. Dr. Richard Gottfried was a graduate of our School of Dental Medicine who taught dental students and regularly provided free care to those in need. Dr. Joyce Fienberg was a generous and caring researcher in Pitt's Learning Research and Development Center, closely allied with our neuroscience programs; she was known for using her intellect to help others. Dr. Jerry Rabinowitz was a greatly respected teacher in our UPMC Shadyside family medicine residency program, from which he also graduated as a young doctor. He was one of the first physicians who would accept appointments with AIDS patients in the early '80s. He was known for his selflessness, humility, and openness; likewise, his patients felt that they could be transparent with him. (Jerry was, for many years, my wife's mother's physician.) Jerry's widow, Miri, is a widely admired PhD research associate in our Department of Neurosurgery.

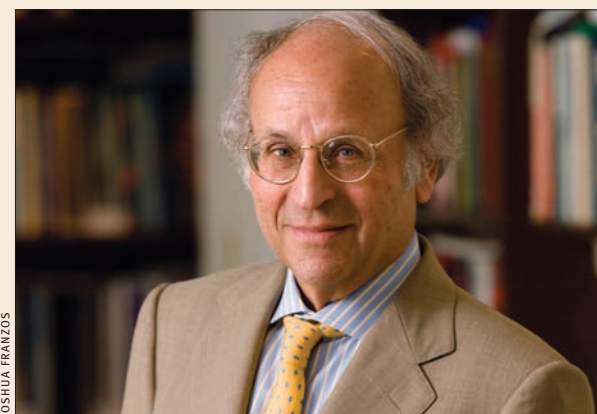
The entire city is grateful to the police and other first responders who were on the scene at Tree of Life Synagogue that day. Pitt trauma doctor Keith Murray, a member of the SWAT team, and tactical EMTs went into the synagogue while the shooter was still armed and firing.

This city is also grateful for the aid to the injured provided by our interprofessional teams, including those in emergency medicine and trauma surgery, who responded brilliantly. They provided sorely needed light in a very dark time. I'm less familiar with what unfolded at Allegheny General Hospital, where doctors treated the shooter. I do know that they treated him as they would any other. That hospital's president, Dr. Jeffrey Cohen, was married at Tree of Life. Dr. Cohen felt compelled to meet the man who had murdered his neighbors and who'd pledged to kill as many Jews as he could. Dr. Cohen told the *Pittsburgh Post-Gazette*, making no apologies for the shooter, that he did not see the face of evil when he met the man. Instead, Dr. Cohen saw "someone all alone, and all he hears is the noise in his head all the time."

Though we may try, how can we fathom unfathomable acts? Part of me doesn't want to fully comprehend such dark, dark hate that took 11 precious lives. I can take some comfort in this: The colleagues we've lost were beacons of light. And we can continue to learn from them.

Dostoevsky, in *The Brothers Karamazov*, describes the scene at the funeral of Ilusha, a young boy. Karamazov makes a speech to Ilusha's schoolmates: "Boys, we shall soon part. But let us make a compact here, at Ilusha's stone, that we will never forget Ilusha and one another. And whatever happens to us later in life, even if we don't meet for 20 years afterwards, let us always remember. My dear children, you must know that there is nothing higher and stronger and more wholesome and good for life in the future than some good memory. . . . People talk to you a great deal about your education, but some good, sacred memory . . . is perhaps the best education. If a man carries many such memories with him into life, he is safe to the end of his days."

The memories of our colleagues that we carry will shield, nurture, and inspire us. As Karamazov said, these memories are perhaps the best education, and also the ultimate and most durable of the many gifts that Richard Gottfried, Joyce Fienberg, and Jerry Rabinowitz have given to us.



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*

WEAKENED ASSOCIATIONS

One approach to keeping a person struggling with addiction away from relapse is to weaken environmental associations. It's a bit like teaching arachnophobes how to reduce their fear of spiders. Doctors can safely expose a patient to the cues that remind them of encounters with spiders; they can do the same for encounters with drug use. Patients eventually learn to experience those cues without fear, craving, or whatever response is targeted.

Mary Torregrossa, associate professor of psychiatry at the University of Pittsburgh, uses a similar method in a rat model for cocaine addiction. She determines the neural circuits responsible for mediating the ability to reduce cravings, and her team uses optogenetics (a neuromodulation method where light controls cells) to mimic the effects of exposure therapy. "We identify the part of the brain where cocaine-related cues are learned," says Torregrossa. "We stimulated this brain circuit in a way that reduced the strength of the cocaine memory, and we were able to prevent relapse." A paper on the study is in peer review.

Torregrossa imagines doctors one day using a similar method to treat addiction. Doctors would replace optogenetics with another type of deep brain stimulation to weaken drug-associated memories. —Evan Bowen-Gaddy

HATCHING PHYSICIAN-SCIENTISTS

Advancing medicine is not going to happen without doctors who also do research. Yet the pipeline for physician-scientists is "uncertain," as a July 3 editorial in *JAMA* noted. Pitt Med has taken a number of steps through the years to address this shortage; the latest is its Physician Scientist Incubator program. Pitt Med will initiate the program with \$2.5 million from the Burroughs Wellcome Fund, a \$2.5 million grant from UPMC, and a \$250,000 grant from the University.

Juggling research and patient care can be tricky for young clinicians, and federal funding uncertainties make the physician-scientist track more difficult. The incubator program will enroll 21 residents in its first five years and help fund their research. It also will connect residents with successful physician-scientist mentors.

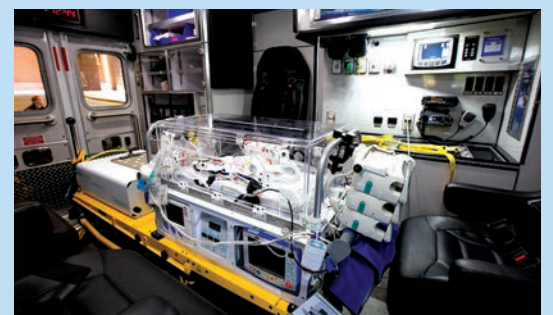
Samer Tohme, a general surgery resident who helped organize the program, says, "How can we attract and try to find those people who are interested and keep them interested? Give them all support to be able to maintain their potential and achieve all they want to."

—EBG

FOOTNOTE

When you hear an

ambulance, you move aside and turn to look. Those are the rules! UPMC Children's Hospital of Pittsburgh has a new ambulance that will make people do a double take. It's built for transporting critically ill babies and children and has a colorful, eye-catching design. The ambulance will travel within a 150-mile radius of Pittsburgh; its features include a backup generator, state-of-the-art medical gas supply, Wi-Fi, a camera system, safety seating for the crew and parents, and a hydraulic lift. "It's designed to give patients a smoother ride," says neonatologist Melissa Riley. "And its accessibility means a faster departure, which leads to a faster response time."





PHOTOS COURTESY DUKER AND DUNMIRE. PHOTO ILLUSTRATION: ELENA GIALMAS-CERRI, AMY P. KLEBANIK

Overheard: “D” Way to Teach

Two Pitt Med favorites retired in June—**Georgia Duker** and **Susan Dunmire**.

In her 31 years at Pitt Med, Duker (PhD '82), an assistant professor in the Department of Cell Biology, won numerous awards, including two Golden Apple Awards, 17 Excellence in Education Awards, and the Chancellor's Distinguished Teaching Award in 1999. Dunmire (MD '85, Res '88), a professor of emergency medicine, was honored with the Chancellor's Distinguished Teaching Award in 2007. A Pitt Med prof for 30 years, Dunmire was a director of several courses and also served as executive director of the Medical Alumni Association. She has earned five Golden Apples and was named Clinical Educator of the Year in 2013. This fall, we connected Dunmire and Duker on a conference call to reflect on their careers and their friendship.

What were the biggest lessons you learned over the course of your careers?

Georgia Duker: I had to get used to saying, “I don’t know.” And I would tell my students, “Don’t be afraid to say to your peers or to each other that you don’t know.” But I said, “Make sure you follow that up with, ‘I will find out.’” Whenever someone asked me a question either privately or in lecture, and I didn’t know the answer, I always made sure that I followed up. I wanted to get the students to see that there’s so much in the body of medical knowledge—you will never know it all. But know that you know how to find out the answers. That’s hard for medical students here. These are such top tier students; they’ve always had all the answers.

Susan Dunmire: I learned it had to be fun. That way, what you taught would stick. We really have a long way to go in the way we teach medicine. I don’t think we’re quite there yet. We’re getting there.

GD: Yeah. Yeah, absolutely. I found that I needed to reread literature and rewrite my lectures. Every single year.

SD: A lot of my teaching was done in simulation. When I trained the people who were going to take over for me, I said, “The biggest thing you can do as you’re teaching is to watch them. If you start to see them look at a phone or zone out, you’ve lost them. Stop right there. Don’t keep babbling, because it’s a waste of your time and their time. You’ve lost them, so you need to back up and engage them again.” It happens so easily.

GD: I did the exact same thing, Sue.

How did you get into your specific fields of medicine?

GD: I initially wanted to be an MD. Did not get into medical school the first time around. It might have been because I did my undergraduate degree in two and a half years. When I was applying to medical school, I had just turned 19. I don’t think anyone took me seriously. So I did a master’s degree in a lab looking at changes in a tumor line. I decided that we don’t know

(continued on page 33)

Next Generation

Out of 119 participants, four Pitt Med students were awarded the Bert and Sally O’Malley Awards for Outstanding Medical Student Research in 2018. Awards are given for clinical science research, as well as basic science research, in both a four-year category and a five-year category.

The four-year clinical research award went to **Arpan Prabhu**, now a resident at UPMC in transitional medicine who will continue his training in radiation oncology. Mentored by Sushil Beriwal, MD professor of radiation oncology, Prabhu analyzed the state of educational YouTube videos surrounding brachytherapy and found that most videos either were too complex for the layperson to understand or, even worse, were intentionally misleading, intent on selling a product. “When I was a medical student, and I was learning about brachytherapy, the first thing I did was go on YouTube, type it in, and see what the procedure actually is,” says Prabhu. “A lot of patients do this as well.” One day, Prabhu would like to make better educational videos.

Xiao Zhu won the five-year award for clinical research for his project studying protein expression in certain kidney cells. Zhu, now a resident in plastic surgery at UPMC, identified a particular protein that contributes to contraction in the kidney, causing high blood pressure. He was mentored by Edwin Jackson, PhD professor of pharmacology and chemical biology.

In the five-year category for basic science research, **James Dolezal** won for a project that used machine learning to identify patterns of ribosomal proteins in human cancers. Dolezal, now a resident at the University of Chicago, found that these ribosomal proteins express themselves differently in regular tissue compared to tumor tissue. He was mentored by Edward Prochownik, MD/PhD and the Paul C. Gaffney Professor of Pediatrics.

Netanya Pollock, now a pediatric intern at Boston Children’s Hospital, won the basic science research award in the four-year category. Mentored by Linda McAllister-Lucas, MD/PhD and associate professor of pediatrics, Pollock identified a breast cancer-related protein, c-Fes kinase, as causing tumor growth. The function of this protein in breast cancers had previously eluded scientists. With this specific protein in mind, Pollock says doctors now have a useful target when thinking about personalized care. “Instead of just giving every patient chemotherapy—no matter what the patient looks like, no matter what their tumor-profile looks like—instead, you give targeted therapy based on what genetic makeup that patient has.” —EBG

A TISSUE-LEVEL SUPERPOWER

When a salamander loses its tail, it builds another one beautifully. But a lizard amputee? Not so much. “It doesn’t get anything right,” says Thomas Lozito, PhD assistant professor of orthopaedic surgery. “There’s no bone; the skeleton is completely cartilaginous, just tubes within tubes,” he adds. Lozito and his research team discovered the reason for this difference. During regeneration, salamanders can produce multiple types of cells from neural stem cells, a process called differentiation. Lizards, meanwhile, can only produce a limited range of cell types.

In an article published in the *Proceedings of the National Academy of Sciences* in August, Lozito identifies the mechanism responsible for enabling salamander cells to differentiate during regeneration: a gene playfully called the hedgehog gene. Lozito and Pitt coauthors Ricardo Londono, an MD/PhD, Megan Hudnall, and Rocky Tuan, a PhD (who is now vice chancellor of the Chinese University of Hong Kong), also discovered that the hedgehog gene will retain its ability to cause differentiation when implanted into a lizard’s tail stump. This discovery could have implications for healing human wounds. Lizard genomes resemble the genomes of mammals more than they do those of salamanders.

“Our approach is to identify animal superpowers that mammals

don’t have,” Lozito explains.

While still a long way from developing a technique to regrow a full limb, Lozito’s discovery could one day help manage pain and facilitate prosthesis attachment.

These are “baby steps,” Lozito says. “But if you can just prevent scar formation and a little bit of tissue growth, that’s significant.”

—Elizabeth Hoover



Bassler Wins Dickson Prize

Bonnie Bassler, the Squibb Professor and chair of molecular biology at Princeton University, accepted the Dickson Prize in Medicine at Science 2018 in October. The Dickson Prize, Pitt Med’s highest honor, is awarded annually to an American biomedical researcher.

“It is a spectacular validation of my group’s work and our research field,” says Bassler, who has been studying bacteria for 30 years.

During her research, Bassler learned that previously unknown molecules were involved in quorum sensing, a process in which bacteria use multiple chemical signals to communicate. The revelation suggests that bacteria harbor an abundance of chemicals with potential medical implications. Bassler, who was awarded a MacArthur Foundation Fellowship in 2002, discovered that bacteria can detect other bacteria and communicate across species. She also showed how bacteria tailor their activities, depending on whether they are surrounded by friend or foe.

“I am constantly surprised by the sophistication of the process [of communication],” says Bassler. “In the early days, we never imagined such capabilities could be possible in bacteria. Plus, I am sure there is more to discover.”

Bassler later demonstrated that quorum sensing can be directed to prevent bacteria from attaching to medical devices and, in medical settings, from forming antibiotic-resistant communities called biofilms.

—Gavin Jenkins

FOOTNOTE

Can you imagine if it were reported that Jeff Capel, Pitt’s men’s basketball coach, fed his players ice cream at halftime? What a scoop! Well, that’s what Henry Clifford Carlson, better known as Doc Carlson, did during the Depression. Carlson (MD ’20) coached Pitt to two national championships; in September, the man known as the “Clown Prince of Basketball” was honored posthumously when Pitt inducted its inaugural Athletics Hall of Fame class. Carlson, a physician who treated all of his players from 1922 to 1953 (including a whole team of med students), entered the Hall with such legends as Dan Marino, Mike Ditka, and Tony Dorsett.



R. BONDE, U.S. GEOLOGICAL SURVEY

GONE GENE GONE

In August, Pitt Med's Nathan Clark published research results in *Science* that change our understanding of the effects of certain neurotoxins in marine environments. Clark is a PhD associate professor of computational and systems biology specializing in evolutionary genomics. His team compared the genomes of aquatic mammals, like dolphins, manatees, and sea lions, with their terrestrial cousins. In doing so, the group discovered that the *PON1* (paraoxonase 1) gene—which defends humans and other land mammals against toxic organophosphates (a kind of pesticide commonly used in agriculture)—has been lost through the process of evolution. Without this gene, marine mammals have no way to combat the paralysis and brain damage associated with the pesticides.

No federal laws currently restrict these pesticides from contaminating agricultural runoff, and that may be a contributing factor to the unusually high mortality rates of certain marine mammals in the Southeastern United States. "The biggest implication is species conservation," says Clark. "A lot of aquatic animals live right below these agricultural fields where these pesticides are being used." It is Clark's hope that this discovery will prompt the Environmental Protection Agency to begin eliminating the use of organophosphates to protect vulnerable marine life. —Jon Kunitsky

Appointments



Gittes

GEORGE GITTES, MD professor of pediatrics, has been appointed director of the Richard King Mellon Foundation Institute for Pediatric Research and co-scientific director at UPMC Children's Hospital of Pittsburgh. Among other initiatives, he will launch the Pittsburgh Study, which will follow thousands of area newborns as they grow up, tracking multiple health indicators. "There is already great strength here," says Gittes of Children's. "Strength that can be built on." Gittes is also the Benjamin R. Fisher Professor of Pediatric Surgery.

In September, **JUSTIN YEH** was named chief of the Division of Pediatric Cardiac Intensive Care Medicine and codirector of the Heart Institute at UPMC Children's Hospital of Pittsburgh. Yeh, an MD associate professor of pediatrics and critical care medicine at Pitt Med, says he's excited to

be mentoring young faculty in his new role. He'll be taking on "many great projects," including continuing his own study of mechanical support devices for heart patients. "There is an incredible opportunity to redefine care for patients with these types of devices," Yeh says.

In July, **AMAN MAHAJAN** was named chair of the Department of Anesthesiology and Perioperative Medicine at the University of Pittsburgh. Mahajan, an MD, PhD, and MBA, hails from UCLA, where he was chair of anesthesiology and perioperative medicine, among other roles. His research examines how neuromodulation can influence heart function. He holds Pitt's Peter and Eva Safar Chair. —EH



Yeh



Mahajan



SOMETHING WAS MISSING

"Although I loved music, I felt something was missing," says Pouya Joolharzadeh, recalling his undergraduate years at the University of California, Irvine, where he studied violin performance.

By the time he was a junior, he started thinking about a career in medicine. But he didn't act on that interest right away. It became a drumbeat inside his head, and after he started volunteering with an organization that paired musicians with ailing adults in hospitals and retirement homes, Joolharzadeh, now a fourth-year student at Pitt Med, couldn't ignore the sound anymore. "With music I provided emotional healing, but I couldn't provide that physical healing. I wanted to be able to diagnose and treat them and combine emotional and physical healing."

While enrolled at Scripps College in California for postbaccalaureate studies, Joolharzadeh learned about the linkage program—a nontraditional route to medical school that connects students to top research universities, such as the University of Pittsburgh, and accelerates the potentially three-year-long postbaccalaureate process.

"These are students who have graduated from an undergrad program, but did not receive a lot of the premedical, prerequisite coursework in order to come to med school," says Clayton Steup, assistant director of admis-



sions at Pitt Med. "The program is designed for career changers."

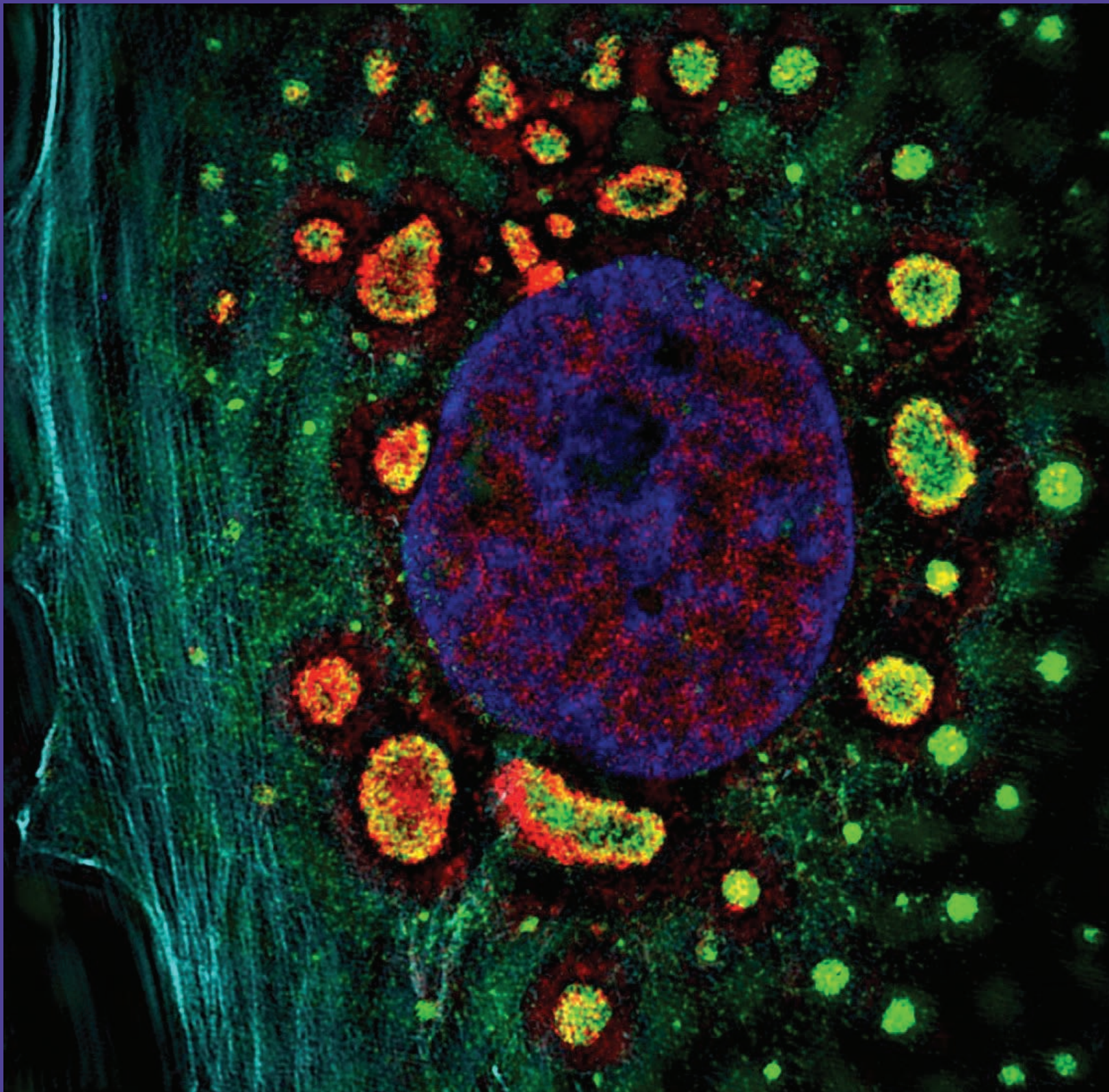
Beth Gordon charted a different path with help from the program. After graduating from Duke University with a psychology degree, she worked for IBM, and then for a health care strategy company called Vynamic. Gordon, 27 and in her second year at Pitt Med, enjoyed these jobs, but felt they didn't give her the opportunity to affect lives. "I was helping strategize with providers about how to deliver care to patients, but I wasn't the person delivering the care," she says. "I wanted to be doing the on-the-ground, individual work at the bedside."

Eleven students matriculated at Pitt Med through the linkage program last year. Graduates from the Class of 2018 went on to competitive residency programs across the United States in internal medicine, ob/gyn, dermatology, pediatrics, and family medicine. —Story by Jon Kunitzky

—Photography by Cami Mesa

INVESTIGATIONS

Explorations and revelations taking place in the medical school



A human cell (components in blue and cyan) infected with reovirus (green and red).

ASSEMBLY REWIRED

A VIRUS HACKS THE CELL FACTORY

BY KRISTIN BUNDY

Virologist Terence Dermody likes to describe viral replication in terms of manufacturing.

Think of a cell as a factory. Maybe a factory that makes flat-screen TVs, he suggests. Then along comes a virus, an inert chemical with instructions for completely rewiring the circuitry.

"It changes the job of the people in the factory," says Dermody. "So now, instead of making flat-screen TVs, the cells make thousands and thousands of iPhones."

The problem with this shift in production, Dermody says, is that it uses up all of the cells' basic building blocks, forcing the factories to shut down. One by one, as these factories close, the whole community—or related tissues, like those of the liver or the heart—shuts down.

"How can that be?" Dermody asks. "How does that little inert package recognize a factory and get in there? How does it do the rewiring business? How does the assembly process take place?"

These questions drive Dermody's current research. Trained in virology, Dermody now focuses on teaching and discovery in his roles as chair of pediatrics at Pitt's School of Medicine and physician in chief and scientific director at UPMC Children's Hospital of Pittsburgh.

His lab team, notably a couple of doctoral students, has worked to decode weak links in viral replication. The goal? To uncover potential therapeutic targets that would disrupt the

replication cycle and inhibit viral infection.

Last March in *Nature Microbiology*, Dermody's team published findings on a late-stage viral replication process that had not been elucidated previously. They showed that a protein complex in the host cell, called the TRiC chaperonin, guides (or chaperones, if you will) the folding process of the virus's outer shell, which then creates new viral particles that go on to infect other cells.

In other words, says Dermody, "These are

likely involved in a process of interest and which ones we thought were probably false positives."

Interestingly, the researchers knew very little about the TRiC chaperonin before viewing the results of this screening. "You could write what we knew about TRiC on your thumbnail," said Dermody. They called upon Judith Frydman—a biochemist at Stanford who discovered the TRiC chaperonin protein more than 25 years ago—and cell biologist Cristina

"How can that be? How does that little inert package recognize a factory and get in there? How does it do the rewiring business? How does the assembly process take place?"

the final steps of the iPhone manufacturing process—the transport of the iPhones to distributors, then the sale of the iPhone, so people have it in their hands."

This discovery was born out of an "unbiased" genetic screen that was designed by Jonathan Knowlton, with assistance from Paula Zamora—two of Dermody's students. They used the screen to identify cellular-protein factors that reovirus, a relatively simple virus that is efficient at factory reorganization, requires to replicate. The screening is called unbiased because the researchers have no idea what they will find.

"We just cast a broad net out into the sea of potential host factors," explains Dermody, "and reeled in what was collected, took a look at the candidates, and ranked them in terms of a priority—which ones were most

Risco in Spain to troubleshoot how to find the precise link between TRiC and the viral assembly pathway. "No one had been able to show that before. That was the main contribution of our paper, and why it was published in *Nature Microbiology*," says Dermody.

Now Dermody and the team are posing three questions they hope will reveal more of a virus's instruction manual on hostile factory takeovers. One: Do other viruses require TRiC to fold their outer shell? That is, is this process generalizable across all types of manufacturing? Two: Can they uncover the complete assembly pathway used to produce the reovirus particles? And three: As it turns out, TRiC is an essential protein for the host and cannot be a target for antiviral therapy. So, are there other aspects of the assembly line that could be a disruption point for treatment? ■

Ask Fred

FOR A BETTER OPIOID RESPONSE
BY HEATHER BOERNER

Policy makers have proposed all kinds of solutions to the opioid epidemic: limiting the number of opioids patients receive after surgery, cracking down on where fentanyl enters the country, expanding the use of medication-assisted treatments for weaning, and more.

But which will work? And which might make the problem worse?

"We want to play this out in silicon first," says Don Burke, an MD and dean of the Graduate School of Public Health who's also a professor in the School of Medicine. "If we could take the same simulation methods that we've developed for contagious epidemics and start using them with the opioid epidemic, we might make some headway."

That's the ambitious goal of the Public Health Dynamics Laboratory. It's gained the endorsement of the Centers for Disease Control and Prevention, which gave the project a two-year \$1.5 million grant to teach infectious disease simulators to model and play out solutions to the opioid epidemic in pixels first.

TEACHING FRED NEW TRICKS

In a lab in the Graduate School of Public Health lives a computer. And in that computer lives a representation of every person, every family, and every community in the United States. It's accurate to the U.S. Census tract, and knows the gender, race, and socioeconomic status of every simulated person and the

relationships between them. The Framework for Reconstructing Epidemiological Dynamics (FRED) was the brainchild of Burke, who is no stranger to tracking an epidemic. An infectious disease physician, Burke cut his epidemiological teeth in the HIV epidemic. With HIV, however, it's a little easier to simulate how the disease spreads. After all, we know how HIV is transmitted, and we can witness a strain of HIV morph over time, showing us which viruses are related to others in the community and a given strain's footprints through a population.

"Drugs aren't infectious organisms," says Burke. "But they do have transmitting properties to them."

For the last two years, Mark Roberts—an MD, MPP, director of the Public Health Dynamics Laboratory, chair of health policy and management, who's also a professor of medicine—and his team have been adapting FRED from an infectious disease model to a more general tool for modeling population dynamics.

"It doesn't necessarily care anymore what specific dynamic it's modeling," Roberts says.

So Roberts and his team are trying to pull together available data—that includes figures on opioid prescriptions, opioid overdose deaths, and incidences of injection drug-related diseases and of infants born with neonatal abstinence syndrome.

But the rest of the story will be harder to tell. The most common drug implicated

in overdose deaths by medical examiners is "unspecified drug"—not very helpful. Law enforcement is not always forthcoming with incarceration data. And efforts to pinpoint the exact mix of street drugs that cause a given overdose are in their infancy.

Yet the researchers already are offering new insight. One finding was featured in *Science* in September, with Pitt Public Health Dynamics Lab's Hawre Jalal, an MD/PhD, as the first author. By casting a wide net on drug overdoses generally (including cocaine, methadone, heroin, prescription opioids, and fentanyl), the team learned that deaths from overdoses have been rising exponentially for at least 38 years, with different drugs taking the main stage in a series of subepidemics.

Sometimes, building a simulation, Roberts says, "Can direct where we need to do more research." Plus, he adds, it could also help researchers narrow in on something that's eluded them for years: What actually causes addiction—and what is just a bystander to the process?

As it is, it will probably take years for the model to accurately simulate the opioid epidemic, and then it will be possible to test the solutions that lawmakers are proposing. It's daunting, but it's a project worth doing, says Burke.

"We approach this with humility. This is an imperfect art. Our job is to help policy makers make better decisions, not perfect decisions." ■

Stiff arteries are not able to cushion the pulsing of blood to the brain and could lead to dementia.

A WAY TO
PREVENT DEMENTIA,
EVEN IN OLD AGE
BY ERIN HARE

CUSHY JOB

For older adults, it may seem as though the die is already cast regarding their odds of developing dementia, but new research from the University of Pittsburgh has identified a dementia risk factor that should be modifiable even well into old age.

The study, which draws on data collected from following hundreds of elderly Pittsburghers for more than 15 years, was published in the *Journal of Alzheimer's Disease* in October 2018. The paper's senior author is Rachel Mackey, an assistant professor of epidemiology in the University of Pittsburgh Graduate School of Public Health. It was coauthored by a team of Pitt scientists that includes the School of Medicine's Oscar Lopez, professor of neurology, director of the Alzheimer's Disease Research Center, and Levidow-Pittsburgh Foundation Professor in Alzheimer's Disease and Dementia Disorders, and Anne Newman, Distinguished Professor of Epidemiology and professor of medicine as well as clinical director of the Pitt/UPMC Aging Institute.

The main finding is that arterial "stiffness,"

or hardening, is a good predictor of who will go on to develop dementia. Meanwhile, they found that even minor signs of brain disease were not as telling. Because arterial stiffness can be reduced by antihypertensive drugs, and likely also lifestyle interventions such as exercise, these findings suggest promising new ways to stave off dementia.

"As the large arteries get stiffer, their ability to cushion the pumping of blood from the heart is diminished, and that transmits increased pulsing force to the brain, which contributes to silent brain damage that increases dementia risk," says Mackey. "Although arterial stiffness is associated with markers of silent, or subclinical, brain damage and cognitive decline, until now, it was not clear that arterial stiffness was associated with the risk of dementia."

The authors analyzed the association between arterial stiffness and dementia among 356 older adults, with an average age of 78, who were part of the Cardiovascular Health Cognition Study, a long-term effort to identify dementia risk factors. This study is unusual because it involved 15 years of

almost complete follow-up of cognitive status and outcomes for older participants. All participants were dementia-free when the study started in 1998.

And although arterial stiffness is correlated with risk factors for cardiovascular disease, these confounding variables did not explain the results.

"It's very surprising that adjusting for subclinical brain disease markers didn't reduce the association between arterial stiffness and dementia at all," says Chendi Cui, first author on the paper and doctoral student at Pitt Public Health. "We expect that arterial stiffness increases the risk of dementia partly by increasing subclinical brain damage. However, in these older adults, arterial stiffness and subclinical brain damage markers appeared to be independently related to dementia risk."

"What's exciting to think about," says Mackey, "is that the strong association of arterial stiffness to dementia in old age suggests that even at age 70 or 80, we might still be able to delay or prevent the onset of dementia."

This story was adapted from *Pittwire*. ■



Braxter



Borrero



Mendez



Shirriel

In the United States, the incidence of maternal deaths and near misses far exceeds that of other industrialized countries. African American mothers are hit especially hard.

LABORS AND LOSSES:

WHY ARE NEW MOTHERS DYING AT AN ALARMING RATE IN THIS COUNTRY?

In 2016, journalist Adriana Gallardo and her colleagues at ProPublica and NPR were tasked with reporting on a worrying trend: Between 2000 and 2015, the number of maternal deaths and near-deaths in the United States rose by 25 percent. And African American mothers are four times more likely to die or nearly die as a result of pregnancy than white mothers.

But who, they wondered, are these women? And why haven't we heard about them?

One reason, they later found, has to do with data collection. It turns out there is no standard means of reporting pregnancy-related deaths. Approaches vary from state to state, leaving researchers and the public alike ignorant of national or even regional trends in the data that could point to a solution. And despite attempts by states to better identify pregnancy-related deaths, for a number of reasons, the data collection is frequently prone to error.

Although the data pose more questions than answers, it's clear that the United States has far more maternal deaths and near-deaths than any other country in the developed world. In every other developed country, these numbers continue to drop. In the United States, an estimated 700 to 900 women die of complications related to childbirth each year, and at least 60,000 women nearly die of pregnancy-related complications. Probably 70 percent of these deaths and near-deaths are preventable.

While the data offered little in terms of reasons for this rise, it was the lack of discourse about these mothers that Gallardo found unsettling. The journalist team scoured the Internet and asked for families to reach out with their stories. More than 4,700 people responded. From their research, the team created the award-winning *Lost Mothers* series, for which Gallardo and her colleagues dissected the data and engaged with communities around the country to illuminate the names, faces, and stories behind the trends.

Momentum is building here to find answers. Gallardo visited the University of Pittsburgh's Oakland campus in May for a maternal mortality forum hosted in part by the nonprofit Healthy Start. Likewise, the Magee-Womens Research Institute and the Jewish Healthcare Foundation (JHF) of Pittsburgh held related

symposia in October. JHF just announced it's partnering with Magee and RAND to develop a center to combat cardiovascular disease in pregnancy, a leading cause of maternal death. And the Commonwealth has established a Maternal Mortality Review Committee.

We sat down with the CEO of Healthy Start, which is charged with improving maternal and child health in Allegheny County, and three Pitt professors who've been appointed to Pennsylvania's Maternal Mortality Review Committee. We wanted their perspectives on why new mothers are dying at an alarming rate and what can be done to spare families from these tragedies. —Susan Wiedel

To paraphrase ProPublica and NPR's *Lost Mothers* series: American women are three times more likely as Canadian women to die in the maternal period. They are six times as likely to die as Scandinavians. In every other developed country, and many less affluent ones, maternal mortality rates have been falling. *The Lancet* noted that in Great Britain the rate has declined so dramatically that "a man is more likely to die while his partner is pregnant than she is."

And, though the data are difficult to get a handle on—the United States doesn't even release an official maternal mortality figure anymore—the situation appears to be getting worse.

What are the data, with all the current limitations, telling us so far?

Dara Mendez (public health researcher):

We've seen on the national scale the rates have been actually increasing quite a bit, although there are no formal national rubber-stamped estimates.

We have seen variations by state. Some states have seen tremendous decreases in maternal mortality—California being one example. There are a few [reasons] they point to: They instituted their maternal mortality review committee in, I want to say, 2006. That state also has what would be equivalent to a perinatal collaborative, which is a group that not only takes the recommendations but applies them. Some of the core elements they've instituted in California [have addressed] postpartum hemorrhage. There are no . . . national protocols . . . for hemorrhage.

Betty Braxter, PhD
Assistant Professor of Health Promotion and Development
School of Nursing

Sonya Borrero, MD
Associate Professor of Medicine; Clinical and
Translational Science; and Obstetrics, Gynecology,
and Reproductive Sciences
Director, Center for Women's Health Research
and Innovation
School of Medicine

Dara Mendez, PhD, MPH
Assistant Professor of Epidemiology
Graduate School of Public Health

Jada Shirriel, MS
Chief Executive Officer, Healthy Start

In addition to hemorrhage, what other conditions are behind these deaths?

DM: Pregnancy-related hypertension or hypertensive disorders, preeclampsia, those are some of the leading causes of maternal death.

If we're thinking about morbidity in general, we also see a tremendous disparity, racial difference, there.

Betty Braxter (nurse midwife): I think we have to look at factors that we know impact healthy pregnancies, and [sedentary lifestyle] is one. And the substance abuse issue, which is not something new. We're just seeing more press now because a different population is being shown as substance abusers who end up dying. [And] we're now beginning to think of preconception counseling. How do we get people more healthy before they even think about becoming pregnant?

I'm just assuming there's more obesity in the United States than in, say, Western Europe. Is that correct?

DM: I believe that is correct.

Yet, I'm reading mostly about conditions that arise during pregnancy, not preexisting conditions, related to these deaths.

Sonya Borrero (internist): Well, they're related. Prior to entering pregnancy, obesity, existing diabetes, and existing dysregulation around metabolism can all contribute to worsening outcomes during pregnancy. Pregnancy is an incredible stress on the body. These preexisting conditions are exacerbated during pregnancy. So, a lot of attention also needs to be placed on the

pre-pregnancy period, although that is incredibly tricky. There is a lot of pushback around the overmedicalization of women's reproduction. How do we talk about this? We don't want to elevate the importance of women's health only because of their reproductive capacity, right? We care deeply about women and women's health for themselves.

A couple of years ago, I did a qualitative study with low-income women in Pittsburgh. We asked them, "What does it mean to you to plan a pregnancy?" Most of them, if not all of them, talked about the need to have your finances in order, to be married. None of them talked about optimizing health. They also recognized that sort of the social normatives that they felt that they needed to achieve were really elusive in their life.

What they conveyed to us is that it is socially more acceptable to have an unintended pregnancy than to explicitly state that they were trying to get pregnant, or open to pregnancy, in these sorts of nonnormative circumstances. This just blew me away. Women also talked about the fact that life had taught them that they did not have much agency around their reproduction. So they just chose to let it happen. All of [this flies] in the face of our biomedical paradigm, which is: You should plan all pregnancies.

We have been recognizing the limitations of this very strict planning paradigm, and that it doesn't actually meet women's needs or match their lived experiences or realities. So one of the first things I did was I removed "planning" language from my counseling. I've been using "preparing" language: *Would you like to talk about this? There are ways to prepare for pregnancy, especially if you are taking some medications or have chronic medical conditions. Do you feel like that's relevant to you right now?* Sometimes providers might seem to be imposing our own normative ideas on who should and should not be reproducing and when they should be. That can really erode the relationship.

What are some contributing factors in the racial disparities in maternal mortality?

BB: One of the factors that HRSA [Health

Resources and Services Administration] called out in international summits this summer was institutionalized racism. [And] unconscious bias. And some of the interactions have left women of certain ethnic groups, not only by race, but socioeconomic status, less enchanted to come in to be served. Or when the services are provided, they are not at the highest level.

DM: Residential segregation has been one of the main ways in which we've measured a form of institutionalized racism in our empirical research.

In the '30s and beyond, communities were redlined on a map—not selected for acquiring home mortgage loans or investments. In Pittsburgh, for example, many of the places that were redlined actually overlay with many of the communities that are historically African American. And you can do that for multiple cities.

We can think about housing security. We can think about poverty and the intersections of race, class, and gender, in this case around maternal health, and a lot of the work around intersectionality points out that women may be more likely to experience adverse outcomes in general.

Jada Shirriel (community leader): Some of the work that Healthy Start does nationally is around looking at those redlined areas in different cities across the country, because it was a federal practice. And looking at the health outcomes of women and babies in those communities. And consistently, across the board, you see the disparities in these specific neighborhoods.

What can be done to address racial disparities in maternal mortality and morbidity?

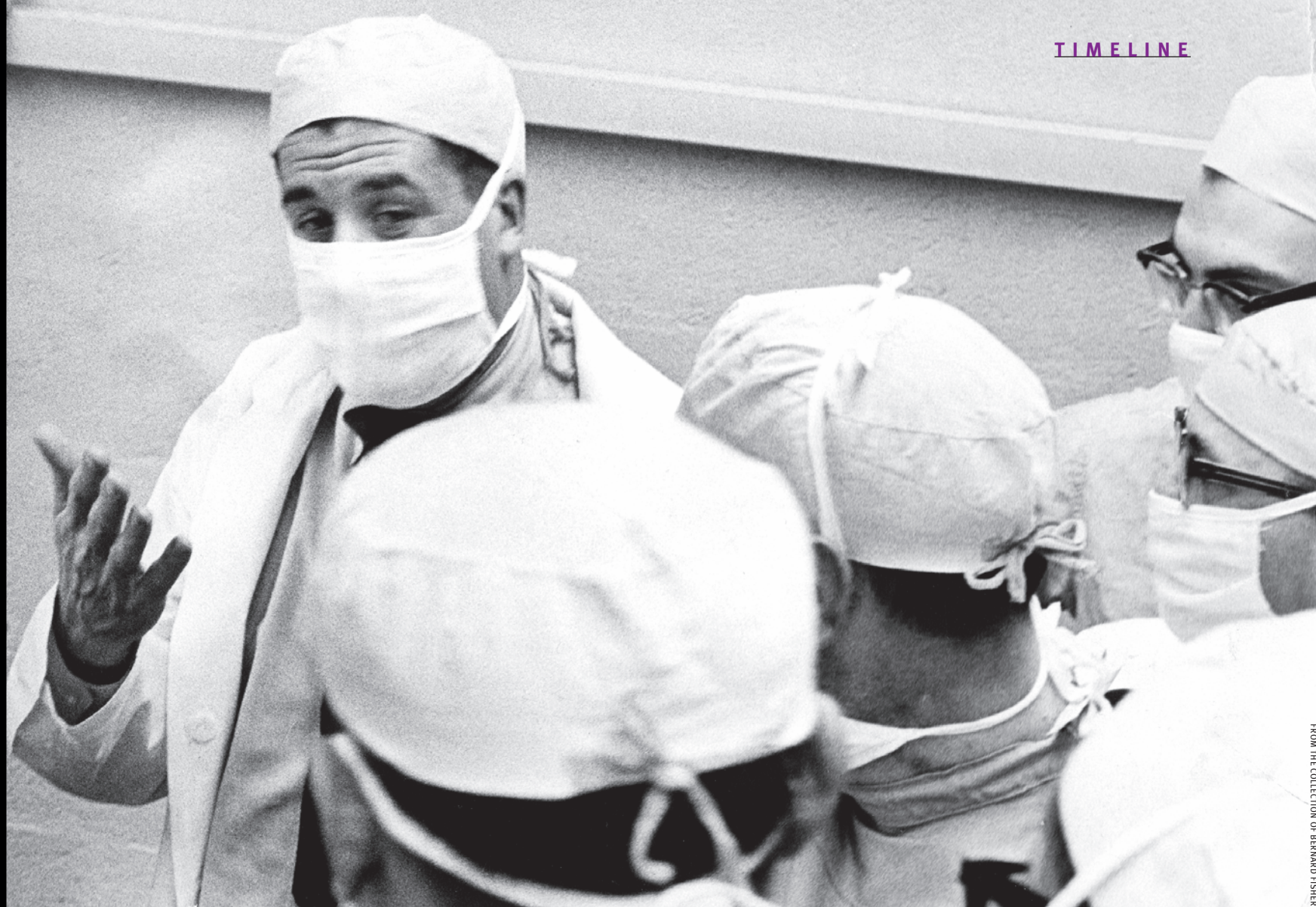
SB: We [providers] use heuristic processes, especially in the time constraints of clinical encounters. This is a natural human cognitive process to stereotype and use shortcuts. We are all guilty of it. And the first step is to recognize situations in which that is happening. We're doing some implicit bias training in the medical school. And we're [having] a meeting of the minds to figure out how to continue doing this throughout training.

DM: There's been quite a bit of work that we've been doing at the health department. There's a local infant mortality collaborative that has included Healthy Start, University of Pittsburgh scholars, folks within the maternal- and child-health space. We've been looking at things beyond just pregnancy and birth, but throughout the continuum. And some of our most recent actions have been around institutional equity. One way that we've done that has been work around undoing racism. And really

(continued on page 33)

WOMEN'S HEALTH PRIZED

To elevate scientific exchange on topics related to early human development and women's health, the Magee-Womens Research Institute at Pitt hosted its first Research Summit in October, drawing scientists from around the world. During the summit, a research team led by Yaacov Barak, PhD associate professor of obstetrics, gynecology, and reproductive sciences, received the **\$1 million Magee Prize**, established to advance "breakthrough research" in women's health. Barak and his team are trying to determine how placental defects can lead to congenital heart disease and how fixing those defects might correct or prevent it. —Gavin Jenkins



FROM THE COLLECTION OF BERNARD FISHER

**BERNARD FISHER
BROUGHT THE
SCIENTIFIC METHOD
TO BREAST CANCER
TREATMENT**

AGAINST THE TIDE

Cancer didn't particularly interest Bernard Fisher (MD '43) early in his career. In 1957, the University of Pittsburgh surgeon was contributing to the development of transplantation and vascular surgery. He performed one of the first kidney transplants. Fisher also directed surgical research at Pitt; as an investigator, he was interested in liver regeneration, hypothermia, and transplant rejection. Then, a mentor from Fisher's training at the University of Pennsylvania, General I.S. Ravdin, invited Fisher to, or rather insisted that he attend, a National Institutes of Health meeting convening in 1958. Participants would create a group for conducting clinical trials on breast and colon cancers. Ravdin, who chaired the NIH's Clinical Studies Panel, was a famed surgeon who had operated on President Eisenhower. "You don't turn down a two-star general," Fisher told this magazine in 2002. And maybe this was a chance, Fisher thought, to do something about the problem that many cancer treatments at the time didn't have strong scientific underpinnings. He became a founding member, and later chair (serving from 1967 to 1994), of the National Surgical Adjuvant Breast and Bowel Project (NSABP) that resulted from the meeting.

Based on research conducted in his Pitt laboratory, Fisher formulated hypotheses that were tested in clinical trials conducted with NSABP in the 1960s and '70s. The findings from those trials led him to challenge the prevailing breast cancer dogma followed since the 19th century, which assumed that patients were best cured through radical

mastectomy—the disfiguring removal of all breast and nearby tissues. Fisher’s ideas did not make him popular among other surgeons at the time. “When radical mastectomy was being evaluated, the idea of performing less extensive operations was considered, at some institutions, to be malpractice,” Fisher said. Besides, he was a rare bird—a surgeon doing science.

“Sometimes, people don’t think of surgeons as the intellectual members of the [oncology] team,” says surgeon Robert Ferris, director of the UPMC Hillman Cancer Center and Pitt associate vice chancellor for cancer research. He says Fisher became a role model for surgeon-scientists.

In 1971, Fisher led the NSABP in a landmark clinical trial in women with primary breast cancer, comparing radical mastectomy with less extensive total mastectomy. In 1976, he initiated a study comparing total mastectomy with less disfiguring lumpectomy, with or without breast irradiation. Neither study showed a survival advantage from the more extensive procedure. Those studies provided a scientific basis for less extensive surgery. Findings from other Fisher-led studies showed that women who also had systemic, adjuvant chemotherapy or hormonal therapy were more likely to survive than those who had surgery alone.

By 1985, the rate of radical mastectomies had fallen from 98 percent of breast cancer patients to only 2 percent. Yet Fisher’s work shaped more than the landscape of breast cancer care.

“He basically illuminated the biology of metastatic cancer in general,” says Arthur S. Levine, Pitt’s senior vice chancellor for the health sciences and the John and Gertrude Petersen Dean of the School of Medicine, who is an oncologist. “His critical observation was that, often, when we make the

Radical mastectomy treatment was based on the Halstedian hypothesis, an idea long entrenched in the medical mindset. Master surgeon William Halsted first performed a radical mastectomy in 1882. (He’s shown here, second from left, as one of “The Four Doctors”—the famed founders of Johns Hopkins.) The Halstedians proposed that cancer spreads in an orderly way, progressing from one anatomical site to another. Thus, stopping cancer’s progression necessitated extensive surgery. The hypothesis, derived from anecdotes and induction, persisted for 75 years.



THE FOUR DOCTORS BY JOHN SINGER SARGENT. OIL ON CANVAS, 1907. COURTESY OF THE ALAN MASON CHENEY MEDICAL ARCHIVES OF THE JOHNS HOPKINS MEDICAL INSTITUTIONS. PHOTOGRAPH BY AARON LEVIN.

1953

Bernard Fisher founds and directs Pitt’s Laboratory of Surgical Research as the first full-time faculty member in the Department of Surgery.

1958

Becomes a founding member of the National Surgical Adjuvant Breast and Bowel Project (NSABP). The group starts its first clinical trial, called B-01, to test the ability of the drug thiotepa to reduce early recurrence rates in breast cancer patients. The trial was a proof of principle that encouraged the group to continue this type of research.

1963

A four-year lab study by Fisher and his brother, Edwin Fisher (MD ’47), a Pitt pathologist, demonstrates that cancer cells can lie dormant for years before developing into detectable metastatic disease.

earliest diagnoses of any cancer . . . it may already have spread microscopic metastases elsewhere in the body. Therefore, it is not sufficient to simply remove the lump.”

If tumors have already metastasized, says Levine, “chemotherapy must be used to kill those metastatic cells—wherever they are in the body—no surgery or radiotherapy will be effective. Fisher’s trials established this fact.

“That is one of the most important contributions to the practice of medicine that anybody has made in our lifetimes.”

Ferris notes that Fisher—who became a Distinguished Service Professor of Surgery at Pitt and has been recognized with many honors, including the Albert Lasker Award for Clinical Medical Research—was an “intellectual driver” of large-scale clinical trials. “That was a conceptual advance—that moving clinical trials forward couldn’t rely on just a single center or two.

“The cooperative clinical trials . . . can answer bigger, transformational, practice-changing questions like [Fisher] did.”

In the 1990s, Fisher investigated the potential benefits of tamoxifen, an anti-estrogen drug, to stave off cancer in high-risk breast cancer patients. “Our 1998 report indicating, for the first time, that breast cancer could be prevented with tamoxifen was probably the capstone of my career,” he said.

“Certainly, in 1958, when I began this journey, the idea of using an agent to try to prevent breast cancer was . . . science fiction.”

Fisher, still writing, publishing, and questioning, turned 100 years old in August. —Cara Masset

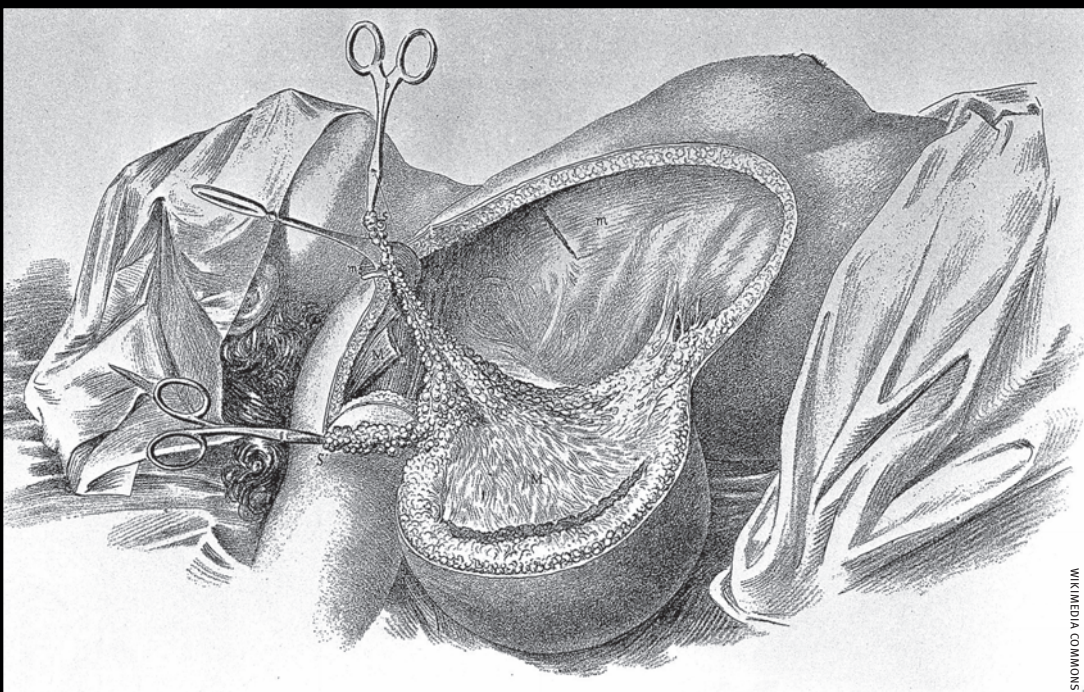
—Timeline adapted from Pittwire



FROM THE COLLECTION OF BERNARD FISHER

Bernard Fisher with his brother, Edwin Fisher.

Before the NSABP studies, radical mastectomy (illustrated below) was the accepted treatment for breast cancer; it involved removing not only the breast but also the chest wall muscles, the nearby lymph nodes, and sometimes even both breasts.



WIKIMEDIA COMMONS

Fisher, c. 2010. He turned 100 in August.



TERRY CLARK

1964

Fisher performs the first kidney transplant in Pittsburgh. It is one of his many contributions to the field of transplantation, which will also include the establishment of Pittsburgh's organ-sharing network and research into skin transplantation.

1977

The first official publication from clinical trial B-04 reports that radical mastectomy provided no survival advantage for breast cancer patients when compared with simple mastectomy. With this evidence, the public begins to question the necessity of traditional radical cancer surgery.

1985

Initial results from the B-06 trial are published, reporting that breast cancer patients with tumors of 4 centimeters or smaller do as well with lumpectomy and radiation as they do with total mastectomy. The results support Fisher's hypothesis of cancer as a systemic disease that can be treated with less extensive surgery.

1998

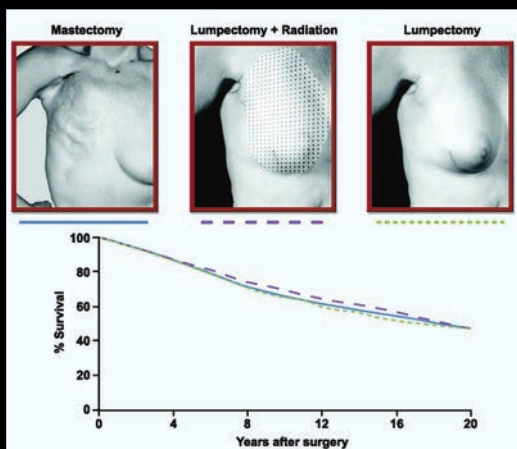
Fisher and the NSABP publish the results of the Breast Cancer Prevention Trial. It shows that the anti-estrogen drug tamoxifen can reduce the occurrence of breast cancer by almost half in women at increased risk for the disease.



GETTY IMAGES

In September 1974, First Lady **Betty Bloomer Ford** had a radical mastectomy. Americans had shied away from discussing breast cancer in anything but whispers until she shared her diagnosis with the public.

While the first lady underwent surgery at the Naval Medical Center, across the street, at the NIH, Bernard Fisher reported findings from studies that would have a profound effect on the treatment of breast cancer for decades to come. Fisher's report showed that less extensive surgery was just as effective as radical mastectomy. He also reported findings from the first clinical trial ever carried out to evaluate the value of postoperative chemotherapy, indicating that a single agent (L-PAM) after surgery led to a better outcome. The first lady was prescribed L-PAM as a result of Fisher's findings.



ABOVE: A Fisher paper shows that survival outcomes are similar for women receiving radical mastectomy, lumpectomy plus radiation, and lumpectomy alone.
BELOW: A scar from a partial mastectomy.



REPRINTED FROM CANCER RESEARCH, 2008, VOL. 68, ISSUE 24, 10007-10020, BERNARD FISHER, "BIOLOGICAL RESEARCH IN THE EVOLUTION OF CANCER SURGERY: A PERSONAL PERSPECTIVE," WITH PERMISSION FROM AACR.

Perhaps Fisher's most important contribution has been the establishment of a scientific approach to the study of breast cancer. In a 2009 video interview shown at that year's annual Pitt lecture named in his honor, Fisher said, "No clinical therapy should be determined by emotion or conviction—the determinant must be the scientific method."

GETTY IMAGES

Once you start noticing it, you see symmetry everywhere in our world. Pitt researchers have figured out one way that vertebrate symmetry gets started.



HOW SYMMETRY ARISES

BY SHARON TREGASKIS

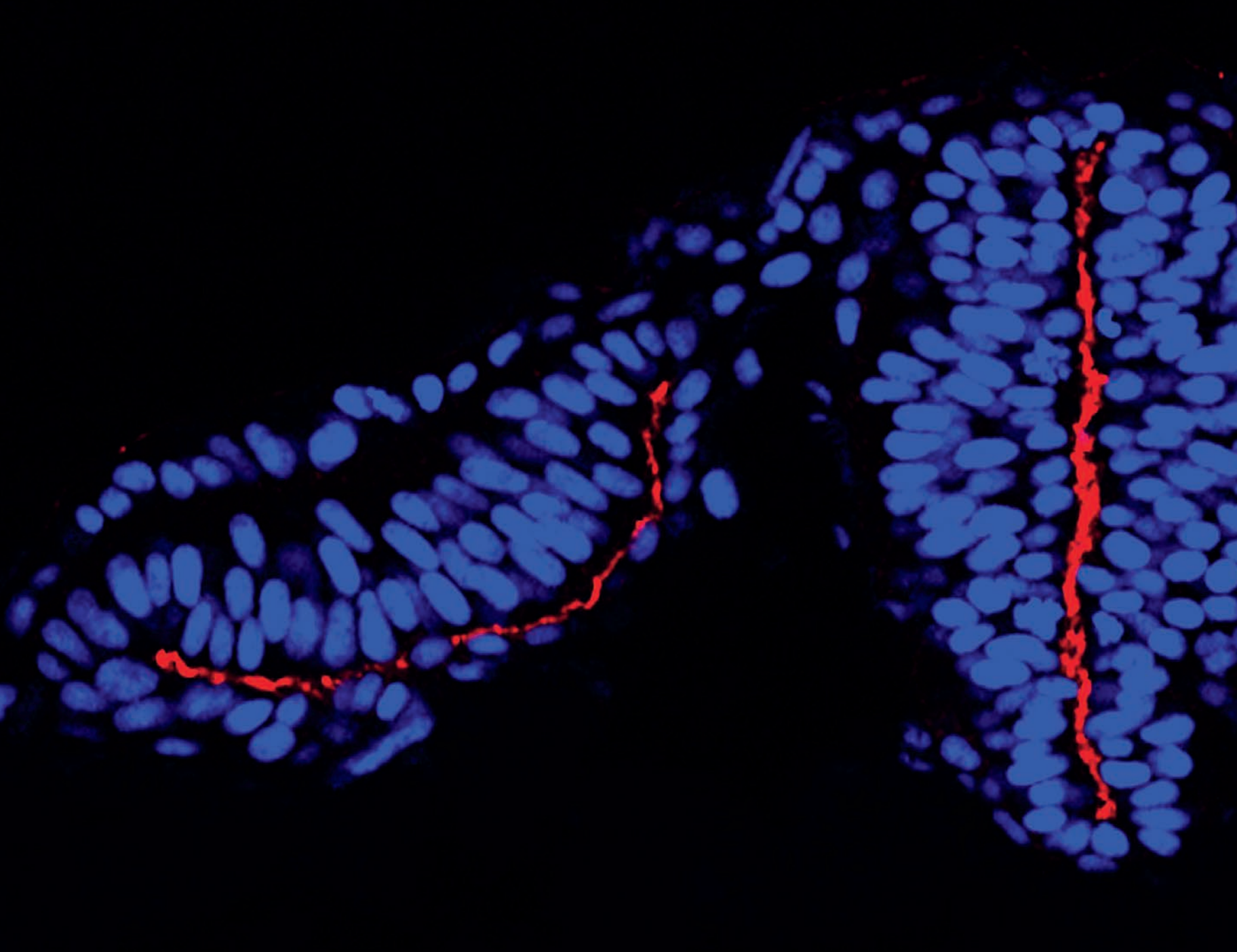
ON BALANCE

I n a chaotic world, we humans crave order. We seek out patterns, then contemplate their deeper meaning. Symmetry—like the bilateral mirror imaging that characterizes our facial features, our brain hemispheres, our limbs—is perhaps the most basic of the patterns found in the natural world, contributing to both our survival and a wealth of discovery.

That creature partially obscured behind a tree trunk? We can fill in the blanks to deduce its size, the breadth of its horns, or the number of claws it may bare if we get too close. That mountain rising up in our path? We assume that if we can make our way to the top, there will be a route back down.

Greek philosophers pronounced such balance a core feature of aesthetic perfection. “The chief forms of beauty,” wrote Aristotle in *Metaphysics*, “are order and symmetry and definiteness.”

PHOTOGRAPHY | GETTY IMAGES



The iridescent train of the male peacock exemplifies Aristotle's ideal. And yet its beauty utterly confounded naturalist Charles Darwin. According to prevailing philosophies of his time, such splendor was a gift from God, a foretaste of heavenly glory here on Earth. But in a world ordered instead by natural selection, what was the point of such a gaudy display as the male's extravagant plumage?

"The sight of a feather in a peacock's tail, whenever I gaze at it, makes me sick," Darwin lamented in an 1860 letter.

It would take the naturalist another decade to dial in on the evolutionary function of such seemingly frivolous elaborations: sexual selection. Such displays, he proposed, broadcast an individual's fitness, boosting one's chances against reproductive rivals. Bighorn ewes pick rams whose racks live up to the species' moniker; even the honeybee has a penchant for balanced blooms.

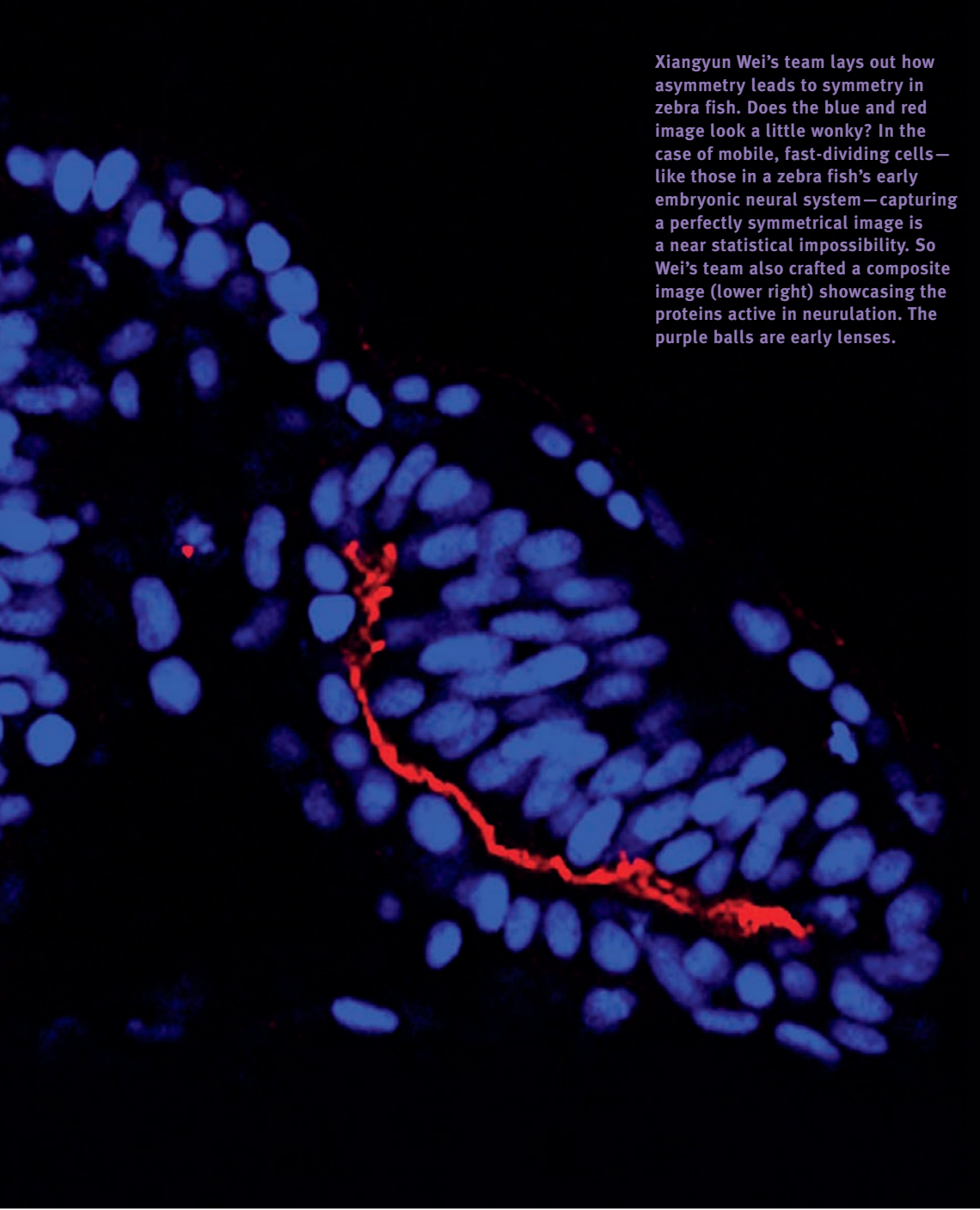
This isn't just about us critters, by the way. Pythagoras hypothesized that the planets must be spherical, the most symmetrical shape of them all. Indeed, symmetry prevails in the physical structures of the natural world—reflected in Einstein's theory of relativity and visible to

the naked eye in the webs spun by orb spiders, the patterns frozen within each snowflake, the nests built by barn swallows. Start looking, and you'll notice it everywhere.

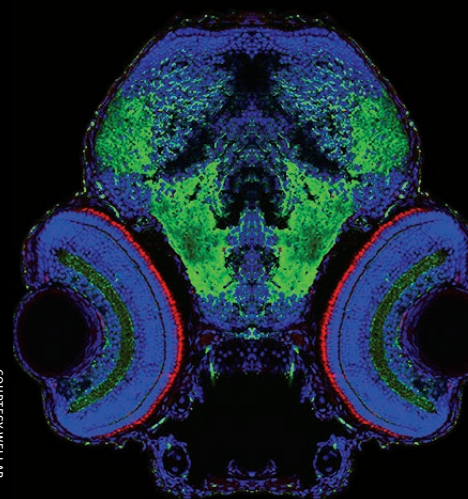
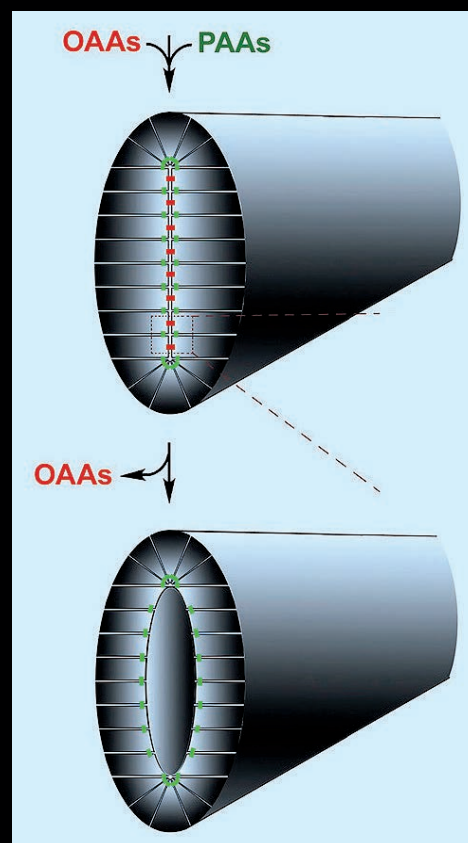
Okay. So, what *about* us? What of the animal kingdom? Does the symmetry of our body plans convey some fundamental reproductive advantage? Is it a byproduct of something deeper—say, genetic architecture, or even an echo of the laws of physics that govern the material world? Deep inside our every cell we harbor the same elements that make up the vast universe.

It's fun to ponder such questions, as Xiangyun Wei has done for a while. He offers this: It appears that, for vertebrates, the coming and going of symmetry propels healthy development.

Back in the mid-'00s, Wei was digging into the process by which a sheet of epithelial cells within a zebra fish embryo differentiates, giving rise to the retina. In humans and zebra fish alike, that process begets a pair of light-sensitive retinas that initiate the gift of vision. In some cases, however, the process unravels, and the resulting disorder within the retina causes congenital blindness.



Xiangyun Wei's team lays out how asymmetry leads to symmetry in zebra fish. Does the blue and red image look a little wonky? In the case of mobile, fast-dividing cells—like those in a zebra fish's early embryonic neural system—capturing a perfectly symmetrical image is a near statistical impossibility. So Wei's team also crafted a composite image (lower right) showcasing the proteins active in neurulation. The purple balls are early lenses.



GUO ET AL., "APICAL CELL-CELL ADHESIONS RECONCILE SYMMETRY AND ASYMMETRY IN ZEBRAFISH NEURULATION," *SCIENCE*, 3, 63–65, MAY 25, 2018. (CC BY 4.0)

GUO ET AL., *SCIENCE*, COVER, VOL. 2, APRIL 27, 2018. (CC BY 4.0)

Wei finds principles of Taoism helpful to explain what he's learned about development. The black fish and white fish depicted in the yin-yang symbol represent the dualities that make up our world. And there's a third, invisible component of the philosophy—what brings the opposing elements together. In planet formation, it's gravity. In the formation of the zebra fish neural tube, says Wei, it's a set of forces known as apical adhesions. **TOP RIGHT DIAGRAM:** Opposing and parallel apical adhesions (OAAs and PAAs for short) pull polarized cells into the form of a rod. After the OAAs dissolve, the rod inflates to form a mirror-symmetric tube.

An associate professor of ophthalmology at the University of Pittsburgh with joint appointments in developmental biology and in microbiology and molecular genetics, Wei wanted to understand the progression of molecular events involved. Very early in vertebral development, the fast-dividing cells of an embryo give rise to primordia of many organs. Among them is the neural tube, a precursor to the central nervous system, including the brain, the spinal cord, and the retina. During embryogenesis, a brisk process of cell proliferation, reorganization, and differentiation introduces the asymmetry that yields heads and tails—while maintaining symmetry across the left and right halves of the body. And somehow fully formed, functional retinas end up right where they belong. Wei studied the genes that transcribe certain proteins (like N-cadherin and Lin7c) implicated in pushing and pulling the optic system into existence. He found that the embryos with certain genetic manipulations were likely to die well before their retinas could fully differentiate. Necropsy revealed a fatal flaw. Says Wei: "The mirror symmetry of the neural tube was messed up."

For example, an early and heavy-handed manipulation of Lin7c resulted in a chaos of branches akin to the six-pointed stars that feature in the old-



time children's game of jacks—instead of an orderly, functional nervous-system-to-be. This suggested the importance of expressing polarity proteins at specific points in time. He and former postdoc Xiaojun Yang published these results in 2009.

Among the dead embryos in Wei's lab, clearly something had gone very wrong. And, for Wei, these shenanigans pointed to a paradox of metaphysical import: How does symmetry *ever* emerge in a biological system that embodies mobile, asymmetric components?

Says the scientist: "That's bugged me for a long time."

Nearly a decade, in fact. In May 2018, *iScience* published a follow-up by Wei and his team (including first author postdoc Chuanyu Guo) revealing key elements that form the foundations of bilateral symmetry of the zebra fish central nervous system.

Other investigators had hypothesized that the mere fact of cross-midline cell division during neural tube formation led to bilateral symmetry. (Each pair of daughter cells splits across a midline.) But

that theory didn't account for the intricate choreography across time and space of myriad proteins known to reposition cells within the embryo.

In their *iScience* paper, Wei's team homes in on the role of "apical adhesions," the bonds that form and dissolve as they coax asymmetric cells into positions of polarity and oppositional alignment. The process creates mirror symmetry, and the mode of the adhesions at work seems to be relevant to the development of many vertebrate tissues.

Wei offers a unifying theory to explain how tissues within the growing embryo simultaneously maintain integrity and also allow the plasticity necessary for fast-dividing cells to change shape and position.

"According to Taoism," says Wei, "everything is made of two things—a yin and a yang, a positive and a negative. They have to interact with each other and sometimes they interchange from one property to another." Only through reciprocal interaction does an entity achieve unity—whether the entity is the neural tube, the gut, or even, says Wei, the two-party system at the heart of American democracy.



We vertebrates embody staggering diversity: trunks and beaks; fins, hands, and wings; gills and bills; fur, feathers, and scales. But in our earliest moments, we bend and fold to the same tune. The development of the neural system, says Chuanyu Guo, “is like a symphony. Each kind of protein plays a unique role; they all need to cooperate with each other to achieve a perfect performance.” That performance happens in three parts, Wei and Guo’s work has shown. In their next act, they mean to reveal the rest of the score and identify the conductor.



You always want to have two things interacting with each other to allow development, Wei adds. “Many tissues and organs start with either a tube or a sac. [That] naturally creates two opponents. These two opponents interact and direct each other to develop.” In the zebra fish and in humans, he says, “the RPE [pigmented cell layer that nourishes the retina] and retina start from the optic vesicle, like a ball, or a balloon. At a certain point, the balloon collapses and forms a cup, at which point there’s an inner and outer layer. The outer layer becomes the RPE. The inner layer becomes the retina. Starting from the optic vesicle, it looks like just one thing; and by changing the folding pattern, you generate two opposing components.” You get differentiation.

“They started as something very similar, and become two things very different,” says Wei. “And the two tissues still interact with each other.

“Nature is very smart.” ■

WHERE SYMMETRY BREAKS

Symmetry may surround us, but mathematicians—Alan Turing most famously—become fascinated at the points where it breaks down.

Pitt’s Bard Ermentrout wrote the book *Mathematical Foundations of Neuroscience*. A University Professor of Computational Biology, he is interested in patterns and the universal mathematics that undergird slips in symmetry. “Left- and right-handedness are a kind of breaking of symmetry,” he says. “If we were completely symmetrical, we would look like really ancient tubeworms.”

The cascade of events that take place in embryogenesis has long been imagined as a process of pure symmetry breaking, as a patterned body plan emerges from a single cell, notes Ermentrout. In their *iScience* paper, Pitt’s Xiangyun Wei and Chuanyu Guo detail how mirror symmetry emerges in neural tube formation. (See story p. 19.) At another point in development, Ermentrout points out, “zebra fish [embryos] form somites, a series of segments. You’re breaking the symmetry by adding more things you have to keep track of.”

And yet pure asymmetry is vanishingly rare in the natural world, says Ermentrout. —SRT



The background of the entire page is a grayscale electron micrograph showing numerous spherical virus particles. These particles have a distinct outer shell and a darker, denser core. They are scattered across the frame, with some appearing in small groups and others in isolation. The overall texture is grainy, typical of electron microscopy images.

WIDE

Leah Byrne uses directed evolution to create more useful species of viral vectors for gene therapy. SHOWN HERE: A new variant of an adeno-associated virus she created.

ANGLE

BYRNE MAKES GENE THERAPY CLICK

BY CARA MASSET

Black and white images of 20-nanometer particles beam out from a computer screen in a structural biology lab in Biomedical Science Tower 3. University of Pittsburgh scientist Leah Byrne examines the viral particles she engineered. Did she get it right this time? Or will she have to go back upstairs to her ophthalmology lab on the 10th floor to re-engineer the particles? The virus she's creating—a variety of adeno-associated virus (AAV)—is a partner in her plan to cure blindness.

If the scientist and her virus continue to succeed, they may write a good portion of the industry operating manual for gene therapy. Many at Pitt and elsewhere are looking to Byrne to turn the holy grail of gene therapy from a good idea into a viable treatment for any heritable neurological disease.



Leah Byrne

PORTRAIT COURTESY BYRNE LAB. ELECTRON MICROSCOPY IMAGE COURTESY JAMES CONWAY AND LEAH BYRNE.

For starters, Byrne is working toward giving sight to patients without vision and preventing patients with degenerative diseases from losing theirs.

The intent of gene therapy—whether it be for retinal blindness, arthritis, or sickle cell anemia—is to transport needed genetic material into cells that aren't functioning properly because of faulty DNA. Give them new genes and—*click!*—eyes will see, joints will swing, and blood will flow. That's the idea, anyway. In practice, it's not easy to do.

We've been covering the promise and challenges of gene therapy in *Pitt Med* magazine since our inception in 1999. When we interviewed Pitt's "gene-therapy point man," Joseph Glorioso, back in 2005, the microbiology and molecular genetics professor predicted that the next advances would involve engineering vectors, i.e., the transporters of genetic material. "Genes already know what to do, but the problem is how to get them there," he said. Glorioso has had success modifying the herpes simplex virus as a vector (without carrying disease), including one vector he patented that targets tumors. It has been partially licensed by Oncorus; clinical trials are expected to start in early 2019.

Byrne, a PhD who joined Pitt in 2017 as assistant professor of ophthalmology, is an expert at engineering AAV vectors. The adeno-associated virus, now in vogue for gene therapy investigations, was identified by Pitt emeritus microbiology professor Robert W. Atchison in 1965. (Byrne regularly cites Atchison's *Science* report when she gives research talks—the Pitt connection is a happy coincidence.) AAVs are ideal as vectors because when they infect cells, they drop off genetic material without causing illness. Scientists like Byrne can engineer millions of AAV individuals that are capable of all sorts of feats. Plus, AAVs are amenable to structural changes.

"It's a highly malleable virus," Byrne says. "You can actually change the way that the virus infects cells. You can change what kinds of cells it infects. You can change how efficiently it infects those cells. That can enable new gene therapies and more successful outcomes for patients."

AAVs are especially good at delivering genes to the retina, the layer of neurons at the back of the eyeball that transmits visual information to the brain.

As a PhD student at the University of

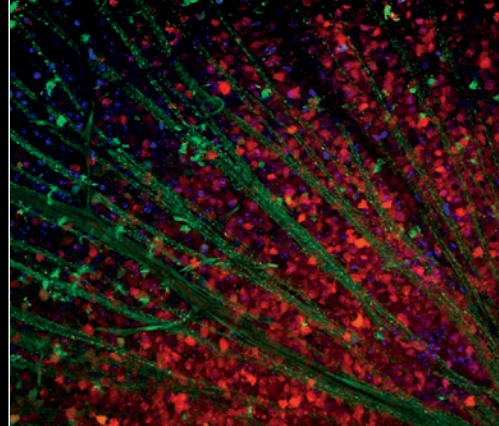
California, Berkeley, Byrne helped to engineer an AAV named 7m8. Mighty 7m8 is capable of traveling from the gel-like middle of the eye, known as the vitreous humor, into the retina, as Byrne demonstrated in rodent and large animal models.

The hope is that this will work safely in humans, as well. If so, it means that rather than undergoing retinal surgery—and risking retinal detachment—patients with retinal diseases could instead receive injections in the vitreous humor. Byrne and her Berkeley colleagues patented 7m8, which has since been licensed by Adverum Biotechnologies. In the fall, the company started clinical trials of intravitreal gene therapy injections for patients with wet age-related macular degeneration, a leading cause of vision loss in patients older than 60.

When the research on 7m8 was originally published in *Science Translational Medicine* in 2013 with Byrne as a first author, it was recognized by National Institutes of Health Director Francis Collins. He posted a blog entry, "Glowing Proof of Gene Therapy Delivered to the Eye," and included an appropriate glowing image—credited to Byrne—that showed that 7m8 had delivered its genetic cargo to all layers of the outer retina.

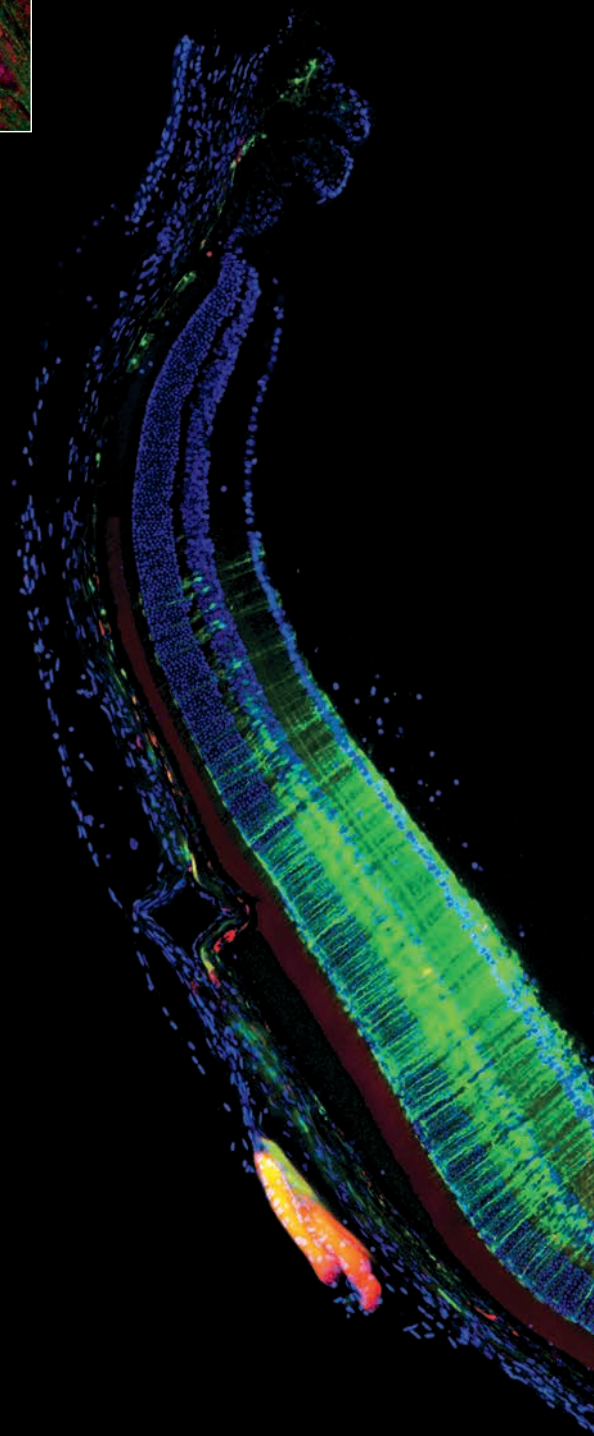
It wasn't the first time Byrne had been credited for a stunning image. Byrne is a photophile who still prefers to shoot on film. The first laboratory of sorts that she built was a darkroom at her family home in Ohio. She began college as an art major interested in photography, then a neuroscience class changed her course. She ended up graduating from Hamilton College with a bachelor's in neuroscience instead.

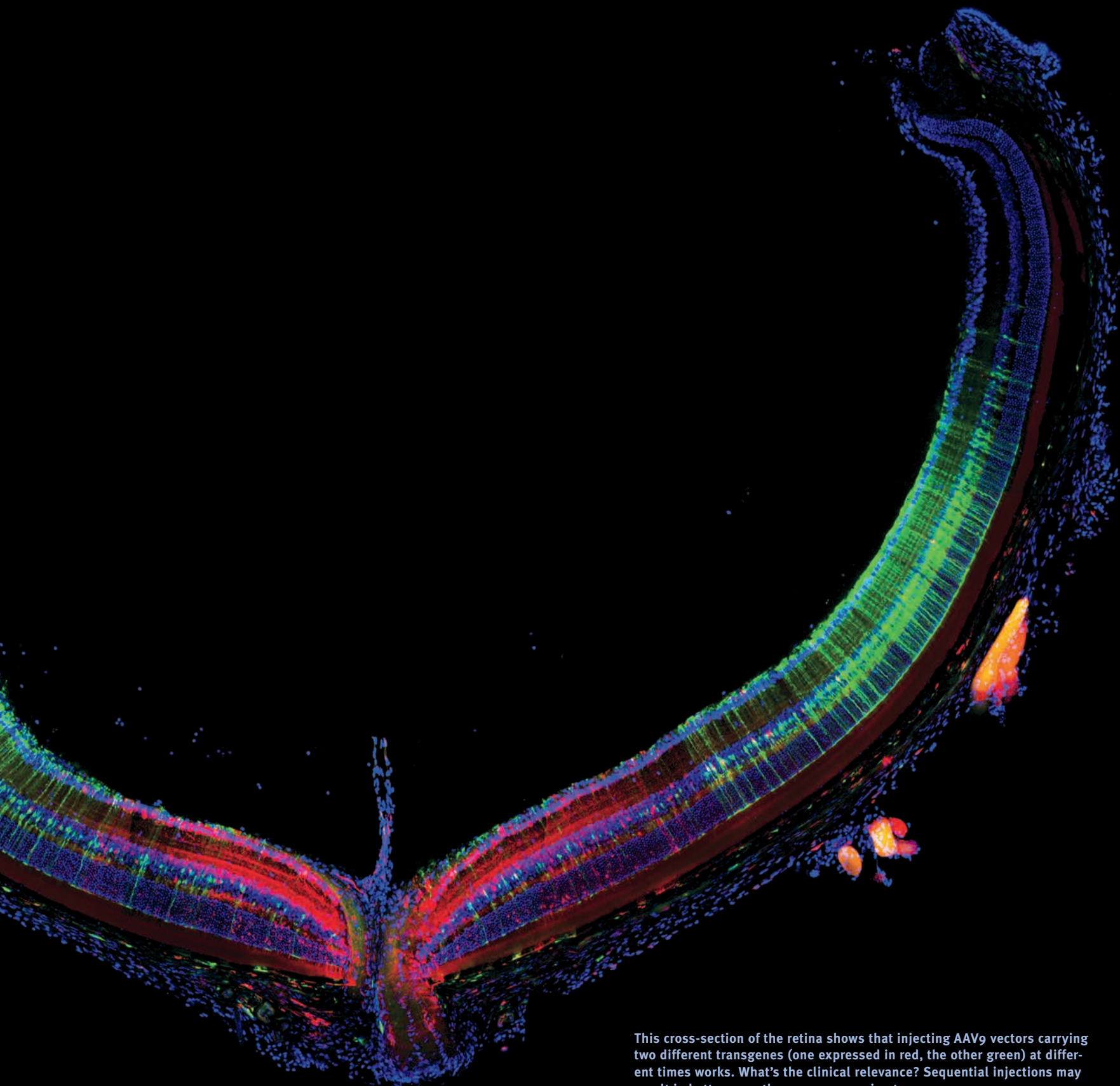
In her early 20s, Byrne "traveled the world for a while doing science," working as a research assistant at labs in Sweden, Oregon,



ABOVE AND RIGHT: Byrne and colleagues found that barriers to gene therapy develop over time with a certain vector they engineered. The cell types infected by AAV9 varied depending on age. Here, axons (green) near the optic nerve express the AAV9-GFP vector after a mouse is 1 day old, and cells (red) in the central retina express another AAV9 vector by the time the mouse is 5 days old.

BYRNE ET AL., "THE EXPRESSION PATTERN OF SYSTEMICALLY INJECTED AAV9 IN THE DEVELOPING MOUSE RETINA IS DETERMINED BY AGE," *MOLECULAR THERAPY* VOL 23, ISSUE 2, 290-296 FEBRUARY 2015 (CC BY 4.0)





This cross-section of the retina shows that injecting AAV9 vectors carrying two different transgenes (one expressed in red, the other green) at different times works. What's the clinical relevance? Sequential injections may result in better gene therapy coverage in utero.

and Lebanon. On her world science tour, Byrne examined how the brain controls food intake; designed molecular biology tools for the diagnosis of mitochondrial diseases; and studied the neuroscience of addiction, neuropathic pain, and schizophrenia.

It wasn't until Byrne landed in California and started her PhD at Berkeley that she decided to specialize in the eye. It was perhaps natural for a photographer to be drawn to the eye, particularly the retina, where images are projected, akin to film in a camera. "It was exactly the right science for me," she says of working in the laboratory of John Flannery, who pioneered the use of AAV vectors for gene therapy for retinal disease. "I loved the engineering side of it. I loved the translational side of it. I loved the imaging."

As a PhD student, Byrne studied the mechanisms of inherited retinal dystrophies, a group of diseases involving mutations in more than 200 genes, all of which can cause blindness. She created gene therapies for retinitis pigmentosa, X-linked retinoschisis, and macular telangiectasia type 2. She developed therapies using 7m8 and then stayed on at Berkeley as a postdoctoral fellow to continue making new tools for gene therapy.

As a postdoc, Byrne mastered an approach called directed evolution to screen for AAV vectors that are best suited for large animal eyes. AAVs that work in mouse models can only take translational research so far, Byrne explains. Rodents have thin retinal membranes, and they lack foveae—the part of the retina that allows people to fixate clearly on an object—so research outcomes don't always translate well to human eyes. Large animal eyes are closer to those of humans. Primates (including humans) have foveae, and canines have streaks that are similar. Both have thick retinal membranes.

To figure out which vectors would excel in large animal eyes, Byrne pooled millions of AAVs and put them through a process of evolution in a controlled laboratory setting. (If you've read about directed evolution recently, it may have been in coverage of the 2018 Nobel Prize in Chemistry, awarded to the inventors of the approach, including Pittsburgh native Frances Arnold.) Byrne injected canine and primate models with pools of AAVs, then allowed the viruses to compete against one another to see which ones were more capable

of reaching the retinas. She repackaged the winners, set up a second competition, then recovered the most successful variants again. She continued the process for six rounds of selection. At the end, she and her colleagues identified and patented the top winners of the evolutionary tournament. The research, soon to be published, not only described the new vectors. It confirmed the importance of creating specific vectors for canine and primate models. "The viruses we evolved didn't infect mice very well, indicating that there are significant differences between the retinas of small animals, in which gene therapies are often tested, and large animals" like dogs and primates, Byrne notes. This insight has led Byrne to create techniques in her new lab that will result in gene therapies that she's confident will work in people.

During her years as a Berkeley trainee, Byrne's wanderlust also took her to Paris for a year to conduct research at Institut de la Vision. It was there that she met José-Alain Sahel, founding director of the institute who became chair of Pitt's Department of Ophthalmology in 2016. They worked together on a new gene therapy for cone-rod dystrophy, a retinal disease that typically onsets in childhood and leads to vision loss over time.

Sahel's team had identified a protein for keeping cones and rods, the light-sensing cells in the retina, healthy. Byrne successfully employed AAV strains, including 7m8, to handle the delivery logistics. They demonstrated success of the gene therapy in mouse models. Clinical trials are expected to begin soon in France, followed by trials in Pittsburgh. (In more photogenic news, when the research hit the *Journal of Clinical Investigation* in 2015, the journal referred to one of the images as a "Scientific Show Stopper.")

Sahel says he was impressed by Byrne's work from the beginning. "She's both a deep thinker—very focused, very well-organized—and at the same time she doesn't create any noise. She's just focused on what's important."

Byrne says she feels fortunate to be mentored by a "true world leader." When Sahel recruited her to Pitt, she was eager to become part of the expansion of the University's vision research that he's leading. For instance, he spurred an agreement, signed in 2017, between

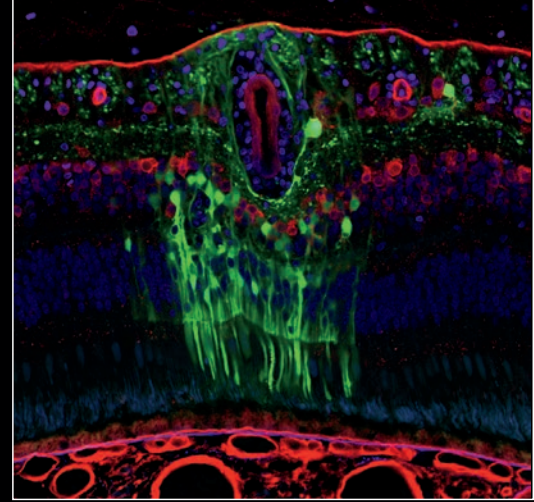
Pitt's School of Medicine and three research institutions in France: the Université Pierre et Marie Curie of the Sorbonne Universités, the Institut National de la Santé et de la Recherche Médicale (which is much like the our National Institutes of Health), and the Centre National de la Recherche Scientifique. The organizations are banding together for research, clinical trials, and joint academic conferences.

This fall, UPMC announced that in spring 2019 it would break ground for a new vision and rehabilitation hospital at UPMC Mercy in Pittsburgh's Uptown neighborhood. Sahel, an MD, will be moving both clinician and research teams there, replicating a model he set up in Paris. Sahel says having patients, doctors, and scientists in the same place is the most efficient way to make progress in bench-to-bedside research. "You have to ask the right questions. And the right questions come from patients," he says.

Byrne is looking forward to moving into the new building. At the moment, her lab is motorizing along in Biomedical Science Tower 3, pursuing the most creative ideas she can dream up. "Dr. Sahel is supportive of me doing the most ambitious work possible," she says. "If they made mugs for World's Best Ophthalmology Chair, I'd get him one."

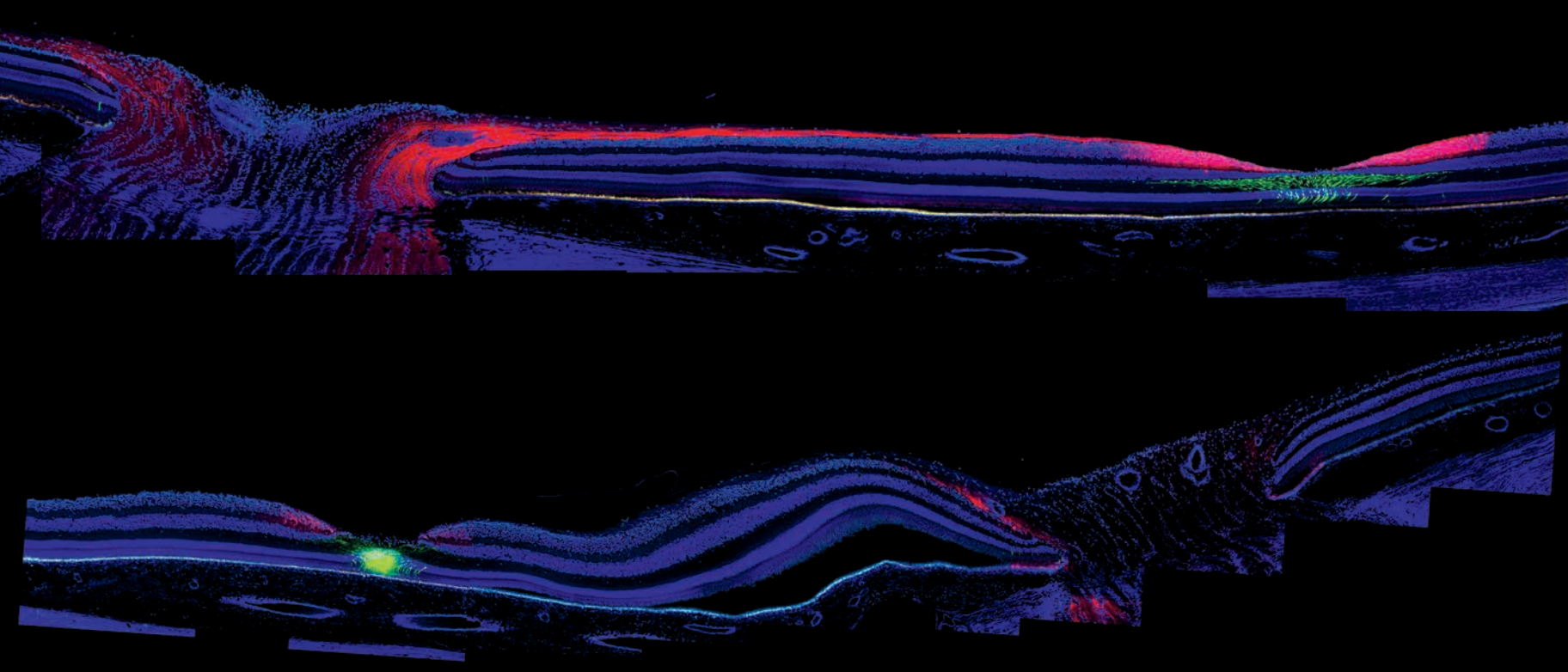
Ambitious Project No. 1 is using high-throughput screening to create a "complete" dictionary of AAVs that can infect every single cell type in the primate retina and brain. In the past, it has taken years to develop a vector for a single target, but Byrne has developed a method to speed up the engineering process; and she can track the behaviors of millions of new viruses in thousands of cells simultaneously. To make this happen, she's working with Pitt and Carnegie Mellon University colleagues as well as the UPMC Genome Center (which just opened in

DANARAO ET AL. "IN VIVO DIRECTED EVOLUTION OF A NEW ADENO-ASSOCIATED VIRUS FOR THERAPEUTIC OUTER RETINAL GENE DELIVERY FROM THE VITREOUS." *SCI TRANSL MED*. 2013 JUN 12;5 (189).



ABOVE: The NIH's Francis Collins called this "Glowing Proof of Gene Therapy Delivered to the Eye." Green shows a protein made from genes successfully delivered to all layers of the outer retina of a monkey with Byrne's 7m8 vector.

COURTESY LEAH BYRNE LAB



TOP: A monkey retina glows with newly expressed proteins (red and green) from a virus evolved in Byrne's lab.
BOTTOM: Another engineered viral vector was able to reach a monkey's fovea (glowing green), which is responsible for visual acuity. This makes the vector (which Byrne named NHP26) a good candidate for macular degeneration or achromatopsia (full color blindness) therapies.

the fall). “We’re making a toolbox of viruses that will be available to the research community,” Byrne explains. “So, for example, if a researcher needed to target photoreceptors and glial cells in the retina, or any other cell type, they could find the optimal virus for that combination of cells in the online database we are constructing.” Byrne received an Individual Investigator Award in 2018 from the Foundation Fighting Blindness to fund the research.

As part of the dictionary project, Byrne has also introduced RNA-tagging, essentially a barcode that can track how much genetic material makes it into cells during gene therapy. It’s an advance from the tracking process she used as a postdoc. The barcode will speed up the process of determining which vectors are most effective.

Ambitious Project No. 2 is figuring out ways to deliver large genes (including the gene that encodes CRISPR-Cas9—the hot gene-editing tool that directly rewrites the genome) into retinal neurons. Transporting CRISPR-Cas-9 into the retina could open up all sorts of solutions. Here’s the problem: It’s too big to fit in an AAV trunk with other molecules that would also need to be delivered for therapy. AAVs are itty bitty things—about 25 nanometers in diameter with room for about 4.7 KBs of cargo.

Byrne and her team have come up with a strategy for splitting genetic cargo, delivering it with engineered dual vectors, and then reassembling the genes inside cells. The approach would be useful not only for delivery of CRISPR-Cas9,

but large genes that are involved with diseases like Stargardt disease (the most common form of retinal degeneration in children). Last year, she received a Career Development Award from Research to Prevent Blindness in support of the work. She also submitted a patent application. If awarded, it will be Byrne’s sixth patented technique.

Besides splitting cargo in two, Byrne’s team is also exploring if they can engineer AAVs with bigger trunks, capable of fitting more cargo. That’s why, soon after Byrne set up her Pitt lab, she began collaborating with structural biology professor James Conway to use electron microscopy to zoom in on the AAVs she’s developed. She heads down to the basement microscope from her 10th floor lab so she and Conway can get a good look at viruses after she creates them. She wants to see how structural changes influence AAV behavior.

Soon, she’ll also tap into the live-video scopes at Pitt’s Center for Biologic Imaging to see the AAVs in action.

Fingers crossed that her team can come up with a structure that increases the cargo capacities of the AAVs by, say, switching from a traditional sedan trunk to a hatchback.

“**W**hat she’s going to do is to the benefit of all of us,” Sahel says of Byrne.

He’s not just talking about the field of vision care. Peter Strick—scientific director of

the University of Pittsburgh Brain Institute, where Byrne also serves on the faculty—calls Byrne an “institutional resource” who is cross-trained and multidisciplinary. (She has secondary appointments in neurobiology and bioengineering.)

“Her skills have been applied to the visual system, but if she solves the problem for one set of neurons [in the retina], it’s likely to be a general solution,” Strick, who is also chair of neurobiology, says.

He has connected her with Brain Institute researchers studying decision-making who need help delivering genes throughout the brain, as well as scientists working on gene therapy for post-polio syndrome.

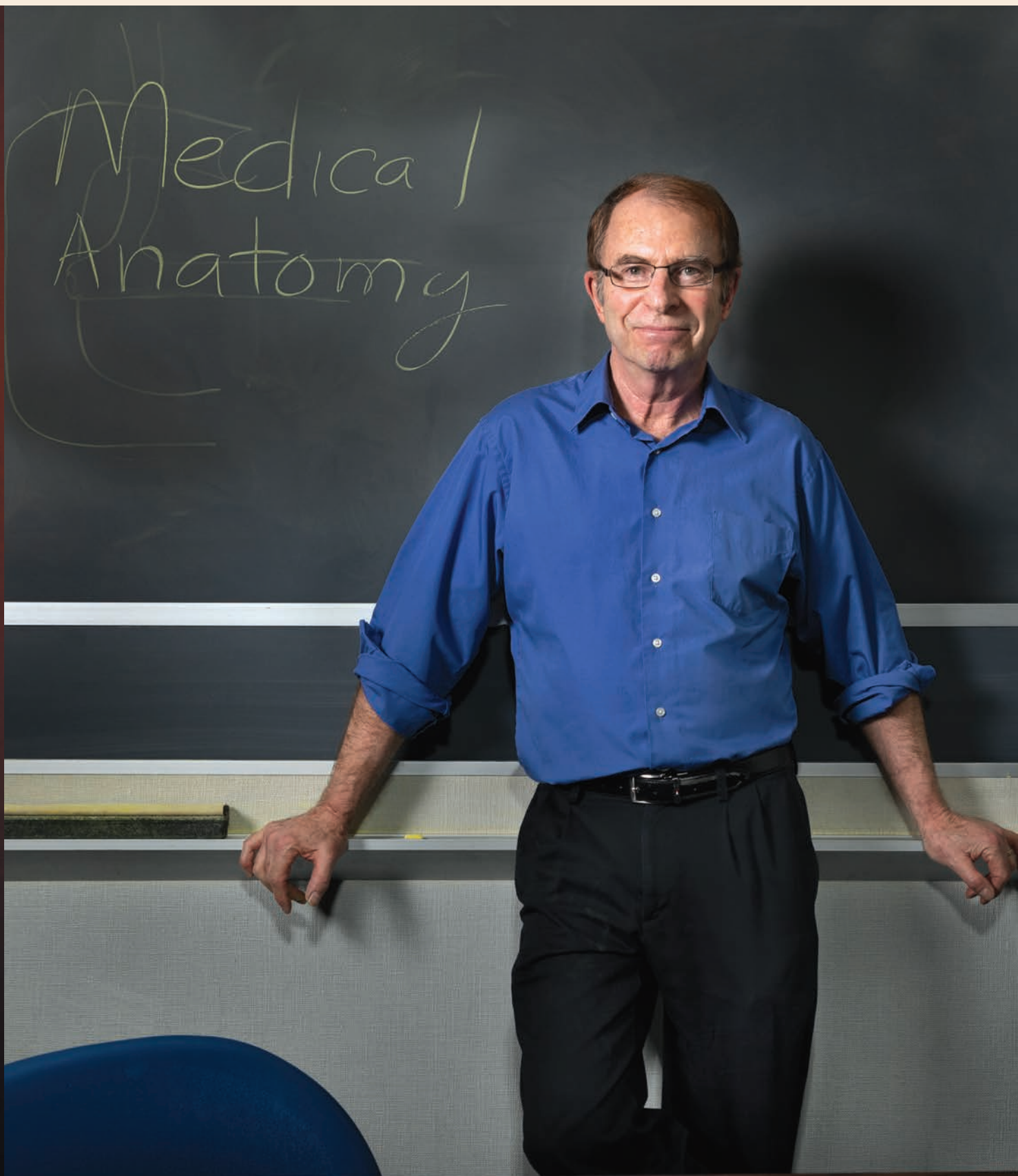
Beyond Pitt, Byrne spent 2017–18 as an associate scientific advisor for *Science Translational Medicine*, writing summary articles about promising gene therapy research for skin regeneration and for melanoma, sickle cell anemia, and other diseases. “That was so much fun,” she says. “It gave me the chance to read in depth in research areas outside the eye.”

The UPMC Vision and Rehabilitation Hospital is set to open in 2021. Once Byrne is situated there, she’ll work with clinicians who will help her, she says, “better understand what the needs of patients are and how my research fits in.”

And that will clarify where to focus her lens next. ■

ATTENDING

Ruminations on the medical life



Jack Schumann teaches students anatomy by going through the trenches with them.

“LOOK AT THAT!”

JACK SCHUMANN GIVES STUDENTS A
ROAD MAP TO THE HUMAN BODY

BY GAVIN JENKINS

PHOTO BY TOM M. JOHNSON

It's a Friday morning in late September, and a Scaife Hall laboratory is filled with 161 first-year medical students. The class, Medical Anatomy, is their first at Pitt Med in the Foundations of Medicine sequence, and this is the end of the fourth week of dissecting the cadavers that line the walls. The room is long and narrow with a low ceiling, and when Jack Schumann, a PhD and anatomy course director, walks out of the lab office buttoning his white coat, the students who greet him have to yell over the cacophony.

Michelle Zhang, a Vassar College graduate, asks Schumann if he'll help her group start the morning's assignment: removing the cadaver's brain.

"Absolutely," he says. "Let's go."

A few minutes later, Schumann is cutting around the cadaver's skull using a handheld electric saw, while Zhang holds the head still. More than 30 students are crammed around the table in this corner of the lab to watch Schumann dissect.

This is what Schumann does. As third-year Mara Rice-Stubbs describes it, he goes through the trenches with his students. When Rice-Stubbs took anatomy, she struggled to memorize the onslaught of information. One day, she visited Schumann in his office, and, though embarrassed to admit it, she revealed that she was falling behind in class. Rice-Stubbs expected Schumann to suggest a review book or a new study strategy. Instead, he told her to drink a cup of coffee and meet

him in the lab.

It was late in the afternoon. Helping her meant going home late, maybe missing dinner. Rice-Stubbs says she would have been grateful if Schumann had reviewed head and neck anatomy with her for 20 minutes.

"He spent the next two-and-a-half hours in the lab reviewing anatomy with me and my classmates," she says.

Schumann's efforts have been noticed. Since becoming Medical Anatomy course director in 1998, he has won 12 Excellence

things tick," he says. Schumann considered studying ecology and zoology before deciding to major in biology at Rutgers University. As an undergraduate, he loved studying photosynthesis, cellular respiration, and embryology. His family pushed for him to attend medical school, but Schumann wasn't interested in becoming a physician. After college, he stayed at Rutgers, earning a master's in cell biology and a PhD in morphology.

He had never even taken an anatomy course before, but when Schumann began

One day, she visited Schumann in his office, and, though embarrassed to admit it, she revealed that she was falling behind in class. She expected Schumann to suggest a review book or a new study strategy. Instead, he told her to drink a cup of coffee and meet him in the lab.

in Education Awards. He received the Kenneth E. Schuit Master Educator Award, the Sheldon Adler Award for Innovation in Medical Education, and the Golden Apple Award. In 2017, Schumann was recognized with the Chancellor's Distinguished Teaching Award.

"I try to set the stage, show everybody the big picture, and then go into the fine detail," Schumann says.

Schumann, 66, grew up in southern New Jersey, near Philadelphia, and as a teenager, he became interested in biological sciences. "I just liked to know what made

working as a professor at another university, he was asked to teach the subject to undergraduates. "My chairman said: *Just keep a chapter ahead of the students*," Schumann says. "It was a struggle at first."

The night before each class, Schumann would stay up late to memorize bones, muscles, and nerves, and after a couple of years of cramming like this, not only did he get comfortable teaching the material, but he also began to enjoy it. In his spare time, he did the coursework for a PhD in anatomy, but because he already had a PhD in morphology, he decided not to write a dissertation.

What his students are going through is not

alien to him. Schumann recalls which material was especially difficult.

And he remembers which sections of the course terrified him—"everything" scared him at first. "It all just seemed overwhelming."

"Even in an undergraduate course, you're learning the names of hundreds of bony prominences, muscles, nerves, veins, arteries, and organs, and relationships of what's next to what," he says. "It's like learning a foreign language."

This is Schumann's favorite analogy for what it's like to learn anatomy; and coincidentally, his wife, Maria, is a linguist who used to work at the United Nations. She's fluent in Spanish, English, French, and Italian.

Rice-Stubbs says that every medical school course feels like the most important one. But she notes that it's easy to argue that anatomy is the most crucial class. Schumann would agree. Some medical schools don't begin with anatomy, and he says that's a mistake. He calls anatomy the "road map" to the human body, an "absolute requirement" for diagnosing patients, and he believes dissecting a cadaver is a rite of passage for future doctors.

Many first-year students have never seen a corpse; fewer have dissected one.

So on their first day of anatomy lab, Schumann has a ritual. He breaks the students into groups and assigns each group a cadaver.

At the end of their anatomy courses, the students attend a ceremony in Heinz Memorial Chapel to honor the donors and their families.

In the closing minutes of Friday morning's class, Schumann stares into a cadaver's skull to inspect Insiyah Campwala's dissection of the middle cranial fossa. He smiles and says, "I'm going to tell people I did this." As students laugh, he steps back and points at Campwala. "She's going to be a surgeon."

Schumann says it's obvious from the first class which students are headed toward a life in the O.R. They're more aggressive about jumping in and dissecting. They pick up the

"Even in an undergraduate course, you're learning the names of hundreds of bony prominences, muscles, nerves, veins, arteries, and organs, and relationships of what's next to what," he says. "It's like learning a foreign language."

Schumann removes the top of the cadaver's skull and peels off the thick dura membrane that surrounds the brain. Anatomy is a seven-week course, and for each lab, he's assisted by five or six physicians who float around the room as he does. Some of the physicians are active faculty members; others are retired doctors who enjoy helping in labs and in problem-based learning sessions.

On this Friday morning, the course instructors are helping the student groups get started. A chorus of handheld saws buzz.

"Now what I'm going to do is cut the cranial nerves from anterior to posterior," Schumann says to a group of 30. "I'm only saying this because I'm being recorded." He nods to my recorder and waits for the students to finish laughing at his joke before adding, "But that means front to back."

After he removes the cadaver's brain, Schumann holds it up and points to the optic nerves. "See them?" he says, excitedly. "Aren't they cool?" Stepping back, he invites other students to look. "Take a look at the optic nerve. Isn't that cool? Everyone see?"

Then each group is given information about the person who lived in the body. As the students sit around a table, they learn the person's age, vocation, and cause of death.

This is a beautiful thing, Schumann will say to them. This person donated their body for your medical education. Maybe they hoped that you'd learn something that will help others.

Course faculty and upper-level med students will walk around the lab, inviting the new students to discuss how they feel. The same first-day ritual will be staged in the spring, when Schumann, who is an associate professor in the Department of Neurobiology and also in the Department of Oral Biology, teaches head, neck, and throat anatomy to dental students. Sarah Albini, a fourth-year dental student, says the first-day ritual is emotional.

"You know you're going to be doing dissections, and you're like: *Oh yeah, it's going to be a cadaver.* But, then when that person's in front of you, and then you're putting that person to a family. So yeah, it definitely has a lot tied to it."

information quickly. "They're not afraid of the material," he says. "It's just very clear."

Campwala, who graduated from Pitt earlier this year with a degree in biology, is interested in becoming a surgeon. She beams after Schumann's remark in front of the group. Campwala tells me later that Schumann will often compliment students with an exclamatory, *You guys should be in medical school!*

His level of enthusiasm never drops. Rice-Stubbs says that when Schumann stayed late to help her in the lab, he gasped as he pointed out nerves: *Wow! Look at that!* "He's seen the same nerve thousands of times," she says.

This Friday morning in the lab, he's checked in on three groups of students so far. He heads to a fourth. He shows them how to fold back the dura, then asks a student to hold the cadaver's head by the jowls while he dissects. He's handed a scalpel, but before he cuts, he points at the brain.

"There's the optic nerve," he says. "Does everyone see the optic nerve?" ■

“D” Way to Teach

(continued from page 4)

how anything works normally. So when it came to getting a PhD, I was 100 percent focused on normal function. Over the years, I've taught in 12 different first- and second-year courses. Almost every single organ system. And my focus was always: How does it work normally? If you understand the foundations of normal, then the diseases start to make a lot more sense.

SD: I was a drama major in college. I guess I went into medicine because I decided there was no way I was ever going to make a living as an actress. Medicine is the only other thing I ever knew. I'm the fifth generation of my family to go into medicine, and my son and daughter are the sixth generation. My father was a surgeon, so I thought I wanted to be a surgeon. But then I read about emergency medicine and thought it sounded cool. It was a brand new residency when I was in med school, so I tried it out, and it's been an absolutely perfect fit for me. I've had so much fun. It fit my attention deficit disorder perfectly.

Do you have a funny story about being colleagues?

SD: The worst thing she ever asked me to do was make gluten-free muffins for her class.

GD: I knew this story was going to come up. So one year in the GI course, every Tuesday morning at 8 a.m. we would do something totally different. One time, we had a hypnotherapist come in and talk about her study treating IBS patients with hypnosis. Another time, we had a yoga instructor come in. And then one Tuesday was healthy breakfast day. We had probiotic yogurt drinks, green tea, and I had asked Sue to make gluten-free muffins.

SD: And I can bake, but I had never baked gluten free before.

GD: She called me and said, “Do you know how awful this is?” She said, “My only option is rice flour, and it's like sand.” But she did it. She came through. Sue, you remember what happened the next week then, don't you?

SD: Oh yes, yes, yes, yes, yes, I do.

GD: I had a real problem getting to sleep one night, and at 4 in the morning, I went to the ER with what ended up being a gallbladder attack.

After a half hour with one doc, shift change occurred, and, lo and behold, Sue Dunmire was my new ER doc. At one point, just Sue and I were sitting in a dimmed room, and she leaned over to me, and she said, “You know what they're going to find when they open you up?” She said, “Your gallbladder is going to be filled with this gritty sand because you made me bake gluten-free muffins.” It hurt so bad to laugh; and you just kept going on, Sue, and making me laugh and laugh.

SD: Yep, that's me.

GD: That gallbladder was taken out by a second-year resident who was our former student.

When you look back and think of the students you taught, what sticks out?

GD: They're very altruistic.

SD: Exactly. They are doing this because they want to learn to take care of patients. And I love that. I love the enthusiasm. I think they are a complete joy to teach.

GD: I still keep in contact with some of them. Last Christmas, I got a card from a graduate of the second year that I taught. He had failed the last course of his first year and had to remediate it over the summer. I chewed him out, told him there was no excuse; he got lazy. And he wrote, “You have no idea how many times I thought about that and realized that that was exactly it.” It feels good to have had an impact. It felt good to have students stop by my office. We must have gone to a dozen weddings of our students over the years.

SD: I went to a conference with my husband. I happened to see five to 10 people who I'd trained. And just to have them come up to you and say, “Hey, tell me what's going on in your life.” It's very gratifying because a couple of them said, “I still remember what you taught me about this.” That made me feel good. And I'm happy I became friends with so many of the students. They knew that they could call me. Or I could pick their brains. And we could get through this together. It was a very gratifying career.

—Interview by Gavin Jenkins

Read more of the conversation at
www.pittmed.health.pitt.edu/story/d_way_teach

Labors and Losses

(continued from page 14)

naming racism as a core element that would be contributing to the racial disparity that we see in maternal health and infant health, as well as in death. We've been working closely with [others] to think about: As practitioners, as researchers, as community organizers that are coming together around these issues, how do we move forward together in a collective impact sort of way?

What is contributing to this disparity at the policy level?

SB: A lot of women, low-income women in particular, become eligible for insurance coverage, Medicaid coverage, during the time of pregnancy—[coverage] which then they often lose 60 days postpartum.

JS: One of the unintended consequences of these policies that we see in community-based programs is moms come to us repeatedly with subsequent pregnancies that are back to back. So if she loses her health coverage and isn't able to continue to manage whatever chronic health condition that she may potentially have, then in that subsequent pregnancy, that condition presents itself again.

[There's a mindset of a mom's value] being centered around her capacity to continue to have children. It's kind of like a backdoor access to things that should be provided anyway. It puts a lot of strain on community-based programs that aren't necessarily meant to cover basic needs.

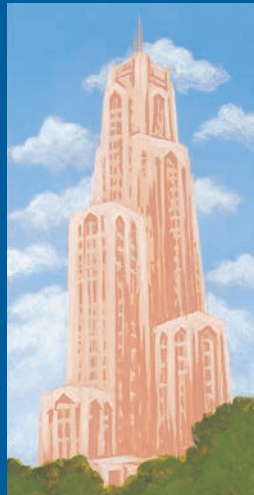
What can be done at the level of the provider, of the community, of the family, to help mothers and babies?

BB: Sometimes [women] just don't know they have the power to tell the provider, *I'm having this dizziness, I'm having these headaches*, and to not necessarily accept it if the provider dismisses them.

JS: The mental health aspect is really important. I think that, as a community, we're doing a better job of making sure that we're paying attention to mom's mental health, and the fact that, at this perinatal period, there is a lot going on. And it's normal to get help. It's normal to recognize that this is a huge change and shift. And that we're not superwomen. Well, we *are* superwomen, but we still need help.

—Interview by Erica Lloyd

This conversation has been edited. To hear more, tune in to our Pitt Medcast: www.pittmed.health.pitt.edu/pitt-medcast



CLASS NOTES

'70s

R. John Solaro (PhD '71), Distinguished University Professor of Physiology and Biophysics at the University of Illinois at Chicago and director of the university's Center for Cardiovascular Research, focuses his



Solaro

research on sarcomeres: the "molecular motors that control the heart." Sarcomeres have captured Solaro's attention since his time at Pitt, where as a student he helped develop the most commonly used method for their isolation. Today, his research has aided the development of drugs for both genetic and acquired heart

failure, including drugs that have proven therapeutic for common inherited cardiac disorders—"[the] biggest killers," says Solaro, "of young adults in the Western world."

'80s

Frank Anania (MD '88) joined the U.S. Food and Drug Administration as a medical officer in 2018. (When we last wrote about him in 2011, he was on the



Anania

faculty at Emory University.) Anania was hired under the 21st Century Cures Act to help the agency jump-start the liver disease review programs in the Center for Drug Evaluation and Research. "What is most amazing to me," he says, "is how important the work of the physician-scientist is to the clinical benefit of our patients."

Shukti Chakravarti (Postdoctoral Fellow '93), after 18 years at Johns Hopkins University, joined New York University in April 2018 as professor of ophthalmology and pathology and director of basic science research in ophthalmology. She credits her postdoc at Pitt Med's Eye and Ear Institute with her ongoing research interest in extracellular matrix (ECM) protein and how, says Chakravarti, "it regulates the cellular micro-environment and functions" in the eye. In her new role, she hopes to grow research efforts in NYU's Department of Ophthalmology. "I am learning something new every day about living in the Big Apple!" she says.

Mark Dias (Neurological Surgery Resident '89) recently received a lifetime achievement award from the National Center on Abusive Head Trauma/Shaken Baby Syndrome for his ongoing dedication to pediatric neurosurgery. It's "for my 20 years of work," says Dias, "trying to reduce the incidence of AHT/SBS through universal perinatal parent education." Dias is professor of neurosurgery and pediatrics, vice chair for neurosurgical education, and codirector for the Clinical Neuroscience Clerkship at Penn

State College of Medicine in Hershey, Pa. He's also the director of pediatric neurosurgery and the pediatric surgical quality and safety officer for the Penn State Health Children's Hospital.

'90s

Paul A. Grabb (Neurological Surgery Resident '95) and his team have started a fetal surgery program that repairs spina bifida in utero. Grabb says that while nationally this procedure reduces incidence of hydrocephalus shunting from about 80 to 40 percent, his team has reduced it to about 12.5 percent. Grabb was named section chief of neurosurgery at Children's Mercy Hospital in Kansas City, Mo., in 2015. The associate professor of surgery at University of Missouri-Kansas City says of his new clinical role: "You are responsible for not only your practice, but the practice of the other surgeons. You need to make sure the whole team is delivering."



Grabb

For years, urine output was not used as a criterion for diagnosing acute kidney injury in patients with chronic liver disease. The argument was that low urine output (oliguria) in these patients may not reflect acute injury. The thinking went that the tests wouldn't work because the urine output of chronic liver disease patients fluctuates widely. But, asks, **Ali Al-Khafaji** (Internal Medicine Resident '99), "Can any of us say that if you don't pee, it's a good thing?" Al-Khafaji, medical director of the transplant intensive care unit at UPMC Montefiore and professor of critical care medicine, teamed up with **John Kellum** (Critical Care Fellow '94), Pitt's vice chair of critical care research, to investigate the significance of oliguria in patients with chronic liver disease who were admitted to the intensive care unit at UPMC. Their findings (published in *Hepatology*) demonstrated that incorporating urine output into the diagnostic criteria increased the measured incidence of acute kidney injury. More importantly, patients with transient oliguria had increased mortality rates compared with patients without oliguria.



Al-Khafaji

'00s

Omar Danner (Minimally Invasive Bariatric and General Surgery Fellowship



Danner

'04) is professor and chief of surgery at Morehouse School of Medicine, as well as Grady Memorial Hospital in Atlanta. His research portfolio spans sepsis treatment, vitamin D deficiency in critical illnesses, and perioperative efficiency. He says he is particularly proud of his work as founding director of the Reach One Each One Youth Mentoring and Medical Exposure Program for high school students, a 10-week course that includes hands-on simulations. "The thing that I realized is that correcting the problems [experienced by] the youth of today was not going to begin and end with a scalpel or laparoscopy."

In our summer issue, we featured a discussion with alumni who are serving as diversity officers around the country. **Stephanie White** (MD '08) was among the voices in "Alum Intel" who commented on race, bias, and otherness in medicine. At the time, she was a diversity liaison for student/resident advising at the Geisel School of Medicine at Dartmouth. This academic year, she was promoted to Dartmouth's associate dean for diversity and inclusion. "This position is the dream job I envisioned while in medical school at the University of Pittsburgh."



White



Moniz

'10s

Michelle Moniz (Obstetrics and Gynecology Resident '12), assistant professor of obstetrics and gynecology at the University of Michigan, completed a policy fellowship last summer at the Center for Healthcare Research and Transformation, a nonprofit in Ann Arbor. She says the experience taught her how research can be publicized to influence policy. "Policy makers are not reading academic journals, so you must find other ways to get that data to people who can change the policy environment," she says. Moniz is working with Michigan's Department of Health and Human Services to give women across the state immediate access to postpartum contraception.

—Ellen Kruczek, Jon Kunitsky,
Rachel Mennies, and Kelsey Sadlek

EYES WIDE OPEN

SHINJINI KUNDU

The human eye can achieve a resolution of approximately 576 megapixels. The latest televisions, by contrast, display more than 33,000 megapixels. Add a third dimension—as in magnetic resonance imaging—and the flood of images overwhelms the naked eye.

That's where transport-based morphometry, or TBM, comes in. Developed by UPMC radiology resident Shinjini Kundu (MD '17), TBM uses artificial intelligence to detect the relevant patterns within an MRI that would otherwise evade detection by even the most expert radiologist.

In a 2017 paper, Kundu demonstrated that up to three years before the symptoms of arthritis manifest, TBM detects structural precursors of the condition—shifts in water diffusion within joints. This year, she began applying TBM to brain imaging. One project investigates how a gene associated with



COURTESY CARNEGIE MELLON UNIVERSITY

autism influences brain structure and function; another examines the subtle injury patterns associated with concussion. "What motivates me is going after the hard problems," says Kundu, who also has a PhD in biomedical engineering from Carnegie Mellon University.

Kundu has garnered praise for both the quality and pace of her research. Two of her papers were deemed best of the year in informatics (for 2016 and 2017) by the Radiological Society of North America. In 2018, *MIT Technology Review* named her among their 35 innovators under 35; in 2017, she was named a World Economic Forum Global Shaper.

Kundu is excited about moving TBM into clinical practice: "With TBM you can . . . identify the target audience or population for whom early intervention would have the most benefit."

In that regard, TBM has unique advantages. "We don't have to have a blanket solution," she says. "That's the advantage of algorithms that learn—you can add shades of nuance and complexity." —Sharon Tregaskis

READY TO GO: DANIEL SINGER

Daniel Singer (MD '96) credits a pair of fourth-year rotations with setting his career trajectory—one rotation was in Zanzibar, an island in the Indian Ocean off the coast of Tanzania, and the other was with the Epidemic Intelligence Service at the U.S. Centers for Disease Control and Prevention in Atlanta. “We got three hours’ notice to pack and get on a plane to Indianapolis,” Singer recalls of the latter. “For several weeks I worked with an officer from EIS tracking an epidemic. I thought it was so cool, that you have to be ready to go—anyplace—and that you’re benefiting whole groups of people.”

Two decades later, Singer has risen through the ranks of the U.S. Public Health Service, holding posts

in Malawi, Liberia, and Washington, D.C. Currently chief of the CDC’s Health Systems Solutions Branch in Mozambique, Singer serves as a point person for programs to promote the prevention, diagnosis, and treatment of HIV, tuberculosis, and malaria. “We’ve been able to drastically increase the number of people being treated for HIV, and when you’re being treated effectively, you can’t transmit the virus,” says Singer, whose



Singer

responsibilities span the entirety of the U.S. government’s \$400 million budget for health in Mozambique. “We’re making progress in that sense.”

The CDC generally enjoys broad bipartisan support in Congress, Singer says, allowing staff to maintain a long-term trajectory in pursuit of evidence-based public health initiatives, buffering the effects of short-term political shifts at home and abroad.

“The United States is the largest funder of HIV work around the world,” says Singer. “And because of that, the financial and political challenges a country faces are not the sole determinants of what [it’s] able to achieve. We’re able to have tremendous effect on health, even when a country is struggling to keep itself up and running.”

—Sharon Tregaskis

MAA SAYS, “REUNITED, AND IT FEELS SO GOOD.”

“We reconnected over zebra fish,” says Elaine Hylek (MD '88), describing her chance encounter with now fiancé Jonas Berman (MD '88). During their 25th School of Medicine class reunion, the pair went on the same tour of Biomedical Science Tower 3. Hylek says, “I thought, ‘Look at this guy—still interested in science!’” She struck up a conversation with Berman, whom she first met in physical diagnosis class in the '80s, and they continued to talk over the weekend. While sharing stories about their children, practices, and previous marriages, they discovered that they lived in neighboring towns in Massachusetts. The proximity made it easy to keep the tête-à-tête going, and now, nearly six years after crossing paths again, they plan to wed this spring.

Vanessa Franco (PhD '11, MD '12) and Ranmal Samarasinghe (PhD '11, MD '12) are also Scaife-crossed lovers. They met during an ice cream social for incoming Medical Scientist Training

Program students. After they started dating, and a year before they were matched for residency in Los Angeles together, Franco and Samarasinghe saved a runner’s life by giving her CPR on a Shadyside sidewalk. The runner, KDKA news anchor Susan Koeppen, reconnected with the couple in Pittsburgh this August; they told the story as part of the White Coat Ceremony. (See p. 38.)

Love was in the air this fall, too. During Homecoming 2018, former MAA President Robert Bragdon (MD '73) renewed his vows with Theresa “Bunny” Clements at Heinz Memorial Chapel’s “I Do, I Do . . . Again!” ceremony. Clements, a nurse, is his partner at work as well as in life. They’ve raised four daughters in their 50 years together.

The Medical Alumni Association delights in campus love stories. Tell us yours at medalum@medschool.pitt.edu. —Kristin Bundy



Hylek and Berman

MEDICAL ALUMNI ASSOCIATION WWW.MAA.PITT.EDU

JAMES PEREL

MARCH 1932–AUG. 27, 2018

When psychiatry professor Neal Ryan stopped by James Perel's office to talk about one of their many collaborations and related research in the field, Perel would often pull a "magic trick" with the stacks of journal articles in his office. "He had a profound knowledge of literature. He'd go to exactly the right stack, cut the stack like a card trick, and choose the right paper," Ryan recalls.



Perel

Perel, professor emeritus of psychiatry and pharmacology, died in August. Before joining Pitt's Department of Psychiatry in 1979, Perel held academic appointments at Emory, Columbia, and New York University, where he earned his PhD in 1964. He served in multiple leadership positions while at Pitt, including acting chair of the Department of Pharmacology, director of the Clinical Pharmacology Program at Western Psychiatric Institute and Clinic, and chief of the Clinical Pharmacology Service for the Veterans Administration Medical Center.

Perel's research centered on psychotropic drug actions and also the prediction of individual responses using biomarker and pharmacogenetic profiling of antidepressants. He accrued a publication portfolio that included more than 330 peer-reviewed articles and was named one of the top 1.5 percent most cited authors between 1982 and 1999 by the Institute for Scientific Information. Perel was also known for his passion for educating students. He earned the Clinician Educator of the Year award from Pitt's School of Medicine in 2013.

Charles F. Reynolds, Distinguished Professor of Psychiatry and the UPMC Endowed Professor of Geriatric Psychiatry, says, "Jim's joining the department turned out to be a wonderful thing for all of us who cared about developing intervention science for people living with mood disorders. His memory is a blessing to all of us." —Jon Kunitzsky

JERRY RABINOWITZ

NOV. 10, 1951–OCT. 27, 2018

When Jerry Rabinowitz attended Jewish services, he always stood when the mourner's prayer, the Kaddish, was recited. If asked why he always joined worshippers who stood in memory of recently deceased family members, Rabinowitz, past president of the Dor Hadash congregation, which met at the Tree of Life Synagogue in Squirrel Hill, said he stood to honor those who didn't have family to stand for them, recalls Brian Primack, a fellow Dor Hadash member and MD, who is a Pitt School of Medicine faculty member and dean of the Honors College.



Rabinowitz

Rabinowitz (Res '80) was one of 11 worshippers killed at the synagogue in October. Standing up for others was a cornerstone of Rabinowitz's spiritual life—and his approach to family medicine.

Rabinowitz's practice partner Ken Ciesielka (Res '83) says Rabinowitz was known as a warmhearted physician, particularly among HIV/AIDS patients. "Word spread that our practice was a safe place to come," says Ciesielka. "We had one of the largest AIDS practices in the county at one time."

At UPMC Shadyside, Rabinowitz was past president of the medical staff and chaired the ethics committee for many years. His wife, Miri Rabinowitz, who manages the neurotrauma biorepository in Pitt's Department of Neurological Surgery, notes, "he was truly passionate" about the ethics work. He was particularly effective helping physicians honor a patient's end of life wishes, says Beth Chaitin, assistant professor of medicine. She counted on Rabinowitz as both her colleague and her family's physician.

Rabinowitz was a clinical instructor in the UPMC Shadyside family medicine residency program for three decades. Elizabeth Baker (Res '91) says he had exacting standards yet never put on airs. "What I learned from Jerry is that doctors do not need to pretend to know everything," says Baker, who also chose Rabinowitz as her family's physician when she lived in Pittsburgh.

At Shadyside, his reputation for good cheer was legendary, says Chaitin. Rabinowitz volunteered for Christmas shifts and donned an elf costume—complete with curled shoes.

—Sharon Tregaskis

IN MEMORIAM

'50s

LEROY W. BOWERS
MD '51
AUG. 17, 2018

RICHARD H. GOLDSBOROUGH
MD '51
JULY 14, 2018

MARVIN Q. SANNER
MD '51
SEPT. 3, 2018

STANLEY P. SILVERBLATT
MD '57, RES '58, '61
AUG. 25, 2018

CHARLES L. WHETSTONE
MD '57
SEPT. 14, 2018

'60s

ISADORE TALESNICK
RES '60
JAN. 16, 2018

FREDERICK J. TERKEL
MD '60

SEPT. 11, 2018

SIDNEY THOMAS LEWIS
MD '61

JULY 7, 2018

RADE PEJIC
MD '66
AUG. 6, 2018

JAMES A. YATES
RES '66
JULY 17, 2018

'70s

LINDA BREUNINGER
MARSHALL
MD '75
AUG. 12, 2018

RASIKLAL B. GANATRA
FEL '77
FEB. 16, 2018

STEPHENSON SWAMIDOSS
RES '78
OCT. 9, 2018

'80s

WERNER M. BLOOS
MD '85, RES '86, '88
JAN. 16, 2018

MARY P. GILLESPIE
RES '85
AUG. 25, 2018

'90s

JOHN G. WASSIL III
MD '94
JULY 10, 2018

'00s

MICHAEL J. KUSH
FEL '00
AUG. 6, 2018

KENT H. CHOU
RES '03
SEPT. 9, 2018

FACULTY

DENNIS O. WAYNE
RES '70, '71, '75, '76
JUNE 9, 2018

UNIVERSITY OF PITTSBURGH SCHOOL OF MEDICINE

PITTMED



SEEN COATED

Since 1998, the School of Medicine has celebrated its incoming class with a ceremony marking their entrance into the medical profession. In what has become a rite of passage, the students are bestowed a crisp white coat (donated by the Medical Alumni Association) and lots of congratulations. This year, the August ceremony, held at Carnegie Music Hall of Pittsburgh, was positively resplendent. Seen at the affair: members of the Pittsburgh Ballet Theatre, Pittsburgh Symphony Orchestra, and Pittsburgh Opera companies (all of whom performed); Dean Arthur S. Levine and other Pitt Med luminaries; KDKA-TV news anchor Susan Koeppen (who relayed the story of how two med students helped save her life in 2011—lifesavers Vanessa Franco and Ranmal Samarasinghe, both MD/PhD '12, joined her at the event); and ceremony hosts and main sponsors, orthopaedic surgery chair Freddie Fu (MD '77, Fel '79, Res '82) and Hilda Pang Fu.

But the real stars of the show were the 162 matriculating students. We invited them to take turns posing as *Pitt Med* cover models at our pop-up photo booth. We're only able to show a few shots here. But as you'll see on these pages, the docs-to-be didn't want to leave out the people who helped them get this far. Among our most popular coverlines: HI MOM! —Erica Lloyd



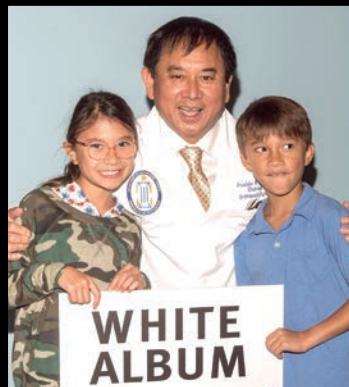
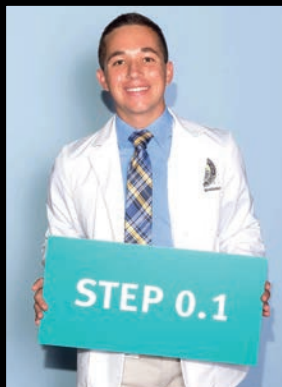
TOP: Josh Ong and his mom.
ABOVE: Lois Wholey (then with the Pittsburgh Ballet), Pitt ENT doc Melonie Nance, Hilda Pang Fu, and Freddie Fu.



Levi Bowers's (shown immediate left) sister, Eve Bowers, is in the Class of '21. Their grandfather LeRoy Bowers (MD '51) also went to Pitt Med. See his story on p. 40.



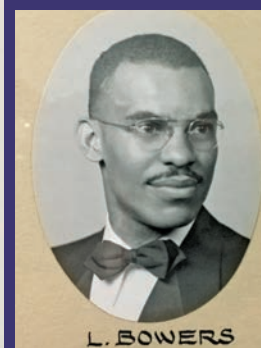
They've worked with NASA and Mount Sinai. They've volunteered for the Hospital Elder Life Program at Shadyside and HIV programs in South Africa. They've run marathons and anatomy courses. And they're all ours. Meet the Class of '22.



That DR. WHO in the fourth row is Victoria Humphrey (Class of '21), who, btw, was Miss National Sweetheart 2016 and runs a non-profit called Apples 4 Education. She's with her mom. Speaking of . . . the HI MOM-er in the fifth row is Stephanie Thermozier (Class of '20), who, like many other students, cheered on the newly coated.

You can't beat this WHITE ALBUM remake (left) featuring Freddie Fu and grandkids Ludivine and Lex (Class of TBD).





ABOVE: LeRoy Bowers's 1951 class photo.
LEFT: The family sets out from New York for Iran via Lebanon. (Photo courtesy Bowers family.)

GOD WILLING

In 1946, seminary graduate and New Jersey native LeRoy Bowers set out for the University of Louisville. He'd been accepted to its medical school. When he arrived to start classes, he was turned away at the door because he was African American. The University of Pittsburgh would later accept him as a member of the School of Medicine graduating Class of 1951. That was after admitting him to the Class of 1950 and, upon realizing he was black, telling him that he had to wait until the following year—the school had already admitted one black student to the class.

Undeterred, LeRoy Bowers would go on to graduate from Pitt Med, train in surgery at Montefiore Hospital, then live and practice in Pittsburgh and rural Blair County, Pa., for four decades. He also supported local churches as an ordained Presbyterian minister.

In 1958, he and his wife, Jean, boarded an ocean liner in New York Harbor to cross the Atlantic with their four small children. They traveled to Hamadan, Iran, where they lived for seven years. LeRoy Bowers learned Farsi so he could serve his newfound community as a physician, surgeon, and director of the local hospital. His son Richard Bowers (Res '90) was born while the family was living in Hamadan. Inspired by his father's work, Richard, an ophthalmologist based in Sewickley, has taken his own family on medical missions. Richard's son, Levi, recalls working vacations in Sierra Leone, Kenya, and Honduras. Hundreds of people would flock to see his father for cataract surgery and other eye care.

Levi is now a member of Pitt Med's Class of 2022 (see p. 39). His sister, Eve, is in her second year here. LeRoy Bowers died in August at the age of 96, just five days after Levi's White Coat Ceremony.

"It is hard for me to imagine that I would be where I am today," says Levi, "without the acts of kindness that my grandfather shared quite literally with the world." —Jon Kunitsky

It's not as though snot is not important.
(Say that fast five times.)



GETTY IMAGES

CALENDAR

FOR ALUMNI & FRIENDS

For more information:
Melanie Sadarananda
at 412-648-9741
or mms239@pitt.edu

**2018 WOMEN IN MEDICINE
AND SCIENCE FORUM**
NOVEMBER 27–28, 2018
University Club

WINTER ACADEMY
FEBRUARY 15, 2019
10:45 a.m., Registration
The Ritz-Carlton, Naples, Fla.

PITT DAY OF GIVING
FEBRUARY 28, 2019

MEDICAL ALUMNI WEEKEND
SEPTEMBER 20–21, 2019
(Celebrating class years ending
in 4 and 9.)

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



FOR REAL! TWEEN SCIENCE

You call it snot. Doctors say *nasal secretions*. And as annoying as it can be to have a nose full of gloopy, gloopy mucus, you actually need the stuff.

Snot contains cells that protect your body from bacteria (like the kind that cause strep throat) and viruses (like the kind that give you a cold or the flu), according to Amanda Stapleton, a Pitt physician who specializes in helping kids keep their ears and throats healthy; she works at UPMC Children's Hospital of Pittsburgh.

Snot cells "have components called *immunoglobulins* that keep these invaders from attaching to the lining of your nose," says Stapleton. Other cells in your body protect you by making little holes in the invaders, to break them up. Then, tiny hairs, or *cilia*, that line your nose move the snot toward your nostrils. It's your job to wipe it away.

You may only think about snot when you're sick. But it helps you when you're well, too. It coats the linings of your lungs so you can breathe easy. It keeps your nose moist and comfortable. And it ushers little particles that might cause allergies, like pollen and cat dander, away.

Snot is somewhat salty. (I'm told.) Some scientists speculate that its flavor appeals to kids because eating it, and the "good" germs it contains, might actually help them fight off diseases down the line. Not to be snotty, but most people think that eating boogers is super gross; besides, picking your nose is likely to spread disease. Better to pick a new hobby instead.

By the way, without snot, "the smell receptors at the top of your nose wouldn't work, and you wouldn't be able to smell—or taste—your food," says Stapleton. We guess you could say that we owe the delicious tastes of pizza and chocolate and strawberries to . . . snot! —Lela Nargi

Is there a topic you'd like us to explore? Drop us a line at medmag@pitt.edu.

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STRONGER THAN HATE

“This senseless act of violence, in a place that many in our community call home, is a source of great pain and sorrow. These acts of hate and terror contradict every human value that we hold dear at the University of Pittsburgh, and we stand united with all of those impacted.”

—Chancellor Patrick Gallagher

A campus gathering on Nov. 5, 2018,
after the Tree of Life massacre.

PHOTO BY MIKE DRAZDZINSKI/UNIVERSITY OF PITTSBURGH