UNIVERSITY OF PITTSBURGH SCHOOL OF MEDICINE | SUMMER 2020

PITTMED

“He’s been hiding my medicine.”

CONTROL AND ABUSE IN INTIMATE RELATIONSHIPS

WITH A SPECIAL COVID-19 REPORT

A TALE OF TWO OUTBREAKS

April 12 was the 65th anniversary of the announcement that the killed-virus polio vaccine—developed here at Pitt—was safe and effective. To mark the occasion, we produced a video to share the perspective and advice of someone who has faced two frightening disease outbreaks up close: David Harding, a Pitt instructor in the School of Health and Rehabilitation Sciences. Check it out at **pittmed.health.pitt.edu/bonus**.

For more on how Pitt's polio work helped move vaccine science forward, visit **bit.ly/poliovaccine65th**.

RECENT MAGAZINE HONORS

2019 Pittsburgh Black Media Federation Robert L. Vann Media Award Magazine/Feature (E. Dyer, "With Love, From Haiti")

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

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Join the conversation on Twitter, @PittMedMag.

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ERIN HARE [COVID-19 coverage and "Build a Beta Heart" contributor] is the Center for Vaccine Research's media relations manager. She has been working seven days a week to share the story of how University of Pittsburgh researchers are pursuing solutions to the pandemic. "I feel very fortunate every day I get to do this job," she says. Hare, who earned a PhD in neuroscience from Pitt, has written for The Atlantic, FiveThirtyEight, Scientific American and STAT, but Pitt Med found her first. Hare's first byline as a freelance science writer appeared in our Spring 2016 issue.

Since RACHEL MENNIES' essay ["Married to Uncertainty"] was first published online in Pittwire in April, docs have reached out to say her story helped their extended families and friends understand the challenges they're facing right now. (Her spouse, Nicholas Goodmanson, MD '13, Res '16, Fel '18, notes that his coworkers hung the essay up in the break room.) BOA Editions will release Mennies' second book, "The Naomi Letters," a collection of poems, in 2021.

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UNIVERSITY OF PITTSBURGH SCHOOL OF MEDICINE MAGAZINE, SUMMER 2020
VOL. 22, ISSUE 1

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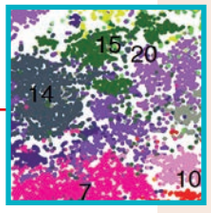

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FEATURES

COVER

Abuse in intimate relationships can show up in the clinic in unexpected ways. (Cover: Dejan/Getty Images.)

PITTMED

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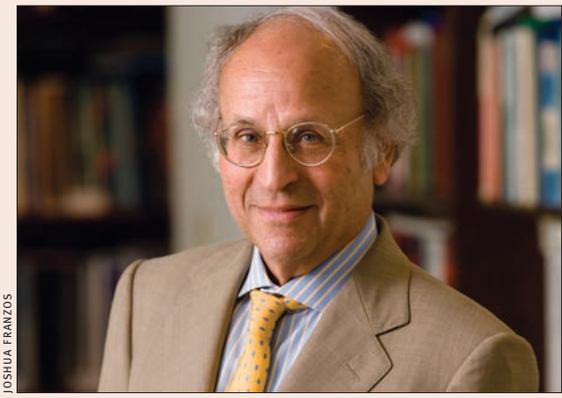
Pitt Med is published by the Office of the Dean and Senior Vice Chancellor for the Health Sciences in cooperation with the Office of University Communications and Marketing. It is produced quarterly for alumni, students, staff, faculty and friends of the School of Medicine. PR 6751

The subway shudders between dark
and light.
The ox plods across the page.
Think of everyone
you ever loved: the boy
who gets off at your stop
is a faint ideogram for each.

Offer him your hand.
Help him climb the stair.
—Mary Karr *(Published in 1993, in response to the AIDS crisis)*



JOSHUA FRANZOS

With my leaving my decanal position in June, this will be my last essay for Pitt Med. Permit me to share another story.

When I was an intern, my department chair often spoke of "experiments of nature," meaning rare mutations that illuminate common—if not ubiquitous—biologic pathways or activities. For example, one out of a million people might fail to produce a metabolic enzyme that would then lead to a disease that can be disastrous, e.g., phenylalanine hydroxylase and PKU, and this would lead us to understand how this enzyme and its pathway, when intact, control biology that is critical for normal brain function. Of course, such insight also leads us to specific treatment or prevention—in this case, a phenylalanine-free diet for those with the mutation. The latter is an "experiment of nurture," i.e., the diet was established after experimental trials.

We've since learned of another experiment of nature, and that is the Christchurch mutation (named for the city where it was identified). There is, in Colombia, a large kindred with the rare, heritable form of Alzheimer's disease. All of the members of this kindred have a known mutation that leads to early onset Alzheimer's, occurring in the 30s and 40s—except for one woman (of 1,200 relatives) who had no symptoms until her 70s. She has a second mutation that protects her from the ravages of the first. Once we understand the molecular role played by the Christchurch mutation, we may be able to devise a therapeutic or preventive strategy for the far more common age-dependent Alzheimer's. Thus my obsession with such experiments!

I am equally obsessed with experiments of nurture. Again in Alzheimer's, we know that two patients with the same detectable amount of the disease's apparent trigger, beta-amyloid, may have very different courses—quite slow or quite fast—and this seems to depend on intellectual reserve (learning something new each day) and overall fitness (i.e., nurture as opposed to nature).

Patients don't live in a vacuum. It's important to note: Are they well-nourished, physically and also mentally and emotionally? Or do they live alone with little stimulation? Or with poor access to resources? The world around us, and how we respond to it, can have an imprint. We have much to learn about disease, yet it seems that everything from our genetics to the microecology of our gut may influence how we manifest with a condition. Further, let us keep in mind that our DNA plays a critical role in our health and longevity, but so do the social and behavioral determinants of health—perhaps even more so. Likewise, it seems helpful to take a larger view of medicine and science as a whole. I trained as a physician and molecular biologist. I'm also a student of literature, a champion and collector of art, a dog lover and a husband, father and citizen. In these essays, which appeared on this page throughout the past 20-plus years while I served as the John and Gertrude Petersen Dean of the University of Pittsburgh School of Medicine and senior vice chancellor for the health sciences, I have shared my decanal perspective—founded on what I have learned from the arts, history and philosophy as well as from science—and from my fascination with the splendid burning torch that is life.

As I write, these thoughts have a new suddenness. Our colleagues are working night and day to save lives and to find a way out of COVID-19. Their zeal and commitment, whether to the care of our patients or to research, define selflessness and, often, heroism. They are reflecting the best of the sciences and the humanities.

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

Special Report

COVID CALLS

Just as we were getting ready to wrap up our spring issue, the University of Pittsburgh, and much of the United States, began operating on modified status in response to the pandemic. We paused the magazine's production to assess the new landscape. It quickly became apparent that Pitt people—healers, discoverers, inventors, activists—were not sitting still; they were not waiting for someone else to come along and find solutions to get us out of these difficult circumstances.

Every day, our magazine team learns of new ways that Pitt people are applying their talents and inspiration to take on COVID-19. We designed this special section to give you a glimpse of those stories. There will be more to share. *—The Editors*

MOVER AND SHEKHAR

In February, we sat down in Pitt Studios with Anantha Shekhar, an MD/PhD who joins Pitt this June as the new senior vice chancellor for the health sciences and John and Gertrude Petersen Dean of the School of Medicine.

The nationally recognized educator, scientist and entrepreneur from Indiana University filled us in on his path, his thoughts on the future of medicine and Pitt's place in it. We'll feature that discussion in our next issue. To hear the conversation now, tune in to our special Pitt Medcast miniseries at **pittmed.health.pitt.edu/pitt-medcast.** *—Elaine Vitone*

PILOT GRANTS FOR COVID-19 RESEARCH

This spring, the University of Pittsburgh Clinical and Translational Science Institute (CTSI) launched the COVID-19 Pilot Grant Program. The grants to 17 projects, addressing different aspects of the pandemic, totaled $900,000.

Funding for the projects was provided by the CTSI, the Office of the Provost, the Office of the Senior Vice Chancellor for Research and the DSF Charitable Foundation, which contributed $350,000.

Steven Reis, director of the CTSI, associate vice chancellor for clinical research, health sciences, and Distinguished Service Professor of Medicine, says that the grant program was created with the intent to support research initiatives that will make immediate progress toward reducing the harm to individuals, groups and society from COVID-19.

"We need to look at all options to deal with the COVID-19 pandemic," Reis says.

The CTSI received applications for 157 projects, and 46 universities were represented on the project teams. Investigators from 14 Pitt schools appeared on the list of applicants.

Nick Beldecos, DSF Charitable Foundation executive director, says that he's confident that the Pitt experts involved in the grant program will help "produce significant and timely advances" in the fight against COVID-19.

The proposals were put through an accelerated and extensive peer-review process.

A team led by W. Paul Duprex, the Jonas Salk Professor for Vaccine Research and director of the Center for Vaccine Research, received $100,000 for its study on the novel coronavirus SARS-CoV-2 and efforts to create and evaluate vaccines. Anita McElroy, assistant professor of pediatrics, and Alan Wells, professor of pathology and bioengineering, are coprimary investigators on the grant with Duprex.

Sources for this special section include Pitt and UPMC reports.

"These grants represent the best of research—creative minds working in collaboration with partners to innovate for benefit to society," said Rob Rutenbar, senior vice chancellor for research. "It's an honor to help support such vital investigation."

RECIPIENTS OF $50,000 AWARDS:

(Programs and project leaders)

Biomarkers for Predicting Viral Pneumonia Severity
John Alcorn (Pitt Med)

Cellular Mechanisms of SARS-CoV-2 Infection
Sally Wenzel and Xiuxia Zhou (Pitt Public Health)

Coronavirus and Lung Microbiome Interactions
Georgios Kitsios (Pitt Med)

COVID-19 Neurologic Manifestations
Sherry Hsiang-Yi Chou (Pitt Med)

COVID-Insight Triage and Monitoring Tool
David Salcido (Pitt Med)

Determinants of COVID-19 Clinical Outcomes
Christian Fernandez, Ernesto Marques, Donald Burke and Philip Empey (Pitt Public Health and Pharmacy)

Generation of Transgenic hACE2 Knock-in Mice
Andrea Gambotto, Louis Falo, Mark Shlomchik and William Klimstra (Pitt Med)

Impact of Maternal COVID-19 Infection on Newborns
Anne-Marie Rick and Judith Martin (Pitt Med)

Lung-Targeting SARS-CoV-2 Therapeutic
Raymond Frizzell (Pitt Med)

Modeling Strategies for the COVID-19 Pandemic
Mark Roberts (Pitt Public Health)

Pediatric Epidemiology SARS-CoV-2 Antibody Response
Sarah Wheeler, Glenn Rapsinski and Megan Culler Freeman (Pitt Med)

SARS-CoV-2 Cellular Imaging System
Zandrea Ambrose (Pitt Med)

SARS-CoV-2 Immune Escape Variants in Treatment
Jana Jacobs (Pitt Med)

SARS-CoV-2 Prevention Spray
Lisa Rohan and Sravan Kumar Patel (Pitt Pharmacy)

Therapeutic Nanobodies for SARS-CoV-2
Yi Shi (Pitt Med)

Therapy for COVID-19 Induced Acute Respiratory Distress Syndrome
Luis Ortiz (Pitt Public Health)

Pitt Moves Quickly,

Develops Two COVID-19 Vaccine Candidates

In February, Pitt joined the global effort to develop a vaccine for the novel coronavirus (SARS-CoV-2) when its Center for Vaccine Research received a sample of the virus from the U.S. Centers for Disease Control and Prevention.

The center's Regional Biocontainment Laboratory is one of a few labs across the country equipped to handle highly pathogenic infectious agents like SARS-CoV-2 (for severe acute respiratory syndrome coronavirus).

W. Paul Duprex, director of the center who holds the Jonas Salk Chair for Vaccine Research, and his colleagues quickly started culturing the virus and producing stocks to be used to assess the efficacy of small molecule inhibitors, antibodies and vaccine candidates. They are developing a COVID-19 vaccine based on the measles vaccine, as well as animal models for testing.

A second Pitt team, led by Louis Falo and Andrea Gambotto, was the first to publish on another COVID-19 vaccine candidate. On April 2, almost 65 years to the day that Jonas Salk told the world that his group had successfully tested a polio vaccine, Falo and Gambotto announced that they had developed a potential vaccine against SARS-CoV-2. Their paper appeared in EBioMedicine (an open-access journal published by The Lancet). Falo is chair of dermatology, and Gambotto is associate professor of surgery.

Duprex spoke of Pitt's expertise and obligation to help find an intervention at a recent University Senate Council meeting: "At Pitt, we have a long history of studying viral and bacterial diseases—and addressing emerging and reemerging infections. We no longer have to deal with the poliovirus because a vaccine was developed here." Pitt's COVID-19 vaccine candidates are two of at least 100 being tested worldwide.

Duprex answered questions about his group's vaccine in a UPMC interview excerpted below.

UNIVERSITY OF PITTSBURGH

Duprex

PHOTOS RIGHT: COURTESY UPMC

Approach

Duprex: "We take portions from the SARS coronavirus—little pieces of genetic sequence that makes SARS coronavirus—and pop those into the measles vaccine. And whenever we inject that candidate vaccine into a person or an animal, as we do in trials, they should make antibodies against measles, because that's what the measles vaccine does. But they should also make antibodies against SARS coronavirus. And that means that if that person, that vaccinee, met the virus in the real wide world, they would have the antibodies that remember what the SARS coronavirus looks like, and they would be ready and primed for action. That's the basis of vaccination."

Timeline

Duprex: "We are working to establish the animal model of disease and select the optimal vaccine candidate to take through the process. [Assuming that goes well,] manufacturing will be taking place in Europe, of that vaccine candidate, to make clinical material that will be produced and ready to be tested in a phase I trial in Europe, hopefully this summer."

Falo and Gambotto described their work at the virtual press conference (sitting 6 feet from each other, of course) in April.

Approach

Falo and Gambotto call their experimental vaccine PittCoVacc, short for Pittsburgh coronavirus vaccine. Their candidate follows an established approach to building vaccines—employing lab-made pieces of viral protein to build immunity. It's the same way some flu shots work.

Gambotto had worked on earlier coronavirus outbreaks—SARS-CoV in 2003 and MERS-CoV (Middle East respiratory syndrome coronavirus) in 2014. They taught his team that a "spike" protein (or "S" protein) is important for inducing immunity against the virus.

"We knew exactly where to fight the new virus," Gambotto said. "That's why it's important to fund vaccine research. You never know where the next pandemic will come from."

Unusual Delivery

A fingertip-sized patch of 400 tiny needles, called a microneedle array, delivers that spike protein into the skin, where the immune reaction is often strongest. After the patch gets applied like a Band-Aid, the needles—which are made of sugar and the spike protein—simply dissolve into the skin.

"It feels like Velcro," Falo said.

When tested in mice, PittCoVacc generated a surge of antibodies against SARS-CoV-2 within two weeks of a microneedle prick. Those animals haven't been tracked for an extended period of time, but the researchers point out that the mice that got their experimental MERS-CoV vaccine produced a sufficient level of antibodies to neutralize the virus for at least a year, and so far the antibody levels of the SARS-CoV-2 vaccinated animals seem to be following the same trend.

Microneedles build on the original scratch method used to deliver the smallpox vaccine to the skin, says Falo. For years, his lab has been focusing on using the tiny patches for inducing an immunological response to combat skin cancer.

From left: Falo and Gambotto

Falo called the scratch method efficient, reproducible and painless. It also is highly scalable. Once manufactured, the vaccine can sit at room temperature until it's needed, eliminating the need for refrigeration during transport or storage.

"For most vaccines, you don't need to address scalability to begin with," Gambotto said. "But when you try to develop a vaccine quickly against a pandemic, that's the first requirement."

Timeline

Falo and Gambotto plan to apply for an investigational new drug approval from the Food and Drug Administration in the next couple of months. The process to begin testing patients takes at least a year, usually longer, according to Falo.

"This particular situation is different from anything we've ever seen," Falo said. "So, we don't know how long the clinical development process will take. Recently announced revisions to the normal processes suggest we may be able to advance this faster." *—Gavin Jenkins*

Dream Teams

Hundreds of Pitt experts in medicine, critical care, immunology, virology, infectious disease, neuroscience, public health and other fields are collaborating to unlock the new coronavirus. Here are a few of the puzzles those dream teams intend to solve:

Drug Screening

Toren Finkel is known for advancing science's understanding about how aging affects disease. He directs the Aging Institute of UPMC Senior Services and the University of Pittsburgh. Finkel is working with a team that includes the institute's Bill Chen and Yuan Liu, as well as investigators in Shanghai. They have extensive experience screening drugs and are now evaluating FDA-approved drugs that may limit SARS-CoV-2 entry into cells.

Finkel is a professor of medicine and the G. Nicholas Beckwith III and Dorothy B. Beckwith Professor in Translational Medicine. Liu is an assistant professor of medicine and expert in lung injury who holds several patents. Chen is an associate professor of medicine, director of the Small Molecule Therapeutic Center and codirector of the Acute Lung Injury Center of Excellence.

Tracking the Evolution of the Virus

Vaughn Cooper is an evolutionary biologist tracking how SARS-CoV-2 moves through populations. That work could reveal where a virus from a given individual likely came from for public health or scientific purposes. He's been studying the evolutionary dynamics of the virus using publicly released genomes, which identify mutations and constraints in the virus that could affect treatment. Cooper is a professor of microbiology and molecular genetics and director of the Center for Evolutionary Biology and Medicine.

Neurocritical

COVID-19 mostly affects the respiratory system, yet some patients seem to have nervous system impairments such as seizures, strokes and encephalopathy. Sherry Hsiang-Yi Chou, associate professor of critical care medicine, neurology and neurosurgery, is leading a multicenter research consortium, endorsed by the Neurocritical Care Society, to study this set of conditions. "There's no ventilator for the brain," as Chou pointed out to The New York Times recently.

A Mysterious Blood Disorder

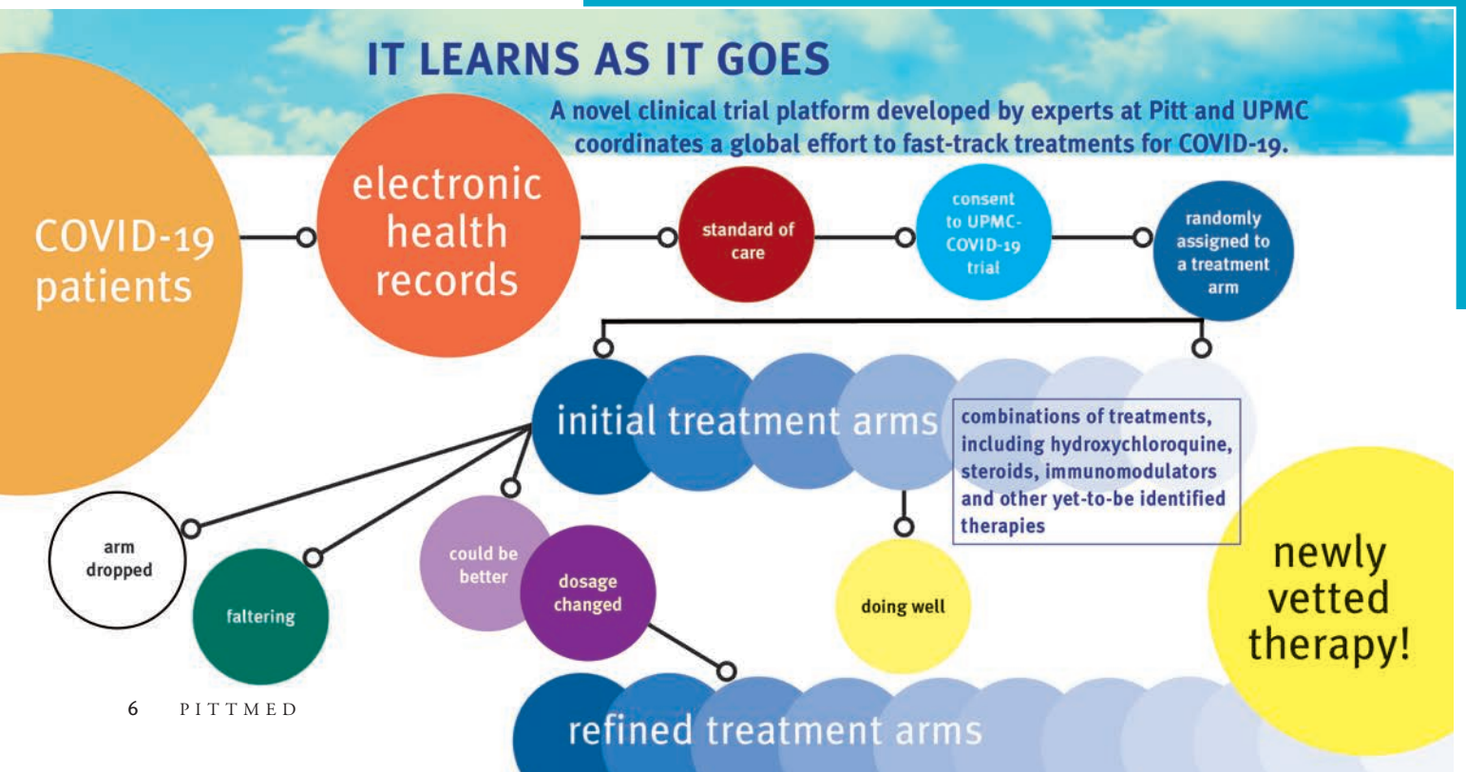
COVID-19 is characterized by a unique disorder, where blood clotting does not happen correctly; this can create severe complications. The mechanisms of the disorder remain unknown. Jansen Seheult and Matthew Neal have established a series of conventional and also novel tests and measurements to understand how the condition unfolds in COVID-19. The team measures samples in conjunction with genomic profiling studies performed by the Immune Transplant and Therapy Center, a partnership between Pitt and UPMC. Seheult is a clinical assistant professor of pathology. Neal (MD '06, Res '14, Fel '15) is also running the anticoagulation domain of the adaptive COVID-19 clinical trial platform directed by Derek Angus. He is an attending trauma and critical care surgeon and the Roberta G. Simmons Assistant Professor of Surgery.

—Compiled by Erica Lloyd and Gavin Jenkins

Answers Needed Now

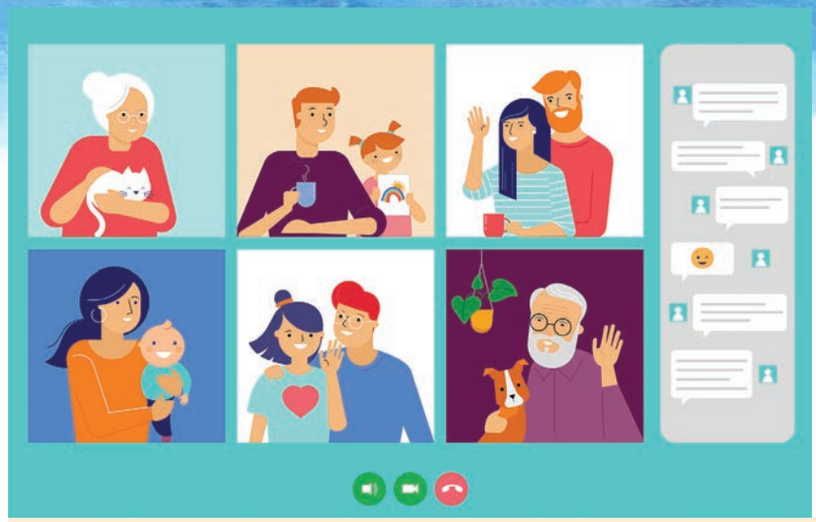
A novel clinical trial platform developed by researchers at Pitt Med and launched at UPMC will address one of the most important questions raised during the COVID-19 pandemic: How should doctors decide which treatments are best for patients when these treatments have not been vetted in long, rigorous clinical trials?

"The solution is to find an optimal tradeoff between doing something now, such as prescribing a drug off-label, or waiting until traditional clinical trials are complete," says Derek Angus, professor and chair of critical care medicine. Their solution, he says, is a clinical trial model that adapts and learns as it goes. It's looped into UPMC's electronic health records and pulls in data from medical centers throughout the world. COVID-19 patients who opt in get the standard of care, as well as two or three experimental therapies.



Coping Strategies for Older Adults

Approaches to Stave Off Depression



At last estimate, depression among older adults in the United States was high—roughly one in 10—and perhaps double that, if you include those just shy of meeting clinical criteria.

And that was on a relatively good, pre-COVID-19 day.

At this writing in May 2020, amid efforts to stop the spread of the virus, risk factors are closing in on this vulnerable population: Loneliness. Sleeplessness. Seeing the very real threat to health and safety in the headlines every day. Maybe a growing roster of friends to grieve—and no one on hand to grieve *with* in the era of social distancing.

Pitt's **Charles (Chip) Reynolds III** notes that social distancing is vitally important (though he prefers the term *physical* distancing) and may continue for some time. However, it's helpful to keep in mind that the connections between loneliness, depression and grief are profound as well as bidirectional, cautions Reynolds, Distinguished Professor of Psychiatry Emeritus.

Further, grief in the time of COVID-19 is emerging differently—not just for older adults, but for all of us.

"The fact that family members are not able to be with loved ones at the time of death because they're physically separated [and] the fact that funerals are not possible or have to be conducted in other ways will definitely be occasions for, in many instances, derailing grief."

Once off the rails, grief can devolve into what's termed prolonged grief; that's when a painful, acute condition becomes chronic, and symptoms like intense longing and searching for the deceased linger for upwards of a year. (Prolonged grief is a longstanding interest for Reynolds and his Pitt colleagues.)

Reynolds serves on the Lancet Commission for Depression and recently finished a stint on the American Psychological Association's depression treatment guideline panel. In partnership with the Depression and Bipolar Support Alliance, he's now working to create support groups to help older adults navigate this difficult time.

He's also part of a five-site collaborative network, dubbed OPTIMUM, that aims to improve treatment for older adults with difficult-to-treat depression. Recently, the OPTIMUM team began interviewing a number of the participants during the COVID-19 crisis, examining how people are feeling and coping. Heading the qualitative research project is **Jordan Karp**, Pitt professor of psychiatry, anesthesiology and also clinical and translational science. **Megan Hamm**, assistant professor of medicine, leads the team that is analyzing the interviews. The study is supported in part by Pitt's Department of Psychiatry and the Commonwealth of Pennsylvania Department of Health.

"For the older adults we interviewed," says Hamm, "one of the most difficult aspects of social distancing is not being able to interact in-person with their grandchildren."

"We're early in this project," says Reynolds, "but we think it will be important to understand how the current pandemic and its progeny of anxiety, depression and grief are affecting older adults who are already living with difficult-to-treat depression."

The team is concerned about the health and well-being of older adults generally. In light of the challenges related to the pandemic, Reynolds suggests a few practical coping strategies (see right).

Care for the caregiver. Some older adults are caring for loved ones with dementia, a round-the-clock job without reprieve. Daily check-in calls are important for such caregivers, Reynolds says. And the Alzheimer's Association sponsors another tool that can be helpful as well: online support groups for commiseration and mutual problem solving.

Take it porch-side. Friends, family and neighbors can stop by and talk—outside, while maintaining appropriate physical distancing guidelines—to lessen the sting of solitude. Offer reassurance that they're safe and cared for, Reynolds suggests, as well as help with a household task or two.

Break out the albums. Flipping through old photos, or putting together new albums—tools in what's called reminiscence therapy—"can be a potent boost to morale," Reynolds says. The reason: It encourages storytelling and meaning-making. "Rediscovering meaning and purpose can have a strong value in promoting a sense of well-being and also in promoting other positive feelings like gratitude, which are key to mental health," he says.

Turn off the tube. Cringe-bingeing newscasts is all too easy now. To avoid overarousal, Reynolds suggests people tune in just once or twice a day.

Set a new schedule. Maintain regular wake times and bedtimes. Stave off boredom by filling the hours in between with things that are pleasant and distracting.

Do what you love. Books, audiobooks, movies, music. Crafts, show-and-tell, charades, storytelling. Virtual concerts or museum tours.

Connect. Social media channels like Facebook can be a rewarding way to catch up with friends, family and communities of faith, Reynolds says. Same with get-togethers through online platforms. (Sometimes it's helpful to get someone with experience with a platform on the phone to guide the novice.)

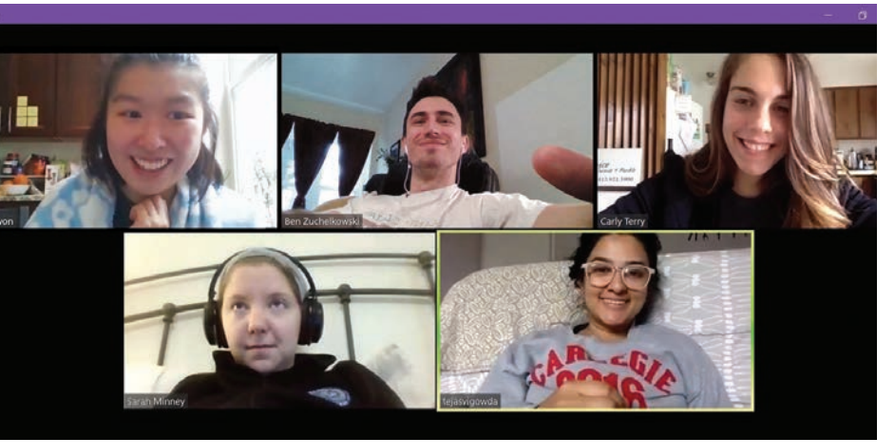
Get moving. Short walks outside (wearing masks and observing physical distancing), seated exercise or gentle stretching can lift spirits.

Eat well, live well. Proper nutrition is important too, Reynolds reminds. Essentially, anything that helps maintain and nourish a body can also maintain and nourish well-being.

—Elaine Vitone

STUDENTS IN ACTION

BOND SHARED BY FIVE STUDENTS FUELS A MOVEMENT OF VOLUNTEERISM



Clockwise from left: Jane Kwon, Ben Zuchelkowski, Carly O'Connor-Terry, Tejasvi Gowda and Sarah Minney

Ben Zuchelkowski says it all started after a conversation with his research mentor, Mark Gladwin, chair of medicine, in mid-March.

"It all happened so fast. I had a meeting with Dr. Gladwin, and we talked about how the coronavirus pandemic was putting big stresses on the health care system. It was getting scary," says Zuchelkowski, a fourth-year med student and research scholar in the Clinical Scientist Training Program. "We thought, 'Wow, there's an opportunity for medical school students to step in and fill the needs that may come up during the pandemic.'"

An hour later, Zuchelkowski texted one of his classmates.

"I felt like we had to do something. We brainstormed and pulled together some more of our friends to start organizing," says Zuchelkowski, a Uniontown, Pennsylvania, native.

From there, Zuchelkowski and classmates Sarah Minney, Tejasvi Gowda, Carly O'Connor-Terry and Jane Kwon put their heads together. "We've all been friends since the beginning of med school," he says.

With medical school rotations shut down because of COVID-19 and while working on any lab work they can from home, Zuchelkowski and his classmates have found new ways to put their skills to use.

"I am encouraged by our students' volunteerism and commitment to coming back to the clinic and engaging as much as possible as student leaders," says Gladwin, who is the Jack D. Myers Professor.

Practicing social distancing, the friends quickly collaborated using online tools to hold meetings around the clock to come up with ways to help the community.

"We decided the best thing to do was play on everyone's strengths and offer help in different areas of life that are being impacted by the crisis. We all have diverse experiences to bring to the table," says Zuchelkowski.

It didn't take long to recruit more than 200 med school students spanning three medical schools—New York University Grossman School of Medicine and Lake Erie College of Osteopathic Medicine, along with Pitt Med—to assist in their volunteer efforts. These include arranging and providing childcare support for medical professionals, helping a Pittsburgh clinic at risk of shuttering, and community and education outreach activities. They've since named their effort 412Med.

WITHIN 5 MINUTES

During her undergrad years as well as medical school, Gowda has volunteered at the Birmingham Free Clinic on Pittsburgh's South Side. She says the clinic was on her mind when COVID-19 hit the city.

"The clinic has a program where uninsured patients can come in and get truly life-sustaining medication. During this time, we reached out to them to see how they were managing," says Gowda, a native of West Windsor, New Jersey.

The clinic has limited in-person visits to reduce risk to its patients and staff to COVID-19. It's also temporarily suspended student participation within the clinic building. But after speaking with Birmingham's clinical director Mary Herbert, Gowda learned there was still a way to be of service: door-to-doorstep delivery of critical medications.

Gowda quickly solicited help from her peers through various Pitt Med student Facebook groups and email lists. The response, she says, was overwhelming.

"Within 5 minutes of posting, the slots to volunteer were completely full," says Gowda. "People were texting me afterwards asking if there was any way to help, disappointed that the spots were full."

"At Birmingham, so many of our patients could never afford just to purchase their medications at a pharmacy—between one-third and one-half of our patients have one or more chronic conditions such as hypertension, diabetes, asthma or a combination of these," Herbert says. She adds that she is "beyond grateful" that the students have stepped in to help. Patients normally would come in from as far as the South Hills, Charleroi and Penn Hills areas.

Approximately 25 students are available to help.

Organized by Gowda, students signed up to work three-hour shifts and be on call to deliver medications to people around Pittsburgh. Students are still practicing social distancing and taking proper safety protocols, says Gowda.

"The clinic has masks, gloves and hand sanitizer that they give our volunteers, and we pass along the CDC guidelines for Allegheny County to our volunteers to make sure they're aware of how to stay safe."

Gowda says they are incorporating the addition of a box of food along with the medication delivery. The addition comes with

Access COVID, an accessible COVID-19 guide for everyone, is brought to you by a caring team of medical students and health professionals at NYU, Pitt, WashU, and the St. Louis Arc.

For more information contact **accesscovid@gmail.com**

Illustration by Ariella Coler-Reilly **Design** by c.design

INSPIRATION DURING CRISIS

• Led by Carly O'Connor-Terry, a group of Pitt Med students created a plain language guide describing what COVID-19 is and what to do if someone experiences symptoms. The guide (shown above) was designed particularly for people with autism or intellectual disabilities; it's also accessible to children and those in older age groups.

• Pitt Med's Class of 2020 decided to donate funds the students contributed toward their Match Day celebration to the Birmingham Free Clinic, which offers free health care to patients without insurance; 412 Food Rescue, an organization that provides surplus food to insecure communities; and chef Claudy Pierre's team that provides hot meals for underserved populations on the North Side. Faculty and students from other Pitt Med classes joined the Class of 2020; the combined effort totaled $25,000 for the local organizations.

help from Thuy Bui, associate professor of medicine and director of the Social Medicine Fellows program and the Produce to People home visit initiative at the School of Medicine.

On a personal level, Gowda says that connecting with Zuchelkowski and her friends is helping her through this difficult time.

"To have my close friends to keep me motivated is very special. It keeps me happy." *—Margo Shear Fischgrund*

ENTIRE PITT COMMUNITY MOBILIZES SOME EXAMPLES THAT WILL MAKE YOU PANTHER PROUD:

• Carla Chugani, assistant professor of pediatrics at Pitt Med, has been running a food pantry from her front porch in Dormont to provide child-friendly staples and basic goods to community members in need.

• Goetz Veser, a chemical engineering professor at Pitt, is using his lab to make hand sanitizer for UPMC hospitals in the area. (He's produced 170 gallons at last count.) Veser is soliciting donations of alcohol from companies and other labs so he can make more.

• Faculty and staff at the Swanson School of Engineering and from the Deitrich School of Arts and Sciences donated five pallets of existing personal protective equipment to UPMC hospitals, such as N95 masks, peroxide and eye protection.

• A team at Pitt Makerspace in the Swanson School has partnered with a local printing company and the UPMC 3D Print Lab to create a single material plastic shield; the group has made the details and design open access—available and free for anyone to use. In the same spirit, Swanson's Manufacturing Assistance Center Makerspace in Homewood is partnering with a local initiative to produce hundreds of 3D-printed face shields a day for health care providers in need.

• With students off campus, Pitt opened up Lothrop Hall, next door to UPMC Presbyterian, to house health care workers during the pandemic.

• The internet has been a lifeline during the crisis. Pitt opened its technology help desk to the larger Pittsburgh community. Other Pitt staff, faculty and students have stepped in to help answer the calls.

• Pitt donated 590 computers to Pittsburgh Public Schools. And Pitt volunteers are among those delivering digital devices so that families can connect from home.

• Pitt faculty and staff have donated canned food, including chow for our four-legged friends, as well as other essential items, like antibacterial soap and disinfectant spray, through the University's partnerships with the Greater Pittsburgh Community Food Bank, the Salvation Army, Animal Friends and the Community Empowerment Association.

• Sometimes listening is the easiest way to help. Through the Office of Community and Governmental Relations, Pitt volunteers are being trained on how to call people in need, listen to what they are struggling with and connect them to appropriate nonprofit organizations for assistance.

• Through the Pitt Shopping Helper program, developed by Ben Rottman, an associate professor of psychology, volunteers deliver groceries and medical supplies to fellow students, staff or faculty who are unable to leave their homes safely. —GJ and EL

2013 New emergency medicine doc Nick Goodmanson with Otto.

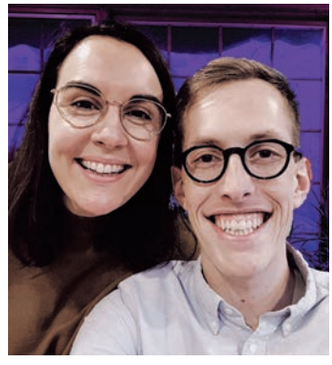
FIRST PERSON:
MARRIED TO UNCERTAINTY

CONNECTIONS AND CONCERNS

STORY AND PHOTOGRAPHY | RACHEL MENNIES

The first big question none of us on the group chat knew the answer to—that we still don't have a certain answer to—"Should we still sleep next to our spouses?"

Since graduation, our group chat of six partners of emergency medicine residents usually hummed quietly over the years, flaring mostly with celebrations of births and new jobs. But in this difficult late winter, questions about how to respond to the COVID-19 outbreak firmly took their place.



PHOTOS COURTESY MENNIES. PHOTO COLORIZATION: ELENA CERRI

Mennies and Goodmanson

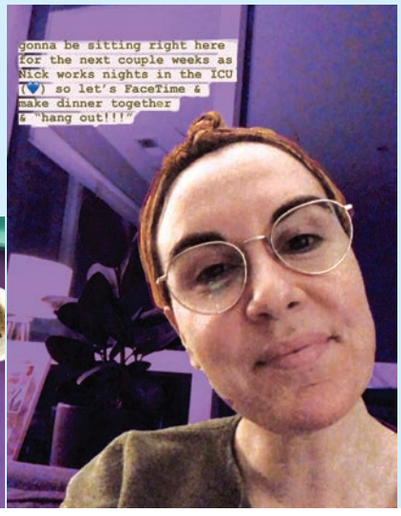
My husband, Nicholas Goodmanson (MD '13), did all his medical training under University of Pittsburgh physicians, including an emergency medicine residency ('16) and a critical care fellowship ('18). Today, Nick works as an intensivist in Chicago. In March, he transitioned from his typical schedule working in several specialty ICUs to a dedicated ad hoc COVID-19 unit at Advocate Christ Medical Center on Chicago's South Side. His group built the unit from other previously allocated hospital wings and recently had to double the capacity by putting two beds in single-bed rooms. The patients, he says, keep coming and coming.

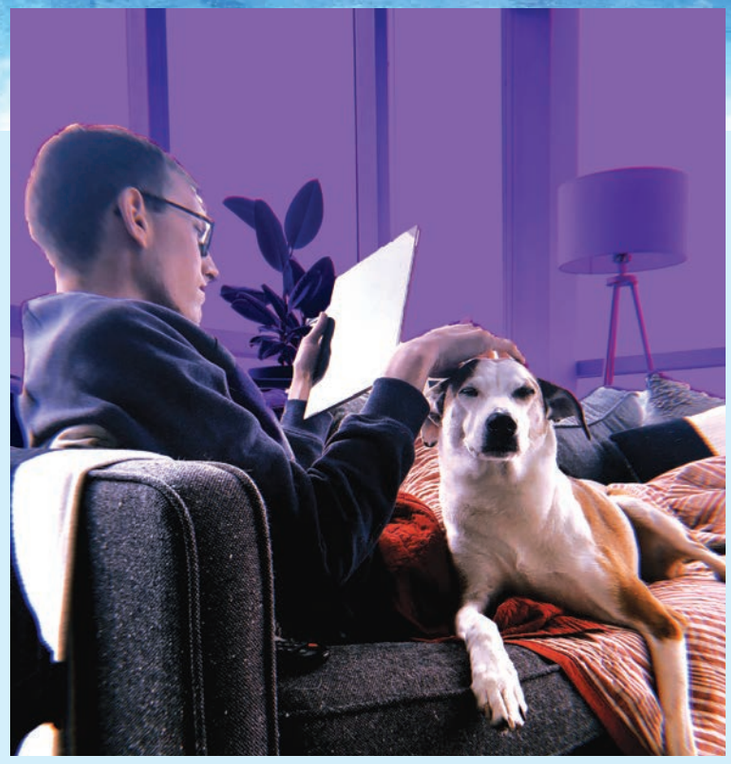
For now, we are both healthy, or at least asymptomatic.

We spouses are texting each other as we isolate ourselves, all of us knowing the additional risk for infection brought into our homes by the doctors we love. Within these spaces scattered

2020 Goodmanson heads out for his shift at a COVID-19 unit in Chicago.

2020 Rachel Mennies has found comfort in connecting with friends from residency and fellow days in Pittsburgh.





2020 Looking over pulmonology studies during a quiet moment in March.

across the United States, from Florida to Boston to Washington state, we've begun to face something unprecedented.

"Is it safe for our spouses to hug our kids after work?" we ask each other. "To hug me?" (Many doctors managing COVID-19 patients are living separately from their families during the pandemic.)

"How do we keep the apartment sanitized—and what about their clothes, or their shoes?" "How many hours are being added to their schedules?" "Does your spouse have enough personal protective equipment?"

"Have any of their colleagues tested positive yet?" we ask. "Have you?"

As folks "married to medicine," as the old joke goes, we partners of doctors and trainees have already learned to live with uncertainty. On Match Day, a slim white envelope determines your fates for the duration of residency. And each new level of training brings the possibility of a cross-country move, job changes and major life events spent apart.

When residency began for our family, I remember the lonely unpredictability of Nick's early, seemingly unending shifts. I remember stuffing his share of dinner-for-two into a Tupperware container. I remember driving to pick him up outside of UPMC Presbyterian at midnight in our Honda Fit, idling on snowy Pittsburgh hills as I waited for him to surface. I remember worrying about him up in the STAT MedEvac helicopter, hovering over the three rivers, zooming out over Western Pennsylvania, maybe even Ohio, West Virginia, Maryland. During those 36-hour shifts, I'd imagine him looking down as he approached another town, en route to a critically ill patient, to life-or-death traumas.

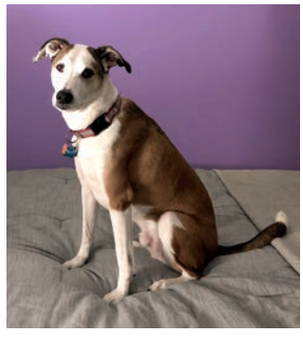
But Nick and I weren't alone. Aside from each other, we were with other people who *got* it—both the deep challenges and the unexpected joys of medical training. With other Pitt Med folks, we built a communal normalcy from this unusual life: We not only got it together, we got through it together.

In both residency and fellowship, perhaps sensing how quickly we'd need one another, we partners immediately made standing monthly dinner dates. We passed around babies at barbecues and house parties; we held showers and happy hours. In this community, despite our many other differences, we all shared this one strange, difficult fact: The people we loved would treat the patients who needed them without question at all hours, even at great personal risk. And when we couldn't be with our spouses, we had each other. We understood our lonesomeness and uncertainty as shared, and we talked about it.

I work as a writer and editor, this month entirely from home. I watch Nick go to the hospital and come back from my vantage point at the desk or the sofa. And we keep each other company at a distance somewhere between 6 feet apart and our usual inches, a compromise between what we need and what we must do. Because we can, we sleep in separate rooms, just to be safe; we walk the dog together when we can, and we eat together when he's free. I worry about him getting sick, or me. And each time my phone lights up, I fear what I might read there from our friends, especially those who are also so proximate to the virus every single day, for however long the pandemic will persist.

By the time this article is published, all of our lives will have changed from when I first drafted the essay on the last Saturday of March. And there are moments when this utter, interminable uncertainty, as it did on the toughest days of residency, renders me useless. Like on a rare-for-Chicago warm day last week, on a walk with the dog alone, when the smell of mulch reminded me that winter had somehow become spring during the stay-at-home order. I wondered if our neighbors had planted tulips, but I couldn't safely get close enough to ask them. I wanted to cry—but I couldn't touch my face.

Instead, I went inside and washed my paper-dry hands for 20 seconds, and I made dinner, leaving part for the freezer in case we need an emergency meal next month. Then I reached out with a video hello to a dear friend from fellowship, a friend whose partner was on the night shift in a Milwaukee ICU. I leaned on the couch as we talked, as if it were her shoulder. ■



Otto does not understand self-isolating.

CATHERINE LAZURE

Ready, Player?

Even before the pandemic, people with cystic fibrosis were advised to keep at least 6 feet from each other. The danger of cross-infection has been a threat they've had to keep in mind throughout their lives. That mandated distancing has impeded commiseration and played into the high rates of depression and anxiety experienced by teens with CF. (Their parents are affected, as well.)

Dmitriy Babichenko is betting that educational video games may improve the health of kids with CF and other conditions. With an interdisciplinary team, he received a Pitt Seed Project grant from the Office of the Chancellor to create games about living well, even when you have a disease. Babichenko, a clinical associate professor in the School of Computing and Information, joined forces with colleagues, including experts from the Schools of Pharmacy and Nursing, as well as UPMC, to develop two games. He credits much of the design to computer science students. Pitt English majors built the story structures, and a music student composed the score.

Combined, these elements form narrative-based, role-playing games (think a digital "Dungeons and Dragons") that kids play as characters who make choices about health. One of the games will provide nutritional guidance to younger children to address obesity. The other is designed to encourage teenagers with CF to become more proactive in their own complex care, which they'll need to manage themselves one day soon. It also gives them an opportunity to get to know others with CF—remotely.

Babichenko will soon begin a study to determine each game's effectiveness. He's already workshopped them with preliminary focus groups. "Ten-year-old kids are brutal," he says with a laugh. *—Alyce Palko*

He's for Kids

Infection is the leading cause of death in children under 5 years old worldwide, and infectious and inflammatory diseases together land more American children in the hospital than anything else. To help kids get and stay healthy, Pitt and UPMC created the Institute for Infection, Inflammation and Immunity in Children (i4Kids) last year.

John V. Williams, who holds the Henry L. Hillman Chair in Pediatric Immunology and is a professor of pediatrics at Pitt, was named i4Kids director. Williams says he spends a lot of time thinking about what is missing from pediatric illness research, and he hopes to make i4Kids an epicenter for research, prevention and treatment of diseases in children.

"Nobody is going to say they don't care about kids; but as a society, we're not putting our money where our mouth is," says Williams.

Williams, along with Anna Wang-Erickson, associate director and assistant professor of pediatrics, will lead the institute that was established under the guidance of Terence Dermody, who is the Vira I. Heinz Professor and chair of pediatrics at Pitt, as well as physician-in-chief and scientific director at UPMC Children's Hospital of Pittsburgh. The institute will support multidisciplinary projects from the health, natural, physical and computer sciences.

Williams

In an effort with Marian Michaels, professor of pediatrics, Williams also oversees a CDC-funded pediatric virus surveillance network with Children's Hospital of Pittsburgh—one of seven national sites. The network seeks to determine the effectiveness of flu vaccines and describes the epidemiology of respiratory infections, including COVID-19, among children hospitalized or evaluated in the emergency department.

Williams is being recognized with the Norman J. Siegel Outstanding Science Award from the American Pediatric Society this May.

—Maggie Medoff

The Imposter Syndrome exhibition hung in a local café.

CAUGHT ON CAMERA

Stories of power, vulnerability and self-doubt among medical students were on display in February as part of Pittsburgh's First Friday showcase.

By organizing the art project, second-year students Catherine Pressimone and Anjana Murali sought to unveil and explore imposter syndrome—the sense that you are not really up to the job before you, that you are an intellectual fraud, however many accomplishments may have qualified you. It's a frequent reason for which medical students seek help, since chronic self-doubt and questioning one's worth can mutually exacerbate stress, depression and anxiety, says Jordan Karp, director of Mental Health Services for Pitt Med and professor of psychiatry.

"It emerges because it's mostly young people transitioning from late adolescence to adulthood," he says. "So, for some people, it's a time of identity instability."

The exhibition hung in Pittsburgh's BFG Café.

Student portraits were strung from a line of fairy lights. Below the photos were comments like: "Having the white coat, you feel like you should be respected . . . people feel as if they should respect you . . . but you come in, and you're like, Do I even remember how to take blood pressure?"

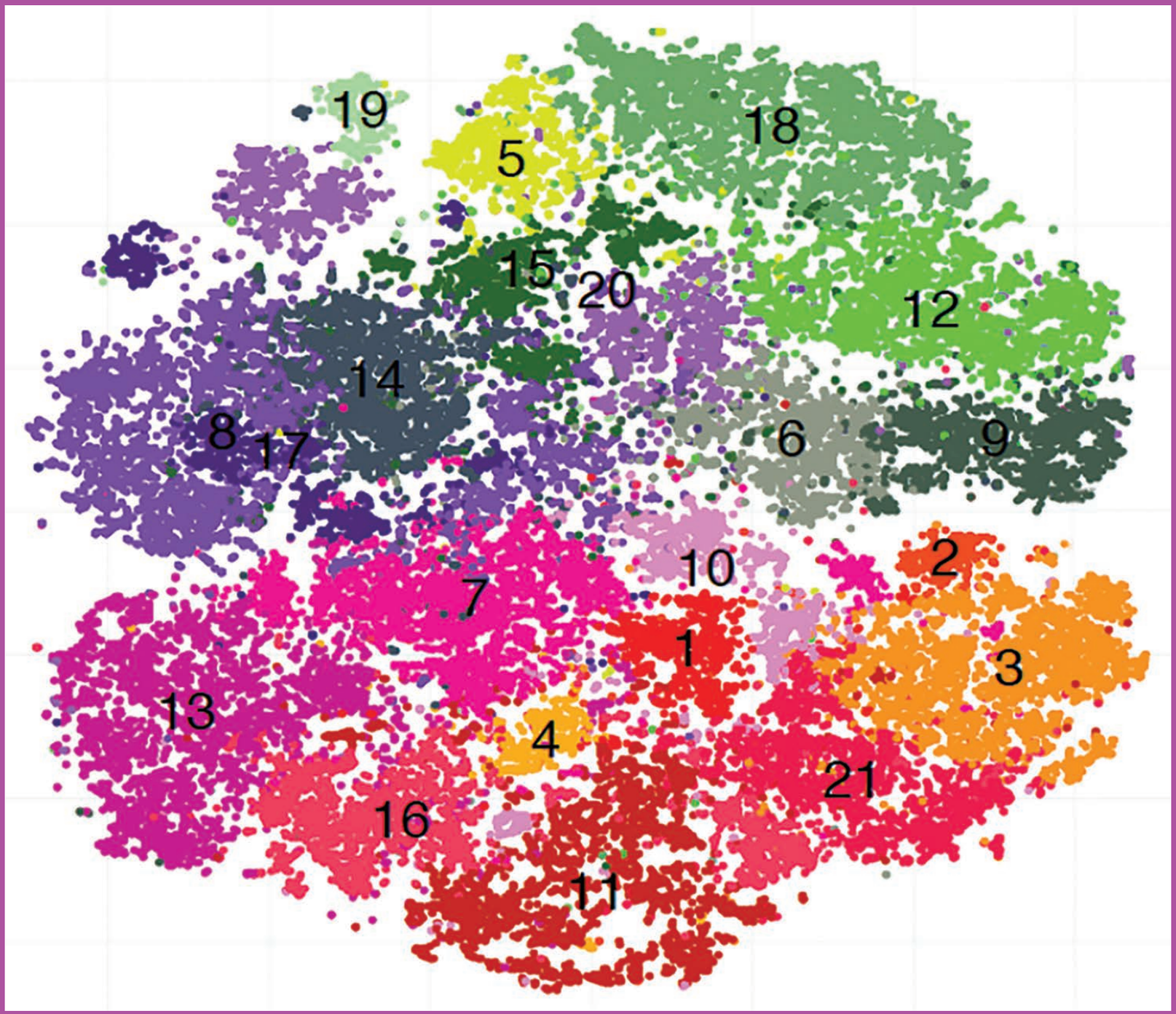
And: "There's been this pervasive worry throughout my medical and preclinical training that I am not emotionally equipped to give that kind of support to another human being. I would like to. . . ."

Murali and Pressimone asked each student questions while photographing them, including, "What are some intrinsically good qualities about yourself that are going to make you a fantastic doctor one day?"

When the interviews began, students filed into the room with nervous smiles. They didn't know what they were in for, and it was much easier to name others' positive attributes than to reflect on their own. As time went on during the interview, hesitance tended to disappear, note Murali and Pressimone. It seemed therapeutic for their fellow students to share their feelings and insecurities.

"It is important to be aware of the fact that we have a whole tribe of people who believe we can do it," says Murali. "With the right education, hard work and passion, there's no reason why we can't." *—Maggie Medoff*

—Photography by Cami Mesa



Using advanced techniques, a Pitt group found fetal cells that develop immune responses much earlier than imagined. SHOWN HERE: Clusters of various types of T cells (indicated by color) in the fetal immune system.

SLICK AS A BABY'S GUT

THE SURPRISING WISDOM OF A NEWBORN IMMUNE SYSTEM

BY ADAM REGER

Much like their brains, babies' immune systems are quick learners, adapting to their environments from the word *go*.

But a recent study from Pitt researchers suggests that, immunologically speaking, go-time might actually start in utero, long before a baby is even born—a notion that turns textbook biology on its head.

Using advanced cellular and genomic analyses, Liza Konnikova, assistant professor of pediatrics in Pitt's School of Medicine and a neonatologist at UPMC Children's Hospital of Pittsburgh, studied the mucosal immune system by analyzing gut tissue taken from fetuses ranging from 14 to 23 weeks of age. Results of the collaboration between Pitt researchers and scientists from Tel Aviv University in Israel were published in the Nov. 4, 2019, issue of Developmental Cell.

The immune system is really two systems: innate and adaptive. The innate immune system is always present in the body and includes natural barriers like skin and dendritic cells. The adaptive immune system, as the name suggests, adapts to encounters with foreign pathogens, growing and learning as it meets new invaders.

"We had presumed there'd be some adaptive component" in the tissue examined, Konnikova says, "but most likely naïve, meaning it's never seen an antigen before."

She and her colleagues were thus surprised to find a significant number of B and T cells, the major cellular components of the adaptive immune system. More strikingly, most of the T cells belonged to what Konnikova calls the "memory pool," responsible for remembering past pathogens to better protect against future attacks.

That finding suggests that the fetuses' immune systems were exposed to pathogens, something that their mothers' placentas are designed to prevent—and that researchers were not anticipating.

Konnikova and others have speculated that the fetuses may encounter molecular byproducts of pathogens through amniotic fluid. But right now, she says, they don't have a clear answer as to how this could be.

"That's the burning question."

These findings raise the possibility of intervening to boost vulnerable infants' immune systems before they're even born, Konnikova says, perhaps through maternal vaccines. She pointed to necrotizing enterocolitis, a disease that affects the intestines of premature infants, causing serious inflammation that can lead to perforation and result in death. Bolstering the defenses of these infants' intestines could be a lifesaver.

Maybe fetuses are exposed to byproducts of pathogens through amniotic fluid.

The paper also sheds new light on how the adult immune system forms, and when—it turns out that the architecture of adult mucosal immunity is set far earlier than previously thought.

By the end of the second trimester, most of the T cells researchers found were of the memory variety. Although significant changes still occur as the fetus becomes an infant and then an adult, Konnikova says, "the major components of the mucosal immune system in adults are already there in fetuses."

Recent technological innovations made these findings possible. These include an approach known as CyTOF that uses sequencing processes in combination with mass cytometry, a measurement technique that tags antibodies with metal isotopes, allowing scientists to sort antibodies according to their mass. The methods used to collect and preserve the tissues are also novel.

"This work is really tricky to do, because you need human tissue," Konnikova says.

As a postdoctoral fellow, she helped develop a technique of cryopreserving tissue that allowed the Pitt-based researchers to save fetal tissue across a range of ages.

"We realized we can save the tissues, and we have all these new techniques," Konnikova says. "The way they're storing these tissues opens up these possibilities."

That includes the chance to delve even deeper into how, and when, the immune system develops.

"We're just starting to do the work." ■

GETTY IMAGES

MIRROR OPPOSITES

MEN AND WOMEN EXPRESS DEPRESSION VERY DIFFERENTLY AT THE MOLECULAR LEVEL | BY JASON BITTEL

Scientists have long struggled to understand why incidences of major depressive disorder (MDD) are higher among women than among men. Pitt's Marianne Seney has found biological evidence that the sexes might be vastly different in regard to this mood disorder.

Not only that, but by some molecular measures, they're opposites.

Seney, an assistant professor of psychiatry, and her team looked at brain tissue taken from 26 deceased men and 24 deceased women with MDD and compared those samples to samples taken from an equal number of deceased men and women who did not suffer from MDD while they were alive.

The researchers measured the genes expressed by three regions of the brain that are involved in mood regulation. When they analyzed each sex, they found that of the 706 genes that showed altered expression by men with MDD and the 882 genes that showed altered expression by women with MDD, just 21 genes were altered in the same direction. At the same time, 52 other genes displayed expression changes in completely opposite directions when it came to men and women with MDD. Further, a sex by disease analysis revealed that more than 1,000 genes were changed in opposite directions in depressed men and women.

These findings suggest that, with the exception of just a few genes, MDD presents in the brains of men and women in vastly different ways at the molecular level.

For example, Seney's team found that men with MDD had lower expression of genes related to synapse function. Conversely, women with MDD had greater expression in those same genes. And it was a similar story for genes associated with inflammation and immune function: Men had increased gene expression and women showed decreased gene expression.

These opposing pathologies were "super-surprising to us," says Seney.

The possible implications for these findings underscore the importance of studying both men and women in drug development—something that might sound like common sense, but has not been the norm in the past.

In fact, the team wrote, "many previous postmortem brain analyses in MDD were performed in mostly (or only) men." Seney says the reasons for this are many, but chiefly, it's long been viewed that men's brains are less complicated to study because men don't have all the hormonal shifts women do. This has caused an enormous bias in medical research that is still being corrected. (For instance, it wasn't until 1993 that the National Institutes of Health implemented a policy that sought to ensure that women and ethnic minorities were included as participants in clinical research.)

Just imagine that you're learning about how the brain works, but you're only studying men's brains. Say you create a drug addressing a neurological change related to depression. Even if that drug works really well for men, it "might push women further into a molecular pathology and potentially further into depression," Seney says.

The team's results were first published in Biological Psychiatry in 2018. Next, Seney hopes to disentangle how some of the genes marked by the study relate to behaviors in living people. Someday, the research may also help bring precision medicine to patients with major depression, and the first step might be sex-specific treatment.

"Maybe in the future we could look at what symptom profile a patient fulfills and then use that to target the treatment," says Seney. ■

GETTY IMAGES

BUILD A BETA HEART

A 60-YEAR-OLD DRUG COULD LENGTHEN LIFE FOR KIDS WITH CONGENITAL DEFECTS

BY ERIN HARE

Surgery can mend congenital heart defects shortly after birth, but those babies will carry a higher risk of heart failure throughout the rest of their lives. Yet, according to a Science Translational Medicine study published in October 2019 by University of Pittsburgh and UPMC Children's Hospital of Pittsburgh researchers, β-blockers could supplement surgery to build infant heart muscle and mitigate the lasting effects of congenital heart disease.

"The question is no longer, 'Can we save this baby?'" says senior author Bernhard Kühn, associate professor of pediatrics at Pitt and director of the Pediatric Institute for Heart Regeneration and Therapeutics at Children's Hospital.

"The challenge for our young patients is that we want to enable them to have a long lifespan, ideally as long as a person without heart disease."

For a congenital heart defect called tetralogy of Fallot, treatment typically involves surgery at around 3 to 6 months of age, which is incidentally when heart muscle cells—cardiomyocytes—are at peak production. Decreased heart function during the first few months may be causing these infants to miss an essential opportunity to build heart muscle.

Kühn's team collected heart tissue from 12 infants who underwent corrective surgery for tetralogy of Fallot and found that more than half of the cardiomyocytes in these samples had started to divide but then got stalled midway through the process; something similar happens with conjoined twins. The ultimate result was fewer cardiomyocytes overall, which makes the heart more vulnerable to damage later on.

"By the time our surgeons operate on these patients, the horse is already out of the barn," Kühn says. "Our data show that they have up to 30% fewer cardiomyocytes than a normal infant has at this age. That's significant. To put that in context, an adult's heart attack can destroy up to 30% of cardiomyocytes."

Through a series of experiments in human and mouse tissue, the researchers traced this cell division failure back to β-adrenergic receptors.

The natural next step was to ask whether the β-adrenergic receptor blocker propranolol—a common blood pressure medication—could enable proper cell division in infants with congenital heart defects and improve heart function.

Indeed, in the heart tissue samples taken from infants with tetralogy of Fallot, the medication enabled dividing cells to separate properly.

And in mice, propranolol treatment during the first weeks of life allowed for better recovery from heart attacks in adulthood. Compared to untreated controls, mice that were given propranolol as pups retained 30% more cardiomyocytes and were able to eject 24% greater blood volume following a heart attack. The treatment did not affect heart function.

According to Kühn, having such promising results with a tried-and-true drug like propranolol means the pathway to clinical translation could be relatively quick.

"This all comes together in a very applicable way," Kühn says. "Propranolol was synthesized nearly 60 years ago, so we're able to bypass a lot of the groundwork that would have to be done if we had identified a receptor that doesn't have a drug for it." ■

PHOTO: DEJAN/GETTY IMAGES

"HE'S BEEN HIDING MY MEDICINE"

HOW CAN WE HELP SURVIVORS OF INTIMATE PARTNER ABUSE?

BY ELAINE VITONE

Years ago, a woman in her 50s came into her doctor's office with diabetes and high blood pressure. Her eager young physician wrote out prescriptions for both, took steps to ensure that these injections and pills were affordable for the patient, and dutifully upped the doses over time as these problems persisted. Still, months and years passed, and the patient's blood pressure and glucose continued to soar wildly out of control.

Then one day as the physician, **Elizabeth Miller**, was scratching her head at the chart again, she looked up at the patient and said, "I just can't understand what I'm doing wrong. I can't seem to help get this under control."

Then, she paused.

The woman on the exam table hesitated. "I'm not sure how to tell you this. He's been throwing my medicines away." And out tumbled a devastating story of brutality and humiliation at the hands of her husband, for years.

In the clinic, abusive relationships, now known as intimate partner violence (IPV), can take on a number of unexpected guises, Miller says. Not following medical advice—nonadherence, as doctors call it—is just one. She's come to see nonadherence as a possible red flag. Because many times, abuse survivors (usually women) are absolutely on board to follow their doctors' orders. But their partners are trashing their pills. Or sabotaging the car on the day of their appointment. Or threatening violence if they go.

One in three women in the United States has experienced physical or sexual violence from a partner at some point in her lifetime. That number doesn't even include nonphysical forms of IPV, like controlling behavior or emotional abuse.

All forms of IPV can have devastating effects on health, both in the short-term and the long haul. Survivors have much higher rates of depression, anxiety, post-traumatic stress, substance abuse and disordered eating. They have more unintended pregnancies and sexually transmitted infections, including HIV.

They're more likely to develop chronic pain and autoimmune disorders. And, as in the case of the woman from Miller's story, survivors often have little control over how well they manage whatever chronic health conditions they may face.

In 2011, Miller, a pediatrician who specializes in adolescent medicine, came to the University of Pittsburgh, joining one of her scholarly heroes—**Judy Chang**, an ob/gyn who studies doctor-patient communication in obstetric care. Miller is the director of Adolescent and Young Adult Medicine at UPMC Children's Hospital of Pittsburgh and a Pitt professor of pediatrics, of public health and of clinical and translational science. Chang is an associate professor of obstetrics, gynecology and reproductive sciences and of medicine. Between them, they have several decades of experience as women's health care providers and community advocates, as well as researchers investigating how social situations affect women's health.

Chang

Recently, we sat down with these two Pitt experts to discuss how we can better help survivors. They explained that physicians are extremely well positioned for this; the clinic can serve as a safe, accessible and confidential hub for information and support. And yet, Chang and Miller have found that the standard way doctors are trained to broach the subject of intimate partner violence (i.e., *Do you feel safe in your relationship?*) is missing the mark. The pair have devised a new strategy that they've shown to be effective at preventing women from falling through the cracks.

The following has been edited for brevity and clarity. For the full discussion, listen to our Pitt Medcast episode at **pittmed.health.pitt.edu/pitt-medcast**.

First, let's define some terms. What is intimate partner violence?

Judy Chang: Essentially it's whenever there is [or is the threat of] either physical or sexual violence being perpetrated from one partner to another, or people being controlled and dominated and afraid to essentially make their own decisions and live their own free will.

Elizabeth Miller: There is still a common assumption it's only about broken bones and bruises, when in fact so much of it is the emotional, the controlling behaviors—the sexual violence, things that happen in the bedroom; the coercion, the financial dependence, threats of taking the children away. All kinds of emotional and psychological abuse.

And, until relatively recently, health care providers had not even acknowledged the extent to which abusive partners can interfere with accessing care, can interfere with use of medication and adherence to medication, and even use substances—including opioids—as a way to control their partner.

JC: There is a new phenomenon sometimes called cyber abuse or cyberstalking. That can involve different technologies that track where people are, monitor their interactions. And in terms of social media, the threats of posting things that would be psychologically, professionally or socially detrimental.

EM: In one of our studies, we surveyed adolescents who were seeking care in confidential teen clinics. Over 40%, both boys and girls, reported experiences of cyber dating abuse in the last three months. Among the projects that we've been working on is: How do you help parents, adult allies, health care providers to actually talk to young people about healthy ways to use social media?

Dr. Miller, you were the first to identify and quantify what's now known in medical literature as reproductive coercion. Can you define it for me?

EM: Reproductive coercion is a constellation of behaviors, often in the context of heterosexual, sexual relationships, where a male partner will explicitly attempt to impregnate his female partner against her wishes. In a study where I interviewed close to 60 young women with histories of being in abusive relationships, about a quarter described these kinds of phenomenon: flushing birth control pills, preventing her from getting to the clinic on time for her Depo-Provera injection, removing the birth control patch, pulling out her vaginal ring, breaking the condom, putting holes in the condom, removing the condom during sex and the like.

There were also stories along the lines of, *Honey, we're going to make beautiful babies together*—pregnancy pressure—as well as threats to leave the relationship if she didn't get pregnant.

Miller

PHOTOS COURTESY CHANG AND MILLER. PHOTO COLORIZATION: ELENA CERRI

We have shown that reproductive coercion is associated with other forms of intimate partner violence.

Often, women, and especially adolescents, do not necessarily recognize reproductive coercion as abusive behavior. *Well, he's never put his hands on me* [violently]. And yet when I talk about it with my patients, inevitably they'll lean in and say, *That's what's going on for me, too.* It is definitely a phenomenon that we need to be talking more about, making sure that young people are aware of and understand the strategies to prevent pregnancies that they don't want. We can offer contraceptive options that a partner can't interfere with, including the intrauterine device, and offering emergency contraception that she can take along with her, for example.

About 30 to 35% of women who are murdered,

What are some common misconceptions among clinicians about intimate partner violence?

JC: The biggest one is the focus on leaving. The assumption that if they really wanted to address the violence, that leaving would be the answer. And I can't completely blame people for thinking that way, because it seems logical. The challenge is that it's not always the safest thing.

About 30 to 35% of women who are murdered, are murdered by either a current or former intimate partner. There's a high correlation between breaking up, filing for divorce, kicking the person out—essentially anything that ends the relationship—with the possibility of a homicidal attack. We can't take that lightly.

It's also not always feasible. There may be issues that person is dealing with financially, socially. Obligations to children and other family members, connections with community and other things that one might rely on. As well as the

very real issue of being in love with that person who is likely not always behaving in this way.

Dr. Chang, you've studied what motivates women to disclose their partners' abuse and seek help from their health care providers. What have you learned?

JC: What was eye-opening to me was that these women said that even if we asked in the best possible way, and we were the nicest person ever, they still might not be ready to disclose.

It's just hard. It's scary. They may not have said it out loud to even themselves before. So what they wanted us to recognize is to have patience, but to also give them the information and resources and support without requiring the disclosure. To not keep all of that information hostage to the "yes" answer, but, instead, make it freely available, so that when they're actually ready—to make a change, do something, tell somebody—that they have those resources.

That was an *Aha!* moment for me, because I was trained in the preventive medicine model of screening, testing, diagnosis and referral or treatment. And that didn't fit in there.

So now, we have a new concept: Maybe I don't need to know the "diagnosis." Maybe the patient actually needs to know that she can make her own diagnosis. And if she does that, then she can access those resources herself. If I make them available.

are murdered by either a current or former intimate partner.

What is a good way into these conversations in the clinic?

EM: *We're offering this information to all of our patients, because far too many have experienced unhealthy relationships that have a huge impact on their health and well-being. And maybe this information is relevant for you. I bet you it's relevant for somebody that you know.*

That makes it easy to take the information, but it also makes them think about the people in their lives whom they care deeply about and reach out to provide more support.

We've tested this approach in numerous randomized trials, finding that not only do the patients like it, their knowledge increases about resources, their ability and their confidence to use strategies to help increase, their safety increases, and especially in our adolescent work, we're seeing significant reductions in experiences of abuse.

JC: I think a lot of health care providers sigh and say, "Yet another thing." Right? And the common reason why they will not add another guideline, requirement, screening topic, et cetera, that we hear is the time issue.

And it's very interesting, because it doesn't take that much time to say what Liz just said. Compare that to not knowing why the blood pressure is not getting under control. Trying to figure out why this birth control method is not being used over and over and over again. Compare it to that, and really, where is the most effective use of your time?

If the usual preventive medicine paradigm—screen, test, diagnose and treat—doesn't fit, what does? How can physicians reframe their thinking?

EM: We can move away from that goal of *I have to get a disclosure, and I need to then get them out of this relationship*—that sort of rescue fantasy—and move toward increasing awareness, building a relationship, being part of our patient's support network and then doing what we can to empower them. Or to partner with them and be part of their solution.

JC: I think oftentimes we feel the responsibility of knowing the answers, having the treatment plan, prescribing "the cure." And what we're saying here is: That burden is not ours to hold by ourselves. We are meant to help the patient identify what will work best for her. We need to trust her in her judgment—and we should. Because there's a good chance we don't know the full context of what she's experiencing. She is the best person to make those decisions. But being able to be there to say, *What can be helpful to you? How can I best help? I'm sticking with you. If that didn't work, let's brainstorm something else. Let's figure it out together.*

In one of our studies, we had a focus group—these were all women who were living at a shelter at that time—and one woman talked about how she had finally disclosed to her health care provider about the physical abuse that she was experiencing. And he had paused and looked at her and said, "I am so sorry. I have to admit I don't know much about this topic, but I am willing to learn with you. Can you tell me everything you learn, so that I can not only help you, but help others who are experiencing this, too?"

And there was this huge *Oh my God* going all around the room, where all of the women are just like, *Wow! What's his name? I want to go to him. He sounds fantastic.*

It doesn't take much. You don't have to be an expert. In fact, not assuming that role of expert is probably helpful. Being able to have the humility to say, *What do you need? Help guide me. Let's work together.* Hopefully that actually makes health care providers feel the burden lift from them.

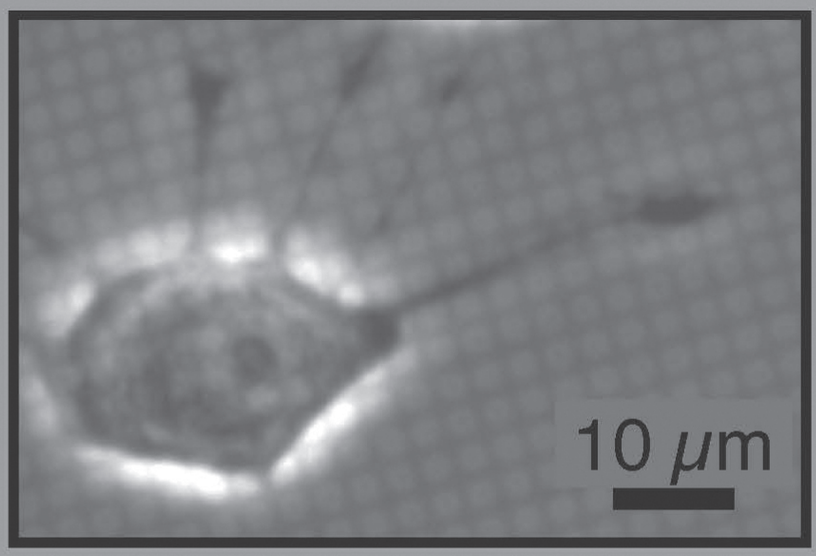
What resources should physicians bring to share with women in the clinic?

JC: The National Domestic Violence Hotline number, 1-800-799-SAFE, is staffed 24/7 by advocates who can link that person to their local resources, provide safety planning and crisis counseling, and be empathetic and a supportive ear for anyone who needs those services immediately. That's easy enough for a person who doesn't feel safe taking anything in writing to memorize.

EM: We have an obligation to know our local resources. To take the time to call the hotline in our region and to get to know who the advocates are, invite them into our clinical space and invite them to be part of our team. The more that we can build that kind of collaboration, I think the better we can serve our patients.

JC: And I want to be empathetic to health care providers, too. This is a hard topic. When one gets a disclosure, that itself can be haunting and traumatizing. One thing on my wish list would be to help create more space and time to allow health care providers to digest, process and heal from some of the secondary traumas that they're experiencing in the care of their patients, not just with regard to this topic, but so many of the other challenging things we're dealing with as health care providers.

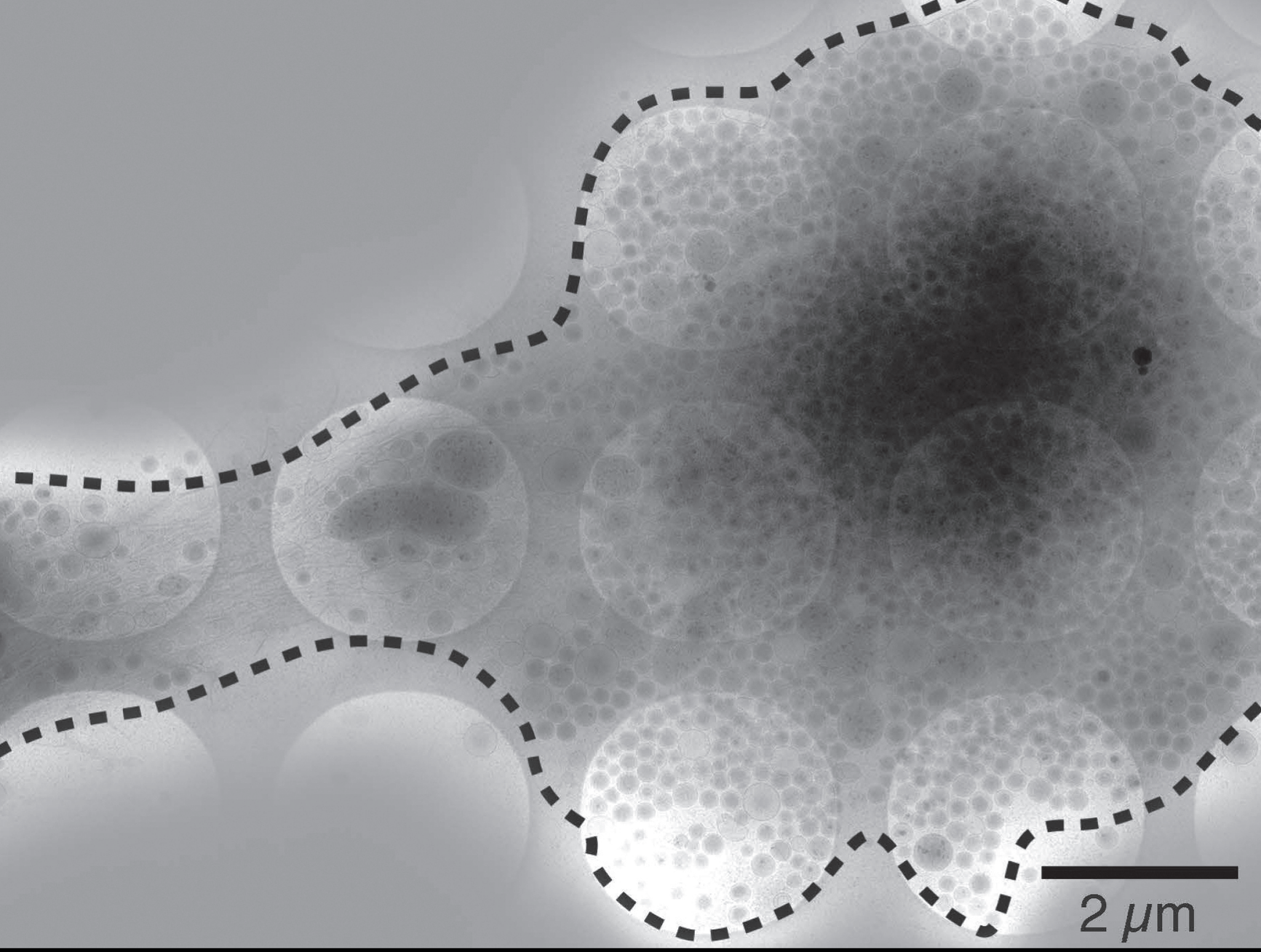
Editor's Note: *In an upcoming issue, we'll explore how community members are challenging harmful masculinities and other social norms that can lead to violence.*



ANOTHER LOOK

NEW TECHNIQUES REVEAL ONCE-HIDDEN CLUES TO GUIDE DRUG DESIGN

BY SHARON TREGASKIS

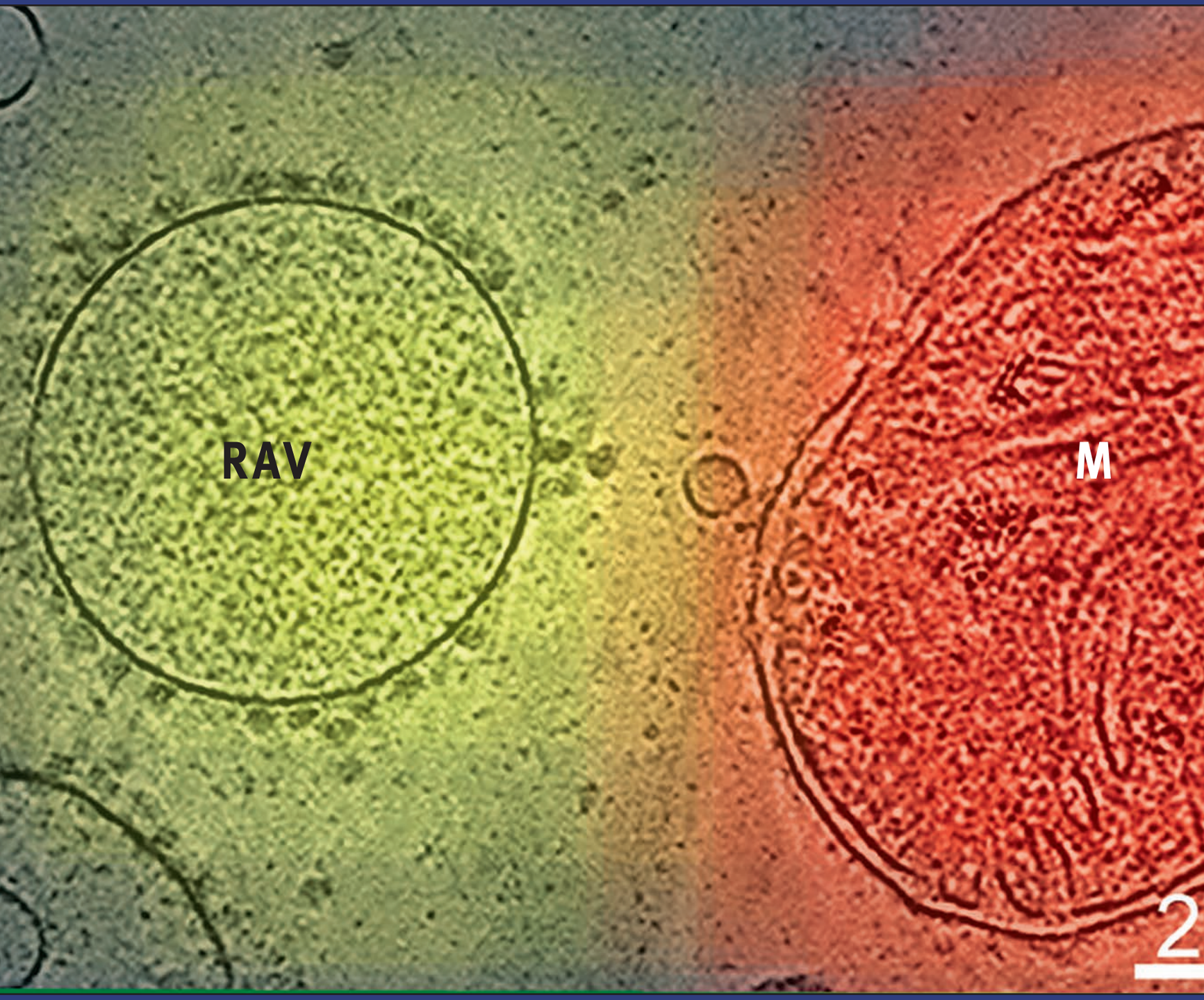


Margaret Bourke-White was 8 years old in 1912 when she accompanied her father to a foundry. The fiery spectacle of molten metal gleaming through smoke and grime captivated the girl. Fifteen years later, as a budding industrial photographer, she would talk her way into Cleveland's Otis Steel Co., intent on recreating the images burned in her mind's eye.

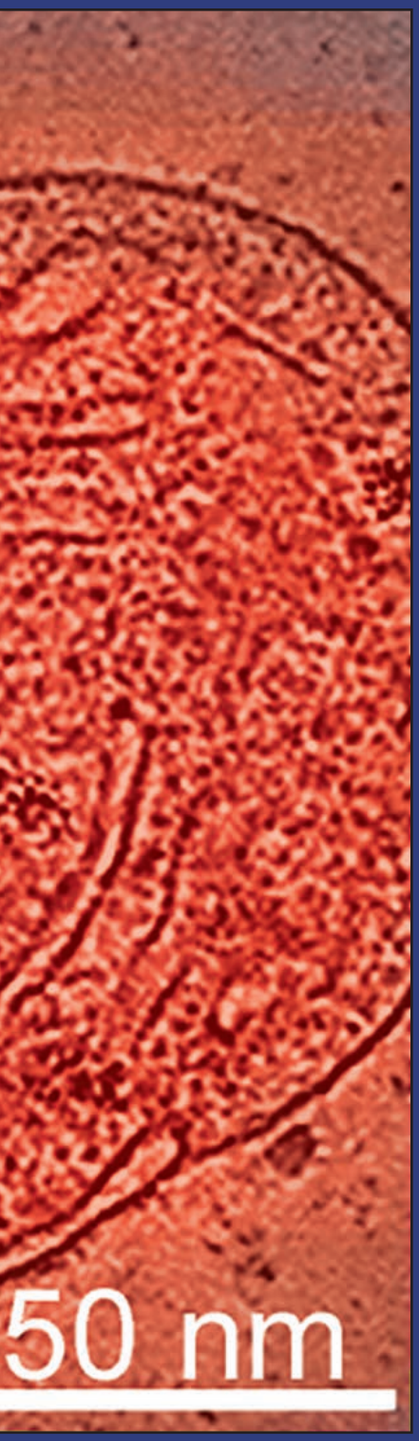
The camera, however, failed to capture what Bourke-White had seen. Her black-and-white film was sensitive only to blue light, and in her early prints, the luminous metal visible to the naked eye was as black as the soot that coated the factory.

Like a photographer modifying aperture, exposure time and lighting to capture a fleeting moment, Zach Freyberg tweaks the tools of cryo-electron microscopy and tomography to visualize the subcellular machines that produce and transport proteins within intact cells. His findings suggest new ways for understanding chemical signaling throughout the human body and rational strategies for drug design. Here, a thin protrusion extends from the periphery of a secretory cell grown directly on a grid to produce images that preserve vital contextual details.

PHOTO: POURED MOLTEN STEEL IN THE OTIS STEEL MILL, CLEVELAND, OHIO, 1928. (BY MARGARET BOURKE-WHITE/ THE LIFE IMAGES COLLECTION VIA GETTY IMAGES)



Consider a tale of two brick towers—one a sturdy, 10-story building and the other featuring the same number of bricks, but at a 20° angle to the ground (an exaggerated Leaning Tower of Pisa). That second tower obviously wouldn't be habitable. But depending on the scale and style of analysis, says Freyberg, that fact might not be clear. "If you just ground up the bricks, ran them on a gel and compared them, those two structures would look the same." So when he started investigating how secretory cells produce and deliver chemical signals, Freyberg was committed to imaging whole cells to preserve context; that choice would unleash a flood of data. To focus its attention, the team, including collaborators in the laboratory of Grant Jensen at Caltech, used a combination imaging technology (dubbed CLEM) to color code: Red shows mitochondria, and yellow is the endoplasmic reticulum (ER). The fluorescence drew their eyes to a previously unknown, mobile form of the ER—the ribosome-associated vesicle (RAV).



Throughout the winter of 1927–28, the photographer tweaked exposure, vantage point, printing process. Her skin burned and her camera blistered. At last, using a lighting technique developed in Hollywood, Bourke-White got her shot. "Saturate yourself with your subject," she would later write, "and the camera will all but take you by the hand and point the way."

Zach Freyberg has spent more than a decade tweaking techniques for another kind of imaging—cryo-electron microscopy and tomography inside cells. He is intent on seeing the engines of subcellular protein manufacture.

In April, Science Advances published a series of images captured by Freyberg that may add a chapter to basic biology textbooks. Freyberg is both a psychiatrist and a cell biologist—and a University of Pittsburgh assistant professor with appointments in both of those departments. His work reveals a previously unknown form of the endoplasmic reticulum. Freyberg collaborated with Nobel laureate Joachim Frank, Caltech's Grant Jensen and others on the study. The newly recognized form is dubbed RAV—for ribosome-associated vesicle. The discovery suggests a mechanism by which secretory cells throughout the body provide instantaneous, localized response to activity among cells. The work also suggests fresh treatment strategies for diseases like schizophrenia, Parkinson's and diabetes that trace their roots to glitches in chemical signaling.

Like Bourke-White's Otis Steel photos, the Freyberg images deploy novel imaging techniques to investigate the synergy of form and function. "If you can see the machinery that's responsible for local [protein] translation, especially in response to different levels of activity in the cell, the next step is learning to control it," says Freyberg, who sees the work as a step toward rational design of medications that coax plasticity in the aging or diseased brain.

Freyberg's work is inspired by a clinical conundrum that has plagued his own psychiatry practice since residency. It's an issue that stretches back to the 1950s, when antipsychotic meds were first introduced.

For every prescription penned for antipsychotics like chlorpromazine or risperidone, psychiatrists hazard as much harm as good. On the upside, after only a few doses, people with schizophrenia often report that their hallucinations have diminished in intensity.

Frequently, however, the drugs also precipitate rapid weight gain, insulin resistance, type 2 diabetes—life-shortening metabolic issues. Some patients are plagued by spasms and other neuromuscular side effects; a few suffer severe cardiovascular symptoms. For some 40 percent of people with schizophrenia, risk outweighs reward, and they quit their meds.

Those stats should surprise exactly no one in medicine. "While we still have many questions and poorly understand the therapeutic benefits of these medications in schizophrenia," says Freyberg, "we have even less understanding of why these medications have such profound metabolic side effects."

By the time Freyberg started his postdoc at Columbia, a growing body of literature suggested that like jostling a radio to boost its audio reception and eventually snapping a part, antipsychotics were rattling dopamine signaling throughout the human body. In one study, Freyberg and collaborators found that the pancreas produces its own dopamine, has its own dopamine receptors and uses dopamine to regulate insulin secretions.

Freyberg set out to figure out how antipsychotics altered that process. He decided to complement more conventional analyses with high-resolution 3D images of the structures within certain cells while the cells were intact. He looked in the pancreas, where dopamine impedes insulin production; in the kidneys, where it helps regulate blood pressure; and in the brain, where it influences the biochemistry of motivation and perception.

As an undergraduate in the mid-90s, Freyberg had become sensitized to the profound ways in which the processes of imaging itself can transform a subject. At the time, he was using various microscopy methods to study living sea urchin eggs. Delicate stuff.

"For the last 70 years, we've been looking at samples that were fixed, sectioned, exposed to heavy metals like lead and uranium," he says. "All of these treatments cumulatively affect the cell, so a lot of what's in the textbooks and what we think we know is a product of these processes."

X-ray crystallography, for example, generates extremely detailed 3D images of proteins, but the crystallization process destroys context. Transmission electron microscopy (TEM) produces detailed 2D images, but only works if electrons can move through a sample. Scientists fix a specimen with chemicals like formaldehyde; mount it in resin; and shave off slices measured by the nanometer. Then they bombard those slices with electrons.

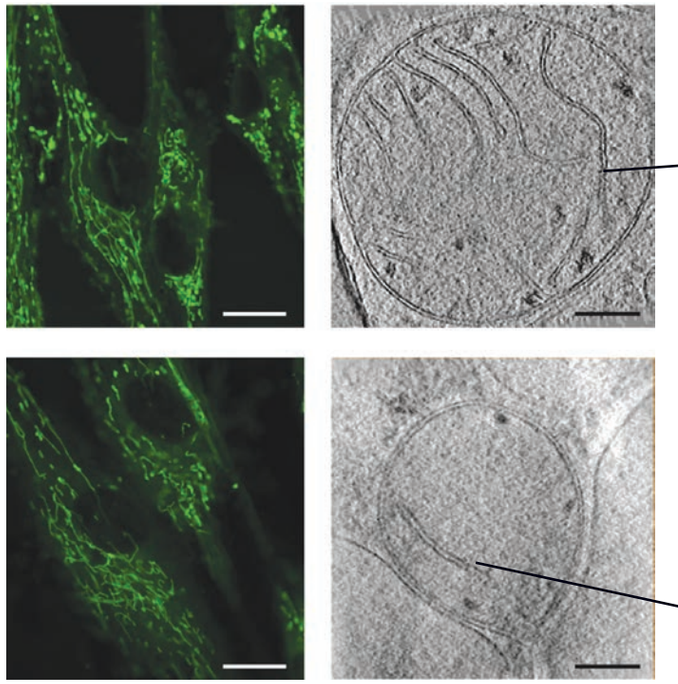
To study dopamine-secreting cells, Freyberg chose a technique that wouldn't be so rough on his samples: cryo-electron microscopy. CryoEM, as it's called, uses a deep freeze instead of chemicals to fix samples and lower-dose electron beams than conventional TEM, allowing the study of single proteins, nucleic acids and other relatively fragile biomolecules. And Joachim Frank was already using cryoEM at Columbia to study protein biosynthesis in the ribosome. So when Freyberg joined Columbia's faculty in 2011, he introduced himself.

Frank was imaging purified organelles in two dimensions. Freyberg opted to sacrifice resolution for context and expose whole cells to the electron beam. First, he grew native cells from the rat pancreas and rat cortical neurons as well as connective tissue from mouse embryos on cryo-electron microscopy grids, the inert scaffolds used to hold samples in place. Then, using a technique known as a "tomographic tilt series," the team captured dozens, and sometimes hundreds, of views of the same intact cell at 1° increments spanning 120° and digitally reassembled them into 3D representations.

"Tomography is definitely an area where we'll see the biggest payoff in the future," says Angela Gronenborn, chair of Pitt's Department of Structural Biology. "We'll do cellular biology in atomic detail, and up until now, that was impossible. It's no longer divide and conquer, but look at your targets or molecules in the normal cellular setting."

The Science Advances paper isn't the first time Freyberg has used such techniques to uncover insights obscured by other methods. In a paper for iScience, he and another team at Columbia, including Frank, identify structural anomalies associated with Leigh syndrome, a fatal neurological disorder caused by mutations that affect mitochondrial energy production.

By growing whole cells from a patient and a healthy control directly on the cryoEM grid, the team could analyze tomograms of the mitochondrial cristae. The cristae are the protruding folds within the organelle's inner membrane where a cell's energy source is synthesized; more cristae mean more energy. They documented profound differences in the cristae volume, shape and orientation from the patient and control.

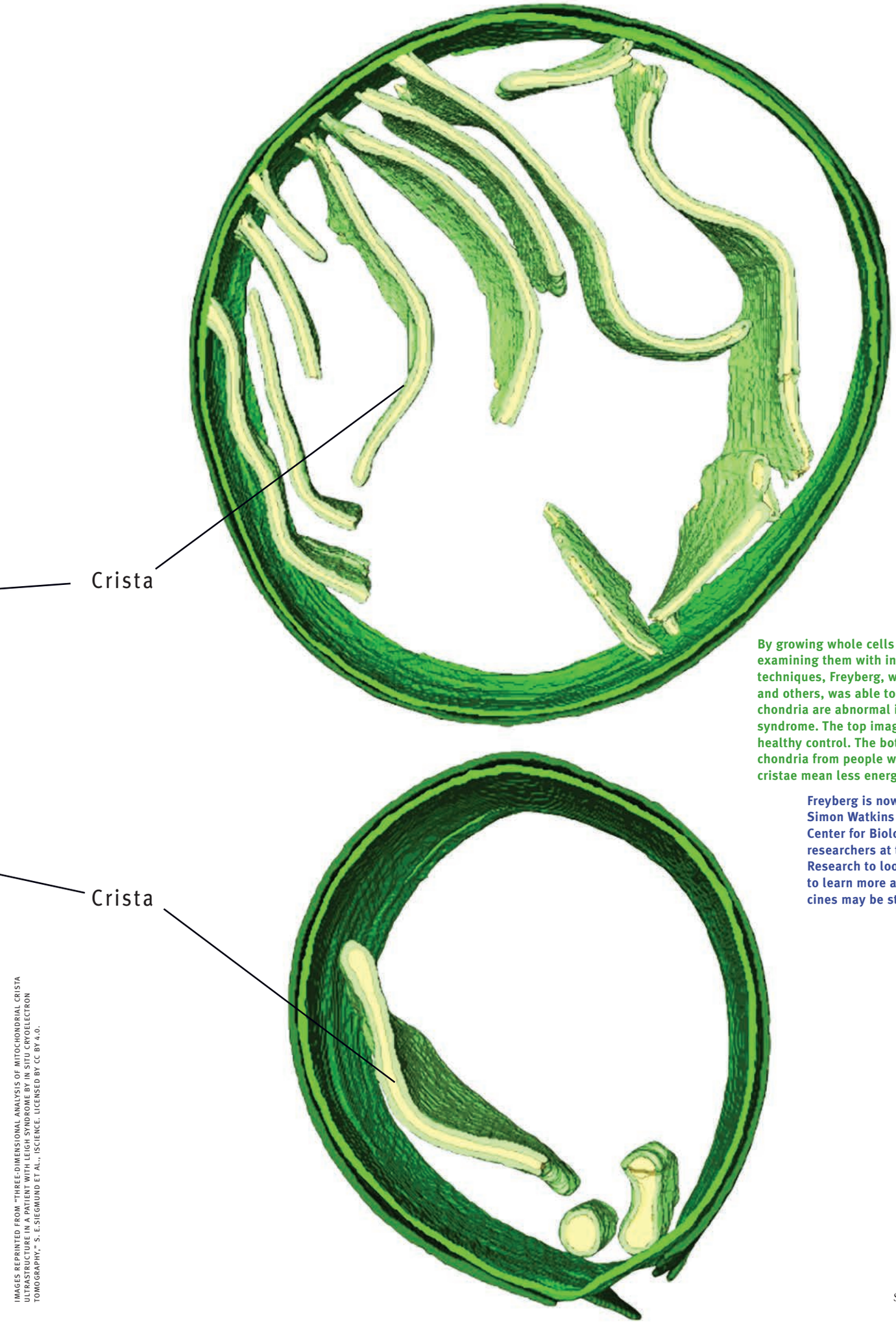


Scale bars represent 5 µm.

Last summer, Pitt acquired a new cryoEM instrument known as the Krios, capable of greater resolution and faster image collection than its predecessor. In partnership with the manufacturer, Freyberg has been refining tomographic imaging approaches to enhance his capacity to capture RAVs at greater resolution within cells. He speculates that the newly discovered vesicle plays a role in neuroplasticity, which isn't always desired. For instance, people with schizophrenia seem to have fewer dendrites. (Pitt's psychiatry chair David Lewis discovered this.) And Parkinson's seems to involve less dopamine production. Maybe figuring out how to alter RAV function will lead to tailored treatments that boost neurological function without compromising signaling elsewhere in the body.

Margaret Bourke-White was not yet 50, covering the Korean War, when she began experiencing the symptoms of Parkinson's disease that would end her career. She had followed her camera for more than three decades as a staff photographer first at Fortune and later LIFE, from the Great Depression to the American civil rights movement. She perched atop the gargoyles of the Chrysler Building, rode in a bomber over Tunisia, learned from Mahatma Gandhi how to spin.

"If you want to photograph a man spinning," she would later write, "give some thought to why he spins. Understanding for a photographer is as important as the equipment he uses."

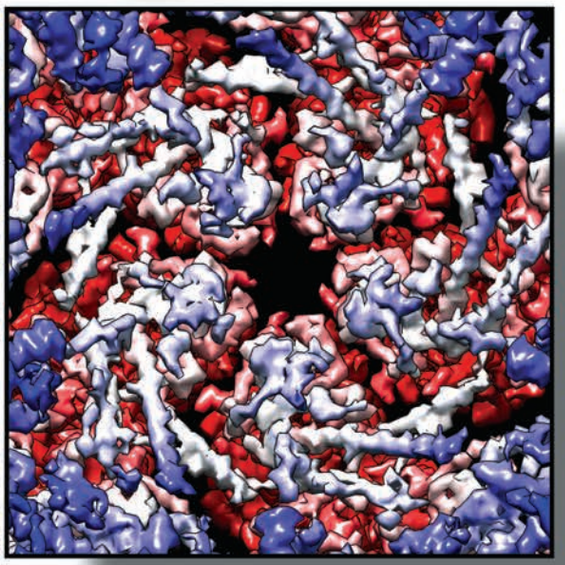


By growing whole cells on a grid, then examining them with inventive imaging techniques, Freyberg, with Joachim Frank and others, was able to see how mitochondria are abnormal in Leigh's syndrome. The top images show the healthy control. The bottom shows mitochondria from people with Leigh's. Fewer cristae mean less energy.

Freyberg is now partnering with Pitt's Simon Watkins and Alan Watson at the Center for Biological Imaging along with researchers at the Center for Vaccine Research to look at COVID-19. They hope to learn more about how the new vaccines may be stopping infection.

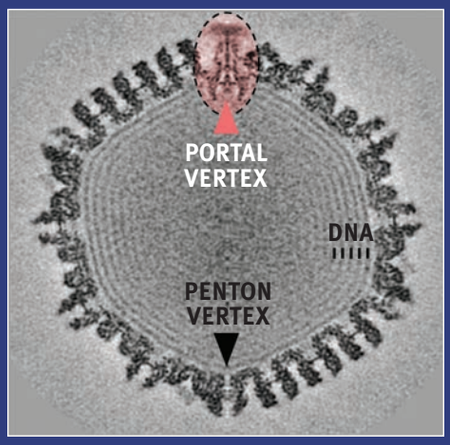
IMAGES REPRINTED FROM "THREE-DIMENSIONAL ANALYSIS OF MITOCHONDRIAL CRISTA ULTRASTRUCTURE IN A PATIENT WITH LEIGH SYNDROME BY IN SITU CRYOELECTRON TOMOGRAPHY," S. E.SIEGMUND ET AL., ISCIENCE. LICENSED BY CC BY 4.0.

James Conway's collaboration with Pitt professor Fred Homa focuses on the herpes simplex virus and the "portal vertex," where DNA moves in and out of the protein shell (or capsid). Shown here, a cryo-electron micrograph of herpesvirions superimposed with a model of the capsid and a close-up of the interior surface revealing numerous corkscrew-like structures (alpha-helices). To understand the roles of the shell proteins, Conway and group member Alexis Huet use genetically engineered variants of the capsid with slightly modified DNA when imaging. This and other approaches are giving them clues about how form affects function. Conway's knack for coaxing forth high-resolution data has led to a wealth of collaborations. He's coauthored structural analyses on hepatitis B virus, papillomavirus, enteroviruses, canine parvovirus as well as bacterial viruses (phages) HK97, lambda and T5, among others. "It's hard to say no," he concedes.



BUT WAIT, THERE'S MORE

BY SHARON TREGASKIS



What makes viruses so formidable? Their protective shells, called capsids, play a large part. Like a fireproof safe, the capsid contains and protects the genetic strands that give HIV, Zika and the flu their destructive powers. Identify each protein within the shell of a particular virus, in its relative position, and a vaccine or antidote designed to target the weakest link can crack the viral defense system without affecting the health of its host. Game over.

That's the hope. Pitt professor of structural biology James Conway has spent more than 25 years using cryo-electron microscopy to produce 3D maps of capsids by knitting together thousands of 2D images. He's shed light on the herpes capsid in particular. Vaccines and medications designed to target the weak links Conway uncovers could furnish more effective protection from Epstein-Barr, shingles and other herpes simplex viruses, with fewer side effects.

When Angela Gronenborn founded Pitt's Department of Structural Biology in 2004, in addition to recruiting talented researchers like Conway, she outfitted the basement of BST3 with the best imaging tools on the market—including a Polara cryo-electron microscope, which Conway has gotten to know quite well. So when the manufacturer announced a few years ago that the Polara would be end-lifed in 2018, Gronenborn wasted no time arranging to replace it with the latest model.

Pitt's brand new Titan Krios was installed last July.

"In structural biology this is *the* equipment," says Gronenborn. At a cost of $6 million, the unit represents a big financial commitment from the University and the National Institutes of Health. "It was very easy for the NIH to give us the money," says Gronenborn, "because we had a major commitment from the chancellor and Dr. Levine."

Conway served as principal investigator for the National Institutes of Health grant that brought the Krios to Pitt, and he managed the installation process to get it online.

Like the slicing, dicing Veg-O-Matic of late-night infomercial fame, the Krios operates in multiple modes. That flexibility makes it an attractive tool for scientists across Pitt's campus and elsewhere who are intent on imaging tiny structures while they are intact, including viruses, enzymatic machines and even suborganelles within whole cells.

In basic imaging mode, the machine generates thousands of single 2D images at extremely high resolution—so high it's measured by the Ångstrom. (That's one hundred-millionth of a centimeter, a unit typically used to characterize wavelengths and arrangements of atoms in space.) Using the Polara, Conway coaxed the resolution of his work from 10 Ångstroms down to 4. With the Krios, he's already reached a target of 2.1 Ångstroms. "[That] is very high," says Conway, "the kind of thing you expect from X-ray crystallography." (That's the technique Rosalind Franklin used that gave us the first view of the double helix.)

Conway expects to use the Krios to analyze particles not suitable for X-ray crystallography.

The machine is also able to bring larger (though still tiny), asymmetric objects into focus. In a tomography mode, it can knit together hundreds of 2D images into 3D representations. The approach has Pitt's Zach Freyberg making waves in cellular biology. (See p. 22.)

Conway is exploring a joint project with Pitt vaccine developers to visualize the spike protein that gives coronavirus its name (corona is Latin for crown). The researchers want to look at how the spike is organized and how antibodies or drugs bind to neutralize it.

His work on solving other viruses will help him hit the ground running. ■

10,000 GENOMES SEQUENCED, AND COUNTING

BY EVAN BOWEN-GADDY

PHOTO: UPMC GENOME CENTER. PHOTO ILLUSTRATION: ELENA CERRI.

A decade ago, if you were a university researcher or a clinician who wanted to sequence some RNA or a full genome, your week might have looked like this: Send out a sample to an off-site, private company, pay them a stack of money, wait for them to sequence it and hope that your sequencing quality wasn't a total dud. "You just dealt with it," says Udai Kammula, director of the Solid Tumor Cell Therapy Program at the UPMC Hillman Cancer Center and associate professor of surgery at the University of Pittsburgh. Now, as Kammula studies RNA and full genome sequences of cancer cells, he does it all at home base, for much less and with a quicker turnaround time.

Since November 2018, researchers and clinicians alike have sent their to-be-sequenced samples to UPMC's own Genome Center. Five behemoth next-generation sequencers, which look more or less like photocopiers, as well as a series of robotic arms have sequenced more than 10,000 samples since the center opened, says Annerose Berndt, director of the Genome Center and faculty member in medicine.

Berndt says that beyond scale, however, the unique part of the Genome Center is

IN THE CLASSROOM

Philip Empey, associate professor of pharmacy and therapeutics, was teaching a pharmacogenetics class in 2014 when he had the idea for a class project: Would students be interested in going through genetic testing personally and using the resulting data in class exercises? With a resounding "yes" from students, thus began his Test2Learn curriculum. A program based on Empey's model has received funding from a $2.8 million grant from the Richard King Mellon Foundation to integrate with the UPMC Genome Center. The grant will equip learners with the Genome Center's ability to do full genome sequencing.

The expanded program will teach practicing providers about applying genetics to care. Mylynda Massart, an assistant professor of family medicine at Pitt who helped write the grant proposal, says the program builds excitement about a topic people may have found unengaging previously.

"Not everyone is as excited about genetics as we are," says Massart. The "secret sauce" in their program, she says, is that "clinicians have the opportunity to learn about genetics using their own DNA. Simultaneously, there's a drive to better understand and better integrate the knowledge." And, she notes, that firsthand experience helps them care for their patients. *—EBG*

that it's embedded within an academic medical center. "It's very valuable to have both the research side and clinical side under one roof," says Berndt.

So, what does this mean for research and for patient care?

For instance—how the capability might be applied in the lab:

Cameras have a feature built in called "white balance," in which the camera can look at a white wall during the golden hour or during a dim, blue dusk and say, "That, right there, is not golden or blue—that's what white looks like." It knows what normal white looks like, so it's able to correct itself if it sees off-white.

Kammula is trying to do the same sort of thing at the Genome Center. If he and his colleagues can sequence some normal RNA, say, from bone marrow, then compare it against RNA in a patient's mutated tumor cell, then they will be able to identify all the abnormalities for that particular patient. They'll be able to see the off-white.

For instance—how it's showing up in the clinic:

As clinicians in the NICU attempt to diagnose an infant's condition, they may spend lots of time iterating through a series of diagnostic tests, says Adrian Lee, director of Pitt's Institute for Precision Medicine and professor of pharmacology and chemical biology. "If they're wrong, they go back and try to figure it out again and order another test; and if that goes wrong, they order another test," says Lee. This kind of reactive testing, what's known as a diagnostic odyssey, has been the standard of care for years.

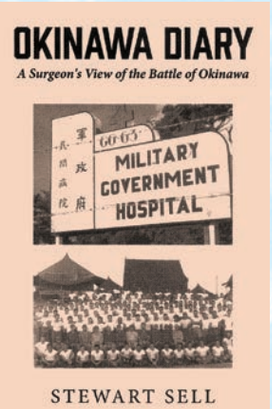
With the capabilities of the Genome Center, however, UPMC's NICUs are turning toward a single genomic test. They are evaluating a new test for children in the NICU, says Lee.

"If you do whole genome sequencing up front, oftentimes you can immediately know the diagnosis, and sometimes that changes medical care." ■

CLASS NOTES

'60s

On June 27, 1945, surgeon and Commander **Oliver Sell** (MD '26) wrote from Okinawa, "I was wondering, as I lay awake last night, if such things as clean people, lighted houses, motion pictures, beds, laughter, etc. still exist in this world." This was just a few days after his unit was ordered to build a field hospital (for locals and U.S. soldiers) behind enemy lines and in a hurry, during the Marines occupation. "Friday morning, June 22nd, we didn't have a tent pole on the area. At 800 hours, we reached the site assigned to us and started setting up. At 1530, the first truckload of patients started to arrive. By the evening we had 500 patients in all stages of disease, injury and starvation. You can't imagine their condition."



In 2019, Oliver Sell's son, **Stewart Sell** (MD '60), self-published his father's WWII diary and letters home, "Okinawa Diary: A Surgeon's View of the Battle of Okinawa," documenting life behind enemy lines, including kamikaze attacks, brain surgery without anesthesia and two typhoons. Oliver returned to his alma mater after the war and served as a Pitt surgery professor from 1945 to 1955. Stewart would graduate from Pitt Med a few years later and go on to uncover surprising discoveries with stem cells. In 2007, one of his papers was cited as a Scientific Landmark in Cancer Research by the American Association for Cancer Research.

Stewart is retiring this year from his role as professor of biomedical sciences at the University at Albany and moving to Williamsburg, Va.

'80s

When the Department of Justice reached out to **Steven Zimmet** (Family Medicine Resident '81) to review a Medicare fraud case, Zimmet agreed. Three years later, in 2019, he testified as an expert witness, an experience he calls "a privilege." Zimmet—the owner and director of Zimmet Vein & Dermatology in Austin, Texas—worked with the DoJ for nearly 300 hours on the case, for which the defendant was found guilty. "While the vast majority of physicians are dedicated and caring," he says, "we also know there is significant fraud and abuse going on. It doesn't serve us, our field or society well."


Zimmet

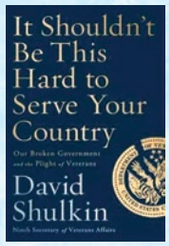
William Sikov (Internal Medicine Resident '85)—or, as Alex Trebek calls him, Doctor Bill—is an associate professor of medicine, obstetrics and gynecology at Brown University. Last October, he appeared on "Jeopardy!"—coming in second place to win $2,000. Sikov is a breast medical oncologist and serves as the associate director of clinical research in the Program in Women's Oncology at the Women and Infants Hospital of Rhode Island. He researches neoadjuvant therapy for breast cancer and the treatment of triple-negative breast cancer.

The ninth secretary of the U.S. Department of Veterans Affairs


Trebek with Sikov

David Shulkin (Internal Medicine Resident '89, Internal Medicine Fellow '90) was the only member of President Trump's cabinet confirmed 100-0 by the Senate. He was also the highest-ranking official to have served under both Presidents Trump and Obama. His new book, "It Shouldn't Be This Hard to Serve Your Country: Our Broken Government and the Plight of Veterans," was published in October. Shulkin is the Distinguished Health Policy Fellow at the University of Pennsylvania's Leonard Davis Institute of Health Economics and president of Shulkin Solutions, which partners with health care and veterans organizations. "Veterans deserve the best care available in this country," he notes.


Shulkin



'90s

Lawrence Wolf (MD '95) of Maimonides Medical Center in Brooklyn, NY, is making changes as the internal medicine residency program director. He says residents needed "more formalized training" in skills like delivering bad news and speaking with empathy. So he helped to create the Humanism Project, which teaches residents communication skills, biomedical ethics and self-care—"the forgotten part of medical education," he says. Wolf hasn't forgotten the funny bone, either: He's exploring the benefits of using humor to teach medical students and residents. His team presented a workshop on the topic at the 2019 Southern Group on Educational Affairs regional conference.


Wolf


Faix

Captain **Dennis Faix** (MD '96) is the executive officer at the Naval Medical Research Unit Dayton at Wright-Patterson Air Force Base in Ohio. His two decades of service as a U.S. Navy preventive medicine officer, focusing on the treatment and prevention of service-related infectious diseases, has included tours in Japan, Denmark, Cambodia and Iraq—granting him "great professional satisfaction." He's also served in Europe with the WHO. From 2014–2017, Faix was the principal investigator of the Millennium Cohort Study, the largest-ever prospective cohort study of military personnel, with more than 200,000 participants; it examines "the health effects," says Faix, "of military-unique exposures such as deployment and combat."

'00s

Ann Cohen (PhD '06) is associate professor of psychiatry at Pitt and the associate director of the Neuroimaging Core for Pitt's Alzheimer's Disease Research Center. She oversees a team of researchers investigating Alzheimer's disease, Down syndrome (DS) and the relationship between the two, among other areas. "Individuals with DS," Cohen notes, "almost universally have Alzheimer's pathology by


Cohen

midlife." Her recently published research indicates that the brain areas where people with DS first develop Alzheimer's pathology are different than those in neurotypical brains—a discovery, she says, that "will be very meaningful for clinical trials" working to prevent Alzheimer's in DS patients.

Justin Baca (PhD '07, MD '09), associate professor of emergency medicine at the University of New Mexico, says Pitt Med got him interested in developing tests that serve patients anywhere. Baca's lab uses a 3D printer to create wearable patches. Those patches have tiny needles for collecting fluid from between cells and could help diagnose and treat high blood pressure and infections. Baca is part of an international project using AI and machine learning to improve point-of-care testing in developing areas for cancer and Zika virus, as well as other conditions. He says their next question is: "How do we integrate the big data?"

Baca

Umamaheswar Duvvuri (Otolaryngology Resident '07) serves as associate professor of otolaryngology at Pitt; he's also the Department of Otolaryngology's director of robotic surgery and holds an additional appointment at the VA Pittsburgh Healthcare System. His department performs about 100 robot-assisted ear, nose and throat surgeries per year. As the medical director for Pittsburgh CREATES, Duvvuri helps connect surgeons with engineers and companies to further bioengineering innovation.

Duvvuri

White

'10s

Patrick White (Hospice and Palliative Care Fellow '12) holds the Stokes Family Endowed Chair in Palliative Medicine and Supportive Care and is chief of palliative medicine at Washington University in St. Louis. He's also chief medical officer for BJC Home Care. In these roles, White helps to train future palliative care doctors. "I fell in love with the field," he says, "doing house calls with my father, who was a community pulmonologist. I was always in awe of how gracious the patients and families were."

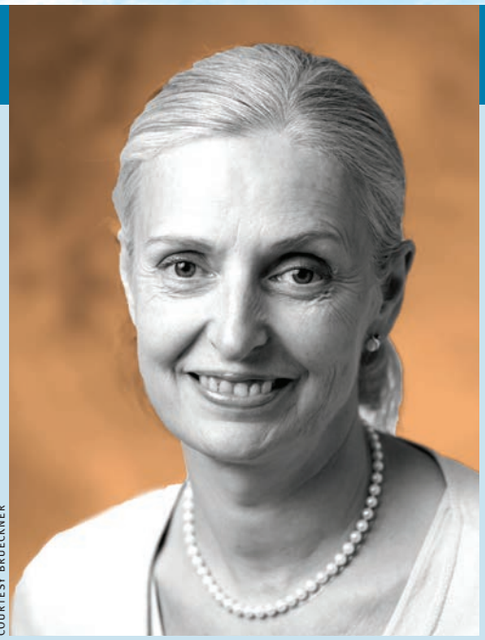
Sabins

Nina Sabins (PhD '13) was recently promoted to associate director at Janssen Pharmaceutical Companies of Johnson & Johnson, where she works to develop novel strategies to measure biomarkers—strategies that can lead to earlier, faster decision-making in the clinical environment. Her research publications, three of which she published while at Janssen, also focus on cancer immunology and immunotherapy—"proof," she says, with a chuckle, "that you can publish in industry." Why translational science? The field, Sabins notes, "is at the interface between the bench and the clinic," giving Sabins the opportunity, ultimately, to help create "better drugs for patients."

—Rachel Mennies and Alyce Palko

BRUECKNER

WHEN GENES OVERLAP



COURTESY BRUECKNER

Brueckner's lab is devoted to fixing congenital heart disease.

When Martina Brueckner (Res '87) established her Yale University laboratory in 1990 to study congenital heart disease (CHD), only 67% of CHD patients lived past their first year. Today, she says, 90% of patients survive into adulthood, but many of them struggle with "major challenges" that aren't properly diagnosed or understood. "Some CHD kids," she notes, "fall under the radar screen for whatever else is going on with them, because everything that's bothering them is blamed on their CHD."

Brueckner, professor of pediatric cardiology and genetics at Yale, is using large-scale genome sequencing to parse out the genetic underpinnings of CHD—work that has yielded insights into the disease's related challenges, too. Brueckner is a primary investigator with the national Pediatric Cardiac Genomics Consortium. In 2017, the group reported in Nature Genetics that a number of genes overlap between patients with CHD and those with autism. (The autism data was collected by the Simon Foundation.) When Brueckner and her colleagues compared the data sets, the overlap was undeniable, but logical. "The same [genetic materials] needed to build your brain," she says, "are also needed to build your heart. It's like a house—you need drywall, bricks, wood for all the rooms of your house. And if those are abnormal, you'll have issues with your kitchen, bathroom and roof."

Drawing a genetic connection between CHD and autism could mean increased diagnostic attention for CHD patients, improving their quality of life, says Brueckner. She maintains a clinical practice in pediatric cardiology. "We need to pay attention to the whole patient—not just the scar on their chest."

Besides "cranking out large sequencing data" with the Yale Center for Genome Analysis, Brueckner's lab is investigating cilia, antennae-like organelles that assist in the heart's development.

Her plan is to keep working to "understand the genetics and biology of CHD . . . and translate those findings into improved care for CHD patients—one gene, and one patient, at a time." *—RM*

BARBARA ANN COHEN LEVEY

MARCH 7, 1935–OCT. 29, 2019


Levey

"They said our class was about a third women, the highest percentage ever at Pitt," says endocrinologist Patricia Bononi (MD '85). "I remember commenting that it was probably because of Dr. Levey."

Barbara Levey, an MD, was the associate dean and director of admissions at the University of Pittsburgh School of Medicine from 1979 to 1991. She was the only woman in her own med school graduating class at SUNY in Syracuse. She served on committees supporting women in medicine for the Association of American Medical Colleges. Levey died in October.

The percentage of women enrolled in classes before Levey's time at Pitt is less clear, pointing to another of Levey's key contributions as admissions director.

"She kept much better records than anybody before her," says Beth Piraino, Pitt Med associate dean of admissions and financial aid and professor of medicine. Levey helped to usher in a more rigorous and systematic approach to the admissions process.

"She was instrumental in making sure there was a thorough vetting of everybody," Piraino says.

Levey's chosen discipline was clinical pharmacology, a field she championed at Pitt and during the rest of her career, most of which was spent at UCLA. There she received numerous National Institutes of Health grants. She also served as associate vice chancellor at UCLA and, from 2002 to 2003, as president of the American Society for Clinical Pharmacology and Therapeutics.

She is fondly remembered as part of a dynamic and influential team with her husband, Gerald Levey, who served as Pitt Med's chair of medicine from 1979 to 1991, and later as dean of the David Geffen School of Medicine and vice chancellor of medical sciences at UCLA.

"They were a wonderful team, she and her husband," says Piraino. "They left a very important stamp on the system here. They did a lot for Pitt." —*Adam Reger*

MICHAEL J. PAINTER

NOV. 30, 1939–OCT. 17, 2019


Painter

An expert diagnostician, neurologist Michael Painter picked up on the subtlest clues to a patient's underlying condition. That was true whether the patient was an infant, incapable of describing symptoms, or an adolescent whose condition Painter suspected to be rooted in psychiatric causes.

Patricia Crumrine, Pitt professor of pediatrics, recalls Painter seeing patients admitted with nonepileptic seizures. "He would go to the ER and see this supposedly unconscious young person lying on a table, and he'd peel back their eyelids and say, 'I know you're in there.' And the person would burst out laughing," says Crumrine, who also trained with Painter at Columbia University.

Painter served as chief of child neurology at Children's Hospital of Pittsburgh from 1978 to 2002, and as professor of neurology and pediatrics at Pitt Med until his retirement in 2013. He died in October.

"There was no situation so adverse that he couldn't dispel some of the adversity with humor," says Nina Schor, deputy director of the National Institute of Neurological Disorders and Stroke, who succeeded Painter as division chief.

As a teacher, Painter modeled the same painstaking attention to detail he used in observing patients.

"He would spend time with you and your patients but, as he realized your capabilities, he would give a lot of leeway," says Robert Safier, clinical director of the Division of Child Neurology at Children's.

"He had a knack for building community and treating his division as a family," says Schor. "We all feel somehow related to one another because of our link to him."

In 2002, Pitt created the Michael J. Painter Award for Excellence in Child Neurology in recognition of his contributions as a teacher and mentor. In 2006, Painter won the Hower Award, given by the Child Neurology Society to a member esteemed by colleagues as both an outstanding scholar and teacher.

"He loved neurology, and he had a way of conveying it," Safier says. —*AR*

JAN D. SMITH

FEB. 6, 1939–SEPT. 6, 2019


Smith

Jan Smith, emeritus professor in Pitt's Department of Anesthesiology and Perioperative Medicine, was "the conscience and soul of the department," says colleague Mark Hudson.

Smith was born in Pretoria, South Africa. He earned his medical degree from the University of Pretoria and trained in critical care medicine, pulmonology and internal medicine at Pitt, first joining the Pitt Med faculty in 1971. From 1974 to 1985, Smith served on medical school faculties in Iowa, Texas, Nebraska and Ohio.

In 1987, Smith returned to Pitt and was appointed chief of anesthesiology at UPMC Presbyterian, a role he held until 1996. He then became chief of anesthesiology and medical director at UPMC Beaver Valley until 2000, when he moved to help develop ISMETT, the UPMC transplant and major surgical center in Sicily.

At ISMETT, Hudson says, "Jan was instrumental in the creation of the academic environment for the institution." Smith used his love of travel for good, Hudson says, "helping to improve the medical care in many places."

Smith again returned to the Pittsburgh campus in 2002 as vice chair for clinical operations until his retirement in 2006 as professor of anesthesiology, internal medicine and critical care medicine.

In his emeritus role, Smith continued teaching and, in 2009, assisted with the development of UPMC Beacon Hospital in Dublin, Ireland, as its associate medical director.

Volunteering as a teacher in sub-Saharan Africa, he also was appointed an Extraordinary Professor of Medicine at the University of Pretoria.

In 2013, his department's Education Office named a classroom in his honor.

Smith "really influenced the educational program for our residents," Hudson says. "He was a remarkable gentleman anesthesiologist."

—*Marty Levine*

JAMIE JOHNSTON
TEACH ONCE, LEARN TWICE

BY ADAM REGER

COURTESY J. JOHNSTON | PHOTO ILLUSTRATION: ELENA CERRI

Johnston (right) with Duker—both beloved professors emeriti at Pitt Med.

If a professor can have a hit lecture, James "Jamie" Johnston's is definitely "Running the Nephron."

"Students will come up to me on clinical services and say, 'Run the nephron for us,'" says Johnston (MD '79), nephrologist and professor emeritus of medicine, who retired in June 2019. "I still have former students tell me it's gotten them through exams or helped solve a clinical problem."

Johnston's famous lecture imagines the kidney as an automobile factory with workers performing specific tasks—transporters handling salt and potassium, for instance—who work in harmony to turn out a product. (In this case, urine.)

"One of the things I enjoy the most is being able to take my really kind of dense area of specialty and make it fun for medical students," says Johnston. By all accounts, Johnston has succeeded in that regard. He's nearly a perennial nominee for the Golden Apple Award given by a medical school class for excellence in teaching. He won the award seven times (not including the National Golden Apple Award he was given in 2004). He won the Excellence in Education Award for preclinical education more than 20 times.

Roderick Tan (MD '07), assistant professor of medicine at Pitt, who trained under Johnston during his fellowship and later worked beside him, recalls being struck by Johnston's diligence.

"You think professors are just great teachers, but he works really hard to keep his lectures up to date and engaging," says Tan.

Johnston's wife, Georgia Duker, has also received several Pitt Med teaching accolades. Through the years, they've been sounding boards for each other's teaching practices. Duker (PhD '82), an assistant professor in the Department of Cell Biology, retired in 2018 after 31 years at Pitt Med.

Cary Boyd-Shiwarski (MD '12), a Pitt assistant professor of medicine who also trained under Johnston, recalls his care in training fellows at patients' bedsides. "He always took the time to teach very small nuances," she says. For instance, examining a patient's fingernails for clues to hidden illnesses, including those typically far outside a nephrologist's scope.

"He had enough clinical experience to think outside the kidney," Boyd-Shiwarski says. "He really treated the whole person."

As highly regarded as a nephrologist as he is as a teacher, Johnston has received numerous recognitions for his clinical work. "Teaching makes you a better physician," he says. "Teach once, learn twice."

Johnston began his studies at Pitt Med in 1975 and spent almost all of a nearly 40-year career here. With Thomas E. Starzl, he coauthored the first study on the drug tacrolimus, used to lessen the risk of organ rejection. His contributions to medical education range from cofounding Pitt's Academy of Master Educators to assisting Pitt with helping a Kazakhstan university establish its own medical school. Nationally, he served on the American Society of Nephrology's executive committee for renal fellowship program directors.

"Always try to learn and teach as much as you can," Johnston says. "If I had to get a tattoo, that's what it would be. Maybe next to my Avengers tattoo."

Science-fiction novels, bird-watching, and grandchildren are on his retirement priority list. He will teach occasionally at Pitt Med. "It's extremely important to me to continue to teach," he says. Asked if he plans to give his "Running the Nephron" talk, he laughs and says, "Medical students are already requesting it." ■

IN MEMORIAM

'40s

JOSEPH M. MAZZEI
MD '45
NOV. 5, 2019

DEAN FRANKLIN KROH
MD '46
JAN. 5, 2020

HARRY J. KERR JR.
MD '48
DEC. 22, 2019

'50s

HARRY K. GILLESPIE
MD '52
DEC. 9, 2019

JOHN O. WOODS JR.
MD '53
OCT. 18, 2019

ALVIN M. BODEK
MD '54
DEC. 10, 2019

ARTHUR D. BOYD
MD '57
JAN. 22, 2020

WILBERT AUGUST ROTH
MD '58
APRIL 24, 2019

DENNY WALTERS
MD '59
JAN. 24, 2020

'60s

WILLIAM J. MCMAHON
MD '60
JAN. 24, 2020

RONALD J. TADDEO
MD '62
OCT. 27, 2019

RICHARD KIERN LANZ
MD '67
DEC. 21, 2019

STANLEY FORD SUMMERSON
MD '67
OCT. 17, 2019

JOSEPH THOMAS NEARY
PHD '69
JAN. 11, 2020

'70s

C. CAROL GUILBERT
PHD '72
MAY 13, 2019

WILLIAM E. NOBLE II
MD '72, RES '73
NOV. 9, 2019

DENNIS AMBROSE EBERZ
MD '73, RES '76, FEL '78
DEC. 10, 2019

RICHARD M. GINSBURG
MD '75
OCT. 24, 2019

SUSAN B. BAILEY
MD '78
OCT. 3, 2019

'80s

KENNETH C. KOZEKA
PHD '83
DEC. 1, 2019

'90s

JOANNE R. OLECK
MD '94
DEC. 12, 2019

FACULTY

DETCHO A. STOYANOVSKY
NOV. 21, 2019

COURTESY NETFLIX

REQUIRED VIEWING

Netflix released a new documentary series "Pandemic: How to Prevent an Outbreak" in January. Fast Company called it "required viewing," saying it "couldn't have come at a more crucial time with the recent coronavirus outbreak."

McGarry

Ryan McGarry (MD '09), an emergency medicine physician, School of Medicine alumnus and cinematographer, is behind the series as an executive producer. Last summer, he invited Pitt anthropology chair Bryan Hanks to help set the stage for the series: The first episode opens at an unmarked grave site near Pittsburgh where an unknown number of bodies are buried—victims of the 1918 influenza. Hanks and a team of Pitt students use ground-penetrating radar to estimate how many people were buried there.

McGarry started work on his first feature film, "Code Black"—which inspired the CBS series by the same name—while in med school. Watch carefully, and you'll see Pitt's Joan Harvey, associate dean for student affairs, in the documentary credits.

McGarry is now on the faculty at LAC+USC Medical Center and on the frontlines of the COVID-19 pandemic there. ***—Micaela Fox Corn***

Least likely to be endangered.

GETTY IMAGES

FOR REAL! TWEEN SCIENCE

Cockroaches—those pesky household guests—were around well before households ever were. Dinosaurs and cockroaches walked the Earth together. The fossils of modern cockroaches date back to the Jurassic period.

The bugs are famously hardy. Sixty-six million years ago a massive asteroid wiped out three-quarters of plant and animal life on this planet, pausing photosynthesis during an "impact winter." But cockroaches? They kept going. Cockroaches seem to stroll through disasters, and they also are somehow able to defend themselves against nasty germs. Some people think they can make us healthier.

The P. americana species has been used in traditional Chinese medicine for centuries. The cockroach antidote is commonly in a powder form, which prevents patients from having to look at bugs during treatment (yuck) and is believed to improve the potency of certain medicinal elements of the roach. Many ingredients taken from P. americana are legal for medical use in China. Injections like "Kangfuxin Solution" are said to promote blood circulation and the growth of human tissue. In some rural parts of China—where farms breed cockroach colonies (yes, that's what I said)—traditional medicine practitioners have prescribed roach formulations for stomach inflammation, pain and respiratory infections.

Don't try this at home.

While doctors practicing traditional medicine may use such treatments, these approaches have not been vetted to see if any of them truly work. There's every indication that cockroach exposure is likely to make you sick. (We know contact with the bug's feces can cause asthma.) Yet scientists are interested in learning how these critters fight disease. In a 2016 report, European researchers suggested that creatures living in dirty environments may help us learn how to kill dangerous germs. Some other examples of animals that thrive in contaminated environments are snakes, crocodiles and water monitor lizards.

So, the next time you spot a creepy cockroach crawling by, remember to pay respect to the reigning champion of survival of the fittest.

—Maggie Medoff

Thanks to Carnegie Museum of Natural History entomologist Andrea Kautz for letting us bug her for insight on this topic.

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