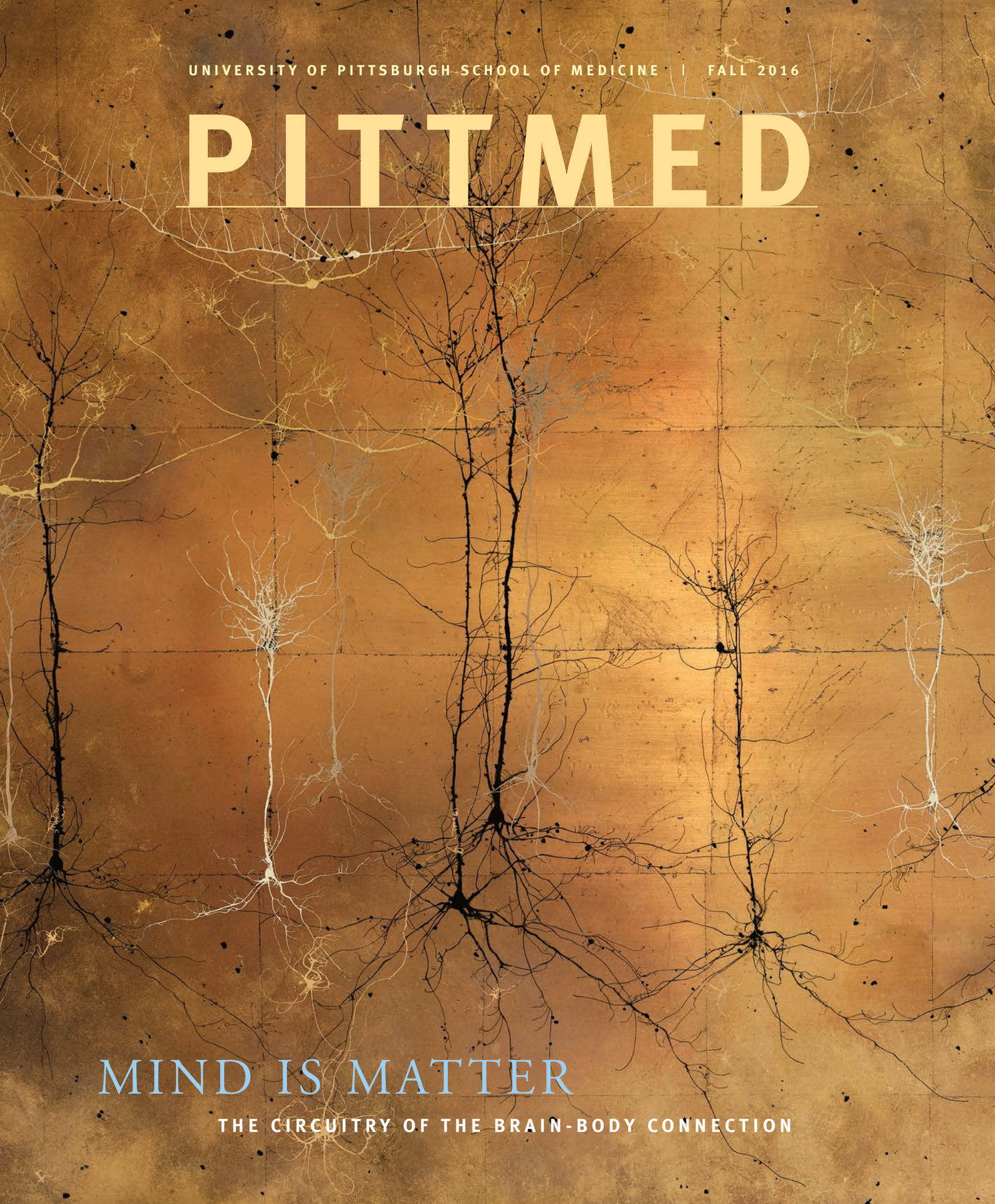
UNIVERSITY OF PITTSBURGH SCHOOL OF MEDICINE | FALL 2016

# PITTMED



## MIND IS MATTER

THE CIRCUITRY OF THE BRAIN-BODY CONNECTION

## BAD CO AND GOOD COMPANY

I read your articles about Dr. Emmanuel Farber and Dr. Jesse Steinfeld (BS '46), U.S. Surgeon General from 1969–1973, two men who warned the public of the health dangers of smoking and supported policies to eliminate it ["The No-Nonsense Pathologist" by Elaine Vitone and "Thank You for Not Smoking" by Thomas H. Maugh II, Spring 2016]. I was not aware of the major influence that Dr. Farber had on these issues, nor was I aware that Dr. Steinfeld was a Pitt alumnus. My sister, Anita Sagone (BS '61, MD '65), also went to Pitt med, taking a residency in pathology. She probably knew Dr. Farber. Unfortunately, she died at age 36 from renal cancer, probably caused by heavy smoking.

After I completed a fellowship in hematology at Ohio State University in 1970, I joined the faculty there and did research on pathophysiology in smokers, publishing work that may be of interest. We concluded that hypoxia caused by carbon monoxide is a major factor for increased vascular disease, heart attacks, and strokes. Our findings were confirmed by numerous others, including Smith and Landaw in a 1978 *New England Journal of Medicine* paper. They coined the name "smokers' polycythemia" for the syndrome. Also, the surgeon general report of 1975 cited our studies.

I remain a strong advocate for policies that discourage smoking. I hope our studies were partly responsible for Ohio's smoking ban in public places—including the OSU campus—which appears to be decreasing the number of smokers in the state.

Arthur Sagone (MD '63, Res '68)
Columbus, Ohio

## LOOKING BACK

A year later still grateful. Touched by human kindness, generosity, love for a friend and a stranger.

Thank you for the gift of sight, and the gift of human touch.

Gugu Mofokeng
Pietermaritzburg, South Africa

*In our Summer 2016 issue ["Sight for Sore Eyes" by Ali Greenholt], we were delighted to cover Ms. Mofokeng's story of traveling to Pittsburgh for treatment.*

MIKE DRAZDZINSKI

## A CALL FOR YOU

**For three Septembers now, the Toast to Diversity and Call to Action event has brought together med students, residents, fellows, and faculty from underrepresented groups to eat, drink, be merry—and make connections. The event has spurred research and other collaborations.**

**How can the School of Medicine encourage future partnerships and continue to build a sense of community? Send Vice Dean Ann Thompson your suggestions and stories: thompsonae@medschool.pitt.edu.**

## RECENT MAGAZINE HONORS

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

**2016 Press Club of Western Pennsylvania Golden Quill Award for Education Feature &**
**Ray Sprigle Memorial Award for Magazines**
**Cara Masset, "Inside the World of OCD"**

**2016 Press Club of Western Pennsylvania Golden Quill Award Finalist, Health/Science/Environment Story, Online**
**Cami Mesa and Elaine Vitone, "Second Lives: A Pitt Medcast"**

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## CONTRIBUTORS

With a number of ADHD-diagnosed loved ones and former students in her life, *Pitt Med* associate editor ROBYN K. COGGINS ["Paying Attention"] says reporting on her latest piece gave her insight into the "science behind the symptoms." She has an ear for patient-focused stories, getting at the lived experiences that intersect the research and treatment of medical conditions. She's always on the lookout for issues that haven't gotten their due attention; most recently, these include the silence surrounding miscarriages. The Minnesota native and her husband, Clint, live in their newly purchased house with dog, Haley Doggins, and two ginger beasts, Oscar and Thomas (who are alternatively known as cats).

GREG DUNN [cover], a Philadelphia-based artist with a PhD in neuroscience (and a background in molecular biology and genetics), embraces his outsider's perspective on the fine arts. To create his brainy images, Dunn uses a handmade lithograph able to manipulate light on the microscopic scale. Dunn developed the technique, called reflective microetching, with artist and applied physicist Brian Edwards. The approach gives the collaborators extraordinary control over metallic surfaces, Dunn says. Dunn and Edwards were awarded a National Science Foundation grant to manufacture an 8' x 12' microetching of the human brain; the piece, *Self Reflected*, is displayed at the Franklin Institute in Philadelphia. Some Dunn pieces are also on display at the Pitt–Carnegie Mellon Center for the Neural Basis of Cognition. Peruse more of his work at **gregadunn.com**.

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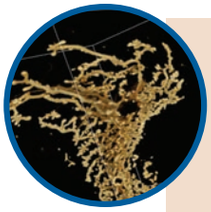

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DEPARTMENTS

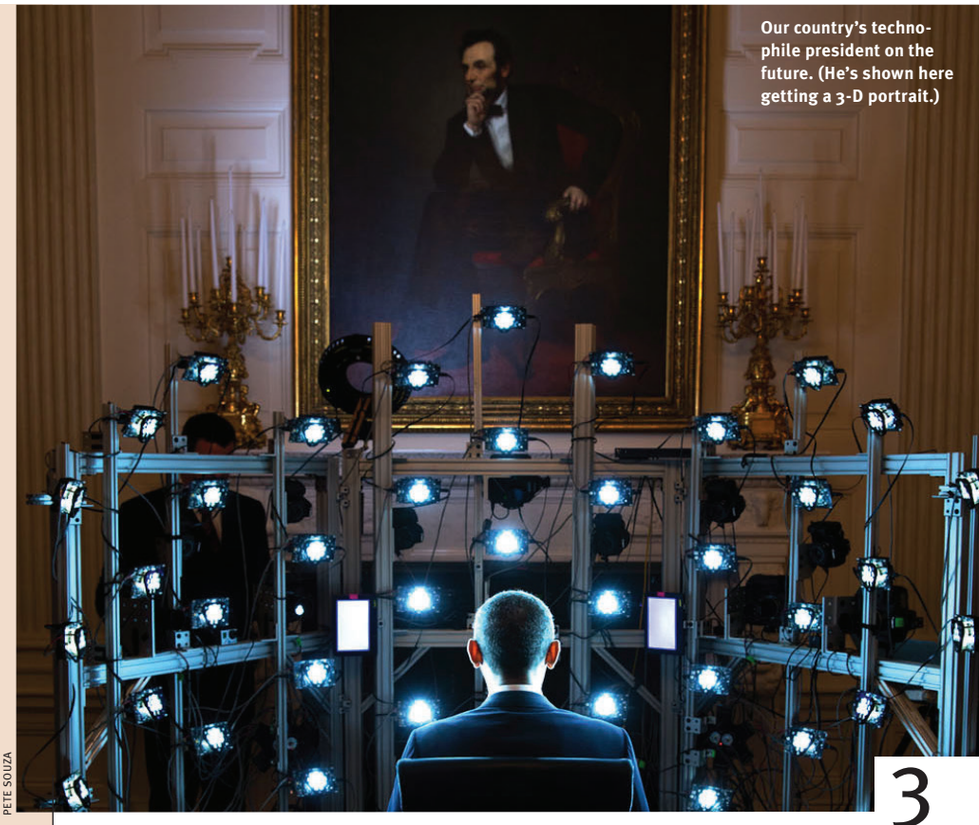


35


40 1/2

**COVER**

Revealing the wiring that undergirds the mind-body connection may help us all. (Cover: Greg Dunn, "Cortical Sunburst," © 2016.)



PETE SOUZA

Our country's technophile president on the future. (He's shown here getting a 3-D portrait.)

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PITTMED

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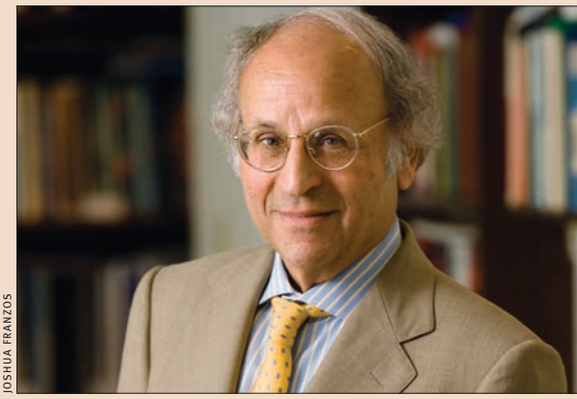
*I shouldda taken that left turn at Albuquerque.*
—Bugs Bunny


JOSHUA FRANZOS

The next time your iPhone helps you get to where you hope to go, think of Albert Einstein. GPS relies on the theories of both general and special relativity to navigate accurately. (If your self-driving Uber car gets lost, it's probably not because of the space-time curve—the global positioning system already accounts for that.)

Examples of the relevance of seemingly obscure discoveries to our daily lives are legion. For instance, in the 1960s at Johns Hopkins, Hamilton Smith was curious about how bacteria defend themselves from foreigners, e.g., viruses, and he found that restriction enzymes (novel bacterial enzymes discovered by Swiss microbiologist Werner Arber) allow the bacterium to cleave foreign, invading DNA at specific points. That Nobel-prize winning advance, allowing DNA recombination ("genetic engineering"), became the basis for what is now a trillion-dollar biotech industry. Certainly that link was not recognized at the moment of pure curiosity-driven discovery. And more recently, while it seemed that everyone else in bioscience was focused on DNA, Berkeley's Jennifer Doudna, our 2016 Dickson Prize winner, was intrigued by RNA. She's no longer in a lonely field, as her work with Emmanuelle Charpentier showed how a mechanism that bacterial RNA and protein use to fight off viruses, called CRISPR-Cas9, can be applied to edit a genome at specific, chosen sites in DNA, and quite easily. The significance of this discovery to biomedical research and biotechnology (and, incidentally, to the ethics of genome manipulation) has been compared to what the transistor portended for electronics and the discovery of electromagnetism by James Clerk Maxwell portended for television.

These scientists set out to understand our world at the most basic level of cause and effect. The fruits of their labors have changed it dramatically. Regrettably, however, support for pure discovery and invention is fading. Federal funding organizations appear to be shifting emphasis to "translational research" out of concern—perhaps, in part, with a political motive force—that "basic" discoveries are not making their way to the marketplace or clinic fast enough. (Also, no doubt, because pure science often seems so abstract, remote, and difficult to grasp.) But I know of no fundamental discovery in biology that has not ultimately been translated to a commercial and/or clinical application when it was appropriate to do so. Let's not forget—you have to discover or invent something before it can be translated.

Our neighbor, Carnegie Mellon's President Subra Suresh, wrote about the situation recently in a *Science* editorial coauthored with Amgen's Chair and CEO Robert Bradway. They noted that America's investment in basic science in the 20th century established its preeminence in science and cultivated the scientific ecosystem that fosters innovation. But now, just as government dollars for basic science are dwindling, industry is also no longer investing in basic research as it once did. (How sad that the unfettered industry research era of Bell Labs, home to many Nobel laureates, is long gone.)

Pitt has been invited to partner with a new group based in Palo Alto called the Science Philanthropy Alliance, founded by a number of this country's major foundations; the Alliance is championing basic science and advising foundations and individual philanthropists about the critical importance of investing in this area. But more needs to be done at the federal level, not to mention our own Pitt-centric philanthropic level. The United States has always attracted among the best, the brightest, the most creative, and the most curious. We must keep it that way.

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*

MICHAEL LOTEN ERO

## VOICES FROM FRONTIERS

**"Patient input is the blockbuster drug going forward."**
*—Margaret Anderson, Executive Director, FasterCures*

**"Some of the most important things we're doing are derived from the difficult questions that patients have asked me about their own health."**
*—David Okonkwo, Pitt Professor of Neurological Surgery*

**"Anybody who said we couldn't do it wasn't invited back."**
*—Elizabeth Tyler-Kabara, Pitt Associate Professor of Neurological Surgery*
*(re: the effort to restore touch with brain interfaces; see photos and story to right)*



**Obama fist-bumps Copeland as Pitt's Jennifer Collinger stands by.**

PHOTOS: UNIVERSITY OF PITTSBURGH

## WHITE HOUSE AT OUR HOUSE

On the chilly October morning of the White House Frontiers Conference, innovators from across the country gathered at the University of Pittsburgh and Carnegie Mellon University to discuss frontiers in science and technology—from driverless cars to precision medicine to missions to Mars. For presenter Michael Boninger, the ultimate frontier is very close to home.

"The next moonshot is the brain," he said. Boninger, professor of physical medicine and rehabilitation and a UPMC vice president, spoke on the promise of pairing artificial intelligence with assistive technology to help people with disabilities. He showed videos of the few patient volunteers who'd undergone a surgical procedure to connect to a Pitt-developed technology that uses a brain-computer interface, or BCI. (The technology is based on studies by Pitt's Andrew Schwartz, Distinguished Professor of Neurobiology.) One video showed a young father, paralyzed from the neck down, grasping his girlfriend's hand for the first time in years.

"This person could reach out and touch a person's hand. But he couldn't feel it." That, Boninger said, became the Pitt team's next frontier.

Recently, Pitt and University of Chicago researchers collaborated to implant BCI electrodes not only in the motor cortex, but also in the sensory cortex. Nathan Copeland, a 28-year-old with tetraplegia, became the first person ever to experience the sensation of touch using a brain-controlled prosthetic limb. The afternoon of the Frontiers Conference, in Pitt's Alumni Hall, President Barack Obama met Copeland. The president would later recall their meeting in his plenary remarks: "We shook hands. He had a strong grip, but he had kind of toned it down. Then we gave each other a fist bump.

"That's what science does. That's what American innovation can do … that's what this Frontiers Conference is all about—pushing the bounds of what is possible." *—Elaine Vitone*

PHOTOS: UNIVERSITY OF PITTSBURGH


# Overheard: President Barack Obama

**"In summer 2005, I was a 16-year-old intern for Congresswoman Barbara Lee, trying to find my way around the Capitol. In my rush to get on an elevator, I almost knocked over the person inside. I looked up to apologize and recognized then-Senator Barack Obama, whose iconic speech at the Democratic National Convention had made him my ultimate role model," said Alexis Chidi, Pitt-Carnegie Mellon MD/PhD student, as she introduced the president of the United States to White House Frontiers Conference attendees in Pittsburgh this October. Since that first encounter with Obama, Chidi has finished her PhD as part of the Pitt Medical Scientist Training Program. She will graduate with her MD in 2017.**

**Obama noted that Chidi neglected to mention that "she started on her premed degree when she was 16." He then added, for the faculty members present, "I hope you already have tenure, because Alexis is coming!"**

**The president joked that his conference hosts are both with the "Obama alumni mafia": Carnegie Mellon's President Subra Suresh served as director of the National Science Foundation under Obama, and Pitt's Chancellor Patrick Gallagher directed the National Institute of Standards and Technology (and now serves on a commission exploring issues of cybersecurity for Obama's administration).**

**What follows are select remarks from the president during a Pittsburgh panel on brain science and medical information, which was moderated by Atul Gawande, a Harvard public health researcher, Brigham and Women's Hospital surgeon, and *New Yorker* staff writer. —*Erica Lloyd***

## On his precision medicine initiative

**Part of our goal here is to shift from what is really a disease care system to an actual health care system.**

**We're being very intentional about making sure that we are reaching out to communities that sometimes are forgotten, whether it's African American communities or women, so that we can really pinpoint what works for whom.**

## On making innovation possible in the health care system

**Even as we're doing all this cool stuff to come up with greater cures, what we're also having to do is try to figure out what are the incentives, the perverse incentives, that are set up in the health care system that prevent [information] from reaching a patient earlier.**

## On privacy and cybersecurity

**The opportunities to hack your information will be just as great or greater in a poorly integrated,**

*Continued on page 34*

## VOICES FROM FRONTIERS

**"I guarantee you will not meet as interesting and diverse a set of innovators and scientists . . . for the rest of the year."** *—Robbie Barbero, White House Office of Science and Technology Policy*

**[There's incredible imaging and science in meteorology,] "yet we are still really impoverished in our knowledge about what's going to happen with that individual storm [like Hurricane Matthew striking inland so forcefully]. . . . With the EMR—electronic meteorology record, I like to call it—small perturbations from the record have an enormous impact on life. It's like the precision medicine initiative."**
*—Eric Dishman, Director, All of Us, NIH Precision Medicine Initiative*

**"We have *Star Wars* medicine in a *Flintstones* [health] system."**
*—Freda Lewis-Hall, Chief Medical Officer, Pfizer*

**"Scenes of parasites, disease, invasion, and suffering have been woven through [life's evolving] tapestry throughout history. But now, that can change."** *—Kevin Esvelt, Assistant Professor, MIT Media Lab*

**"What would a medical selfie look like?"** *—Steven Keating, MIT Engineer, Patient Advocate*

**"Can you imagine what happened when the first woman built a controlled fire? [Maybe her people were concerned], but they were warmed by it."** *—Tim O'Reilly, CEO, O'Reilly Media*

**"It's about time for another giant leap for mankind."** *—Rod Roddenberry Jr., CEO, Roddenberry Entertainment (President Obama has confessed, unapologetically, that he's a big fan of* Star Trek*, which Roddenberry's father created.)*

**"Thank you so much for the world we are going to have in 50 years. It's going to be better."** *—Zoë Keating, Cellist, Composer, Patient Advocate*

# Lasting Effects

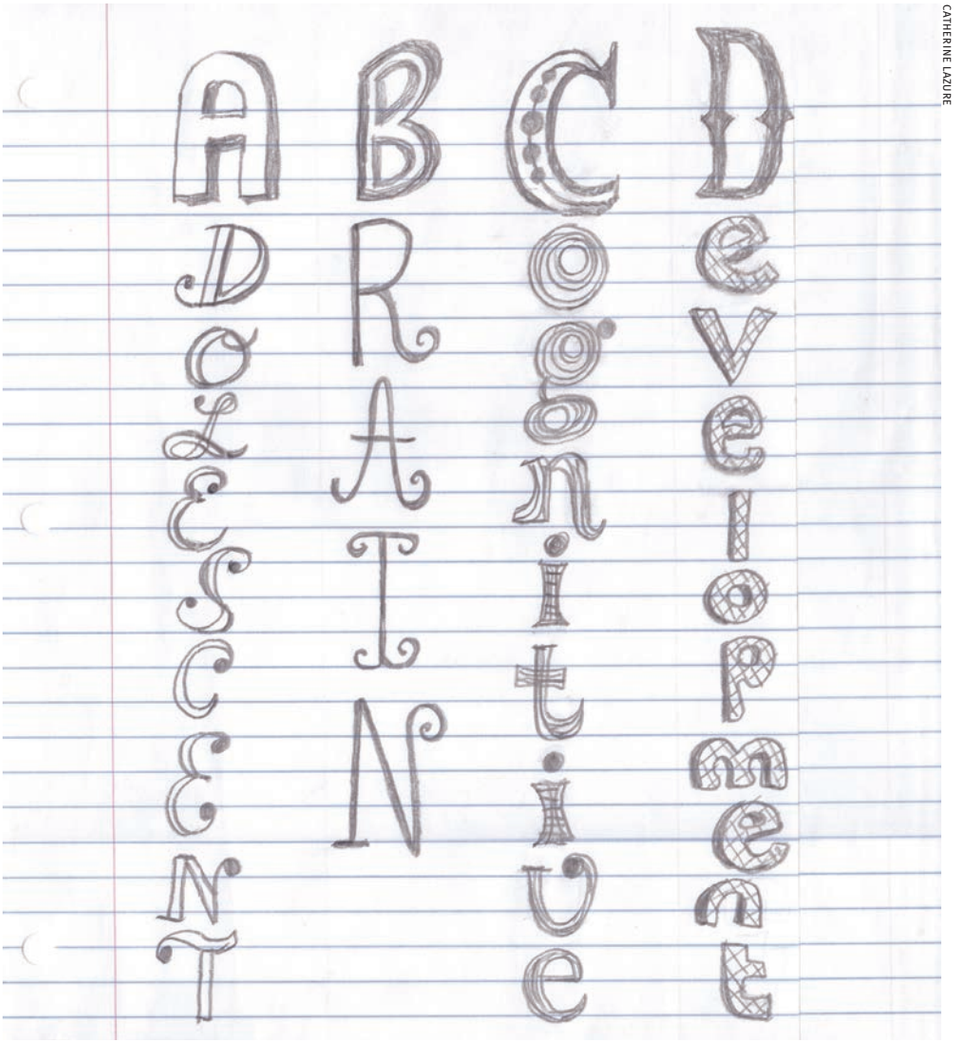
Studies have linked alcohol, cannabis, and other drugs to changes in the maturing mind's structure and function. But to draw concrete conclusions about how and whether such substances change the adolescent brain, researchers need to take a before-and-after look at a very large population. No one has undertaken such a study with this purpose in mind—that is, until now.

This year, Pitt received a $5 million grant from the National Institutes of Health to participate in a multicenter effort called the Adolescent Brain Cognitive Development (ABCD) Study, wherein 9- and 10-year-olds will be assessed to capture a baseline view of the brain before any drug use occurs. Then, over the next 10 years, investigators will observe whether lifestyle choices disrupt brain development. The study will include more than 10,000 kids nationwide, 500 of whom will come from the Pittsburgh area.

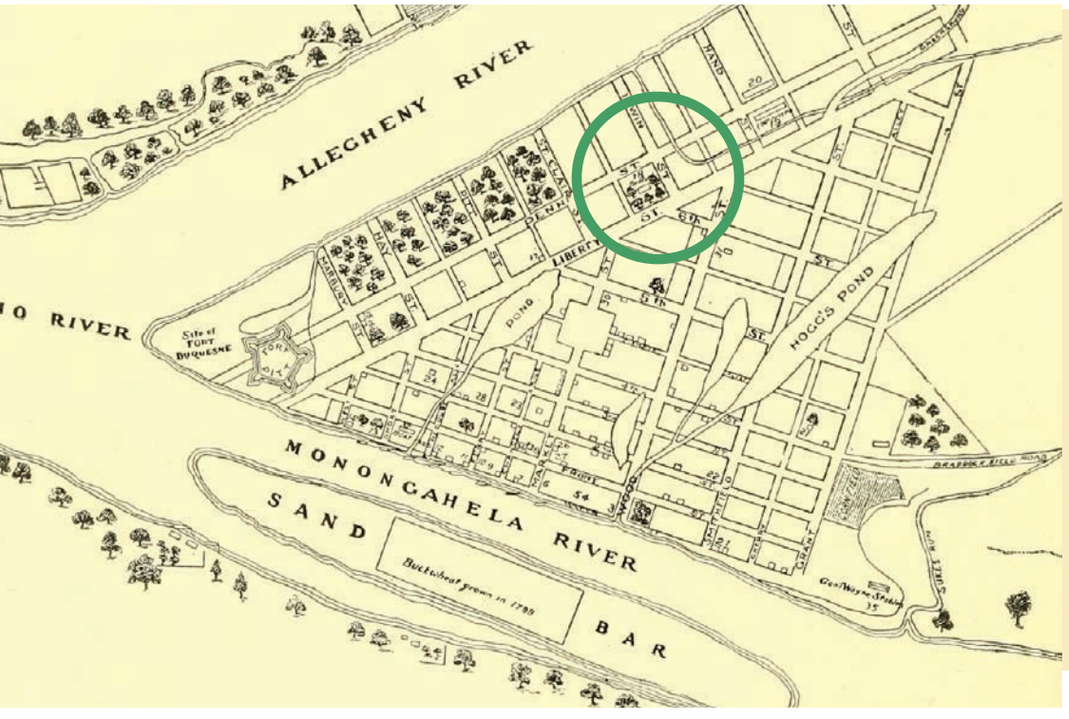
"The goal is to determine which types of substances, at what levels, during which age periods have lasting effects on brain development," says Duncan Clark, an MD/PhD, "and to understand those effects in the context of individual vulnerabilities and resilience."

Clark, a professor of psychiatry, is heading the Pitt team, which includes Rolf Loeber, a PhD and Distinguished Emeritus Professor of Psychiatry; Beatriz Luna, a PhD and the Staunton Professor of Psychiatry and Pediatrics; Claudiu Schirda, a PhD assistant professor of radiology; and David Lewis, an MD who holds the Thomas Detre Chair in Academic Psychiatry.

*—Kristin Bundy*



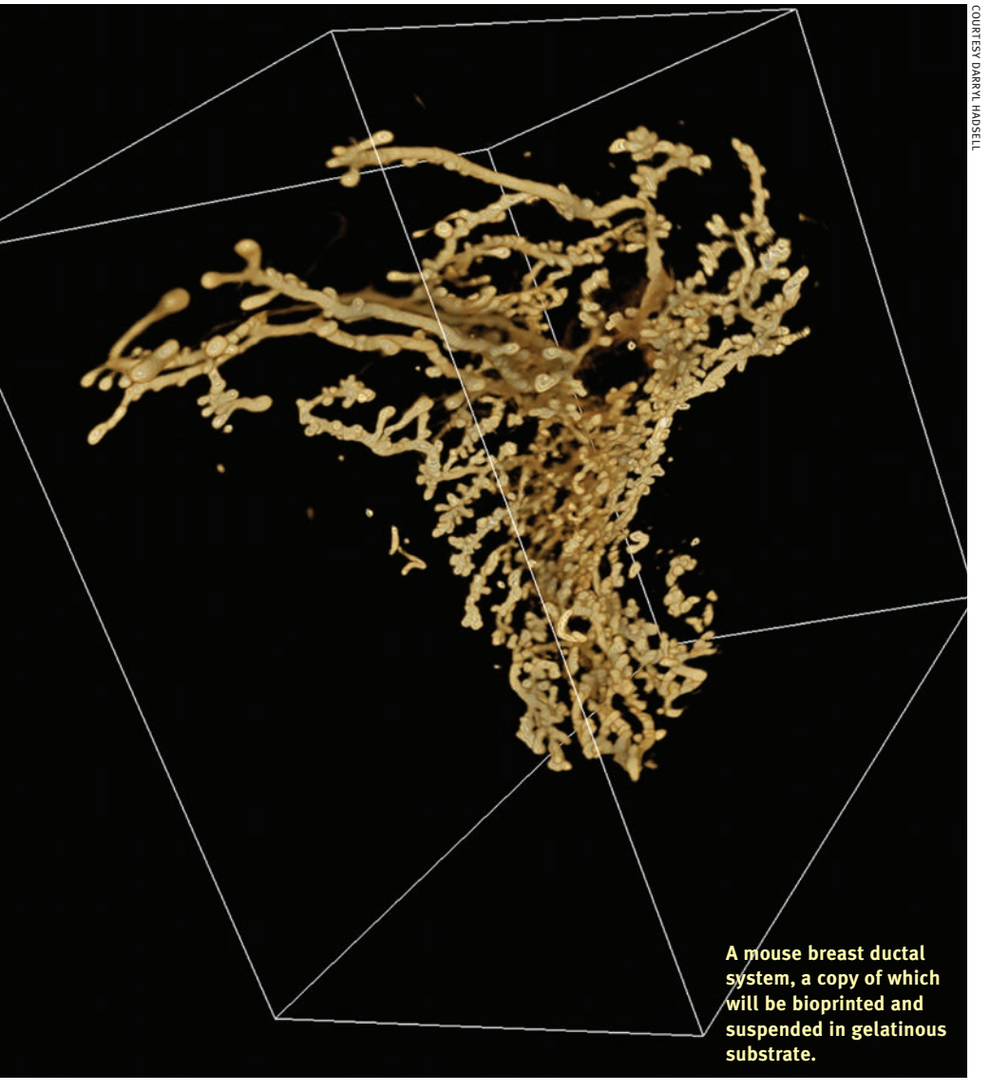

CATHERINE LAZURE




## FLASHBACK

**Around 1770, former military surgeon Nathaniel Bedford established what is believed to be the first private practice in Pittsburgh. He prospered and laid out the town of Birmingham—now the South Side (still undeveloped on the map, left)—naming the streets after his wife and her siblings: Jane, Sarah, Mary, and Sidney. In 1787, Bedford became a trustee of the Pittsburgh Academy, the original incarnation of the University of Pittsburgh. His homestead (in what is now now downtown) is circled in green.**

COURTESY LIBRARY OF CONGRESS



COURTESY DARRYL HADSELL

A mouse breast ductal system, a copy of which will be bioprinted and suspended in gelatinous substrate.

## TUMOR PRINTS

Every year, 60,000 women in the United States are diagnosed with ductal carcinoma in situ (DCIS), a type of premalignant tumor that grows in the breast ductal system—and rarely progresses to other organs. Yet, because of improved screening technologies and lengthening life spans, more women are being diagnosed with DCIS and undergoing potentially unnecessary preventive treatments.

Adrian Lee, PhD director of the Women's Cancer Research Center, coleader of the Breast and Ovarian Cancer Program at the University of Pittsburgh Cancer Institute, and new director of the Institute for Precision Medicine (among other positions), has teamed up with Adam Feinberg, associate professor of materials science and biomedical engineering at Carnegie Mellon University; Priscilla McAuliffe, an MD/PhD assistant professor of surgery and member of Magee-Womens Research Institute; and Darryl Hadsell at Baylor College of Medicine. The team has an $800,000 Department of Defense grant to create a new model for diagnosing DCIS.

"To understand [disease progression], you need models—what we call tractable models—where you can change genes, turn genes on, turn genes off, and try to understand the biology," Lee says.

With this 3-D model, Lee will be looking for genetic biomarkers that provide insight into how and why some cases of DCIS are harmless and some cases spread from the duct. *—Ali Greenholt*

# Appointments

**Gwendolyn Sowa**, MD/PhD associate dean for medical student research and professor of physical medicine and rehabilitation, became the new chair of that department in July. Sowa also holds appointments in orthopaedic surgery and bioengineering and is the medical director of UPMC Total Care—Musculoskeletal Health.

At the Ferguson Laboratory for Orthopaedic and Spine Research, where Sowa is codirector, investigators are digging into the mechanobiology of the spine, studying stressors on intervertebral discs and the cartilage where vertebrae meet to find novel and personalized treatments for what she calls the "clinical conundrum" that is low back pain. In her new position, Sowa hopes to emphasize collaboration in order to harness and showcase the educational, research, and clinical talent in the department.

Sowa

**Donald P. Taylor**, a PhD (who also has an MS and an MBA), has been named assistant vice chancellor for commercial translation in the health sciences. Taylor's additional appointments include codirector of the Center for Commercial Applications of Healthcare Data and codirector of the Clinical and Translational Science Institute's Innovation program. He is an associate professor of both biomedical informatics and bioengineering.

Taylor

In his new position, Taylor is responsible for cultivating the "enormous market potential" of Pitt's basic and clinical research to fill unmet market needs, such as technologies surrounding personalized medicine. To do this, Taylor emphasizes the importance of collaborative relationships across scientific and business disciplines, institutions, and mindsets. "You've probably heard of team science," says Taylor. "We are now activating team translation."

Methé

At its grand opening and researcher retreat this June, the Center for Medicine and the Microbiome (CMM) welcomed its codirectors, **Barbara Methé**, a PhD professor of medicine, and **Alison Morris**, an MS and MD professor of medicine, immunology, and clinical and translational science (see p. 34). Methé comes to Pitt from the J. Craig Venter Institute in Maryland, where she studied microbial and environmental genomics. "She was a member of the original human microbiome project," notes Morris.

Morris

Professor of pediatrics **Patrick McKiernan**, an MD, is now director of the Pediatric Hepatology Program at Children's Hospital of Pittsburgh of UPMC. McKiernan will also join Children's Center for Rare Disease Therapy. While a consultant pediatrician in the liver unit at the Birmingham Children's Hospital in England, McKiernan led a study that injected adult stem cells into children with metabolic liver disease as an alternative to liver transplantation. Although these phase 1 and 2 trials proved safe, the stem cells didn't permanently correct the defect. "That's work that I would like to continue here in Pittsburgh," says McKiernan. *—AG*

McKiernan


## MOST POPULAR

**The most matches went to these UPMC/Pitt specialties* this year:**

| | |
|---|---|
| INTERNAL MEDICINE | 92 |
| PEDIATRICS | 34 |
| FAMILY MEDICINE | 28 |
| ANESTHESIOLOGY | 17 |
| PSYCHIATRY | 17 |
| EMERGENCY MEDICINE | 16 |

Source: UPMC Office of Graduate Medical Education
* Dual specialties, such as internal medicine/global health, were counted in both categories; transitional years excluded from count

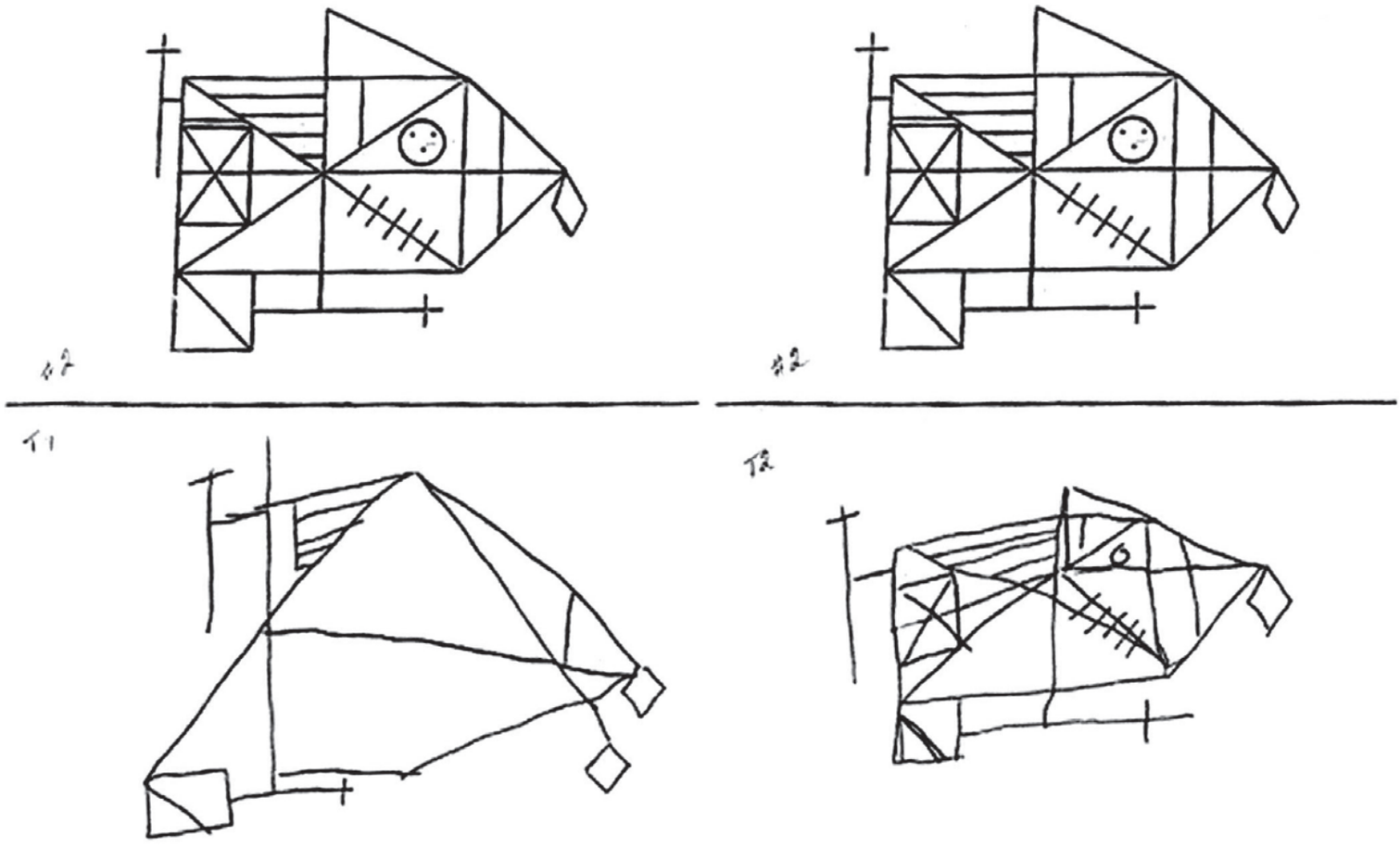
## MATCHES MADE IN PITTSBURGH

Match Day rightfully commands the med school's attention each spring, but what about all the envelopes being opened at other schools? Who are the brand-new docs coming here?

Some impressive stats on the newest house staff: This year, 312 new residents said "Yes!" to Pitt and UPMC, and a total of 650 trainees (residents and fellows) came here. Nationwide, more than 30,000 graduate medical positions were offered this year. At Pitt, 98 percent of spots offered were filled—two points higher than the national average. *—Robyn K. Coggins*

*—Illustration: Michael Lotenero, based on a photo by Mervin Stewart (MD '53)*

## COMPLEX FIGURE TEST



**BASELINE** **6 MONTHS**

**In a recent trial using stem cells that promote healing and reduce inflammation, patients who were treated months or even years after a stroke showed marked improvement in tests similar to this one. Patients were asked to study a complex figure (top row) and then draw it from memory.**

# OPENING THE WINDOW

## A NEW TIMELINE FOR STROKE TREATMENT

BY JILL NEIMARK

When a stroke occurs, it's a desperate race against the clock. Current treatment can help dissolve clots, improve blood flow to the damaged part of the brain, or limit brain bleeding. But the IV (or, in a minority of cases, endovascular treatment) must be administered within hours of the stroke. And even when patients are fortunate enough to be rushed to the hospital within that brief window, prognosis is grim. Seven out of 10 stroke survivors suffer lasting disabilities.

A new approach—using adult stem cells—could change that, says Lawrence Wechsler, MD professor of neurology and neurological surgery who holds the Henry B. Higman Chair at the University of Pittsburgh and is founding director of the UPMC Stroke Institute. Wechsler was an investigator on two recent multicenter adult stem cell studies, which he helped design. He hopes that an array of targeted therapies could pry that window open by days, months, or even years and ultimately improve patient outcomes.

In separate trials, Wechsler's team looked at two delivery methods—IV infusion in subacute care and brain surgery to infuse stem cells directly into damaged cerebral tissue months or even years after a stroke. Both methods proved safe.

The first, a double-blind, placebo controlled phase 2 safety trial, conducted in collaboration with more than 30 hospitals and universities in the United States and Great Britain, followed 126 acute stroke patients for a year. Sixty-five patients were given an IV infusion of mesenchymal stem cells, and 61 were given a placebo infusion. David Hess of the Medical College of Georgia, Wayne Clark of Oregon Health and Science University, and Wechsler presented the results to the American Heart Association International Stroke Conference in February of 2016.

The researchers used multipotent adult progenitor cells (MAPCs), which are usually derived from bone marrow (these mesenchymal cells can also be found in fatty tissue, dental pulp, umbilical cord blood, and other tissues). MAPCs can be multiplied in the laboratory and stored frozen for several years. They are well tolerated, do not require tissue matching, and appear to have profound anti-inflammatory and tissue repair effects.

As the patients recovered, the researchers looked at their neurological deficits and degree of disability in daily activities. They also imaged the brain via MRI and examined blood for levels of inflammatory chemicals circulating. A higher number of patients treated with stem cells achieved an excellent or good recovery by day 90 poststroke. Hospital stay, time in the ICU, infections, and readmissions went down. The key, the team found, was early treatment—meaning within 36 hours of a stroke—a far cry from currently available therapies. A year out, "there was a clear, statistically significant benefit for treated patients," says Wechsler.

"Stroke has an effect on the immune system itself," he explains. "In the early stages, inflammatory immune cells rush to the site of damage in the brain, and they may actually impede the recovery process. Suppressing that inflammatory reaction appears to be beneficial."

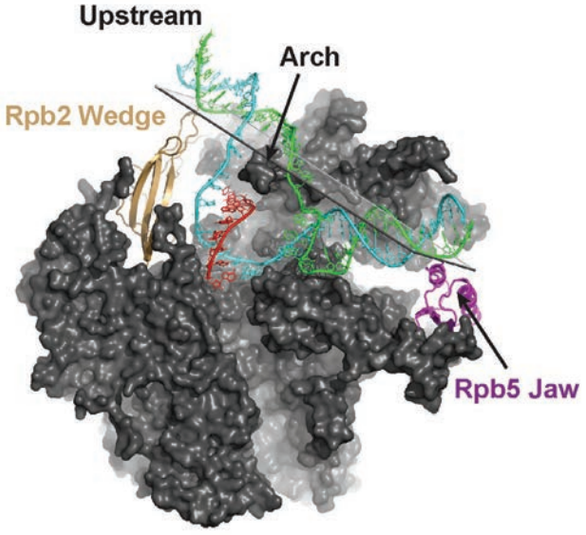
And, in what Wechsler calls "a completely different stem cell approach," 18 patients suffering from chronic stroke underwent brain surgery to infuse another kind of specialized mesenchymal stem cell directly into the damaged area of the brain. Called SB623, these cells secrete factors that protect neurons from hypoxic injury, help repair damaged cells, support neural growth, quell inflammation, and promote blood vessel growth. The study was published online in *Stroke* this June.

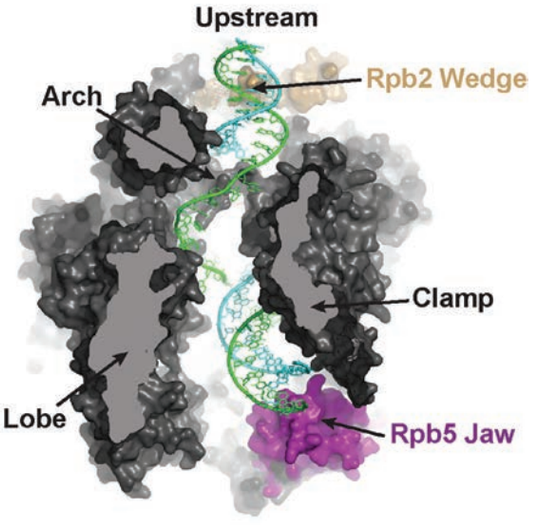
These patients were six months to several years out from a stroke, and the natural recovery process had plateaued. To rekindle healing, the team delivered stem cells every 5–6 millimeters along a track in the damaged area of the brain.

"The cells secrete a variety of growth factors to enhance recovery at a later stage," Wechsler says.

There were no complications directly related to the cells. All patients had at least one treatment-related adverse effect—from headaches to, in the worst case, a seizure related to the surgery. But those complications completely resolved. Moreover, the participants experienced gains possibly related to the treatment, such as improvement in ability to stand and the disappearance of tremor.

It's early yet—more patients will need to be studied for the researchers to be confident of the results (a large, multicenter, phase 2 study is now under way). Wechsler is optimistic. This new approach to therapy has "tremendous promise for enhancing stroke recovery," he says. ■




**Calero and collaborators demonstrate the inner workings of Pol II, the RNA polymerase protein. Pol II's "wedge" and "jaw" hold the double helix together above and below the region being transcribed as the protein moves upstream. Pol II's "arch" coordinates the process by which the transcribed strand recombines with the other strand to re-form the double helix.**

**CALERO SHOWS HOW TRANSCRIPTION HAPPENS**

**BY ALLA KATSNELSON**

# RNA IN ACTION

Structural biologists the world over have an unofficial motto: Structure is function. Figure out a protein's shape, in all its nooks and crannies, and you'll find meaty clues to the role it plays in the cell. It sounds straightforward, but there's a constraint. In order to determine a protein's structure with the traditionally used technique, X-ray crystallography, you have to coax it to crystallize. It's a state that many proteins resist—particularly large or otherwise complex ones, or groups of proteins interacting in some sort of cellular tango.

Such complicated proteins or protein groupings are the specialty of Guillermo Calero, an MD/PhD assistant professor of structural biology at the University of Pittsburgh. Calero decided to tackle a mystery of RNA polymerase II, or Pol II for short. Pol II is one of the most important players in the cell; its job is to read the cell's DNA, transcribing it into messenger RNA. Accuracy is essential, because that RNA will eventually travel to the ribosome and get decoded into the proteins that keep almost every single cellular process running.

Pol II had been studied extensively, and scientists had even solved its structure, but it still wasn't clear how exactly it latched onto a section of unzipped DNA and got down to business. Calero and his lab team set out to catch the polymerase in the act.

Their initial efforts fell flat, however, because, predictably and unfortunately, the crystals wouldn't grow.

So the researchers decided to dive in for a closer look: They picked through the detritus of their failed attempts and found tiny aggregates they were able to examine with electron microscopy, which uses electrons rather than light to image a specimen super close-up. "We were able to look at precipitates that most researchers would claim were useless and find that they did indeed contain very small crystals with nice lattices," he says.

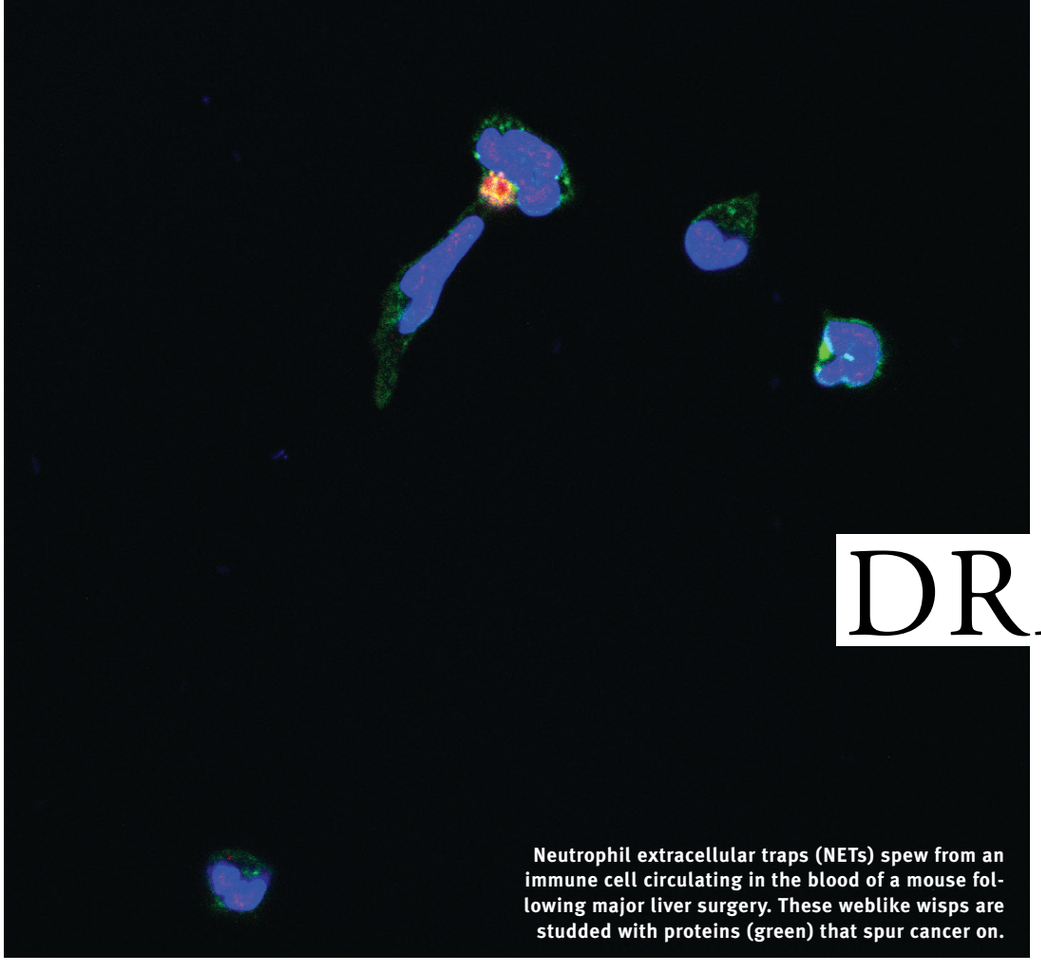
Growing crystals involves fiddling with a set of parameters—the concentration of the protein, for example, or various reagents in the solution. By optimizing the conditions under which the electron microscope showed nanocrystals, Calero and his colleagues were able to grow those tiny nuggets larger. "It's essentially electron microscopy–guided crystal growth," he says.

The structure they determined of the RNA polymerase complex in yeast cells, published in *Molecular Cell* in July 2015, provided the first complete look at a transcription bubble passing through a polymerase protein. "It's like if you were able to go to the nucleus of the cell and open your eyes and look for a polymerase molecule," he says.

They could image the protein as it simultaneously grabbed both the upstream and the downstream part of the DNA, using its main subunits to keep the transcription bubble open at one end while coordinating the DNA's annealing of the other end. More recently, Calero and his colleagues used the same approach to solve the structure of the HIV protein Vpr bound to three human proteins. In August, they revealed how Vpr interferes with DNA repair in human cells by inactivating one of the three proteins, and later by earmarking it for degradation.

Calero is now taking his nanocrystal detection technique a big leap farther by teaming up with a beam-wielding collaborator, Tamir Gonen at Howard Hughes Medical Institute's Janelia Research Campus. Gonen recently devised a technique called MicroED for generating high-resolution structures; he puts nanocrystals in an electron microscope and shoots them with an electron beam to diffract them.

"You can actually obtain a structure with only three crystals that are super small—we're talking less than one micron," says Calero. "It's a completely new way to get structures."



COURTESY TSUNG LAB

**Neutrophil extracellular traps (NETs) spew from an immune cell circulating in the blood of a mouse following major liver surgery. These weblike wisps are studded with proteins (green) that spur cancer on.**

## CATCHING A CULPRIT IN CANCER'S SPREAD

BY ERIN HARE

# DRAGNET

Surgery is the only possible cure for metastatic colorectal cancer, the third most common and third most deadly cancer in the United States. "But there has always been anecdotal evidence suggesting that [surgery] can also cause the cancer to recur quicker," says surgeon Allan Tsung, codirector of the UPMC Liver Cancer Center, Pitt's Roberta G. Simmons Professor of Surgery, and vice chair of research for the Department of Surgery.

In March, Tsung's team published a paper in *Cancer Research* that helps to explain this paradox—a finding that *The Scientist* later highlighted as an editor's choice in cell and molecular biology.

It all started when Tsung, curious about the link between the immune response after surgery and subsequent cancer, was examining serum samples from his post-op patients and noticed something that piqued his interest: Weblike structures known as neutrophil extracellular traps (NETs) were flooding their blood.

Historically, the presence of NETs had been thought only advantageous. During infection, they capture bacteria—like dragnets catching fish—to help the body clear away pathogens and heal. "We weren't sure initially whether NETs were beneficial or harmful in cancer progression," Tsung says. He thought it was possible that NETs just trap tumor cells and help immune cells get rid of them, but they found the opposite. The release of NETs actually supported tumor growth.

First, the team compared the prevalence of NETs in colorectal cancer patients who had undergone surgery on their livers—that's the site where colorectal tumors most often metastasize (the liver is where the primary cancer's lymph fluid and blood drain). The researchers found that patients who had more major liver-resection surgery formed more extensive NETs—and also had a four-fold higher rate of recurrence compared to patients with little NET formation. (They also looked at healthy controls with no NETs.)

Patients with colorectal cancer often have cancerous cells and undetectable tumors throughout their bodies, Tsung explains. Thus, he hypothesized that the released NETs—which are known to be triggered by inflammation—may interact with cancer cells he couldn't remove in the OR. Unfortunately, because the inflammatory response is global, NETs form everywhere. "Any time you have any surgery, everyone thinks, *Oh it's just localized to that organ.* But in fact, multiple parts of your body actually can go through changes" after surgery, Tsung says.

Next, using surgery to induce NET formation in a mouse model of cancer, the team watched via *in vivo* imaging as NETs corralled free-floating tumor cells into clumps—which spelled trouble. Divided, the tiny tumor cells had floundered, but in the inflammatory aftermath of surgery, the milieu seemed to change. Gathering strength in numbers in the NETs, the cells became much more likely to invade tissue and spread.

The team then tried pharmacologically inhibiting NETs with DNase—an enzyme that disbands their DNA backbone—and were pleased to see drastically reduced tumor formation. NETs seemed critical for cancer recurrence initiated by tumor cells that evade a surgeon's scalpel.

Further, they also found that NETs actually changed the behavior of tumor cells via cellular-signaling pathways. NETs are studded with proteins that interact with a receptor called TLR9 on cancer cells to make them more aggressive, Tsung says. When the team manipulated the cancer cells to lack TLR9, the mice grew far fewer tumors in the post-op period.

Having shown in mice that DNase blocked NET formation—and in turn cancer progression—Tsung's team recognized DNase as a potential cancer therapy. DNase is already FDA approved as a treatment for cystic fibrosis; whether it will be safe for people who just underwent major surgery remains to be seen. Tsung expects clinical trials could begin in the next couple of years. ■

**A Pitt team is the first to map the neurocircuitry connecting a visceral organ (the adrenal medulla) to the brain. Researchers throughout the neuroscience community are calling this a landmark finding that will help scientists understand more about how what we are feeling and thinking influences other aspects of our health.**

# MIND IS

THE CIRCUITRY OF THE BRAIN-BODY CONNECTION

BY ELAINE VITONE

# MATTER

Just about every field of medicine has patients with stories like this: *I can't catch my breath,* they tell the pulmonologist, but then the CT scans check out fine. *I have chest pain,* they tell the cardiologist, but their ECGs are all clear. *My stomach is killing me,* they tell the gastroenterologist, and yet imaging, endoscopy, and sometimes even surgery fail to turn up reasons why.

Patients with various kinds of psychosomatic illnesses can seem "kind of like the same person," says David Levinthal (PhD '04, MD '06, Fel '12). And often, they're "*literally* the same person who has symptoms across multiple body systems." Levinthal directs UPMC's Neurogastroenterology and Motility Center, a tertiary-care clinic where patients go when neither their primary care physician nor a community gastroenterologist has been able to help. Plenty of referrals for severe, unexplainable, intractable irritable bowel syndrome come to his door. And typically, GI symptoms aren't all these patients are dealing with. Panic attacks, depression, and early life trauma are all over their charts. So are meds for chronic pain, meds for high blood pressure, meds for fast heart rate, and more.

ARTWORK | GREG DUNN

So if all of the standard test results are normal, asks Levinthal, "What's more likely? That you have 10 things independently wrong with you, or that the master regulator is off?" That master regulator being the neural network that governs organ function. Or, in an another way of putting it which these patients hear way too often: *It's all in your head.*

"Well, it *is* all in your head—because your brain is in your head," says Peter Strick, Levinthal's scientific mentor and collaborator. Ultimately, this network answers to one command-central, the brain.

Strick is the Thomas Detre Professor, chair of neurobiology, and scientific director of the Brain Institute (among other titles) at the University of Pittsburgh. A decade ago, he and Levinthal got together over a shared curiosity about the intersection of the mind and the body and tackled the problem from a perspective that's been largely missing from this field. Rather than focusing on more downstream measures of brain-body interactions (like hormone levels), they sought out the neural connections themselves. In August, their efforts culminated when Strick, Levinthal, and Strick's longtime collaborator Richard Dum, a research associate professor of neurobiology, published in *Proceedings of the National Academy of Sciences* (*PNAS*) a study that cuts to the crux of a paradox in modern medicine:

We all accept that stress is terrible for us, and that when our mental health suffers, the rest of our health follows suit. And yet the branch of medicine that's devoted to this integral relationship—psychosomatic medicine—is often written off as pseudoscience. The actual anatomical "connection" part of the mind-body connection was unknown.

In this study, the Pitt team became the first to map the elusive networks that connect an internal organ all the way to the brain. The researchers say the adrenal gland (specifically, the region therein known as the adrenal medulla, which is central to the fight-or-flight reaction), is the first of many internal organs that they plan to trace, a prospect that offers hope for broadening our understanding of how the brain influences the rest of the body.

And in this first paper, they've made unexpected discoveries about the inverse: how the body (or rather, certain muscles therein) can be used to influence the brain.

They found brain regions, hardwired directly to the adrenal medulla, involved in core-muscle movement—a finding that offers a possible explanation for why activities that focus on engaging these muscles, like yoga and Pilates, are said to be such stress relievers. (By the way, they knew it was the core muscles, specifically, because the movement aspect of the cortex covers "areas we've spent the last 30 years studying," says Dum. "We were the perfect people to do this.")

They also found circuits to brain regions involved in certain mood disorders—a new "stress-and-depression connectome," as Strick puts it. As these networks sharpen in focus, eventually it may be possible to intervene in mental illness right where it lives, in the wiring itself. "Deep brain stimulation is in major growth in neurosurgery" for a variety of diseases and disorders, notes Strick. He believes the new tools his team has developed offer hope for defining these multiple, distinct, yet interconnected networks at a level of detail that has never been possible before.

This new stress-and-depression connectome also includes a brain region that lights up in mindful meditation, adding to a list of findings that show the ancient practice actually does influence the brain. "It's only in the last 25 years that Western medicine has acknowledged, *Oh, those things have worked for people for thousands of years*," Levinthal says. "I think we just need to be open to the fact that, if done the right way, mind-body interventions could be just as valuable as everything else we do."

In his clinic, it all starts with listening—*lots* of listening. Then he explains that gut-churning agony doesn't always stem from the gut; often, it's a reaction to anxiety, depression, or some other poison of the psyche. (Remember, at this point, just about everything else has been ruled out.) Then, as he carefully takes the patient off the pills that have Band-Aided so many symptoms through the years, he works with the patient to confront the problem at its source.

"Amazingly," Levinthal says, "getting help for the mental health issues seems to make a huge impact on the GI symptoms."

In the Western world, prior to the 19th century, if you went to your doc with a complaint, his first thought would have been that something was amiss upstairs. His Rx: *Get thee to the beach.* Then medicine became more of a heads/entrails coin—germ theory taking over on the one side, and later, psychoanalysis and psychopharmaceuticals on the other. For the most part, the brain and body parted ways.

In college in the '60s, Strick was already curious about the brain-body bond. He did a summer research project for Barney Dlin, a famous physician-scientist in the field of psychosomatic illness. "It was always there in the back of my mind, the whole notion [that people think it's] imaginary," says Strick. "Just the name, *psychosomatic*, it's like calling somebody a psycho."

After his BA in biology and PhD in anatomy (both from the University of Pennsylvania), Strick worked for four years as a fellow in Edward V. Evarts's Laboratory of Neurophysiology at the National Institute of Mental Health, where Strick probed brain structure–function relationships and, in some cases, developed new techniques to do so. The dye-based tracing methods that were available at the time had big limitations—namely, when a tracer was injected into the brain, the tracer lost potency before passing any farther than the next neuron over. To get anywhere with this research, he realized, he would have to reveal networks in their entirety.

Through the '80s and '90s, at the VA Medical Center at Syracuse, N.Y., Strick honed the use of certain viruses, previously used to trace neural networks in rodents, for nonhuman primates. He started out with the cold-sore virus (herpes), then switched to rabies, because it moves very quickly. It travels along the central nervous system backwards, toward the brain, replicating from neuron to neuron in predictable 8- to 10-hour cycles. The path of the infection can be tagged with antibodies to reveal a clear road map.

Using this viral-tracing strategy, the Strick lab has uncovered previously unknown fundamental networks of movement—especially voluntary movement. His group also revealed a division of the cortex that's likely responsible for the uniquely human capacity for fine-motor movement, discovered the cerebellum as a potential new target for dystonia treatment, and uncovered previously unknown connections between brain regions, among many other high-profile findings. Strick, who joined


Strick


Levinthal


Dum

the University of Pittsburgh in 2000, is now a member of both the American Academy of Arts and Sciences and the National Academy of Sciences.

Levinthal is the son of a psychologist (his dad was chair at Hofstra University) and grandson of a human factors engineer for an aerospace company. Levinthal always knew he wanted to be a scientist, too. One of his very first school projects used biodots—little color-changing stickers that indicate skin-surface temperature—which 11-year-old Levinthal compared to his test subjects' reported emotional states throughout the day. Even as a fifth grader, he was getting at the idea "that how we think and feel and what we're doing matters for how our body is responding."

Levinthal came to Pitt for the Medical Scientist Training Program (MSTP)—a dual-degree track for physician-scientists—and completed his neuroscience PhD and his MD in 2004 and 2006, respectively. (The overachiever cofounded the Pittsburgh Center for Pain Research while he was still a med student.) Six months before he was bound for an internal medicine residency at the University of Michigan, he met Strick and in short order joined his lab. Levinthal was fascinated by the possibilities that viral tracing presented for his research interests in the cerebral-cortical processing of pain. They continued their collaboration long distance, publishing a 2009 paper on what's called the spinothalamic tract—a study that was "full of surprises," Strick says. (Ascending pain signals to the cortex, it turns out, seem to influence not only cognition and sensation, but also motor planning and execution.)

Levinthal returned as soon as he could, in 2008, as a GI fellow, eager to begin a project on the stomach. This work would later snag him a career development award from the National Institutes of Health. Though the paper is still in the works, Levinthal has already presented his findings at professional meetings.

At the same time, Strick was spearheading projects on other organs, starting with the adrenal medulla. (Remember: That's a subregion of the adrenal gland—not a part of the brain, much as it sounds like it should be to a layperson's ear.) In speculating which parts of the brain were the origins of the adrenal medulla's wiring, most neuroscientists figured that the cerebral cortex—that wrinkled, gray outer layer of the brain—had maybe one or two areas connecting to the organ. A highly developed cortex is one of those brain features that separates us from other animals—think higher-level stuff like controlling your emotions, fine-tuning your body movements, and so on. Fight or flight, on the other hand, is universal across vertebrates—so it is likely linked to deeper, old-brain sort of stuff, the thinking went.

The team conducted tracing studies, first in the rat and then in the nonhuman primate, eager to see what had changed in the course of evolution. And they were surprised by what they found: A whole mess of connections—several times more than those in the rat—many of which were in regions of the cortex that the rat didn't even have.

Though this finding was unexpected, it had a certain logic. When we humans get stressed out, we're capable of far more than merely throwing punches or high-tailing it out of there. We can make jokes, talk it over, hold our tongues.

The team was intrigued to learn that most of the cortical connections were plugged directly into the areas for movement planning and performance, especially the primary motor cortex region for the core—those deep, stabilizing muscles stemming from your spine and pelvic bone. Given this, it's no wonder people who do core exercises say they're so much happier for it, Strick says.

When you make even simple movements, like twisting a light bulb, there's plenty of stuff going on behind the scenes: adjusting your heart rate to maintain your blood-oxygen level, redistributing blood to muscles that need it—automatic functions that control your adrenal medulla, kidney, heart, and so on to keep you alive. We've long known that these housekeeping chores happen concurrently with voluntary movements, but we've never been sure how they fire together so precisely—there was no evidence that they were part of the same system, says Dum. The *PNAS* paper offered some explanation: "Top-down" signals are plugged not only into the system behind your voluntarily moving, lightbulb-twisting arm, but also into your autonomic nervous system, of which the "fight or flight" network is a part—and they appear to have overlapping circuitry after all.

**So if all of the test results are normal, asks Levinthal, "What's more likely? That you have 10 things independently wrong with you, or that the master regulator is off?"**

So perhaps, says Strick, if your core muscles are weak and have to strain with every move you make, the brain has to work harder to make them keep at it. And that hard work amounts to stress. (This is all speculation, he adds—he's eager to see others put his findings to the test.) And so, as Strick recently told *The Atlantic*: "My kids would tell me, 'Dad, you ought to take up Pilates. Do some yoga.' But I'd say, 'As far as I'm concerned, there's no scientific evidence that this is going to help me.'" Well, out of the mouths of babes. (His kids are grown, but you get the point.) Now he's found some evidence.

Second to the motor cortex, the brain areas with the most connections to the adrenal medulla were in a region known as the anterior cingulate cortex, or ACC. Which was fascinating, because the ACC is involved in our very thoughts and feelings—not old-brain stuff at all.

The ACC is part of what can be described

as our emotional and self-referential system—the machinery behind how we decide what events in our lives mean to us, says Tor Wager, a leading researcher in this field and director of the Cognitive and Affective Neuroscience Laboratory at the University of Colorado Boulder. In brain scans, you can see evidence that the self-referential system is altered in people affected by trauma, abuse, poverty, and neglect. It's also linked to chronic pain.

"I think this is a landmark paper," Wager says. "It provides a really solid physiological foundation for some of the relationships we're seeing with human fMRI of stress." Human imaging can be used to identify correlations with responses in the body, he says, "but this neurological tracing in the nonhuman primate is another level of detail. I'm really enthusiastic."

Fight or flight is essential. In the event of real danger, you need your adrenal medulla to kick in, widening your pupils to attention, pumping blood to muscles, and pausing digestion as you mobilize your energy stores to be ready for whatever comes next.

But a chronic state of all the above can be a damaging system overload, literally from the top down. And unfortunately, the Pitt team found, we are hardwired with a vulnerability to that overload: The ACC, that region so connected to the adrenal medulla, lights up even when we perceive a mild conflict, or beat ourselves up over a mistake, or reimagine what we regret from the past. Which means all of the body's potent stress-response effects are kick-starting, too. Hence, the team believes, post-traumatic stress disorder (PTSD)—a condition characterized by haunting flashbacks, nightmares, and survivor guilt—may well be a mix-up in this wiring. A person's pulse might shoot through the roof every time he thinks a certain thought, says Levinthal, because he's "essentially reliving the stress response from the initial inciting event and . . . getting stuck in this pattern."

One of the adrenal medulla–linked subregions they found in the ACC—the subgenual—has been implicated in the neuroanatomy of mood disorders, a subject that Helen Mayberg, professor of psychiatry, neurology, and radiology and the Dorothy Fuqua Chair in Psychiatric Neuroimaging and Therapeutics at Emory University, has been studying since the 1980s. Over that time she has drawn a map that was highly informed by Strick's work, in a kind of "collaboration by proxy," as she puts it. This map has enabled her to bring to clinical trials a new therapy that the field of psychiatry is abuzz over: deep brain stimulation for severe, intractable depression. "For people who are ill who basically have run out of options, it's another chance," she says.

There have always been clues that movement and depression are linked, Mayberg notes: Babies tense up and freeze when they cry, and young animals stay put when they're separated from their mothers. People with depression have a hunched posture to them,

**The team members also revealed a "stress-and-depression connectome," raising hope that mental illness may one day be treated at its source, in our wiring.**

as well as a sluggishness that, as the illness progresses, can devolve into a kind of "virtual paralysis."

But this relationship between depression and movement was unclear. Was an altered movement network the cause or the effect?

Mayberg's PET and fMRI scans show that depressed people have aberrations in their limbic-cortical networks (including the subgenual and pregenual ACC). This, along with corroborative evidence in the Strick lab's *PNAS* paper, has provided a new lead: "What we can see now," says Strick, "is cortical motor areas are really influencing regions involved in stress," to which depression is directly linked.

The other main ACC subregion Strick's team found in the stress-and-depression connectome—the pregenual ACC—is of particular interest for Wager, who throughout his career has been fascinated by how our thoughts and beliefs can affect health. The pregenual ACC, he explains, is among the areas that respond most reliably in his human brain-imaging studies of the placebo effect, a major area of focus in his lab. He says the Pitt team's paper "provides a firmer scientific foundation" for findings on placebo effects on the body.

The pregenual ACC has another claim to fame. In addition to its link to the placebo effect, it's also the region that lights up in mindful meditation. Strick has always been skeptical about this mind-realigning technique.

Well, not anymore.

It might sound a little "out there," but it's true: We are brilliant, electrified beings. Our neurons are live-wired together in stunningly complex arrangements. Electrical signals shift into chemical signals and back again, crossing from synapse to synapse every moment we're alive. That is the basis of everything we think and feel and do, and it does not end at our necks; it continues all the way down through our beating hearts and churning guts and into the extremities that ground us.

Many drugs in common use target only the chemistry parts of this spark-chemical-spark chain. And drugs don't just patch our faulty circuits; they affect the entire machine. Hence your blood-pressure pills disrupt your digestion, and your bipolar meds put you to sleep in your chair.

If we had a clear road map for the wiring within us, it could change how doctors diagnose, treat, and measure progress in patients.

The Strick lab aims to draft that map—from head to toe, from childhood development all the way through the aging process—as well as this map's many perplexing variations. How does it change as we acquire knowledge and experience? And how is it altered in trauma? In cerebral palsy? Or in addiction?

Besides the ACC, the Pitt team also found a separate adrenal medulla–influencing system beneath the cortex, mainly in the basal ganglia—a site involved in reward processing and addiction. There's evidence that people caught in the damaging cycle of substance use have actually formed new connections in their brains, Strick notes. "This puts a whole new perspective on it. It's a brain-based approach." Those 12-step programs, unfortunately, don't work for everyone—only 5 to 10 percent. "For those people, it's fantastic," he says, so what is it about their brains and connections that makes that effective?

Picture a world where we could know the distinguishing features of a particular person's case of alcoholism, or PTSD, or IBS, or chronic pain. Brain structure–function correlates could be charted as patients progress—or fail to—and a careful study of the patterns that emerge could give rise to subtypes within each of these illnesses. Perhaps one day, doctors could look at your brain scan and instantly know, for example, how likely cognitive behavioral therapy, or deep brain stimulation, or a particular pill would be of help. (Mayberg has already published on exactly this.) Or maybe your doc could even tell you what you—given your genetic susceptibilities, or traumatic childhood, or adrenaline-fueled job—can do to minimize your chances of ever getting sick in the first place.

"You're talking about personalized medicine," says Strick.

In the clinic, Levinthal sees plenty of people who've been stuck in a loop of doctors' appointments for decades, with lengthy lists of diagnoses and misdiagnoses in between. And while undoing such deeply ingrained brain-to-body circuits isn't something patients can accomplish overnight, there's heartening news: The successful path to therapy may be something they can actually gain some control over.

Levinthal's favorite scenario is when he first meets a patient as a college student. A snarl of stress and indigestion, the kid shakes his hand and tells him her story. And then the GI doc gives his pitch:

*It's okay. You're just the kind of person whose body does this when you're stressed out. I want you to learn how to not do that. And you can learn. If you invest now in these coping skills, your life path is going to be awesome.*

"And often," says Levinthal, "it's just a few visits, and they're feeling better." ■

*Editor's note: This is the first of a two-part series on brain-body biology.*

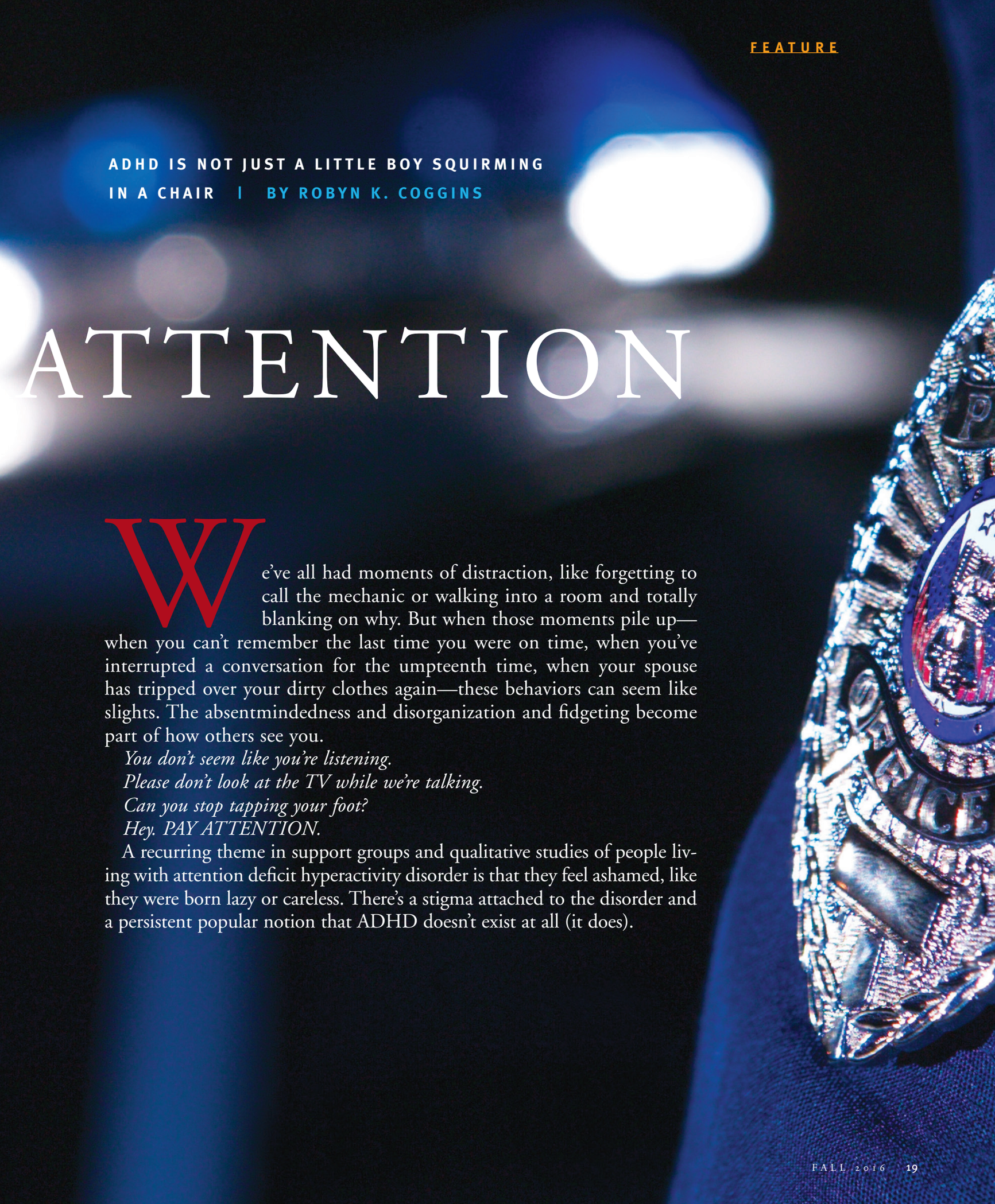
Although he has struggled with ADHD, one local policeman with the condition says that it's also an asset at work.

# PAYING

THINKSTOCK

ADHD IS NOT JUST A LITTLE BOY SQUIRMING IN A CHAIR | BY ROBYN K. COGGINS

# ATTENTION



We've all had moments of distraction, like forgetting to call the mechanic or walking into a room and totally blanking on why. But when those moments pile up—when you can't remember the last time you were on time, when you've interrupted a conversation for the umpteenth time, when your spouse has tripped over your dirty clothes again—these behaviors can seem like slights. The absentmindedness and disorganization and fidgeting become part of how others see you.

*You don't seem like you're listening.*

*Please don't look at the TV while we're talking.*

*Can you stop tapping your foot?*

*Hey. PAY ATTENTION.*

A recurring theme in support groups and qualitative studies of people living with attention deficit hyperactivity disorder is that they feel ashamed, like they were born lazy or careless. There's a stigma attached to the disorder and a persistent popular notion that ADHD doesn't exist at all (it does).

ADHD used to be considered a childhood disease, and one that kids would outgrow, at that. Children do in some cases, but researchers are just starting to understand what happens when kids with ADHD grow up.

"Sometimes you'll see symptom reduction, but not necessarily improvement in function," says Brooke Molina, a PhD and principal investigator of the Pittsburgh ADHD Longitudinal Study (PALS). The National Institute on Alcohol Abuse and Alcoholism and National Institute of Mental Health–funded project—which has followed almost 650 participants with and without ADHD—just wrapped up its 18th year. Some of its participants are in their 30s now, and their adolescence and young adulthood have provided unprecedented insight into the trajectory of the disorder.

A major finding: In their teen years, at least two-thirds of PALS participants still had symptoms, including making seemingly careless mistakes, having trouble staying focused, and being easily distracted, among other issues.

All of us fall somewhere on an inborn spectrum of attention, from distraction to utter absorption. Molina explains: "Human beings vary on all kinds of dimensions. We vary on height. We vary in weight. We vary in our tendency to put on weight or to stay skinny. We vary in our tendency to have high or low blood pressure. Our ability to regulate our attention and to sit still in a long, boring meeting and to stop and think before we act varies naturally in humans."

When a person lands on the extreme end of that continuum and has trouble functioning day to day, clinicians call it ADHD. The disorder is chronic and extremely heterogeneous. There is no cure (though medication can subdue symptoms).

Depending on their symptoms, people with ADHD fall into three subtypes: inattentive, hyperactive-impulsive, or combined. Symptoms usually begin in childhood and may present differently as people age.

As they move past their teen years, adults with persistent ADHD—some 40 to 60 percent of those diagnosed in childhood—have challenges in various aspects of life, including educational attainment, finding an occupational niche, and relationships. Separation and divorce rates are higher in families affected by ADHD, too.

The disorder is so much more than a little boy squirming in his seat at school.

"It's a beautiful and mysterious disorder," says Hank Bauer (not his real name). He's a police officer in the Pittsburgh area, a father, a husband, and a person with ADHD. He was diagnosed at 5 years old. "It was never a negative diagnosis. It was always framed like, 'You have abilities other people don't! You are able to look at the world [from] a perspective that most people don't have.' And that actually came from Dr. Molina."

"[ADHD] can be the best asset," Bauer adds. He says he can work a 24-hour shift and not blink an eye (not that he wants to anymore, at 41), and he can summon almost unlimited energy when he needs it (that energy shows in his extremely detailed arrest paperwork).

Bauer was one of the earliest participants in PALS. The study involved children from a Pitt project called the Summer Treatment Program. Each morning, just like summer camp, a dozen kids around the same age would gather to learn social and sports skills, strategies for controlling negative behaviors, and goal setting; they'd also have circle time to update the group on how they were doing at home, at school, and with friends. The program was based on a point system and positive validation of behaviors. If you said, *Good game,* during softball, you'd get 10 points, Bauer recalls. Punching another kid would dock your total by 50. And parents were trained in point systems and positive reinforcement, too.

"We, as ADHD kids, seek validation from our peers. We seek validation from our parents. We seek validation from our partners," Bauer says. He recounts recently purchasing a vacuum. He told his wife what a great deal he got—he was proud. *Isn't it the best thing you've ever seen!?!* He knows how outsized that reaction sounds. His wife replied gamely, with a *Good job, way to go.*

"God bless her," he says. Through the years, and with some guidance from Molina, his wife has learned to respond lovingly to Bauer's bursts of enthusiasm.

At times during our conversation, it feels like riding in a car with a person learning stick shift—a bit of a jerk in an unexpected direction or a swerve to a tangent. But who doesn't like talking about their pets? Who doesn't occasionally return to a conversation thread that's passed?

Bauer grants that what we'd call "deficits" and hyperactivity obviously affect his everyday life, but he notes they're symptoms of the condition of his brain—not the definition of him as a person. He wishes they'd rename ADHD something more positive.

Bauer appreciates the friends he made in that summer program and PALS as a teen and the social skills he learned: "I have better insight to do my job and be a more well-rounded police officer. I wouldn't have that without Dr. Molina."

## MOLINA AND PALS

Molina, who's a professor of psychiatry and psychology, as well as the director of Pitt's Youth and Family Research Program, came to Pitt as a postdoc with a background in adolescent substance abuse and longitudinal research.

A grad school friend had connected her with William Pelham, then an associate professor of psychology and psychiatry at Pitt, who was investigating the connection between alcoholism and ADHD. In the '90s, Pelham was the primary investigator of the Pittsburgh arm of a multisite, 14-month study called the Multimodal Treatment of ADHD (MTA). The MTA was the first randomized, longitudinal study to look at the effects of medical, behavioral, and combination treatment in children with and without ADHD (nearly 600 total). Molina was invited to join the MTA investigators to study risk for addiction and other outcomes.

The MTA's major findings, published in 1999, marked a milestone in ADHD research. One noteworthy discovery was that stimulant medication had the strongest effects on symptom reduction, and when medication was combined with behavioral therapy, they saw even more improvement in kids like Bauer.

The MTA findings led Pelham to begin another study—one that would follow children diagnosed with ADHD even longer, into high school and adulthood.

The teen years are a time of explosive changes in the brain, as well as changes in social pressures. And it's often when kids start experimenting with drinking and drugs. That's where Molina came in.

"[Pelham] had become interested in the connection between ADHD and alcoholism, and also in lack of treatment for adolescents with ADHD," Molina recalls. "And I had a background in adolescent substance abuse." So she came to Pitt.

That partnership resulted in Molina's very first grant—a pilot study for $9,000. That study tracked down kids Pelham had previously treated to see whether they were willing to be reinterviewed.

The researchers' persistence paid off: "They did indeed seem to have higher rates of early substance use as teenagers," Molina notes. Now they could make a case for following larger samples of children into adolescence and adulthood.

on the schedule.) In 2014, the team expanded its interview subjects to friends and partners of participants. PALS has taken many millions of dollars and thousands of woman-hours to give us insights on ADHD, and its participant retention rate is high—nearly 90 percent.

In January 2015, PALS branched into neuroimaging. More than 200 of the PALS participants—many from the earliest PALS groups who had dropped off the radar but whom Molina managed to find again—have undergone functional magnetic resonance imaging, enabling researchers to see inside their brains in real time. Those results are yet to be published, and those data will provide yet another view on this much-measured

Molina

Pedersen

ues," Molina says. Positive bias can lead people with ADHD to stop taking their medicine or drop out of therapy, which indeed happened to Bauer. In his teens, he refused the Ritalin he'd been prescribed; he didn't resume medication again until his 30s. Once he did, "it was night and day."

Bauer faces this medication battle with his own children, who have the diagnosis, as well.

**Between April 2015 and March 2016, PALS researchers made 4,512 phone calls and completed 250 visits with parents and young adults. (It can take more than 20 attempts to contact a participant before he's on the schedule.)**

Molina and Pelham used those results to apply for more grants to conduct larger studies, and that's how PALS began. Pelham left Pitt in the mid-1990s, and Molina assumed leadership in Pittsburgh. (Pelham is now at Florida International University, and the two continue to work together.)

Unlike the MTA, which began as a randomized controlled trial, PALS arose from the Summer Treatment Program conducted between 1987 and 1996. Pittsburgh-area clinicians, schools, mental health workers, and parents referred children to the well-known program at what was then the ADD Clinic at the Western Psychiatric Institute and Clinic. The average age at enrollment was about 9 years, and the PALS crew comprehensively diagnosed and assessed the kids yearly until age 23, then every three to five years thereafter. Molina and her team set out to study many aspects of their lives: family and other relationships, employment, school performance, substance use, and overall mental health.

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A study old enough to vote has revealed many aspects of ADHD and the paths of those with it. One revelation: ADHD can be sneaky.

Molina describes what her former Pitt colleague Betsy Hoza coined as "positive bias," or a lack of insight about one's condition: "Parents would bring kids to the clinic, but the kids would say, 'ADHD? What problems paying attention? I'm fine!'" Hoza launched a series of studies and found that often—not always, reminds Molina—these kids didn't realize the true extent of their attention issues.

Molina has continued this work on positive bias with the older PALS (that's what some participants call themselves). "We ask our young adults, who've been followed since childhood, to rate their symptoms. And then we ask, still, their parents to rate their symptoms. There's still an appreciable discrepancy." Other studies, notably those by internationally renowned ADHD researcher Russell Barkley (who spoke at Pitt this September), have found similar discrepancies between ratings by patients in their 20s and their employers.

"So, at least for samples of children who've been diagnosed and followed longitudinally, we see that often this lack of insight contin-

It turns out that ADHD is 75 to 85 percent heritable, and its cause is likely a handful of genes plus some environmental factors. (One preliminary study published by a team in Spain this summer found that microRNAs—noncoding molecules that regulate genes—might play a role, too.)

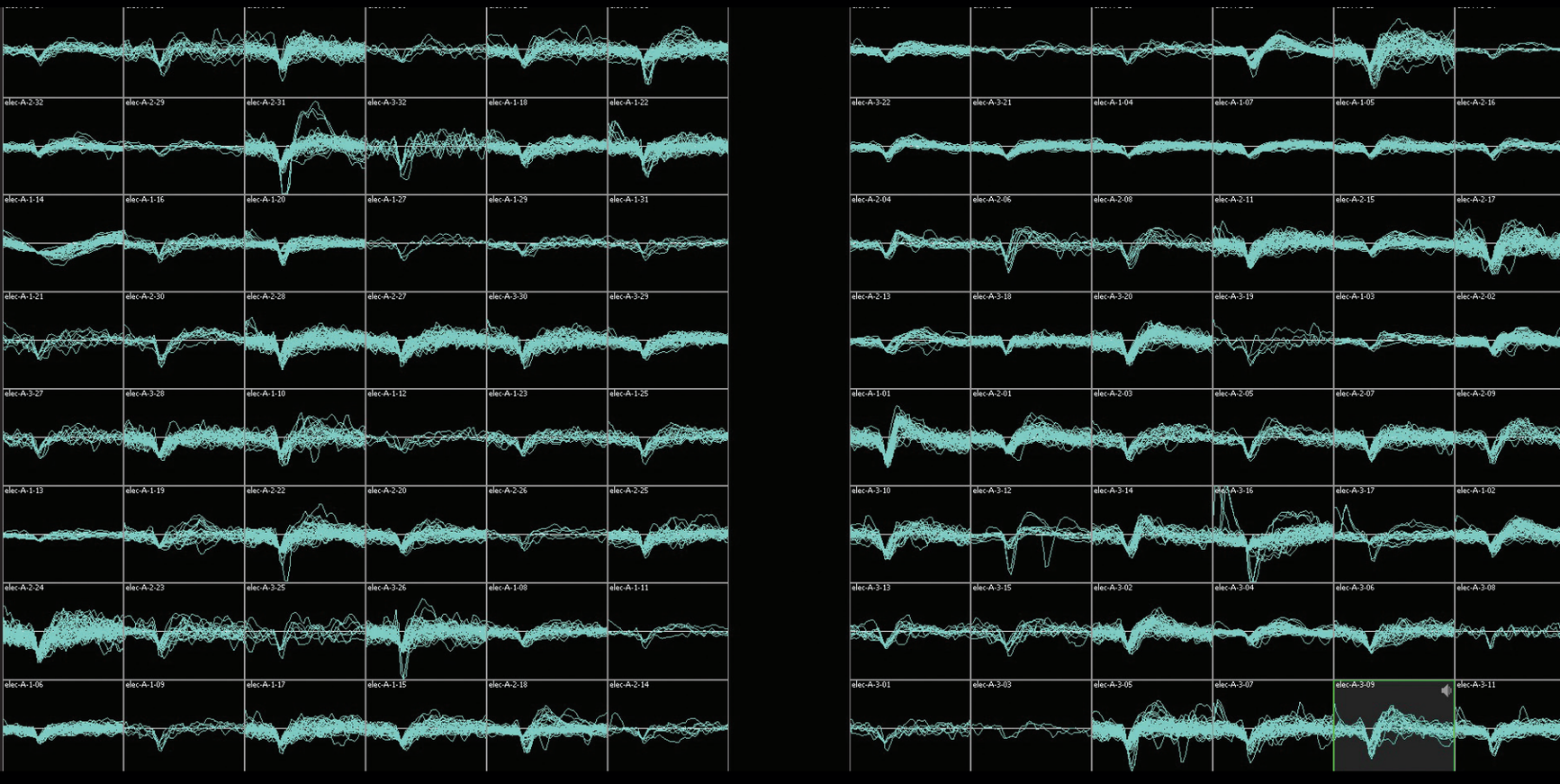
PALS might trace the lineage of ADHD in families like Bauer's someday. But for now, one of its most impactful areas of study is substance use and abuse in those with ADHD—and the behaviors that accompany inebriation, including drunk driving, partner violence, and absenteeism at work and school. Many of these behaviors have a common source: impulsivity.

## NO GO

Sarah Pedersen is a PhD assistant professor of psychiatry and an expert on impulsivity.

She breaks the concept of impulsivity into these parts: lack of planning (not arranging a designated driver, for instance), lack of perseverance (difficulty following through), positive and negative urgency (acting rashly because of a good or bad mood), and sensation seeking (hopping helmetless on a friend's motorcycle).

In a study published in *Addiction* this



**Cohen's lab tracks the behavior of neurons during visual attention tasks, recording multiple signals in one area of the brain. Taken together, these signals reveal how visual information is encoded in the brain and modulated by attention.**

September, Pedersen, Molina, and others (including Pelham) examined impulsivity and alcohol use among PALS participants.

They discovered that, for adults who were diagnosed with ADHD as children, all of those impulsivity factors except sensation-seeking remained elevated into adulthood. The tendency to act rashly while emotional may explain why those with ADHD have more alcohol use issues than those without, Pedersen says.

The intersection of Pedersen's work and PALS has provided novel insights. While Pedersen describes most of her studies as "intensive snapshots," she can also look at the participants' longitudinal data. "We actually have their alcohol response with what they experience, and then we have assessments from when they were in childhood." That gives Pedersen a much fuller picture.

Like Molina, Pedersen came to Pitt as a postdoc and was quickly folded into PALS. She came to study differences in how people with and without ADHD respond to alcohol; she also examines how factors like gender and race can play roles.

"One of the main goals of my research [is] to understand and decrease health disparities and substance use outcomes. When you get into clinical populations where there's already some stigma involved, and then you add on racial discrimination, we're talking about a really stigmatized population at that point."

Pedersen's current study of 120 people with and without ADHD diagnoses intentionally includes 60 participants who are black—a nearly unheard of proportion in this type of research.

Pedersen brings participants, some of whom are from PALS, into her lab, where she doses them with alcohol up to a precise 0.08 blood alcohol content, the legal driving limit. Then she has them complete a simple computer task.

On screen, a cue—"go" or "no go"—pops up, along with a target. Participants are instructed that if "no go" appears, they should not hit the target. The task is a test of ability to withhold a response.

The study also has a real-world component. After the lab's drinking session, the participants track their own drinking for 10 days using their smartphones so Pedersen can compare a controlled drinking environment to one where mood, friends, and setting might affect actual drinking behavior. She also follows up with them in six months.

**In one study, Cohen even found that attending too closely to a particular feature, say, a change in orientation of an object, can impair one's focus.**

In non-ADHD research, difficulty with the no-go task has been associated with binge drinking and drinking more than intended. In Pedersen's study, those with ADHD perform significantly worse on this task after drinking, relative to those without the disorder. She's also found that, in the real world, just one drink increases emotional impulsivity significantly for people with ADHD—more than in

Cohen

those without the condition. For black drinkers, a shift in stress is more strongly related to alcohol cravings than in white participants, she says. These factors add up to poor decision-making while drinking.

Pedersen expects that her impulsivity findings will also be relevant to other substances like cannabis, which she plans to study in more depth soon.

Pedersen and Molina are now conducting research with primary care providers in the Pittsburgh area. They hope to improve the rate of screening for substance abuse as well as other risky behaviors while improving ADHD treatment. Molina says pediatricians and family medicine physicians are thus far welcoming the partnership.

## TUNED IN

Bauer used to bombard people with information before saying hello. At the Summer Treatment Program as a kid, he recalls, "We were taught basic social skills. . . . We're not . . . *Hey buddy, how ya doing?* We don't know how to do those things."

To keep their behavior in check, people with ADHD need to tune their attentional antennas. Sometimes that means therapy or counseling for adults to help them organize, prioritize, and motivate. It could mean training for parents in behavioral management strategies. And it could mean medication to regulate neurotransmitters.

A boost of norepinephrine can hone scattered attention; to curb impulsivity, a surge of dopamine can do the trick. Physicians generally prescribe stimulants such as amphetamines (perhaps Adderall) or methylphenidate (better known as Ritalin or Concerta) to up the attentional signal. Not everyone with attention issues needs medication, though it's currently recommended as a first-line therapy for all but preschoolers.

But the connection between chemicals in the brain and behavior is still murky. Pitt's Marlene Cohen, a PhD assistant professor of neuroscience and member of the Center for the Neural Basis of Cognition, studies real-time electrical signals in the brain that follow the neurochemical flood and lead to action.

Cohen says attention is a process of selection. "It's what lets you home in on the thing that's most important to you. If it's a visual thing, it makes you see that thing better. But it's also at the exclusion of other things, so you're not paying attention to everything at the same time."

"The challenge is that the visual world is so rich!" she says. Lighting, depth, movement, color, shape . . . there's so much to process—and to be distracted by. In one study, Cohen even found that attending too closely to a particular feature, say, a change in orientation of an object, can impair one's focus.

Vision happens to be the most easily measured kind of attention—Cohen uses a precise infrared camera that tracks where a subject's pupils point.

To get at the attentional nitty gritty, Cohen records electrical impulses from a few dozen neurons using a group of electrodes similar to those used in deep brain stimulation. When a neuron fires, an electrical signal blips, and she measures its change in voltage.

"We know the exact millisecond that that neuron fired an action potential. We know what's going on on the screen, we know what the subject is doing with their eyes, and then we know what all the neurons are doing, so we can start to make links between those three things," she says.

Cohen records each neuron's reaction and charts them. The collective result looks a bit like the spikes of an electrocardiogram or a stereo's equalizer display. What she's found is that a single neuron doesn't tell us much about attentiveness; it's the cumulative interaction of neurons that signifies attention.

While a brain has something like 100 billion neurons, Cohen has found that studying a few dozen is sufficient to make preliminary conclusions. "In the primary visual cortex, which is sometimes called V1," she says, "you have neurons that encode the orientation of something—a neuron will fire to say something is vertical or that it's horizontal. In V4 [another visual area], there are neurons that are selected for color or for texture.

"What attention does to them, [and the] characteristic ways that attention changes the way neurons interact, seems to be the same no matter which area you look in." (These results likely have relevance for other neuronal processes beyond attention, too.)

Neurons work together somehow—the *how* is the million-dollar question—to create focus.

## PLANNING AHEAD

"We may have results in the lab," says Molina, "and we may even have results on whatever device or task we put out there to train the child. But will we see meaningful results in the day-to-day life functioning of that child that endure? That's ultimately the important question to ask of our neuroimaging paradigms."

A combination of medication and behavioral therapy can produce those meaningful results. When treating children with ADHD, including parents and teachers is especially helpful. But the most mind-boggling finding from PALS has been this: When treatment stops, the benefits of treatment disappear.

"Just like if you have chronic back pain, ibuprofen is going to make you feel better," Molina says. "But it's not going to fix that ruptured disc. [Similarly] stimulant medication and behavior therapy work when they're being used. We unfortunately have not been able to document long-term [behavior] change as a function of using these evidence-based treatments."

Molina says the PALS participants have had "more than their fair share of distressing outcomes, including dropping out of high school and incarceration."

Unmanaged ADHD becomes boredom, stress, a short fuse. Divorce, broken friendships, overwhelming frustration. Bauer sees the results of mental illness, including ADHD, all the time as a police officer. He tries to help. Rather than just toss a guy in jail, he'll offer him a list of community resources that can keep him out of the cell. When he can, he'll give a break to an honest person who admits he's struggling—because Bauer has been in those shoes.

"I personally used to drink a little too much with the guys," he concedes. He also barely passed high school—it took two years of summer school for him to pass with Ds. But once he found what he was good at and focused on it, his life started to turn around. First it was firefighting, then becoming an EMT (first in his class), then paramedic training (top of the class, again), and finally the police academy (he was top cadet).

Molina notes, "There are people with ADHD who are happy and well-adjusted with fulfilling lives. I'm looking forward at some point in the future to writing an article that describes their paths to happiness.

"Instead of focusing only on the negative outcomes, I'd like to also understand more, in a targeted, focused way, what factors lead to good outcomes, because we know they happen for some. I'd like people to know that, too." ■

COURTESY COHEN LAB

# STEPPING OFF "THE

PITT PEOPLE LOOK TO NEW WAYS TO END THE OPIOID EPIDEMIC | BY JENNY BLAIR WITH ERICA LLOYD AND KATY RANK LEV

# PATH TO HELL"


In August 2015, a 26-year-old mother in a Walgreens southwest of Pittsburgh collapsed from an opioid overdose, her toddler locked in the bathroom stall with her. It was part of a rash of opioid poisonings in Washington County, Pa., which led to 25 overdoses and three deaths in two days. David Hickton, U.S. attorney for the Western District of Pennsylvania, called the outbreak "apocalyptic."

A bad situation had gotten worse. Since its origins around 2000, the opioid abuse epidemic has devastated the United States. What began with a well-intended rise in pain reliever prescriptions has led to widespread, entrenched pill and heroin addictions. Heroin is now increasingly laced with fentanyl, as was probably the case in that Washington County outbreak, often without the user knowing (though some now seek out its high); and fentanyl is many times more potent and deadly. Accidental drug overdose is now the leading cause of death by injury in this country, with 78 people dying of an opioid-related poisoning every day.

ILLUSTRATIONS | STACY INNERST

Amid the wreckage, Pitt Health Sciences faculty are studying the problem and developing new ways to approach it. They're also tackling the issue in Western Pennsylvania, an especially hard-hit area. Pitt faculty were a part of the U.S. Attorney's Working Group on Drug Overdose and Addiction, which issued its first action plan in 2014. Mark Nordenberg, Pitt chancellor emeritus, has made the issue a priority at the University's Institute of Politics, of which he is chair. The institute catalyzes public-private sector conversations about regional policy. In 2014, an institute advisory group led by Hickton issued a set of recommendations relating to pill abuse; it released another in October about the opioid epidemic as a whole. Nordenberg also connected Hickton (JD '81), who is his former law student, to Donald Burke, dean of the Graduate School of Public Health, sparking new conversations about Pitt's role in addressing the epidemic.

"Nobody's saying we should never use opioids," says Susan Meyer, the School of Pharmacy's associate dean for education, who codirects the Pitt Center for Interprofessional Practice and Education. "We just have to understand better about avoiding indiscriminate use of them."

On March 29, the Association of American Medical Colleges released a letter signed by 69 medical schools, including Pitt, that pledged a renewed commitment to training students to meet the epidemic. (The Schools of Nursing and Pharmacy have signed similar pledges.)

For Pitt Health Sciences students about to graduate, Arthur S. Levine, senior vice chancellor for the Health Sciences who is the John and Gertrude Petersen Dean of the School of Medicine, charged his staff with rapidly organizing an April 14 panel on the topic. The event included harrowing talks by Hickton; Burke, who holds the UPMC Jonas Salk Chair in Global Health; and Gwendolyn Sowa, who is now chair of the Department of Physical Medicine and Rehabilitation.

Levine attributed the epidemic to inappropriate pain medication prescribing, noting that the medical profession, the pharmaceutical industry, and failed federal regulatory mechanisms sowed the seeds of its creation.

We now know that between 5 and 15 percent of people who are prescribed opioids for pain will develop an abuse problem. They might receive opioids for chronic or acute pain in an internist's office, in the ED, in a pain management clinic, or for surgery.

Hickton called this "the worst epidemic in our history." He noted, "A person who gets addicted to prescription pills is basically on the path to hell at the rate of a dollar a milligram."

As part of the panel discussion, Hickton shared details of the outbreak in Washington County. Burke showed a time-lapsed map of accidental poisoning deaths in the United States, with counties colored according to their death rates. In the 1980s, sporadic counties showed elevated death rates; by the mid-2000s, the map displayed explosive color all around the nation (with a red hot spot indicating poisonings in Western Pennsylvania). Sowa explained how little evidence there is to recommend opioids for low back pain, yet how commonly physicians prescribe them anyway, contradicting guidelines.

"It's very challenging to change provider behavior," Sowa noted. It's easier, of course, to persuade students; and Pitt and UPMC will be training both emerging and established providers.

In the pages that follow, we show how Pitt people are working to help end the devastation. The first steps involve changing how people think about the problem.

*—Jenny Blair with Erica Lloyd*

# DOCTORS COME CLEAN

When it comes to treating pain, health professionals across the country are embarking on a massive shift of mind-set—their second in recent history.

Opioids include morphine and its relatives, all of which can relieve pain and cause euphoria and dependence. Less than two decades ago, doctors tended to be cautious about prescribing these drugs for fear of addicting patients.

However, in the 1990s, patient- and physician-activists began to call attention to the serious problem of undertreated pain. The American Academy of Pain Medicine and other professional societies adopted pain as the "fifth vital sign." Physicians accepted the supposition that addiction was unlikely if opioids were given for significant chronic pain, an optimistic claim later found to be based on thin evidence.

Around the same time, drug companies manufactured and began marketing powerful new opioid formulations, like the extended-release form of oxycodone, OxyContin.

"One of the only tools that primary care physicians had was providing opioids," recalls Ajay Wasan, an MD professor of anesthesiology and vice chair for pain medicine. Pain clinics offering multidisciplinary treatment—considered cutting-edge prior to the opioid epidemic—have been in short supply for decades.

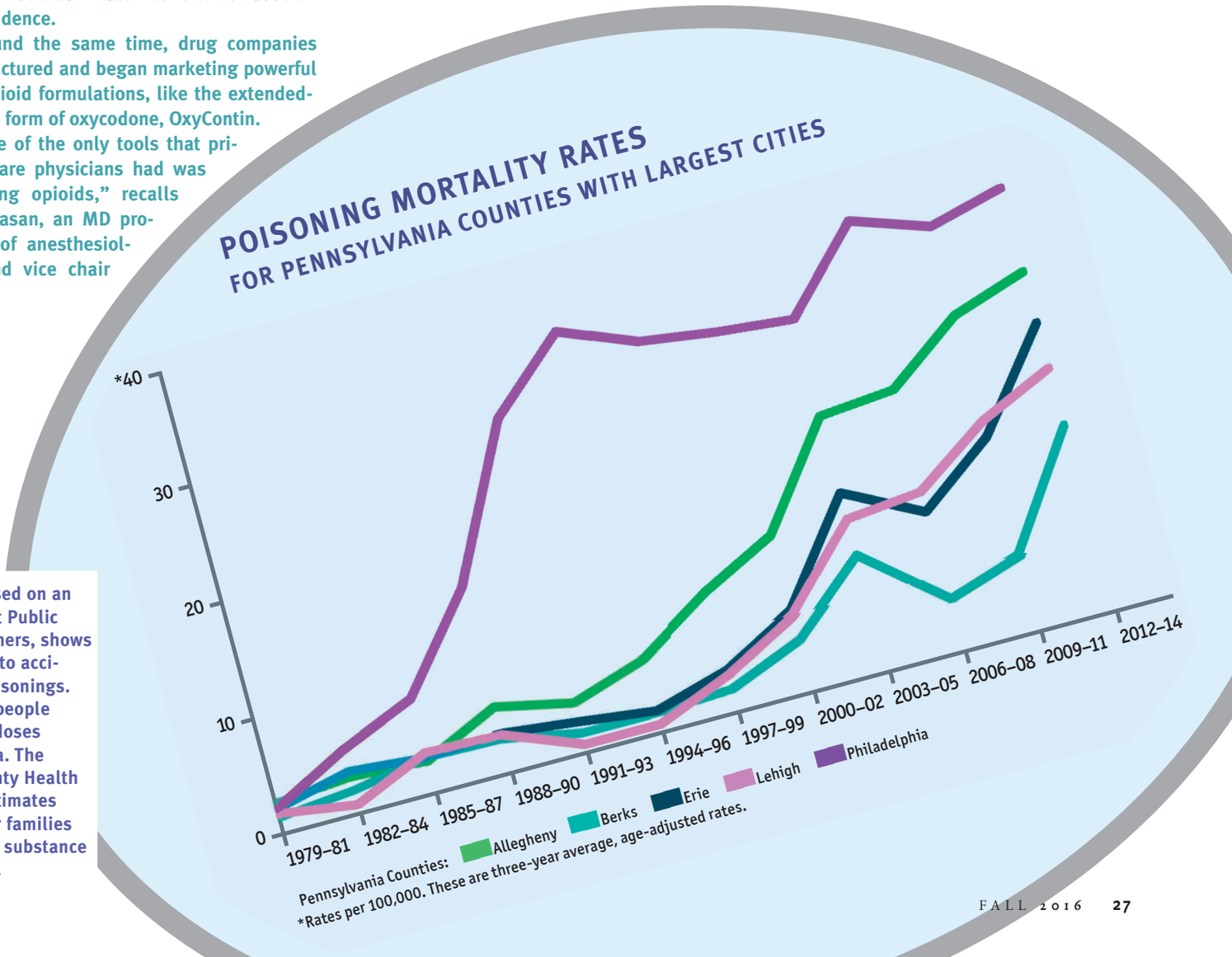
Several years into this movement, signs of a crisis emerged. Opioid painkillers did addict a substantial portion of patients, as well as their families and friends. In the meantime, dealers hawking cheap heroin began to fan out in U.S. cities, tempting people whose pill habit had gotten expensive. Deaths began to rise.

"The supposition was wrong," says associate professor of anesthesiology Michael Mangione, an MD. "[Patients'] pain isn't controlled indefinitely. They don't go back to work. They do have side effects. Tolerance is a big issue. They get opioid-induced hyperalgesia, where being on the opioids chronically actually makes their pain worse. And, obviously, it has led to an enormous addiction and abuse problem."

Indeed, many opioid abusers overdose and die—some 28,000 of them in 2014, the highest rate of opioid-related deaths on record. Eighty percent of all new heroin users got their start using prescription pain pills. And physicians widely acknowledge their role in starting it all.

"In retrospect, sometimes we rely on experience and a consensus of experts when we don't have good objective data. We truly believed 10, 12, 14 years ago that what we were doing was correct," Mangione says. "But we were wrong.

"Over the first 10 years of my career physicians were part of the culture that created this problem," Mangione adds. "I'm spending the latter part of my career trying to clean it up." *—JB*




This graph, based on an analysis by Pitt Public Health researchers, shows deaths related to accidental drug poisonings. In 2015, 3,500 people died from overdoses in Pennsylvania. The Allegheny County Health Department estimates that one in four families struggle with a substance abuse problem.

GRAPH BY PICTOGRAM STUDIO BASED ON "PATTERNS AND TRENDS IN ACCIDENTAL POISONING DEATHS: PENNSYLVANIA'S EXPERIENCE 1979-2014," FIGURE 4, BALMERT L, BUCHANICH J, PRINGLE J, WILLIAMS K, BURKE DS, MARSH G, PLOS ONE, MARCH 10, 2016.

# OLD WAY

## A CASE THAT ENDS BADLY (c. 2000)


A man gets hurt at work lifting something. His low back pain becomes chronic. Eventually, he goes to his doctor. The physician hands him an opioid prescription, saying, "There's no serious injury, but this will help with the pain."

Patient fills it, takes it. He finds himself sitting more, thinking, *I'm afraid that if I move I'll really hurt myself*. This inclination is called "fear avoidance."


Turns out the man is in the unfortunate subset of patients who develop tolerance and dependency to the drug.

Pills get expensive; he switches to heroin.

"Where we've really missed the boat as a medical community is getting these patients reactivated. They start taking pain medications, they start having a little lower energy and motivation, they become less and less active, their pain becomes worse, they start taking more pain medications, and it becomes this vicious cycle. Maybe a decade or so ago, we would have told them to rest for a few days. Now we're doing quite the opposite. We're telling them that they need to keep moving."

*—Gwendolyn Sowa, Chair, Department of Physical Medicine and Rehabilitation*

"Between 5 and 15 percent of patients who are prescribed opioids for pain will develop either an abuse or addiction problem."

*—Ajay Wasan, Vice Chair, Pain Medicine, Department of Anesthesiology*

About one in four people who try heroin become addicted. In 2014, 586,000 people in the United States had a heroin abuse problem.

Fear avoidance can make low-back pain related disability worse and can block recovery.

An illicit prescription opioid habit can cost hundreds of dollars a day.

# NEW WAY A CONSERVATIVE APPROACH


A man gets hurt at work lifting something. Eventually, he goes to his doctor. The physician tries a conservative approach, newly recommended by the Centers for Disease Control and Prevention.

In 2016, the CDC released these best practices for chronic pain unrelated to cancer or palliative care. Conservative practices are being folded into Pitt's Health Sciences curricula, as well.

- Use nonopioid therapies, such as acetaminophen, nonsteroidal anti-inflammatory drugs, anticonvulsants, antidepressants, physical therapy, assessment for anxiety and depression, cognitive behavioral therapy, and nerve blocks.
- Start low and go slow: if using opioids, begin with a low dose.
- Follow up: monitor patients for efficacy and possible harm.

"A lot of times we've been, as providers, a little too quick to pull out the prescription pad and try to quickly fix the problem, as opposed to spending the time and resources needed to tease out all these other complicating factors." *—Gwendolyn Sowa*

## Fear Itself

Pitt's School of Health and Rehabilitation Sciences is leading a $12 million national trial to see if patients with fear avoidance who are given extra cognitive behavioral therapy heal faster than patients given conventional treatment.

"We're trying to identify patients who tend to think in this way [i.e., are afraid to move] and intervene with them early on when they're still acute, to characterize their pain in the right way and encourage activation and encourage confrontation of the pain process. [We will] see if that reduces the incidence of an acute situation becoming chronic.

"All the while, we're monitoring opioid use in both of the groups."
*—Anthony Delitto, Dean, School of Health and Rehabilitation Sciences*


With a new kind of prescription plan built into UPMC's electronic medical record system, a man with back pain is likely to hear this from his doctor: "I want to help you address the root cause of your back injury and pain. I'm writing you a prescription to help you with your activity level and fitness. Call this health coach. In six weeks, let me know how you're doing."


## Lessen Suffering

Pain has two components. The sensory component, called nociception: *Ouch. I feel that.* And the suffering component: *This is horrible—make it stop!* The latter is the emotional, behavioral, and cognitive interpretation of the pain stimulus—the story we tell ourselves about it, so to speak.

It's prolonging suffering—perhaps from dread, anxiety, anger, or sadness—that mires us in misery. Pitt physical therapy students are being taught to observe this distinction and explore ways to mitigate suffering for patients. Opioids treat the sensory part of pain—not suffering.

## PREVENTION PLAN

A doctor's prescription carries an aura of authority that helps motivate the patient to fill it. Mike Parkinson, an MD and UPMC Health's senior medical director of Health and Productivity, wants to employ what he calls the "power of the white coat" toward addressing the root causes of disease.

The National Institutes of Health has recognized the School of Medicine as a Center of Excellence in Pain Education. Pitt has been developing online case-based teaching modules on how to handle opioids in patients with problems like low back pain, dental pain, and fibromyalgia.

UPMC Health Plan's Prescription for Wellness lets doctors click a box in the electronic medical record (EMR) to print a paper prescription for health coaching. The coaches help patients take on unhealthy behaviors and habits (like smoking or not exercising). The prescription comes with the coach's phone number; Parkinson says many patients call from the parking lot right after a visit. The EMR then periodically reminds office staff to call patients and check if they've "filled" the prescription.

Parkinson says, "These types of innovations give [staff] the opportunity to engage patients and their families in the prevention, treatment, and even reversal of some of these conditions with lifestyle." Physicians say, *It makes me feel like a doctor again*, he notes.

Begun as a pilot in the General Internal Medicine Clinic, Prescription for Wellness doubled tobacco-cessation and weight-loss rates compared to standard coaching. It's rolling out across UPMC this fall. "We're the only system in the country that does [EMR-based lifestyle-change prescriptions]," says Parkinson. "We're getting calls from leading systems in the country asking, *How did you guys do this?*" *—JB*

# POST-OP DEPENDENCE DROP

Surgery is a big reason why patients get opioids. But cutting back on narcotics, doing without them, and using other pain-control approaches can help post-op patients heal faster. An approach called enhanced recovery after surgery (ERAS) is getting patients home as much as three days sooner.

For colorectal surgery, at least, standard surgical practice means patients get opioids while asleep during the operation. After the operation, they're put on a patient-controlled intravenous narcotics pump (called patient-controlled analgesia, or PCA). The drugs naturally slow bowel activity, which is already a problem after surgery, so patients might sit in the hospital for almost a week before being able to eat, switch to oral opioids, and go home.

"The more opioids patients take before surgery and the more they're given during their surgery, the more they require after their surgery," says Pitt assistant professor of anesthesiology Stephen Esper, an MD and MBA.

By contrast, ERAS patients get other pain medications—like acetaminophen, ibuprofen, and ketamine—before, during, and after a procedure (as well as some opioids). That means the bowel "wakes up" sooner, so many patients are eating solid food just hours after their operations. They might get oral opioids, but only 17 percent wind up needing a PCA pump. By the time they go home, the pain tends to be modest. And these patients aren't more likely to be readmitted to the hospital than patients treated the old way.

"We don't want [patients] to be tethered to an IV or other catheters. We want them to walk. We want them to get out of bed," says Esper. "Many patients and providers feel that physicians, nurses, PAs, or CRNPs are responsible for patient recovery. Truly, it is the patient who is the team leader. We are the patients' support staff and encourage and empower them to take responsibility for those healthier steps toward a recovery, which includes walking after surgery, on the same day."

"I can't say [the rate of opioid] abuse is high after colorectal surgery, but I think abuse altogether is high, so we have to be careful as to how we're sending patients home [and how we're] controlling their pain," says UPMC colorectal surgeon and Pitt assistant professor of surgery Jennifer Holder-Murray.

She and Esper, a cardiothoracic anesthesiologist, learned about ERAS during their fellowships at Mayo Clinic and Duke, respectively. The ERAS approach was developed in the late 1990s in Denmark but has been slow to make inroads in the United States.

At three UPMC hospitals, however, it's now standard practice in colorectal and pancreatic operations. The physicians plan to expand to other surgical specialties and more UPMC hospitals. (And there's much more to ERAS than easing up on narcotics for pain. Watch for more *Pitt Med* coverage in future issues.)

Shorter hospital stays, no extra re-admissions, better patient satisfaction. Is there a downside? "No," says Holder-Murray. "There's really none." *—JB*

## No Tolerance?

A hallmark of opioids is that people can develop tolerance, or the need to take ever-higher doses to maintain the same pain-relieving (or euphoria-inducing) effects. In the lab, Pitt's Howard Gutstein and his team have discovered a mechanism that causes tolerance—they've also found a way to completely eliminate it. They're about to start clinical trials of tolerance-blocking compounds to see if they can prevent or reverse tolerance. Such an approach could help people suffering from addiction and/or pain cut down on opioid doses.

"These are revolutionary breakthroughs. If it works in humans the way it does in rodents and monkeys, Pitt may be able to provide the first effective treatment to help eradicate the opioid epidemic."

*—Howard Gutstein, Chair, Department of Anesthesiology*

# FORECASTING AN EPIDEMIC

Donald Burke, dean of Pitt's Graduate School of Public Health, notes opioid overdose deaths have surpassed motor vehicle accidents and are now the leading cause of years of life lost for persons under age 65 in Pennsylvania. Yet in terms of the scope of the epidemic, he points out that those deaths are just the tip of the iceberg.

Pitt Public Health researchers made headlines in recent years with a modeling platform (called FRED), which they developed for predicting infectious disease outbreaks. The platform helped one California legislator, Richard Pan (MD '91), persuade colleagues of the need to vaccinate against measles. Burke believes his team can use the same kinds of tools to pinpoint outbreaks and activity around the noninfectious epidemic of opioid use disorder. Such a model would predict actions of "virtual people" without infringing on privacy rights. Burke and his team are now working on a model of all 4 million people in Western Pennsylvania that simulates and forecasts prescription drug use, addiction, overdoses, and deaths into the future. They then will use the model to evaluate the effectiveness of public health interventions, such as reducing the number of opioid prescriptions.

In an October report on opioid use disorder released by Pitt's Institute of Politics, U.S. Attorney for the Western District of Pennsylvania David Hickton notes that we can't prosecute or incarcerate our way out of this epidemic. What's needed, he says, is a true partnership between law enforcement and health care to get people help when they need it. Burke says his model would offer decision support for leaders to "contain and reverse the opioid epidemic." *—EL*

## ACCIDENTAL POISONING DEATHS IN PENNSYLVANIA*

| | | 1979 | | 2014 | |
|---|---|---|---|---|---|
| | | *Deaths* | *Rate* | *Deaths* | *Rate* |
| **Overall** | | **134** | **2.04** | **2458** | **29.16** |
| **Sex** | Male | 96 | 3.02 | 1633 | 38.89 |
| | Female | 38 | 1.12 | 825 | 19.50 |
| **Age Group** | 15-24 | 43 | 2.38 | 277 | 16.25 |
| | 25-34 | 30 | 2.04 | 654 | 39.87 |
| | 35-44 | 18 | 1.70 | 555 | 36.69 |
| | 45-54 | 24 | 2.17 | 616 | 34.10 |
| | 55-64 | 19 | 1.70 | 356 | 20.10 |
| **Race** | White | 118 | 1.98 | 2160 | 30.73 |
| | Black | 16 | 2.85 | 283 | 27.00 |
| | Other | 0 | 0.00 | 15 | 4.24 |

** Poisonings linked to drugs. Rates are per 100,000 accidental poisoning deaths among persons age 15 to 64, by selected characteristics.*

GRAPH BY PICTOGRAM STUDIO BASED "PATTERNS AND TRENDS IN ACCIDENTAL POISONING DEATHS: PENNSYLVANIA'S EXPERIENCE 1979-2014, TABLE 1, BALMERT L, BUCHANICH J, PRINGLE J, WILLIAMS K, BURKE DS, MARSH G, PLOS ONE, MARCH 10, 2016.

## ADDICTION TREATMENT

With its relapses and remissions, life-threatening complications, and periods of stable control, opioid addiction (to painkillers and heroin) is a chronic disease, also called substance use disorder. It's not curable, but it's "very treatable," says Antoine Douaihy, a Pitt professor of psychiatry and medicine and an addiction specialist. Unfortunately, up to 80 percent of patients aren't in treatment, not even a 12-step program. The most effective approach is multidisciplinary and long-term—much more than expecting a patient to "stop using," says Douaihy. Some medications help. Naltrexone is an opioid antagonist that prevents opioids from activating receptors, thereby helping to control cravings and prevent relapse. A long-acting form of naltrexone, originally approved for alcohol addiction, is FDA approved to treat opioid addiction. Other medications like buprenorphine and methadone can help patients control their opioid use, prevent cravings and relapse, and also achieve social stability and better functioning. This year the FDA approved a long-acting implant of buprenorphine that releases a constant low dose for six months. Douaihy is conducting clinical trials of medications that target heroin and prescription opioid painkillers.

Douaihy says, "Research has demonstrated that the combination of behavioral therapies, motivational interviewing, psychoeducation, family interventions, mutual support groups such as [Narcotics Anonymous], and medication-assisted treatments produces long-lasting positive outcomes and helps patients to establish and follow a recovery program." Starting this fall, Pitt med students are learning about treating clinical addiction with these approaches. *—JB*

## HAVEN FOR MOMS

"Are you thirsty?" The question rocked Jenifer Lake (not her real name) as she sat in the intake room at Magee-Womens Hospital of UPMC's Pregnancy Recovery Center (PRC). Not once before in her pregnancy had anyone asked how she was feeling. She began to cry as staff members congratulated her for both her pregnancy and her decision to battle her substance use disorder.

"We understand that addiction is a chronic illness, and that the women coming to us are taking steps to control that disease, doing the best thing for themselves and their children," says PRC medical director and Pitt clinical assistant professor Michael England, an ob/gyn, whose patients tend to hug him both in the halls of Magee and on the streets of Pittsburgh. (He choked up when he mentioned a patient's recent relapse to this writer.)

A couple of years ago, Lake and her mother had driven from Pittsburgh to Texas, stopping at each state along the way in search of a rehabilitation program that would accept a woman pregnant with twins. Despairing, they returned home only to learn of a new program beginning here, at Magee, in July 2014.

Encouraged by research suggesting babies have better health outcomes when their mothers take buprenorphine (a stabilizing drug that prevents mothers from going through withdrawal) compared to methadone, Magee researchers partnered with Medicaid insurance providers to develop a comprehensive outpatient program for pregnant women with substance use disorder: the PRC.

Lake joined nearly 200 other women in the PRC receiving behavioral health and social services as well as prenatal care, while taking buprenorphine. Lake was able to remain living at home and even continue working throughout her pregnancy.

England feels the true benefit of the PRC lies in the behavioral health services branch of the program because, although medication manages the symptoms of the disease, it doesn't help anyone "understand why [patients] are using substances, what led to the behavior initially, and how we can help them control this disease." Each woman gets help navigating housing, transportation, and legal issues. The program also helps with job training in addition to providing individual counseling, group sessions, and classes ranging from yoga to art therapy.

"Our philosophy is to focus on the pregnancy and wrap recovery around this major life event," says England.

Pregnancy was certainly a turning point for Lake, who had attempted sobriety several times, only to relapse. Her inability to find help terrified her, because she knew withdrawal could trigger miscarriage, but she desperately wanted to stop taking illicit drugs.

The PRC became a haven for her. Lake feared cesarean delivery for her twins because of the pain medication she'd likely have to take post-surgery, so the PRC supported her through vaginal delivery of healthy, full-term babies.

England says the PRC results have been promising. More than half of the babies born at Magee to women on methadone had neonatal abstinence syndrome, which can occur when babies are exposed to opioids in the womb. Those newborns can go through withdrawal after birth and may need pharmacological treatment to help with symptoms. However, the PRC's neonatal abstinence syndrome rate is 34 percent, which means the majority of the babies born in the program require no medication or NICU stay.

England says of the PRC mothers, "They should feel proud—we are proud of them."

Lake stays home full-time with her twin daughters, now 2 years old. Both are thriving, as is their mother. After delivery, Lake transferred her care to an outpatient rehabilitation facility near her home. She visits support groups once a week but feels her daughters are the real ticket to her continued recovery.

"I don't have time for cravings when I'm constantly keeping toddlers from climbing the bookshelves," she says.

*—Katy Rank Lev*

# Obama: continued

**broken-down health care system as it will be in a highly integrated, effective health care system. So I think it's important for us not to overstate the very real dangers of cybersecurity and ensuring the privacy of our health records. We don't want to so overstate it that that ends up becoming a significant impediment to us making the system work better.**

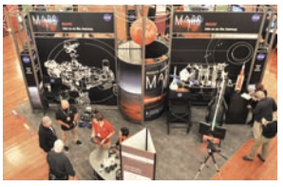
## On the value of informed debate

**One of the ironies . . . of the Internet has been the degree to which it's bringing us unprecedented knowledge, but everything on the Internet looks like it might be true.**

**Any scientific revolution is by definition contesting the status quo. And we're going through a period in which our knowledge is expanding very quickly. It's going to have a wide range of ramifications, and you've got a whole bunch of legacy systems that are going to be affected.**

## On keeping information curators in our modern world

**The most important curator to be able to sort through what's true and false, and sustain those scientific values, is the human brain; and [we're] making sure our kids are getting that ability to analyze and do that sorting early. And so part of the reason why we've been emphasizing STEM education is not because we don't value the humanities—I was a political science and English major, and I've probably learned more reading novels than textbooks. What [STEM] does is help everyone as citizens. Even if you don't become a doctor or a scientist or a physicist, it helps you evaluate information in a way that allows you to make good decisions in your own life but also allows you to participate in the country as a whole.**



## On the advice he gets from tech leaders in the private sector

**Government will never run the way Silicon Valley runs because, by definition, democracy is messy. This is a big, diverse country with a lot of interests and a lot of disparate points of view. And part of government's job, by the way, is dealing with problems that no one else wants to deal with.**

**So sometimes I talk to CEOs; they come in and start telling me about leadership, and, *Here's how we do things.* And I say, *Well, if all I was doing was making a widget or producing an app, and I didn't have to worry about whether poor people could afford the widget, or I didn't have to worry about whether the app had some unintended consequences . . . that would be great.***

**Sometimes we get, I think—in the scientific community, the tech community, the entrepreneurial community—the sense that we just have to blow up the system, or create this parallel society and culture, because government is inherently wrecked. No, it's not inherently wrecked; it's just government has to care for, for example, veterans who come home. That's not on your balance sheet, that's on our collective balance sheet. . . .**

**Let's get to work.**


**Frontiers had five tracks—personal, local, national, global, and interplanetary—plus exhibit halls and a plenary. Pitt's Jeremy Berg (editor in chief of *Science*) is shown above (second row) with Chancellor Patrick Gallagher. Hundreds of science luminaries, as well as students and patients, participated. (Pitt student Jesse Irwin, nominated for a regional Emmy Award for hosting *Pitt Tonight*, live-streamed from the conference; he's shown stalking a robot on the exhibit floor.)**

See more of the White House Frontiers Conference online: **frontiers.pitt.edu** and **frontiersconference.org**

## PRESIDENTIAL INVITES

A $4.2 million grant from the National Institutes of Health will help Pitt recruit study volunteers and collect their biological, genomic, and lifestyle data for **President Barack Obama's precision medicine initiative, now called All of Us**. The grant could total up to $46 million throughout the next five years. "The program will focus not just on disease, but also on ways to increase an individual's chances of remaining healthy throughout life," a White House news release says.

Pitt's Clinical and Translational Science Institute—with **Steven Reis**, MD associate vice chancellor for clinical research, health sciences, professor of medicine, and CTSI director as principal investigator—is leading data collection through an effort called Precision Approach to healthCARE (PA CARES). His team plans to recruit 10,000 patients in the first year and 175,000 people total as part of Obama's goal for 1 million enrolled by 2020.

It's perhaps no surprise that the content of a person's saliva affects his dental health—but are there hints of heart disease swimming in there, too? Pitt's new Center for Medicine and the Microbiome (CMM) faculty aim to find out.

In conjunction with the School of Dental Medicine's **Alexandre Vieira**, codirectors of CMM **Alison Morris**, an MS and MD, and **Barbara Methé**, a PhD professor of medicine, have collected saliva samples of more than 3,500 people to examine what microbes teem between our teeth. Then they will connect those findings to each anonymized patient's electronic health record.

"We have the ability to really look at how the microbiome impacts disease in well-phenotyped cohorts," says Morris. **CMM's efforts are part of the National Microbiome Initiative**, supported by the White House.

This July, **Ivet Bahar** was invited to speak at the White House as part of the **National Strategic Computing Initiative**. Bahar, a PhD, is a Distinguished Professor who holds the John K. Vries Chair of Computational and Systems Biology at Pitt. The NSCI was established to support the development of faster computations so researchers can tackle larger, more complex systems. "The idea is to extract useful information from extensive data," says Bahar, noting this is especially important in this "postgenomic era" of the life sciences.

*—Robyn K. Coggins*

PHOTOGRAPHY: UNIVERSITY OF PITTSBURGH

CAMI MESA

Parker (left) and Kuchinskaya

# INVISIBLE LOSS

## THE LANGUAGE OF MISCARRIAGE

INTRODUCTION AND INTERVIEW
BY ROBYN K. COGGINS

For many women, miscarriage is a life event with meaning far beyond the medical.

Recent findings of Olga Kuchinskaya, a PhD assistant professor of communication at the University of Pittsburgh, are bringing such nuance to light.

While writing her first book, *The Politics of Invisibility: Public Knowledge about Radiation Health Effects after Chernobyl*, Kuchinskaya got interested in other forms of "invisible" health topics, namely pregnancy loss.

"[Kuchinskaya's work] brings medicine and ethics into conversation with the methodology of looking for the invisible," says Lisa Parker, PhD director of Pitt's Center for Bioethics and Health Law and a professor of human genetics in the Graduate School of Public Health. The two presented on miscarriage at this year's Humanities in Health conference. (The event showcased researchers at Pitt who are breaking down disciplinary walls and collaborating across what were once institutional silos—like communications and medicine.)

In 2015, Parker encouraged Kuchinskaya to pursue a project analyzing written narratives about miscarriage. Parker suggested including biomedical peer-reviewed literature, as well as the social media and online forums Kuchinskaya was already analyzing. Kuchinskaya used a technique called grounded theory to identify textual patterns. She discovered that women who write about miscarriage often want to do something about the loss, besides try for another pregnancy.

"Doctors give well-meaning but general answers about the cause of miscarriage," Kuchinskaya found. "They assume it's chromosomal without testing, that it's the age of the mother, or it's bad luck. . . . It's not medically explained in 50 percent of cases." That's not the case with, say, dementia or heart disease, adds Parker: "Everybody wants to explain those. And with miscarriage, there doesn't seem to be quite the same groundswell of trying to understand."

*Pitt Med* sat down with the scholars to talk about their collaboration.

### Can you describe the analysis you conducted?

**Kuchinskaya:** I looked at specific issues that different authors (researchers, doctors, patients) focus on when they talk about pregnancy loss . . . especially recurrent pregnancy loss. For example, one theme noticeable in texts of women with recurrent pregnancy loss is that [the women] "need to know" what caused recurrent pregnancy loss. Another common theme [was] frustration with doctors' "bad luck" explanations for recurrent pregnancy loss.

### You call miscarriage "socially invisible." What does that mean?

**Kuchinskaya:** Compare it with pregnancy. Pregnancy is physically visible, right? There are clear signs of pregnancy, at least in later stages. But when somebody's going through a miscarriage, especially early miscarriage, there aren't any [obvious] signs. And . . . there isn't as much discussion about it; it's not covered in movies; a lot of women don't [bring it up].

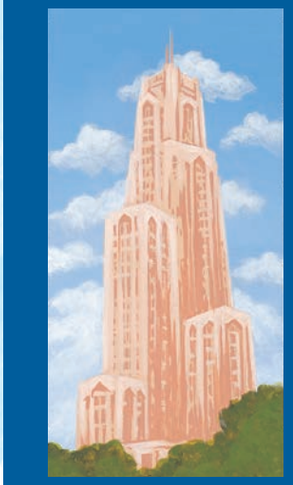
**Parker:** I would add that there's uncertainty: Do you offer condolences or sympathy, or do you just ignore it? It's not even discussed how people should respond to miscarriage.

**Kuchinskaya:** Miscarriage is kind of an in-between experience. It's between infertility and fertility; the woman is not pregnant, but she's also not *not* pregnant. And the little embryo is between life and death, and it's not quite [a] human but it's not quite other. So it's this very particular space, but it affects women's identity very strongly.

### What can doctors do to help women cope with miscarriages?

**Kuchinskaya:** Tell them it's not something they've done wrong . . . and join them in the search for answers.

**Parker:** In other contexts, we talk about the "diagnostic odyssey" and the benefit that can be afforded by just having an explanation. Not a cure for the disease—to give it a name, to understand where it came from. That can—not for everybody, but for a lot of people—be very helpful to end the odyssey. ■



# CLASS NOTES

## '60s

**Philip Raskin** (MD '66), an endocrinologist and the Clifton and Betsy Robinson Chair in Biomedical Research at UT Southwestern Medical Center, focuses both his patient care and research exclusively on diabetes. Recently, he and his team found that pregabalin, a drug used to treat fibromyalgia and epilepsy, may also be effective in treating peripheral neuropathy in diabetic patients. The results of the study, which were published in the *Clinical Journal of Pain*, showed that pregabalin reduced pain and improved sleep. "There's half a dozen treatments for peripheral, painful diabetic neuropathy," Raskin says. "Some drugs work where something else didn't. This is another option." Raskin is also the principal investigator of four National Institutes of Health–sponsored diabetes trials that strive to better understand how diabetes treatments work.

Among his more than 600 papers in refereed journals, **Naranjan Dhalla's** (Pharmacology PhD '66) most significant contribution may well be establishing that the oxidized products of catecholamines (rather than catecholamines themselves) contribute to arrhythmia. Dhalla, the principal investigator of experimental cardiology at St. Boniface Hospital in Winnipeg, Canada, credits **Paul McLain** (MD '32) and other Pitt mentors for his success. "Pittsburgh had a long-lasting effect on my career. It gave me experience doing very independent research." An honorary MD and editor in chief of *Molecular and Cellular Biochemistry*, Dhalla also serves as the executive director of the International Academy of Cardiovascular Sciences, which promotes awareness of cardiovascular-health education and research.

One morning, **Mike Lieberman** (MD '67, Pathology Resident '70, Biochemistry PhD '72) wrote a dark short story. Later, he appropriated aspects of Homer's *The Iliad*, rewrote all of it in iambic pentameter, and created a book-length poem set in Houston, his home of nearly 30 years. The result is a 4,500-line poem, *The Houstiliad* (Texas Review Press, 2015). Lieberman—former pathology chair at Baylor College of Medicine and founding director of the Houston Methodist Research Institute—didn't realize that *The Houstiliad* was about the "rage of modern men" until he had finished. Lieberman has authored seven volumes of poetry and three novels.

Lieberman

## '70s

**Rebecca Hughey** (Biochemistry PhD '76), a Pitt professor in the Departments of Medicine, Microbiology and Molecular Genetics, and Cell Biology, as well as assistant dean for medical student research, first began studying MUC1 glycoprotein in collaboration with Olivera Finn, Distinguished Professor of Immunology and Surgery, in 1996. Among Hughey's current research interests is MUC1's role in kidney health, including in kidney epithelia survival and recovery after acute kidney injury. With colleagues, she has shown that MUC1 protects kidney cells by enhancing two pathways (HIF-1 and ß-catenin), causing the organs less injury from restricted blood supply. She's now collaborating with researchers at the Broad Institute of MIT and Harvard to study MUC1 kidney disease.

Hughey

**Freddie Fu** (MD '77, Orthopaedic Research Fellow '79, Orthopaedic Surgery Resident '82) is easily one of the most storied orthopaedists in Pitt history, and we don't just mean in our magazine. His double-bundle ACL surgery technique inspired Sandy Havercroft, who attended his workshop in Cape Town, South Africa, back in 2007, to write a song (you can catch this catchy tune on our website—or in Fu's OR). In 2012, Tony Siragusa, a former defensive tackle for the Indianapolis Colts, Baltimore Ravens, and Pitt Panthers, gave Fu a shout-out in his autobiography, *Goose: The Outrageous Life and Times of a Football Guy*. And in more recent news, the Pittsburgh City Council declared September 13, 2016, "Dr. Freddie Fu Day." Fu, Distinguished Service Professor as well as the David Silver Professor and chair of orthopaedic surgery, is celebrating 30 years as the head team physician of Pitt's athletic department. In April, he was inducted into the American Orthopaedic Society for Sports Medicine Hall of Fame for his contributions to the field and his innovations in personalized orthopaedic surgery.

## '90s

**Lori Birder** (Neuropharmacology PhD '92) has long had a hunch that epithelial cells are more than just a protective barrier. The Pitt professor of medicine first started researching them in the bladder wall two decades ago, and her team has since become one of the first to reveal sensory properties of the bladder uroepithelium. She subsequently expanded the scope of the research to include epithelial cells in other parts of the body. "Neuroepithelial interactions between epithelial cells and the underlying tissues can influence every single tissue, every single organ," she says. In regard to the bladder, Birder's team has been researching the effects of aging on incontinence and other lower urinary–tract conditions. She hopes to provide fundamental insights into how cell-to-cell interactions can alter bladder function.

## '00s

**Suresh S. Ramalingam** (Hematology and Oncology Fellow '03), Pitt assistant professor of medicine from 2003 to 2007, remembers his colleagues here fondly: "I was fortunate to be mentored by Dr. Chandra Belani and the late Dr. Merrill Egorin." In February, Ramalingam was named deputy director of Winship Cancer Institute and assistant dean for cancer research at Emory. He also chairs the Thoracic Malignancy Steering Committee within the Eastern Cooperative Oncology Group–American College of Radiology Imaging Network, funded by the National Cancer Institute. Ramalingam has been involved in clinical trials for several newly FDA-approved treatments for lung cancer, including the immune checkpoint inhibitor nivolumab and epidermal growth factor receptor inhibitor osimertinib.

In child neurology, the patient population

is "unique, because they are very fragile and vulnerable. Many times they go years without being diagnosed," says **Hoda Abdel-Hamid** (Child Neurology Resident '05, Neuromuscular/Neurophysiology Fellow '06). Abdel-Hamid is part of a multicenter trial of a genetic-modifier drug for Duchenne muscular dystrophy, recently FDA-approved for a subgroup of these patients. An associate professor of pediatrics at Pitt, she directs the EMG Laboratory and Neuromuscular Program as well as the Muscular Dystrophy Association Clinic at Children's Hospital of Pittsburgh of UPMC.

## '10s

After a residency in anatomic pathology in her native Brazil, **Mariana Morais Cajaiba** (Anatomic and Clinical Pathology Resident '10) came to the United States for further training in pediatric pathology and decided to stay. At Pitt, she worked under Trevor Macpherson and Ronald Jaffe researching disorders of sex development and renal medical pathology. Now an assistant professor of pathology at Northwestern University, Cajaiba leads the team that recently discovered the first two known cases of primary renal myoepithelial carcinoma (both in children)—findings that will help the specialty refine diagnoses of pediatric renal tumors. She is also a central pathology reviewer for the National Cancer Institute–supported clinical trials group COG (Children's Oncology Group). "I review over 800 renal tumors in children every year." *—Imaz Athar, Jessica Boddy, Ali Greenholt, Rachel Mennies, and Susan Wiedel*

# ROBERT SANDERS

## OF SEA AND SPACE

PHOTO COURTESY OF NASA; WILLIAM BRASSARD

**Sanders at NASA's Neutral Buoyancy Laboratory**

As 100-mile-an-hour winds blasted across the frozen landscape, Robert Sanders (Res '08) waited out the storm with five other researchers. "If our hut failed, we were dead," he recalls of that time in Antarctica. Still, he didn't regret coming. The skilled diver had been tapped by the New York Department of Health just out of college for the mission; and in the waters among icebergs he went on to catalog 12-inch sea spiders, swimming scallops, and creatures known as *Astrammina rara*—single-celled carnivores that secrete a biological superglue.

"That learning was so enjoyable that it helped set me on the path for med school," he says. An avid diver since age 14, he gained expertise that led to adventures galore. An advocate for scuba diving safety and emergency care, he later worked for the films *Cast Away* and *Stuart Little*, for the Los Angeles County Sheriff's Department, and on Catalina Island, a diver's paradise 22 miles off the LA coast. He helped divers avoid potentially fatal illnesses like decompression sickness and air embolism.

Sanders realized becoming a doctor would offer even more scientific adventures and opportunities to ensure diver health, so he went to med school at Rosalind Franklin University in Chicago, then did an emergency medicine residency at Pitt. While in Pittsburgh, he trained river rescue teams.

Today he's in charge of the NASA medical team's Neutral Buoyancy Laboratory in Houston, a 6 million–gallon swimming pool with a mock-up of the International Space Station (ISS) on the floor. Astronauts train there, lowered in by crane while wearing full space gear, to rehearse station repairs and other tasks in this simulated zero-gravity environment.

As medical director and crew health and safety flight surgeon, Sanders oversees the safety crew and operates the hyperbaric chamber. He supervised aspects of training for Scott Kelly prior to the astronaut's groundbreaking year-long mission on the real ISS to study the human body's reaction to long-term space travel.

Though Sanders still dives around the world, frequently taking his daughter to her favorite snorkeling spots in the Caribbean, he's hoping for his biggest plunge yet: Perhaps, one day, a trip to space? *—Liberty Ferda*

# MAA SAYS, "BRIGHAM BACK!"

**Kang**

Just over a year ago, seasoned Pitt orthopod **James Kang** (Res '92) left the Burgh for Boston, accepting the mantle of orthopaedic surgery chair at Brigham and Women's Hospital. This fall, he returned to Pittsburgh for a happy homecoming indeed—as the recipient of the William S. McEllroy Distinguished Resident Award. The reception doubled as the Medical Alumni Association's reunion weekend kickoff event at the Phipps Conservatory.

Kang, who studies osteoarthritis of the spine, is interested in the biomechanics as well as the biochemistry of disc degeneration. An international leader in this area, he has been on the forefront of novel disc-degeneration therapies, including stem cell and gene-transfer interventions.

As the spine surgeon blazed these trails in research and clinical practice at Pitt, he rose from trainee to executive vice chair of clinical services, professor of orthopaedic and neurological surgery, and director of the Ferguson Laboratory for Orthopaedic and Spine Research—experiences that prepared him well for his new role in Beantown, he says: "How a department runs and how it fits with the overall enterprise, what levers to push, how to negotiate." His first year marks an exciting time for Brigham and Women's as the hospital grows aspects of its research portfolio, and he's especially excited about one development in particular: a translational orthopaedics and arthritis research center that opened October 3.

This isn't the first time a Pitt orthopaedist has led a Harvard department. Henry Mankin (MD '53) was chief of orthopaedic surgery at Massachusetts General for decades; and Harry Rubash (MD '79, Fel '81, Res '84) was at the helm from 1998 until his retirement this year. Both were also honored with Pitt's Philip S. Hench Distinguished Alumnus Award. *—Imaz Athar and Elaine Vitone*

**MEDICAL ALUMNI ASSOCIATION MAA.PITT.EDU**
**ON INSTAGRAM AND TWITTER: @PITTMEDALUM**

## MAURICE S. ALBIN

### MARCH 18, 1923–JULY 2, 2016

"A Giant of Neuroanesthesiology has Passed," reads the title of a paper eulogizing Maurice Albin this October in the *Journal of Neurosurgical Anesthesiology*. The author, University of Pennsylvania's W. Andrew Kofke (MD '78), is president of the Society for Neuroscience in Anesthesiology and Critical Care, which Albin helped found 43 years ago. Kofke credits the neuroanesthesiologist for inspiring his choice of specialty in the '70s at Pitt.

Albin

After serving in the U.S. Army during World War II, Albin graduated from New York University, completed his MD at Universidad Nacional Autónoma de México, and went on to a residency in anesthesia at the Mayo Clinic. In the 1960s, Albin and renowned neurosurgeon and ethicist Robert J. White did pioneering work in canine brain transplantation. Albin was also a historian of medicine and war, and he published several papers on the use of anesthesia during the Civil War.

A native of Brooklyn, Albin ended his 60-year career at the University of Alabama at Birmingham, with appointments at Case Western Reserve University, the University of Michigan, the University of Pittsburgh (where he was director of the Spinal Cord Injury Research Center), and the University of Texas at San Antonio before that. In 2005, UAB established the Maurice S. Albin, MD, Endowed Professorship in Anesthesiology.

"He was a model physician-scientist," says his son, Roger L. Albin (MD '82), a neurologist at the University of Michigan.

"An exceptional person in all respects," Maurice Albin was "an unusually warm and generous father" who at one point spoke four languages fluently, Roger Albin says. "He was an excellent example of how to pursue a rewarding life." —*Sarah C. Baldwin*

## DONALD A. HENDERSON

### SEPT. 7, 1928–AUG. 19, 2016

By the time Donald "D.A." Henderson began to lead the global effort to eradicate smallpox in 1966, the disease had already killed 300–500 million people. The World Health Organization recruited him from his post at what is now the Centers for Disease Control and Prevention to lead the 10-year charge, which would become the first such successful effort in history. As Donald S. Burke—dean of Pitt's Graduate School of Public Health—noted in the jacket copy he wrote for Henderson's 2009 book, *Smallpox: The Death of a Disease*, Henderson's day-to-day tasks in this seemingly impossible effort "were to cajole indifferent health ministers; upgrade woeful vaccine quality control; outflank unsupportive superiors at WHO; bargain vaccination plans with anti-government rebels; snatch funds from other accounts; repair broken-down vehicles. . . . This is the heroic stuff of true public health leadership!"

Henderson

Henderson was a distinguished scholar in the UPMC Center for Health Security, which he helped found and direct at Johns Hopkins University in 1998 as the Center for Civilian Biodefense Strategies before it moved to Pitt in 2005. He was 21st Century Professor of Medicine and Public Health at Pitt, as well as Distinguished Service Professor and dean emeritus at the Johns Hopkins Bloomberg School of Public Health. His work garnered him numerous honors and awards, notably the Presidential Medal of Freedom in 2002, the National Medal of Science in 1986, and the National Academy of Sciences's Public Welfare Medal in 1978.

Tom Inglesby, director of the health security center since 2009, noted that "D.A. . . . always took the time to meet with the rising generation in public health. Just watching him with new students considering careers, mid-career people—he was always generous with his time and spirit." —*Marty Levine*



## SHUNZABURO IWATSUKI

### MAY 24, 1940–MAY 14, 2016

Iwatsuki

Shunzaburo "Shun" Iwatsuki was at the University of Colorado when he made the pledge of loyalty that would set the arc of his career. "Wherever you go," he told his mentor, esteemed liver transplant surgeon Thomas E. Starzl, "I come too."

Iwatsuki died in May. A longtime faculty member at the University of Pittsburgh and Pitt's Thomas E. Starzl Transplantation Institute, Iwatsuki authored or coauthored more than 300 papers elucidating the science and surgical techniques behind liver transplantation; 213 were coauthored with the institute's namesake. "If not for Shun," says Starzl, "human liver transplantation likely would have been forestalled for another 50 years, if not permanently. He was also my most valuable ally in establishing the transplantation program in Pittsburgh."

Iwatsuki moved to Pittsburgh in 1981. By that time, Starzl wrote, "One could make the argument that he had undergone the most extensive surgical training of almost any surgeon in the United States." Having already achieved the rank of chief transplant surgeon at Chukyo Hospital in his hometown of Nagoya, Japan, where he had earned his MD in 1965, Iwatsuki spent three years training to pass his boards in the United States.

John Fung, director of the University of Chicago Medicine Transplantation Institute and former head of the transplantation program at Pitt, says, "Shun will be remembered by all who passed through the University of Pittsburgh as the gruff but lovable Jedi master who was a master clinician, a skillful surgeon, and, most of all, a friend." —*Sharon Tregaskis*

## IN MEMORIAM

### '40s

**JAMES R. DORNENBURG**
**MD '40**
SEPT. 24, 2016

**EUGENE (CZEMERYS) EMERSON**
**MD '43**
MAY 28, 2016

**WILLIAM N. DAVIS**
**MD '48**
NOV. 3, 2015

### '50s

**MERVIN S. STEWART**
**MD '53**
SEPT. 16, 2016

**WILLIAM W. WARING**
**MD '53**
JULY 14, 2016

**ROBERT L. EISLER**
**MD '55, RES '59**
JULY 15, 2016

**SANFORD M. KLEIN**
**MD '56**
MAY 12, 2016

**HOWARD L. HUDSON**
**MD '57**
JULY 15, 2016

### '60s

**PHILIP P. RIPEPI**
**MD '60**
AUG. 7, 2016

**F. DONALD COONEY**
**MD '63**
JUNE 26, 2016

**ANTHONY R. HARADIN**
**MD '63**
AUG. 26, 2016

**JAMES J. MARKOVICH**
**MD '63**
JULY 6, 2016

**DAVID LEE SAWHILL**
**MD '63**
JUNE 19, 2016

**ROBERT J. ROMA**
**MD '66**
MAY 5, 2016

**ROBERT G. CARROLL**
**MD '68**
AUG. 13, 2016

### '70s

**ROBERT G. DUNWORTH**
**MD '76**
AUG. 1, 2016

**JOHN J. NERNEY**
**RES '77**
JULY 6, 2016

# KARL WILLIAMS FORENSICS OF THE OPIOID EPIDEMIC

BY SHARON TREGASKIS

PITTSBURGH POST-GAZETTE © 2016

Williams (right) on the job as Allegheny County medical examiner.

In January 2014, a spate of fatal overdoses in Western Pennsylvania sent 17 bodies to the Allegheny County Medical Examiner Facility, run by **Karl Williams** (MD '74, MPH '03). One clue seemed to link the deaths—small packets of heroin, known as "stamp bags" on the street, branded "Theraflu" by the dealer.

Williams

Within three weeks, Williams and his staff had linked autopsy, toxicology, and crime scene evidence to those designer packets and issued a public health warning urging heroin users to beware of the deadly mix of fentanyl and heroin they contained. "Because I was getting bodies, blood, and stamp bags, I could put together a running tally and make it public knowledge—not only what was killing people, but also what stamp bags it was in," says Williams, who credits members of his toxicology and drug chemistry teams for their roles in the case.

Williams also credits a unique feature of the Medical Examiner Facility, the first accredited crime lab in Pennsylvania, which he has overseen since it opened in 2009. In most parts of the United States, crime scene evidence, bodies, and fluid samples from a single case each take a distinct path through the chain of custody, with medical examiners, police, and distant toxicology labs each operating in isolation. It can take weeks or even months for the resulting reports to make their way back through the investigative food chain.

Not so in Allegheny County, where the $26.8 million Medical Examiner Facility—an 80,000-square-foot building in Pittsburgh's Strip District—puts pathologists, toxicologists, ballistics experts, and other scientists under the same roof. Under Williams's leadership, the team investigates well over 1,000 deaths annually, including those of anyone who dies accidentally, suddenly, unexpectedly, or outside of a doctor's care. In 2015, 451 people died due to natural causes in the county; there were also 116 homicides and 179 suicides.

But nothing compares to the accidental overdoses (attributable to 424 deaths last year), the vast majority of which feature opioids—heroin, fentanyl, and their ilk (see our feature story on p. 24). Unlike motor-vehicle accident fatalities, which have plummeted in the past two decades because of improved vehicle engineering and seat belt use, fatal overdoses have climbed precipitously. In Pennsylvania, drug-overdose deaths have increased 14-fold in the last 35 years. "The number of opioid overdose deaths nationwide is getting very close to the total number of Americans killed as a result of the Vietnam War," says Williams. "That's a mind-boggling statistic."

To help public health officials wrap their heads around those numbers—and optimize interventions—Williams has dedicated himself to making data on overdose deaths in Pennsylvania freely available. He takes pride in OverdoseFreePA.pitt.edu, an online collaboration of Pitt's School of Pharmacy with a half-dozen nonprofit organizations and 16 communities.

"It's my belief that that information is essential to trying to deal with the problems," says Williams, who also serves on the Allegheny County Overdose Prevention Coalition's executive committee. "The people at the ground level—working on resources for education, treatment, and prevention—they need an idea of the numbers involved."

Drug trends differ by county, says Williams, pulling up the OverdoseFreePA website and clicking on the data tab. "You can see gender, age, top 10 drugs, even [view the data] by zip code where [overdoses] are happening," he says. "It's different in each county in terms of age, sex, distribution." Allegheny and neighboring Westmoreland Counties currently make their data available through the site. Over time, Williams hopes to recruit other counties. It's an uphill climb, he notes, because most coroners in Pennsylvania are funeral directors without medical degrees and have very limited resources for toxicology analyses.

"This is the single-most important public health issue of my career," says Williams, "and I have the ability to generate a really unique data set." ■

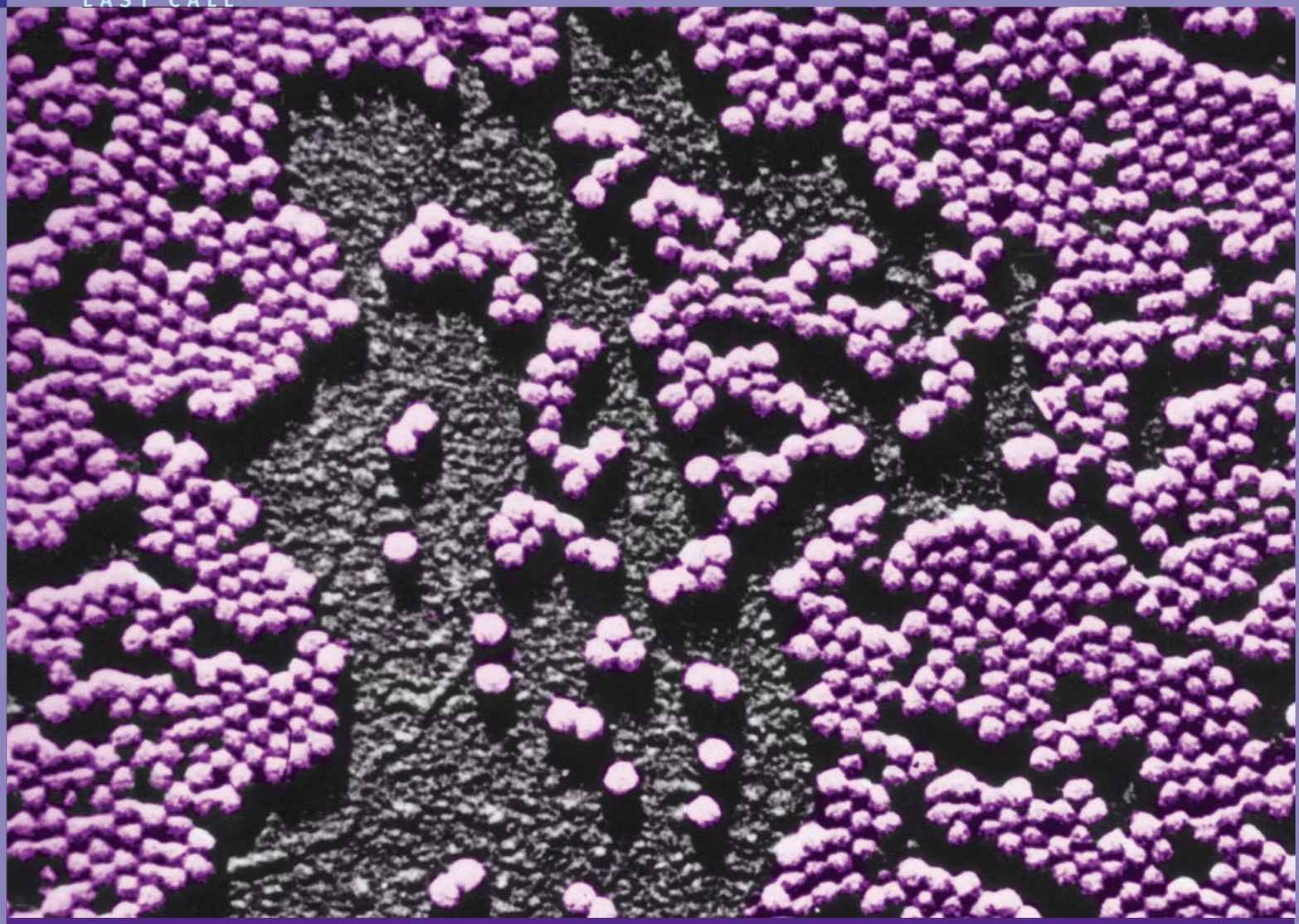
## '80s

**SAMUEL J. BLACK II**
**RES '80**
JULY 6, 2016

**CHRISTOPHER J. LYNCH**
**FEL '80**
JUNE 10, 2016

## '90s

**STEPHEN D. MULLINS**
**RES '99**
SEPT. 16, 2016



VIRUS IMAGE BY OMIKRON/SCIENCE SOURCE
CHILDREN GETTING VACCINE: UNIVERSITY OF PITTSBURGH HISTORIC PITTSBURGH IMAGE COLLECTION

TOP IMAGE: The poliovirus, which is nearing extinction. ABOVE: Children receive the killed-virus polio vaccine in Pittsburgh, c. 1955.

## OVER AND NEARLY OUT

**As we put this magazine to bed, Jonas Salk would have turned 102. In September 2015, 60 years after the killed-virus polio vaccine was licensed, a global commission declared wild poliovirus type 2 eradicated and instructed labs worldwide to destroy their stocks. (Though the virus reared its head again in Nigeria earlier this year.) Virologist Julius Youngner, 96, a key member of the team assembled by Salk, duly sacrificed his viral store to the autoclave, "like a good citizen," he says. We wondered, how did it feel to observe that historic milestone? Momentous? More bittersweet, he says.**

**Like the rest of the country, Youngner, Distinguished Service Professor Emeritus, was euphoric when the vaccine proved viable and, decades later, immensely satisfied as he witnessed the march toward world eradication of polio. And then he was told to send off his constant labmates—"the noninfectious mutant virus strains I developed and raised like babies"—onto their last trajectory.**

**Youngner reassures: "The commission is doing exactly the right thing."**

**Thanks to vaccinations, at last count (in 2010), 1.09 million lives in the United States alone were spared the curse of polio.**

***—Erica Lloyd***

***Ali Greenholt contributed to this report***

# CALENDAR

FOR ALUMNI & FRIENDS

**MEDICAL ALUMNI ASSOCIATION EXECUTIVE COMMITTEE BOARD MEETING**
NOVEMBER 9, 2016
6 p.m.
University Club
For information:
Ashley Knoch at 412-648-9059
akk57@pitt.edu

**WINTER ACADEMY**
FEBRUARY 15, 2017
The Breakers, Palm Beach, Fla.
FEBRUARY 17, 2017
Ritz-Carlton, Naples, Fla.
For information:
Jen Gabler at 412-647-3792
jag188@pitt.edu

**PITT DAY OF GIVING**
FEBRUARY 28, 2017
For information:
Kelsey Thayer at 412-648-9090
kelsey.thayer@pitt.edu

**CLASS OF 2017 MATCH DAY**
MARCH 17, 2017
Petersen Events Center
For information:
Joy Trybula at siz13@pitt.edu

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


GETTY IMAGES

Miami 2016

## FOR REAL! TWEEN SCIENCE

**The Zika virus is making its way around the world with the *Aedes aegypti* mosquito.** People bitten by an infected insect can get rashes and red eyes; some babies are born with very small heads. Scientists are trying to figure out how to conquer Zika. But with every possible preventive measure, there's a potential trade-off. What do you think of the pros and cons of these approaches?

1. Don't get bitten! The simplest way not to get Zika is to stay nibble free. Yet no repellent is 100 percent effective. And what happens if the repellent wears off before you have a chance to reapply it?

2. Attack! Some communities have started spraying insecticides over whole neighborhoods. This kills both grown mosquitoes and their larvae. Are these chemicals safe for people and other animals? What if mosquitoes become resistant to insecticides?

3. Vaccinate! Researchers have already developed a promising vaccine and are testing it in humans. How quickly can they get it to people who need it?

4. Create an anti-superinsect! British researchers have genetically engineered mosquitoes to breed offspring that quickly die. They want to try releasing them in Florida. But some residents are concerned: What effect might these bugs have on the ecosystem? *—Lela Nargi*

*Thanks to Pitt's Ernesto Marques Jr., a scientist with an infectious drive to find answers to this threat, who helped us understand how Zika works.*

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*THE OWL*, 1964

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| AGE | PAYMENT RATE | CHARITABLE DEDUCTION |
|---|---|---|
| 60 | 4.4% | $2,410.30 |
| 65 | 4.7% | $3,096.00 |
| 70 | 5.1% | $3,797.80 |
| 75 | 5.8% | $4,348.20 |
| 80 | 6.8% | $4,850.40 |
| 85 | 7.8% | $5,542.70 |
| 90 | 9.0% | $6,216.90 |

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