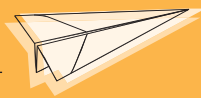


UNIVERSITY OF PITTSBURGH SCHOOL OF MEDICINE | FALL 2018

PITTMED

HELP AT THE SEVERE END
OF THE AUTISM SPECTRUM



ANESTHESIO-POLOGY

I read *Pitt Med* the day I receive it. I love hearing about all the advances in medicine that are happening at Pitt and following up on classmates and faculty. Over the past several weeks I've found myself thinking of both Peter Safar and Tom Starzl, both of whom have been featured in the magazine. My wife and I have retired here in Pittsburgh after 25 years at a major trauma center in Baltimore, and it's good to be back.

I was delighted to read the article about Henri Ford and his team's separation of conjoined twins in Haiti ("With Love, From Haiti" by Ervin Dyer). My trauma center, the R Adams Cowley Shock Trauma Center, sent a team to Haiti after the earthquakes in 2010. Although I was unable to participate because of pending knee surgery, I helped with supply acquisition and followed their travails.

I was disappointed, however, to read that Dr. Ford often brings with him "physicians, nurses, and anesthesiologists." It should be noted that anesthesiologists are physicians, who, after medical school, complete a one-year internship, three years of residency, and, often, a one- to two-year fellowship. While I'm sure that the article was not meant to slight us, it does a disservice to our specialty. Anesthesiology, along with antibiotics and modern blood banking, forms the foundation upon which surgery is based.

John W. Blenko (Med '79, Res '82, Fel '83)
Sewickley, Pa.

Editor's Note: Here at Pitt Med we respect the important work that anesthesiologists do. We regret the error and hope you keep reading.

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FOLLOW-UP



Join in the conversation @PittMedMag. Because you seem like someone interested in healing and discovery.



Pitt Med Magazine @PittMedMag · 18h
Four diversity and inclusion officers from US med schools and hospitals talk about race, #bias, and otherness in #medicine. Discussion moderated by Pitt SNMA president Nia James. bit.ly/2kYWHB

#meded #PittMedAlum #Pitt #AcademicMedicine @SNMA
#DiversityDrivesExcellence

"There's such empathy that's inherent in the choice to provide relief of suffering. Sometimes people make the mistake of thinking, *I can't be biased, because I'm in this pursuit.*"

1 2 4



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Replying to @PittMedMag @SNMA

Nia James is an inspiration! Young and wise. Savvy and kind. Just like you, Paula Davis.



anne-ruxandra carvun
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Here is a nice overview of my work and trajectory by @PittMedMag. It was fun reflecting and exchanging during the process!

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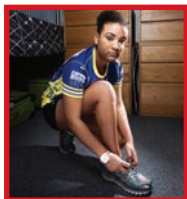
Making her *Pitt Med* debut, **CARRIE ARNOLD** ["Severe End of the Spectrum"] writes about a subject close to her heart. Arnold, who has written for *National Geographic*, *The Atlantic*, *Quanta*, and *Women's Health*, has a cousin with autism; she became interested in writing about the condition while searching for information to help her relatives. A Michigan native who has lived in Virginia the past decade, Arnold was surprised to learn how few resources there are for families in crisis, even in metropolitan areas. Arnold is the author of *Decoding Anorexia: How Breakthroughs in Science Offer Hope for Eating Disorders*, and she has a 15-year-old cat named Aria.

ELLEN KRUCZEK ["Really Out There" and other stories] was *Pitt Med's* talented summer intern. Majoring in nonfiction writing and biology, with a chemistry minor, Kruczek is entering her senior year at Pitt and plans to earn a master's in public health after graduation. She also is thinking of applying to medical school in order to focus on clinical human research. A Beaver, Pa., native, Kruczek hopes that as a science writer she can improve communication between experts and the general public. The most shocking fact she learned while reporting for *Pitt Med* was that there are no official protocols in place for medical emergencies, except: "Go back to Earth."

PITTMED

UNIVERSITY OF PITTSBURGH SCHOOL OF MEDICINE MAGAZINE, FALL 2018

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(Cover: Illustration by Frank Harris © 2018)



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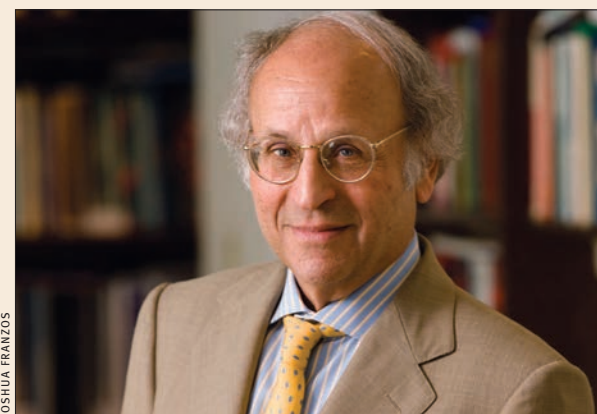
During the summer, I attended a talk about culture by the extraordinary musician Yo-Yo Ma, and I read an article about basic science by the highly regarded journalist George Will. Here I put the two together.

Ma noted that he is first a person, second a citizen, third a musician, and only fourth a cellist. (Of course, he is one of the world's greatest cellists.) Both Ma and Will used the platform of their widely recognized but specific expertise to speak transcendently about matters that should concern us all, reaching far beyond what we might expect them to say as cellist and journalist and speaking profoundly as citizens. Ma spoke of how art, music, literature, biology, and even shipbuilding all contribute to a culture; these disciplines each have their own distinct culture, as well. Further, Ma noted, with great insight, that the circles of politics and economics can be polarizing and divisive, absent the imposition of culture's circle in a Venn diagram.

What is a citizen and what is culture? The *Oxford English Dictionary* tells us that the latter can be thought of as "manifestations of human intellectual achievement regarded collectively" or "the cultivation of bacteria or cells in a medium containing nutrients." A citizen is "the character of an individual viewed as a member of society." Science certainly can be understood through these definitions. Scientists contribute their achievements (and nutrients) to our culture collectively; and as citizens, as Ma would put it, they may also bring their analytic and intuitive ideas at the edge of society back to the center.

What about basic science? Will suggests that this definition is a great challenge: Basic science helps us understand our environment, ourselves, and one another; but it seems abstract, risky, remote. And it's hard to attract philanthropy to it: *No one ever died of biochemistry*. Basic scientists jump into a dark hole and hope that there is water in it. James Clerk Maxwell's curiosity revealed electromagnetism, and a century later, we have video streaming and MRI. Japanese marine biologist Osamu Shimomura changed the course of cellular biology, though that wasn't his intention. In the early '60s, he was trying to understand why the jellyfish *Aequorea victoria* glows green. At the end of a not very fruitful day in the lab, he had tossed a specimen in the sink and witnessed a flash of blue. He later learned that the addition of calcium in seawater would make the jellyfish flash green and found the protein responsible, which he called GFP (for green fluorescent protein). Scientists now widely apply GFP to track cellular activity in healthy physiology, as well as in models of every disease you can imagine. In the rush to find concrete applications for science, let us remember that we cannot apply what hasn't been discovered! This is understood within the culture of basic science and by the "citizens" who practice or value it.

Our school focuses on the development of physicians who are also scientists. Their culture is driven by their curiosity, and their citizenship is granted by a fascination with discovery that will benefit all of us. The author Saul Bellow (*Herzog*) writes of the "human millions who have discovered what concerted efforts and thoughts can do. As megatons of water shape organisms on the ocean floor. As tides polish stones. As winds hollow cliffs." What might Ma say? Citizens and culture form the soul of our planetary architecture.



JOSHUA FRANZOS

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*Devoted to noteworthy happenings
at the medical school*

Pittsburgh Atlas

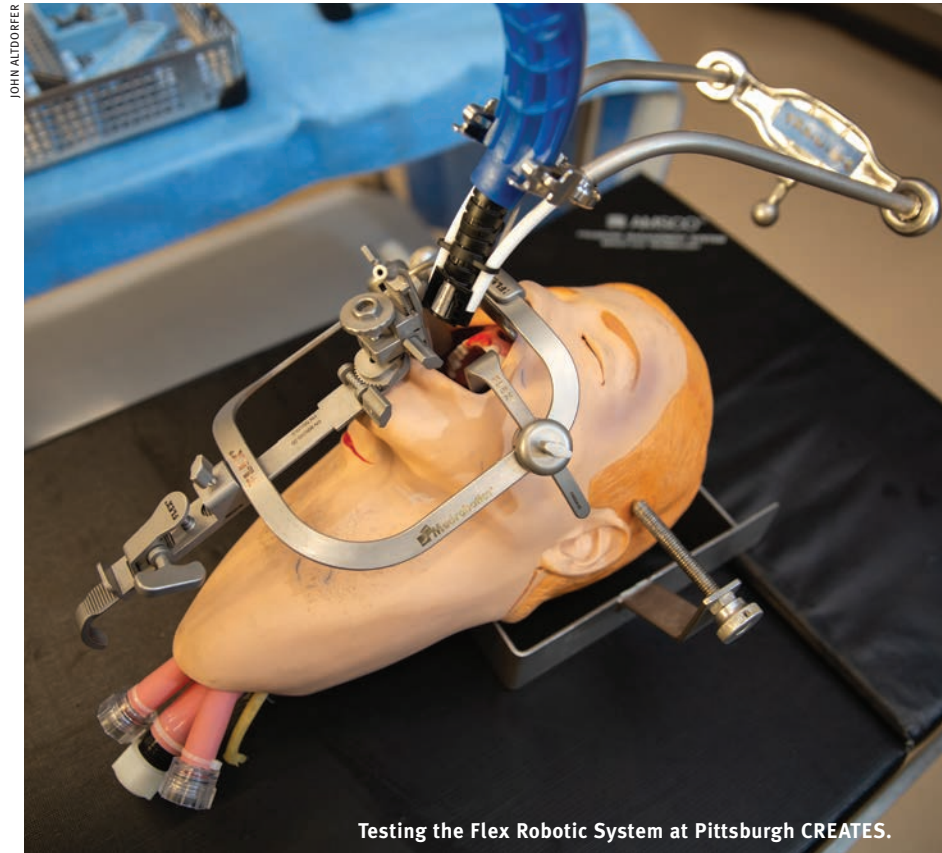
Researchers at Dartmouth set out more than 20 years ago to create a map that would describe both where people lived and where they went to get their health care. In the first iteration of what they called the Dartmouth Atlas of Health Care, they split the nation into 306 regions, but many of them crossed state and county lines—there was no way for policy makers or public health agencies to use the map if they had jurisdiction over only part of a region.

“No one has ownership of a Dartmouth Atlas region,” says David Wallace (Fel ’11), an MD/MPH assistant professor in the University of Pittsburgh Department of Critical Care Medicine. “You don’t have natural stakeholders. If a county is cleaved in half by the Dartmouth Atlas, who takes ownership of the parts?”

Seeing the potential for health care policy to shift toward state powers, Wallace and his team created the Pittsburgh Atlas, a map of care referral regions that factors in state and county borders. The team designed the map using data on where people were receiving emergency care for heart attacks, major trauma, and strokes, as well as data on the outcomes of that care. Wallace says now investigators will be able to compare states and say, “State A has done X, Y, and Z. Has that had a meaningful impact on groups of patients that we can epidemiologically draw dotted lines around?”

“The Pittsburgh Atlas is a way of moving beyond comparing apples to apples and into thinking about orchards,” he says.

—Evan Bowen-Gaddy



Testing the Flex Robotic System at Pittsburgh CREATES.

Creative Surgical Tech

On the first floor of the UPMC Eye and Ear Institute, a clinician tests a new surgical robot with a flexible arm. The device was developed at Carnegie Mellon University, tweaked at Pitt Med, sold by a private company in Boston, and has found its way back to Pittsburgh, where surgeons are now using the robot for transoral and colorectal surgery. How did engineers, clinicians, and entrepreneurs find their way into the same room? They collaborated at Pittsburgh CREATES, Pitt Med’s new lab where clinicians and engineers work side by side to build and evolve surgical technologies.

“What we’re there for is to bring thought leaders together with clinicians who probably have the greatest insight into how to improve the outcomes for patients,” says Max Fedor, executive director of Pittsburgh CREATES. The lab was developed by Fedor, Umamaheswar Duvvuri, assistant professor of otolaryngology, Carl Snyderman, professor of otolaryngology and neurological surgery, and Jonas Johnson, chair of otolaryngology. It differs from other innovation labs around the country in that it operates on a fee-for-service model; surgeons work on single assignments rather than large research projects. “When we need to bring in clinicians, they’re nearby. They can come in for an hour; they can work with us; they can go back to the OR,” says Fedor. —EBG



Overheard: Culture Shock

How do you say “contractions” in Uzbek? **Daniel Lattanzi** (Res ’82), assistant professor of obstetrics, gynecology, and reproductive sciences, works with video translators regularly at UPMC Magee-Womens Hospital. He sees an increasing number of patients from North and Central Asia. But he’s finding that communication challenges span more than just vocabulary. For example, Lattanzi learned that in Uzbek culture, women aim for four children. “That’s good for business,” he says with a laugh. It also emphasizes how much he and his residents have to learn about his patients’ various cultures, particularly how those cultures conceptualize motherhood and pregnancy issues.

How do cultures around the world view postpartum depression differently than we do in the United States?

Many cultures do not accept depression as a problem that can be treated and addressed. There are cultural issues related to how you are supposed to behave and feel after having a baby, and there can be stigma or repercussions for the entire family if a woman deviates from these norms. We have to accept the fact that, in other cultures, women have different roles. That’s not right or wrong. A lot begins with understanding the cultures we are interacting with and being supportive rather than making everyone American. Many of our patients are separated from family, which puts them at an increased risk for postpartum depression. So many other countries have wonderful systems to take care of women after childbirth, with relatives coming in to take care of the home and other children and the mother herself. Here, there’s nobody to help.

How have you adjusted your standard postpartum depression screening tools to better serve this foreign patient population?

Written screening forms are often easier for women to fill out because they feel like they have some privacy, but I will often see women just randomly circling answers because they don’t understand the questions. Not only is the concept or perception of depression different in some cultures, but concepts like “sometimes” versus “often” are difficult to grasp. Our forms need to make sense culturally. We collaborate with our social work staff to gather these patients’ histories and provide the total care they need.

Has this awareness changed your practice model?

We are trying to establish a specialty subclinic where patients with limited English proficiency can come and be treated in a culturally comfortable way. Our immigrant patients have the same interests and needs as all women. They want a relationship. Someone they can trust. We want to create that environment for them. It starts with good communication. A dream of mine is that everyone will consider that not all patients have the same background and see this as an important part of providing care. —Katy Rank Lev

Faculty Snapshots

In March, **Bernard Fisher (MD ’43)**, Distinguished Service Professor, received the 2018 Charles M. Balch Distinguished Service Award from the Society of Surgical Oncology. David Bartlett, Bernard F. Fisher Professor of Surgery, says, “[Fisher] changed the way we approach cancer treatment by addressing the systemic process in which it is spread. This lifetime achievement is given to a surgeon who has the greatest impact on surgical cancer care.”

The American Academy of Arts and Sciences has elected **Angela Gronenborn**, a PhD, to join its ranks. Gronenborn is the UPMC Rosalind Franklin Professor, a Distinguished Professor and chair of structural biology, and a professor of bio-engineering. “It is a great honor to join a truly outstanding society of scholars, artists, and thinkers in all fields. It is a privilege to be a scientist,” Gronenborn says. She was also just given the Mildred Cohn Award in Biological Chemistry from the American Society for Biochemistry and Molecular Biology.

In March, **associate vice chancellor Maggie McDonald**, a PhD, received the **Group on Institutional Advancement Distinguished Service Award** from the Association of American Medical Colleges. “What began as a small group of colleagues has grown into an ever-expanding circle of friends,” McDonald says. “For any advice I may have shared, I’ve gotten that back several times over.”

Jane Schell received the **Hastings Center Cunniff-Dixon Physician Award for developing NephroTalk**, a communication skills training program that helps doctors discuss end-of-life care decisions with patients suffering from advanced kidney disease. “I think that what I am most proud of is that this award is really honoring kidney palliative care,” Schell says. She is an MD assistant professor of medicine within the Section of Palliative Care and Medical Ethics and the Renal-Electrolyte Division.

For being one of the leading surgical scientists of the last 50 years, **Richard L. Simmons** was awarded the **Medallion for Scientific Achievement by the American Surgical Association**. Simmons is chair emeritus of the Department of Surgery. Current chair Timothy Billiar says, “He has always understood that it is through helping others to achieve what they want to achieve that he realizes his greatest fulfillment; and in doing so, he’s recognized for greatness.” —Nichole Faina



Fisher



Gronenborn



McDonald



Schell



Simmons

BURDEN OF GENIUS

It's a *Rocky*-esque story in the world of medicine—that's how Carl Kurlander, a film studies senior lecturer at Pitt, describes *Burden of Genius: Dr. Thomas Starzl's Journey into Organ Transplantation*, a documentary he coproduced with Laura Davis about the legendary Pitt Med surgeon. *Burden of Genius* chronicles the medical and professional challenges Starzl overcame to give hope to patients with liver failure. Starzl, an MD/PhD who died in 2017, performed the world's first successful liver transplant in 1967 at the University of Colorado.

The film, directed by Tjardus Greidanus, won the Cleveland International Film Festival's Global Health Competition prize in April. The heart of the documentary, says Kurlander, is Starzl's unrelenting belief in science's ability to heal. He adds, "If [*Burden of Genius*] was just a movie about a brilliant, innovative surgeon . . . that would have been enough. But in watching this film you realize that it was all driven by a man who had a vision, and he would not be stopped, which is what made him one of the greatest medical figures of the 20th century."

Starzl, who joined Pitt in 1981, also is credited with developing the organ procurement and immunosuppressant protocols necessary for successful transplants. Early in his

career, the surgeon acquired many detractors who believed that transplantation was ethically unwise. In fact, it was when one of Kurlander's Pitt film students showed him a 1983 clip of *Nightline*, during which Ted Koppel asked Starzl if he was giving people false hope, that Kurlander realized the narrative potential of Starzl's story. —NF

PITTSBURGH POST-GAZETTE/JOHN KAPLAN, PHOTOGRAPHER



ABOVE: Starzl and Oscar Bronsther in a photo shown in *Burden of Genius*. BELOW: A statue of Starzl now sits next to the Cathedral of Learning.



MIKE DRAZDZINSKI/UNIVERSITY OF PITTSBURGH

Overcoming the Brain's Defenses

What do you do when you're performing brain research and the brains fight back? If you're Tracy Cui, you improvise. Cui, Pitt's William Kepler Whiteford Professor of Bioengineering, is studying why young adults are more susceptible to drug addiction, specifically to cocaine.

But brains (in this case, those of rats and mice) have a way of rejecting sensors. Cui says immune cells tend to damage tissue surrounding the sensor, and the resulting scars block its ability to communicate. To overcome this issue, Cui's team of bioengineers developed a synthetic "zwitterionic" polymer (these neutrally charged molecules like binding with water). The team spreads the polymer on the implant sensors. The approach gives them up to 72 hours to record the effects of cocaine. The previous approach yielded just 5 to 10 minutes.

The sensors have multiple electrodes spanning 5 millimeters in depth.

"We can actually get multiple measurements, and we can compare adult rats and young rats and see if the cocaine concentration ends up being different between them," Cui says. Funded by a National Institutes of Health grant, the two-year study on addiction is aimed at discovering whether the age effect is the result of differences in neuron sensitivity to cocaine or whether it's a result of where in the brain the drug concentrates. "We care about the real-time cocaine concentration in different regions of the brain," Cui says. "How can we [learn about] that? By reducing the foreign body response to the implant, by inhibiting the new cells that are activated because of the insertion."

If the sensors are successful, Cui says, they can be used to measure other substances, like alcohol or opioids. —Gavin Jenkins

FOOTNOTE

George Harrison—the quiet genius of the Beatles—helped popularize Indian music in America in the 1960s. Vijay Bahl, MD codirector of Pitt Med's endocrine fellowship training program, has been championing the genre for local fans for more than 40 years. Bahl (Res '74, Fel '77) cohosts *Music from India* at 8 p.m. on Sundays on 90.5 WESA with Harish Saluja, who started the show five years before the Pitt Med doc joined. *Music from India* is the longest-running Indian music program in the country, and it features the genre in all its forms, from classical to modern.

SOUND CHECKS

How can one of the smallest communication systems be studied? A prototype developed in a Duke/Pitt/Carnegie Mellon/MIT collaboration probes what's happening in the fetus. The method uses acoustics to isolate exosomes, extracellular vesicles used in cell communication. With the new technique, separation takes less than an hour and lessens sample damage compared to the standard method. Pitt's Yoel Sadovsky, executive director of Magee-Womens Research Institute and Elsie Hilliard Hillman Professor of Women's Health Research, was a coauthor of the resulting publication in *PNAS*. Sadovsky imagines one day using the approach for determining the health of placentas through their exosomes, which circulate in the mother's blood during pregnancy. —Ellen Kruczek

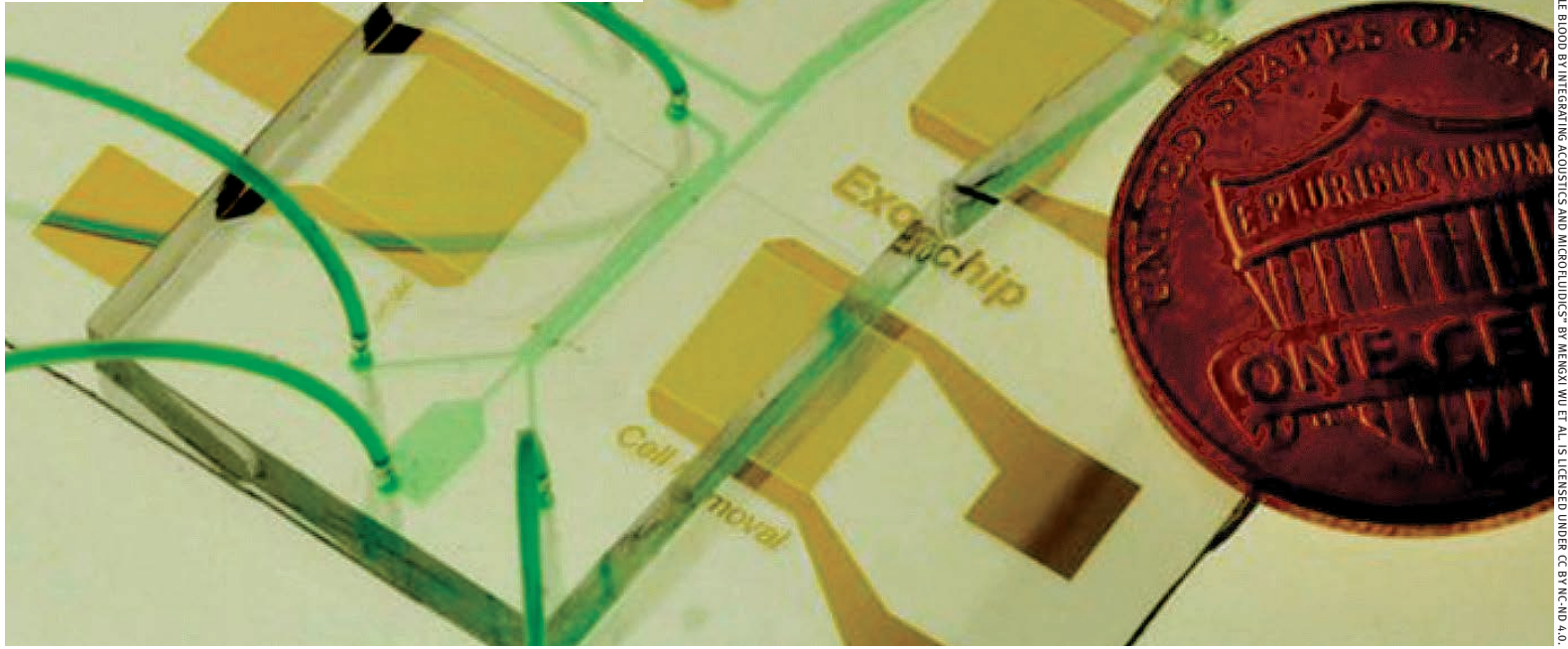


FIGURE 1B FROM "ISOLATION OF EXOSOMES FROM WHOLE BLOOD BY INTEGRATING ACOUSTICS AND MICROFLUIDICS" BY MENGJI WU ET AL. IS LICENSED UNDER CC BY-NC-ND 4.0.

Name Dropping

On May 10, Pitt's 2018 Laureate Lecture Series kicked off when **Botond Roska**, MD/PhD professor of medicine at the University of Basel, Switzerland, delivered his talk, "The First Steps in Vision." The lecture series is a yearlong program featuring top biomedical researchers in their fields. Roska, the founding director of the Institute of Molecular and Clinical Ophthalmology Basel, studies the structure and function of visual circuits in search of new ways to repair visual dysfunction in patients with retinal diseases like retinitis pigmentosa, which affects 2 million people worldwide and can lead to incurable blindness.

Roska and his labmates investigate cell types within the retina, thalamus, and cortex using a number of tools, many of which they invented. With optogenetic methods (which use light to control cellular functions), Roska seeks to restore retinal photosensitivity in patients. It's rare for retinitis pigmentosa to cause complete blindness. Roska explained to the Pitt audience that this can be an obstacle in the lab, because without complete blindness, some photoreceptor cells are intact—and the researchers don't want to change healthy cells. So Roska and his team have begun altering optogenetic wavelengths for people with partial blindness.

Roska's visit took place just as his review on restoring vision came out in *Nature*. His coauthor was Pitt's **José-Alain Sahel**, chair of ophthalmology and the Eye and Ear Foundation Professor;

Sahel also heads L'Institut de la Vision in Paris.

The series continued on June 14, when **Bruce Beutler**, MD and director of the Center for the Genetics of Host Defense at the University of Texas Southwestern Medical Center, presented "Studying Immunity by Randomly Inactivating Genes in Mice." Beutler earned a share of the 2011 Nobel Prize in Physiology or Medicine for the discovery of a family of cell receptors that enable mammals to sense the presence of infections, triggering an inflammatory reaction.

The three remaining 2018 Laureate Lectures will be given by . . . **Hopi Hoekstra**, a PhD and the Alexander Agassiz Professor of Zoology at Harvard University, as well as a Howard Hughes Medical Institute investigator, will discuss "The Genetic Basis of Parental Care" on Sept. 27.

Pitt's **Yuan Chang**, an MD and Distinguished Professor of Pathology, and **Patrick Moore**, an MD/MPH and Distinguished Professor of Microbiology and Molecular Genetics, are both American Cancer Society Research Professors. On Nov. 8, they will present "Why Do Viruses Cause Cancer?" The Pitt Med duo discovered two of the seven known human viruses that directly cause cancer.

Alan Hinnebusch, a PhD and National Institutes of Health Distinguished Investigator, will deliver a talk titled "The Molecular Mechanism of Scanning and Start Codon Selection in Translation Initiation" on Dec. 5. —GJ



THE LONG RACE

On a spring day at 5 p.m. in her Tower A dorm, Monica Henderson began her routine—right sock, left sock, right shoe, left shoe—and tied her running sneakers. Bending down to touch her toes, she commenced her lengthy stretching sequence, needed for muscles she says are always tight. Then she tied her shoes one more time—just to make sure they were secure.

Henderson is among hundreds of biology and sociology majors at the University of Pittsburgh, but the 18-year-old is anything but standard. She just ran across the United States in support of the Ulman Cancer Fund for Young Adults. Henderson started at the Golden Gate Bridge in San Francisco with her relay team on June 17 and finished at the Brooklyn Bridge on Aug. 4.

UCF helps alleviate the hardships young adults battling cancer commonly face. It hosts the annual 4K for Cancer—that “K” is for thousand, not kilometers—during which participants cover a total of 4,500 miles to raise money for the fund.

Henderson, who is going into her sophomore year, says many of the runners don’t have a personal connection to cancer. But for her, the cause hits close to home.

When Henderson was 2 years old, doctors found a tumor growing on her left cheekbone. She was diagnosed with rhabdomyosarcoma, an aggressive soft-tissue carcinoma. Rhabdomyosarcoma accounts for only 5 percent of all pediatric cancers in the United States. Fortunately, after two years of treatment, Henderson was—and remains—cancer free.

Cancer blindsided Henderson’s family in 2012 when her oldest aunt was diagnosed with breast cancer. Henderson’s mom was diagnosed a year later, and her youngest aunt was diagnosed in the spring of 2017. Henderson’s mother and oldest aunt have since fully recovered.

It was never easy for Henderson to verbalize her experiences with cancer. Now that she’s a young adult, however, she’s finding her voice.

“I always had like this, something inside me telling me that people should know or do something about [childhood cancer],” Henderson says. “It’s always been my passion to give back.”

Henderson hopes to become a pediatric oncologist.

“My story’s not finished,” Henderson says. “I’m not done with this fight yet.”

—by Hannah Schneider

—Photography by Theo Schwarz

Adapted and reprinted with permission from The Pitt News.

INVESTIGATIONS

Explorations and revelations taking place in the medical school



In a clinical trial published in the *New England Journal of Medicine*, trauma patients who received plasma while in transport via air medical service had a 10 percent reduction in mortality.

BLUE SKY IDEA

A TEST FLIGHT FOR PREHOSPITAL
PLASMA | BY KRISTIN BUNDY

Say a STAT MedEvac helicopter is flying a patient, a nonresponsive 44-year-old man, from the scene of a car accident. He is bleeding and at risk of hemorrhagic shock. His systolic blood pressure dips dangerously—below 70. But the patient is still 20 minutes from the hospital.

“Giving early plasma in the emergency department was thought to be beneficial,” says Jason Sperry, MD professor of surgery and critical care at Pitt. He wanted to see what benefits a prehospital infusion would give a patient like this. So Sperry and coprincipal investigator Francis Guyette, a Pitt MD associate professor of emergency medicine and the medical director of STAT MedEvac, launched a clinical trial, Prehospital Air Medical Plasma (PAMPer). The results came out in the July *New England Journal of Medicine*.

Collaborating with seven other large trauma centers with busy helicopter units, the team collected data to determine if plasma given in addition to standard resuscitation efforts during a flight would affect 30-day mortality rates post-trauma in a randomized controlled trial.

Funded by the U.S. Army, Sperry and Guyette’s study was no small task. Because the patients could not give consent at the time of the intervention, the FDA had to approve the study design under a protocol known as exception from informed consent (EFIC). This was in addition to seeking approval from the Department of Defense (DoD) and the institutional review boards of each study site.

EFIC criteria are stringent. Investigators

must first demonstrate that not only is there a potential benefit for the patient, but also that there is no time for the patient to give informed consent and no other way to do the research. Second, the primary endpoint has to represent a significant outcome—in this instance 30-day mortality rates. Third, the researchers have to make the community aware of the upcoming study.

Outreach for PAMPer came via bus ads, newspapers, YouTube and other sites, and radio. People who chose to opt out wore a “No PAMPer” bracelet. In all, it took two and a half years of planning and four years to complete the study, Sperry says.

It was worth the wait. Plasma was shown to save lives (improving the 30-day mortality figures by 10 percent). In addition, it reduced blood transfusion requirements and improved a measure of coagulation.

What’s more, benefits were found in a broad patient population. The inclusion criteria required that participants have either one episode of low blood pressure with a high heart rate or an episode of severe low blood pressure at any time before reaching the trauma center via air medical service. Some patients had liver injuries, some had traumatic brain injuries (TBIs), and some didn’t have significant injuries at all, Sperry says.

For him, the most interesting finding was the rate at which mortality improved in a subset of patients with TBI. Of the 87 in that treatment arm, two thirds survived, representing a 21 percent relative improvement in survival. “No other intervention on the

planet” can do that, says Sperry. “Now, that’s a subgroup,” and not statistically significant, he says. “It deserves further investigation.”

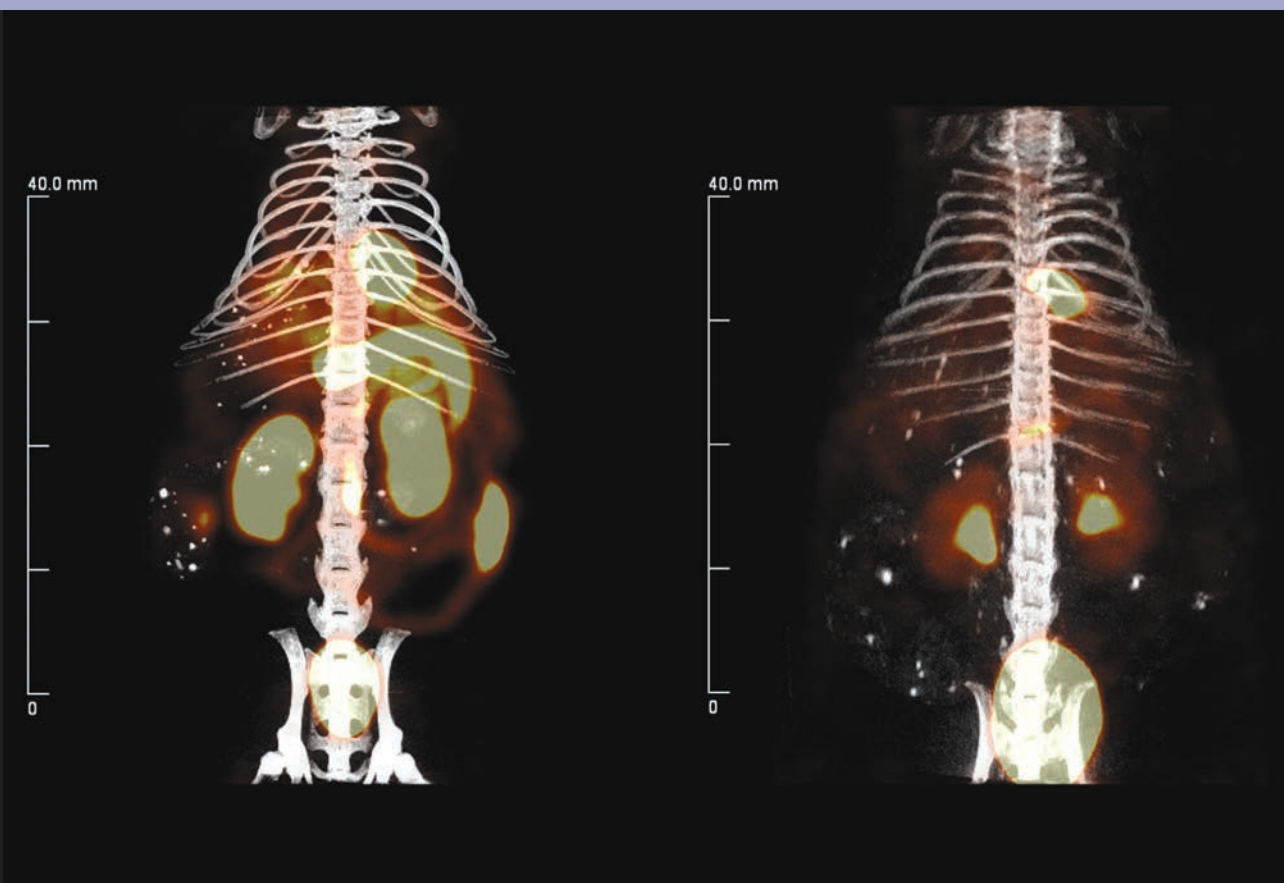
Although they don’t know how the plasma works, they have a theory. In addition to treating the bleeding and preventing further bleeding, the plasma might provide some additional protection:

“Newer evidence suggests that plasma may give back,” says Sperry. “It may protect the endothelium—the cells that line the blood vessels—which is almost an organ in and of itself. When they’re in shock, these endothelial cells release cytokines that cause inflammation, and plasma may have certain pro-endothelial cell mediators that benefit.”

Thawed plasma is just one stepping stone along the path of products Sperry is studying to try to improve outcomes after trauma. In addition to further investigating data from the PAMPer study, he wants to learn what advantages other types of plasma may have when given immediately post-trauma.

“This impact—this 10 percent reduction in mortality—could change practice across the country,” he says. “It may not be able to be done using thawed plasma, which only has a five-day shelf life, but it could be done with liquid plasma [which has never been frozen]—and in the future, potentially freeze-dried plasma that has no shelf-life or storage limitations.”

Because injury is one of the leading causes of death in people ages 1 to 44, the new approach has the potential to save a huge number of lives, notes Sperry. ■



Zahid aims to reduce the amount of radiation that patients are exposed to during cardiac stress tests. Here, the organs of a mouse injected with traditional imaging agents (left) show higher exposure (yellow) than Zahid's more targeted approach (right).

**A BETTER WAY TO
IMAGE THE HEART
BY AMERIGO
ALLEGRETTO**

CORDONED EXPOSURE

COURTESY MALIHA ZAHID

When patients describe chest pain as coming from the heart, they are often prescribed stress tests that use a radiological scan for diagnosis, prognosis, or treatment monitoring.

"During these tests, the radiation goes everywhere—it goes into the liver, the lungs, and the gut, to name a few organs," says Maliha Zahid, assistant professor of developmental biology at the University of Pittsburgh. Because the gut is so close to the heart, she explains, it can sometimes cause images to be difficult to interpret.

So Zahid, a cardiologist, has created a way to alleviate both of these problems: deliver radiation straight to the heart. "By sending the radiation only to where it's needed for imaging, you can reduce the amount of radiation by as much as 80 percent," she says. "We are hypothesizing that this will also lead to higher image quality."

These specific stress tests are "the biggest contributor to radiation that patients receive in the course of medical treatment," notes Zahid.

A study published in 2011 by the National Center for Biotechnology Information showed that such scans performed annually in the United States could result in 7,400 additional future cancer cases.

Her research led to the creation of a novel non-naturally occurring 12-amino-acid peptide—peptides are molecules made up of links of amino acids that are the building blocks of proteins—called the cardiac targeting peptide. It intravenously transports radioisotopes needed for stress test scans and is designed to be taken up only by cells that make up the heart muscle (cardiomyocytes). The radiation, therefore, doesn't spread to other organs and, unlike the course for current stress tests, the peptide then leaves the heart and is excreted through the kidneys, sparing the liver.

Zahid says this took about two years and six attempts to get right.

"The last attempt, I told myself, 'If this doesn't work, I'm going to give up,'" she says. "It worked, and we found a peptide that we were able to manufacture in the University's peptide synthesis facility."

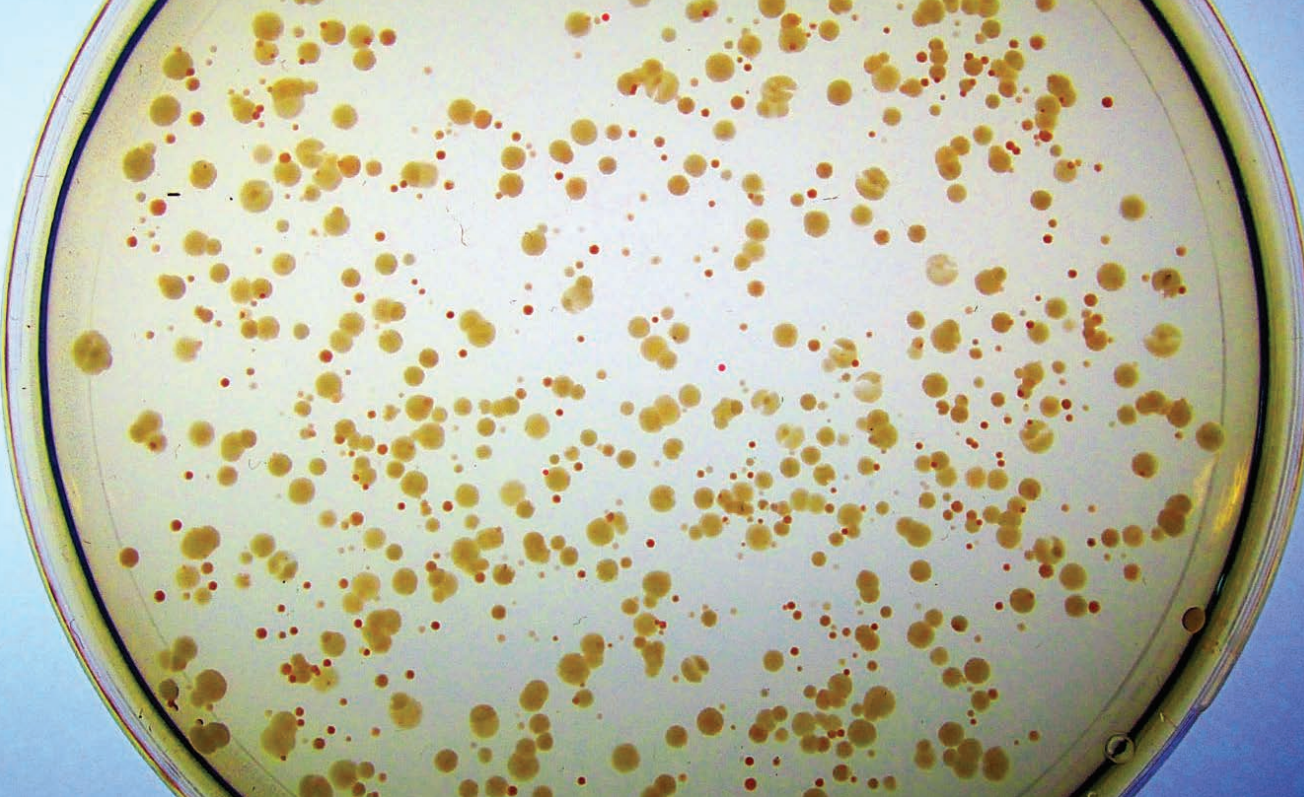
Zahid's peptide won first place at Pitt's Clinical and Translational Science Institute 2016 Pitt Innovation Challenge (PInCh); the \$100,000 in winnings will advance Zahid's research findings toward clinical application. Zahid received assistance in translational research strategy from sciVelo, a Pitt Innovation Institute program aimed at accelerating life and health sciences translational research and commercialization.

And she recently also received an American Heart Association Scientist Development Grant for \$231,000.

Pitt, Zahid, and her co-inventor, Paul Robbins, a former Pitt faculty member who's now a molecular medicine professor at the Scripps Research Institute in Jupiter, Fla., have been granted a U.S. patent on the peptide technology and are planning a startup company, CardioTrak.

"The past year has been fun and fast-paced like a roller coaster ride," Zahid says. ■

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Donnelly constructed Syn-F4, the first-ever artificial enzyme capable of working in a living organism—in this case, *E. coli*. Pictured here are engineered *E. coli* lacking the Fes enzyme, either expressing Syn-F4 (large beige colonies) or a control protein (small red colonies).

A LIFE-SUSTAINING
CREATION
BY ALLA KATSNELSON

ENZYMES FROM SCRATCH

Enzymes are the workhorses of the cell—and of all biological systems. These specialized proteins set into motion all the cells' chemical reactions, making sure they run fast enough for life on a biochemical level to proceed. Each enzyme precisely aligns with the cellular processes it regulates. Thanks to evolution, our world is full of these meticulously well-suited proteins.

A study published earlier this year by Ann Donnelly, a research specialist in the Department of Biomedical Informatics, has revealed that scientists can also make working enzymes from scratch.

The study was e-published in January in *Nature Chemical Biology*. Donnelly, who came to Pitt in 2017, did the work as a PhD student in the lab of Michael Hecht at Princeton.

"We showed that you can take novel protein sequences that nature has never seen before and put them in natural systems—and they can function," Donnelly explains.

The findings hint at some fascinating dimensions of our primordial history, she says: Namely, the reactions that governed early cellular processes were much more flexible than they are now. "The enzymes we see today have a lot of evolutionary baggage and have been really refined to do the things they do," Donnelly says.

But evolution's solutions weren't the only ones, it turns out. "Our work suggests it's possible to replace what we have now with something completely different."

The synthetic enzyme Syn-F4 was one of a big batch made in Hecht's lab a decade ago. The group routinely produces synthetic proteins, designing them to conform to a folding pattern called a four-helix bundle and then testing them in mutated strains of the bacterium *Escherichia coli*. The idea is to see whether any of the synthetic enzymes they make can replace the functions of *E. coli* genes that have been knocked out. And sometimes the artificial versions do work. Mostly they come into play in a pinch—by switching on cellular processes that can have functions similar to what's called for.

"But the case with Syn-F4 was a little different," Donnelly says.

Syn-F4 and its synthetic cohort were evolved to fill in for an *E. coli* enzyme called Fes that had been hobbled by a mutation. The job of Fes is to release iron from a compound in *E. coli* that nabs the metal from the environment so that it can be used for healthy growth in the cell. Without Fes, the bacterial colonies grow poorly, speckling with red as iron builds up around them. But when Donnelly added Syn-F4 to these sickly colonies, the red began

to disappear, returning the *E. coli* to its healthy state. "It was clear as day," she says. "It was unbelievable for me to see this happening in real time."

So unbelievable, in fact, that she kept mum about it until she had repeated the finding several times. In addition to testing the synthetic protein in living bacteria, she also mixed it directly with its iron-grabbing substrate and biochemically analyzed the ensuing reaction.

Later, she tweaked the substrate by chemically reversing its orientation. She found that this prevented Syn-F4 from working its magic, demonstrating its specificity and supporting the idea that it was working as an enzyme.

What's interesting, says Donnelly, is that the natural enzyme and the artificial one look completely different. The natural one is about four times as big, and it is known to connect to the substrate through a site that includes the amino acid serine. The artificial enzyme, though, has no serine residue in it whatsoever.

"It's difficult to pinpoint exactly how it's working, but at minimum we know that they are not catalyzing the reaction the same way."

These days at Pitt, in the lab of Erik Wright, an assistant professor of biomedical informatics, Donnelly's using her ingenuity to focus on understanding how pathogens evolve to become resistant to antibiotics. ■

REYES

END

A PLACE OF BEST
RESORT FOR FAMILIES
BY CARRIE ARNOLD

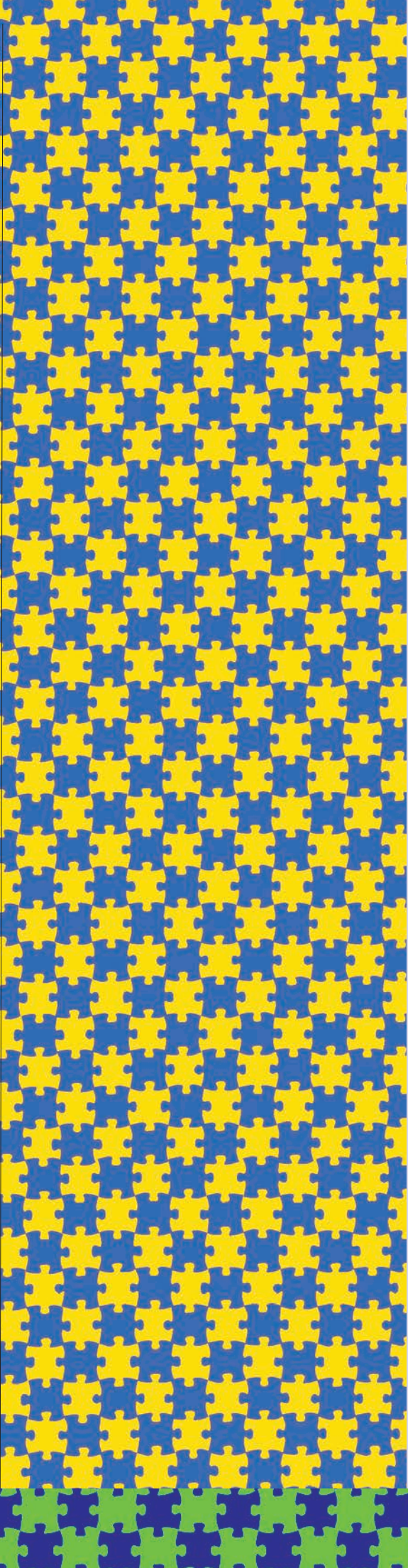
OF THE SPECTRUM

David and Emily Tate had run out of options. Since the birth of their daughter, Joy, 16 years ago, the Tates had struggled to manage her sudden, intense outbursts that grew into a tsunami of fury and frustration. Joy, who is on the autism spectrum, didn't always have the ability to express her needs and understand the tumult of emotions that coursed through her young body. Despite the best efforts of her parents and a cadre of teachers, therapists, and psychiatrists (Emily stopped counting professionals at 15), Joy's emotions daily whirled her into a destructive force that no one could contain or control. Most local psychiatrists couldn't or wouldn't help. The family would sit in local emergency rooms when Joy was in the throes of rage only to be sent home because the psychiatric unit wouldn't take teens with autism. Probably about one-third of people with autism demonstrate severe behavior issues like Joy's. Behavioral meltdowns can become so extreme in this subgroup that one in three are hospitalized for psychiatric reasons before their 18th birthdays.

ILLUSTRATION | FRANK HARRIS

Pitt faculty at the Merck Inpatient Unit offer a calm in the storm for families in crisis. Merck staff develop strategies to deter self-injury and aggression by children, teens, and adults on the severe end of the autism spectrum.





Emily and David placed their hopes in an Ohio residential treatment facility for teens on the spectrum, a three-hour drive from their home east of Pittsburgh.

“It was one of the hardest things we ever had to do,” Emily says.

While Joy was there, her behavior deteriorated even further. One week into her stay, a late-night phone call from the facility informed the Tates that Joy had gotten so violent they had no choice but to hospitalize her in a psychiatric unit. The Tates had heard of UPMC’s Merck Inpatient Unit for children, teens, and adults with neurodevelopmental disorders, but their insurance would never approve a stay—until now. At the time, Joy’s parents thought this was the worst thing that could happen to their daughter.

But what started as an awful turn of events became a glimmer of hope. When Emily and David arrived at Pitt to visit Joy, they met with psychiatrist Joseph Pierri. From that moment,

as of the Center for Autism and Developmental Disorders at Western Psychiatric Institute and Clinic.

When the Merck unit opened its doors in 1974, it was the only specialized inpatient unit for people with autism in the United States. More than 40 years later, only a handful of such units exist across the country, almost all of them concentrated on the Eastern Seaboard. Part of what continues to make Pitt’s unit unique is its commitment to helping affected individuals across the life span.

“It’s not just through childhood, and then falling off the cliff. We treat children, teenagers, and adults,” says Lubetsky.

Whatever their age, the individuals admitted to the Merck Inpatient Unit are at a crisis point. Many have symptoms of serious psychiatric disorders such as major depression, bipolar disorder, and schizophrenia, in addition to autism. Others are admitted after run-ins with police. Nearly all

In January 2017, West’s son froze while trying to cross a busy intersection near their home in a Pittsburgh suburb.

At that moment, West knew her son needed more help than she could provide.

everything changed.

“If we wouldn’t have met Dr. Pierri, and [Joy] wouldn’t have made it to the Merck center, I don’t think we would be where we’re at today,” David says.

A bespectacled, soft-spoken University of Pittsburgh assistant professor of psychiatry with a salt-and-pepper beard, Pierri is one of the many Merck providers who becomes the calm in the storm for families of children with autism whose behavior has become too difficult to safely manage at home. Pierri is medical director of the Merck Inpatient Unit, an acute care psychiatric facility. His team’s primary goals are to adjust medications, identify potential triggers of behavioral problems, and improve patient and family safety after discharge.

“Coming into the inpatient unit is not like a surgical approach. It’s not like you’ll come in, you’re here two weeks, four weeks, six weeks, eight weeks, we’ll fix it all, [and] you’ll go back out. So what’s really critical is the idea that it takes a village,” says Martin Lubetsky (Fel ’86), Pitt professor of psychiatry and clinical service chief of child and adolescent psychiatry, as well

are physically aggressive, both to caregivers and to themselves. Headbanging, scratching, skin picking, punching, kicking, and headbutting often occur multiple times each day at home, and the behaviors don’t stop on the unit. For a long time, Pierri says, staff on the unit had the highest rates of workplace injuries at Western Psychiatric Institute and Clinic. The addition of specially trained staff to observe patients, learn their unique quirks, and defuse outbursts before they happen has helped injury rates decrease. The behavioral therapists also teach their skills to parents to be used at home and school.

The challenging behaviors exhibited by Merck inpatients can cause serious burnout among staff, says social worker Tara Krelic. Yet people who work on the unit get a break as soon as they clock out. The parents of these children don’t, and the strain can cause serious problems for families, she explains.

“The people who bear the burden are caregivers. The people who are on the receiving end of the aggression are often family members,” Krelic says.

For Jessica West, whose 14-year-old son (we’ll

call him Ronald) was treated at Merck last year, the coaching has been nothing short of a godsend.

"I don't know where we would have been without that time and without the guidance and support of the medical team," West says.

Her son's violent behavior followed episodes of catatonia, during which her son would freeze and become unresponsive for upward of an hour. In January 2017, West's son froze while trying to cross a busy intersection near their home in a Pittsburgh suburb. At that moment, West knew her son needed more help than she could provide.

"Because you can't explain to somebody who's in a car that he has autism. You can't explain to the onlookers who are seeing you out in the middle of the street and you're not moving, why you're not. It just looks like you're just being a jerk. It doesn't look like there's something that's going wrong with my son," West says.

"My husband and I looked at the situation from a safety perspective. And I really felt like there was nothing more that we could do to keep him safe."

Ronald's verbal abilities are pretty good. Because his language is better than some on the spectrum, West says that it's easy to think his problems aren't as severe as those of nonverbal children.

That's not how things work, according to Lubetsky. In 2017, Pitt's Carla Mazefsky and colleagues showed that verbal children hospitalized on the Merck Inpatient Unit had just as many outbursts and instances of aggressive behavior and self-injury as minimally verbal children. (Learn more about Mazefsky's work in the adjacent story.)

On admission, the teams at the Merck Inpatient Unit provide each inpatient with a targeted behavioral plan that focuses on the nexus of issues that led to the hospitalization. As staff track how each patient adjusts to life on the unit, they can learn what might set off a person and how best to de-escalate the situation.

Joy spent several weeks at Merck. When she was discharged, her behavioral issues weren't gone. But her time as an inpatient gave her a start on more effective medication, as well as a chance to learn new strategies to keep her frustration from boiling over.

And this spring, Joy had the chance to compete in a beauty pageant for teens with special needs. She dressed in a teal gown, her light brown curls framing her face. For once, Joy got to act like any other teenage girl. Her mother says the opportunity was made possible by the new start offered by her stay at the Merck Inpatient Unit. ■

Note: To protect privacy, we have changed names of patients and families in these stories.

"I HONESTLY HAD NO IDEA IT WAS COMIN

A SEARCH FOR WARNING SIGNS

BY CARRIE ARNOLD

W

hen inviting colleagues and visitors to the inpatient wing where she leads a research study, psychologist Carla Mazefsky sends them a long list of dos and don'ts. Avoid large earrings, scarves, and anything else that can be grabbed by an excited or distressed child. Wear trousers and comfortable shoes "in case you have to get out of the way quickly."

Mazefsky specializes in kids on the far end of the autism spectrum who are prone to aggression. The Merck Inpatient Unit (which has treatment wings for adults, teens, and children) was designed for individuals in crisis who can't be physically safe in their day-to-day lives. Doing research to help them, as Mazefsky has pursued since she arrived at the University of Pittsburgh in 2006, seems like it would be nearly impossible. Most people would be deterred, or at least intimidated. After spending years working with this population, however, Mazefsky has gained tremendous insight into what drives the aggression and outbursts most likely to cause harm and lead to hospitalization.

Popular accounts of autism often portray people with the condition as emotionless automatons. Yet more than a decade of work at Pitt has convinced Mazefsky that emotional dysregulation (the inability to control emotional responses) plays a key role in autism.

What results are angry outbursts and meltdowns, as well as aggression toward self and others that can drive families to

their breaking point. If she's right that these intense emotions are central to autism, her work won't just change how doctors and other providers think about autism, but also will help them develop strategies to prevent meltdowns before they occur.

Mazefsky is also a codirector of the Center for Excellence in Autism Research, which was founded by codirector Nancy Minshew, who holds Pitt's Endowed Chair in Autism Research and is an MD professor of psychiatry and neurology.

Sitting in a small alcove in the cafeteria of the Western Psychiatric Institute and Clinic, Mazefsky outlines the difficulties and idiosyncrasies that form the core of how many researchers think about autism: language delays, difficulty making eye contact, trouble understanding what another person might be thinking and feeling, repetitive motions such as hand flapping or rocking to self soothe. These traits have been codified into the diagnostic criteria for autism.

As she leans back in her chair, Mazefsky notes that these differences are very real. The problem, she says, is that the focus on this particular set of challenges overlooks the profound emotional dysregulation faced by many

G.”

with autism.

Mazefsky has found that many with autism are overwhelmed by emotions they can neither identify nor control.

Most clinical researchers spend their time trying to improve how children on the spectrum interact with the world around them.

“The early interventions are focused on increasing communication, cognitive skills, social interaction—which all make sense. But it’s very hard to even make gains in those areas if you’re really dysregulated,” Mazefsky says.

It’s as if people on the spectrum are being taught to make cakes; and if their skills improve, their teachers say, they’ll add more layers. Maybe even elaborate fillings and icings. Yet instead of an oven that works at 375 degrees Fahrenheit, those with autism must contend with one that shoots up to 600 degrees at random. The result is a cascade of effects that reverberate throughout the life span. And someone is bound to get burned if you don’t regulate the temperature.

Parents use another metaphor when describing this phenomenon: Their kids’ emotions rev up from zero to 100 in the blink of an eye. One second, everything is fine; the next, chaos.

“It’s a problem when they’re little. And then, as they’re older and their behaviors are more difficult to manage, and it’s less acceptable to have a tantrum, it almost creates more of a divide between even the verbal kids with ASD and their peers when they’re so dysregulated emotionally,” Mazefsky says.

Even Mazefsky can be taken aback by how quickly things can unravel. Last year, she administered a diagnostic test to a nonverbal teenage girl being discharged from the unit. At first, everything seemed to be going well, Mazefsky recalls. The girl appeared to be engaged and even enjoying the activities. Then, seemingly with no warning, she headbutted Mazefsky, leaving the researcher bruised and shaken, but otherwise okay.

“And I honestly had no idea it was coming. Despite my knowledge of her [long history of headbutting], knowing she was still doing it, and all of my years and years of training. And her parents were in the room, and they had no clear indicator that it was coming either,” she says.

“If I had had one minute of warning, how different that situation could have been.”

Looking back, Mazefsky realized that she shouldn’t have let her guard down. Testing was intense and required social interaction, which many with autism find stressful; and stress, she’s found, can often set the scene for an outburst. But the experience left Mazefsky with more than just a goose egg. She realized that some sort of warning that her young charge was getting overwhelmed could have helped both of them through the incident unscathed.

“Once you’re that aroused, it’s really hard to back down. But we do think there’s stuff going on beforehand that we’re just not picking up on,” she says.

Mazefsky began to wonder whether there was a way to capture the internal signs that someone was beginning to get overwhelmed.

Identifying these precedents wouldn’t be easy, however. For one, people with autism don’t always have the ability to identify, in

aggression occurrence based on preceding biological signals. To do this, they had to determine whether participants would be able to tolerate wearing Fitbit-like devices to measure heart rate, electrodermal activity (like changes in body temperature and sweat), and movement.

Mazefsky and her ADDIRC colleagues intend to use machine learning to see if they can tease out any factors that can predict these events.

“It’s almost never out of the blue, but it does *appear* to be out of the blue,” she says.

Preliminary results from the pilot study suggest that they’re on the right track. The researchers reported at the 2017 meeting of the American Academy of Child and Adolescent Psychiatry that the physiologic data could predict aggression one minute before it occurs with 71 to 84 percent accuracy. Mazefsky has begun a larger trial at UPMC’s Merck Inpatient Unit and hospitals

The girl appeared to be engaged and even enjoying the activities. Then, seemingly with no warning, she headbutted Mazefsky.

the moment, what they’re feeling. The other major barrier is the heterogeneity of people with autism—even among the small subset treated at the Merck Inpatient Unit. IQs can range from 30 to greater than 140. Some kids are verbal, others not. And patients range from 4-year-olds to full-grown adults. Since little had been done on emotional dysregulation in autism, Mazefsky would have to adapt tests designed for other disorders and get them to work for everyone in her study.

Laying the groundwork took years. Mazefsky drew from her experiences working with this population. And she partnered with other experts through the Autism and Developmental Disorders Inpatient Research Collaborative (ADDIRC), a multisite study of severely affected youth with autism who are admitted to specialized psychiatric units, including the one at Merck.

Mazefsky and her collaborators—Matthew Siegel at Maine Medical Center and Matthew Goodwin at Northeastern University—completed a pilot study to see if they could predict

in Rhode Island and Maine to more definitively test this idea and improve accuracy.


Her ultimate dream is to create an app for a Fitbit or other smartwatch that can provide something like a green-, yellow-, and red-light system for potential problem behaviors.

In the meantime, Mazefsky is working with Pitt clinicians treating outpatients with autism to implement a new therapy. It’s called Emotion Awareness and Skills Enhancement Program (EASE). EASE starts by teaching awareness of emotions as a foundational skill that promotes the ability to manage intense feelings. Then patients build tolerance for distress through different strategies.

Although it’s still too soon to say whether EASE is effective, Mazefsky remains optimistic.

“Parents live with this every single day. I really feel for them,” Mazefsky says.

“The families are in crisis, but they’re also excited to work towards doing something to help the problem and get their kids represented.” ■

A high-magnification fluorescence microscopy image of brain tissue. The image shows a dense population of cells. Many cells have bright blue nuclei, indicating they are stained with DAPI. Interspersed among these are cells that exhibit green fluorescence, which, according to the text, indicates they are dying of ferroptosis. The background is a complex network of red and orange-stained structures, likely representing the cytoplasm and extracellular matrix of the tissue. The overall image has a dark, almost black, background, making the fluorescent signals stand out.

Pitt investigators are illuminating a kind of cell death called ferroptosis, which likely plays a role in many acute and chronic diseases. Here, in a model of traumatic brain injury, cells dying of ferroptosis glow in green.

COURTESY BAYIR LAB AND CENTER FOR BIOLOGIC IMAGING

IRONS

UNDERSTANDING DEATH

BY ELAINE VITONE

IN THE FIRE

On a recent afternoon, the University of Pittsburgh's Valerian Kagan explains the tolerance of living things. Life, in its many forms, only has so much wiggle room, he says.

"You'd be surprised to see a polar bear in Miami, right? And similarly, nobody has reported on hummingbirds on the North Pole?"

Birds, bears, whatever earthly inhabitants you might imagine—all life is defined by two things, he continues: one, the raw material imparted by genetics; and two, “everything else.” Food, microflora, temperature. Viruses, pollutants, and heaven forbid, the ionizing radiation from a nuclear bomb. All of the above interact with genomes and their translations, and that, essentially, is life—at least from his particular scientific perspective. Kagan is a Graduate School of Public Health professor and vice chair of environmental and occupational health and School of Medicine professor of radiation oncology.

Well, that’s life until, of course, it’s not. Once a given biochemical point of no return is crossed? “Bye-bye.” Cells die. “It’s difficult to recreate the chicken from a boiled egg, right? Did you try it? No? Well, I tried several times. Don’t waste your time.”

Death always has a reason, he says.

“Hello—nice to meet you,” says Kagan’s coinvestigator, Pitt Med professor of critical care medicine Hülya Bayır, walking in a couple of minutes later after driving from UPMC Children’s Hospital of Pittsburgh, where she directs pediatric critical care medicine research. Her accent is Turkish. Bayır first came to Pitt as a pediatric critical care fellow in 1999 and cut her teeth as an investigator under Kagan’s tutelage. They’ve been collaborators ever since. For her work in the fields of pediatric neurocritical care, traumatic and ischemic brain injury, and redox biology, Bayır has been elected to the esteemed American Society for Clinical Investigation and won several honors from the Society of Critical Care Medicine.

Where were we? Oh yes—death. It always has a reason.

You’ve got your very quick, smash-into-a-truck ways for cells to die—mechanical reasons. That’s called necrosis. And then, as has been discovered over the last couple of decades, there are a dozen other types of cell death that occur naturally, preprogrammed by genetics as a normal part of our life cycle and general upkeep. Balance is key, though. Too much death is not good, for obvious reasons, and too little death is a recipe for cancer.

Usually, programmed cell death is first

sparked by factors outside of the body, Kagan says. For example, in one program called apoptosis, the death sequence switches on when DNA is damaged beyond repair. Bayır and Kagan have made significant contributions to the literature on apoptosis.

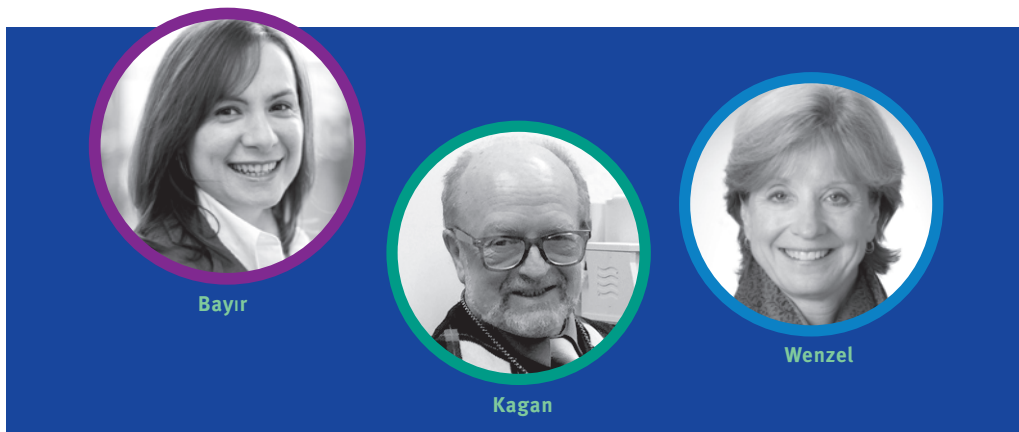
Then, a few years ago, the pair decided to take on another kind of cell death called ferroptosis.

It was first described in 2012 by Columbia University’s Brent Stockwell, who’s now a collaborator with the Pitt duo. Stockwell had been looking for new drug candidates that

from multiple fields of medicine, along with biochemistry, molecular biology, structural biology, and computational biology, they’ve uncovered new insights with potential relevance to a number of diseases. They hope to find ways to stem ferroptosis when it contributes to the degradation of tissue, as it does in brain trauma, asthma, kidney disease, and more—and, in the case of cancer, to better urge ferroptosis into action.

“LOX contains iron—*ferro* means iron,” says Bayır.

“And we live in Pittsburgh, the Iron



could hit the cancer cells that apoptotic drugs missed, and came upon something never seen before: When he chemically depleted tumor cells of an antioxidant called GSH, a chain reaction ignited. Somehow, this reaction seemed to be using an enzyme called LOX to attack—and kill—the cancer cells.

Within the massive field of programmed cell death, ferroptosis is exploding. Of the 350-plus papers on the topic, 270 were published by labs around the world just in the past couple of years. Pitt researchers are among those leading such efforts, having developed a new technology for the study of ferroptosis—Pitt is one of the few places in the world with this capability.

In a series of papers, Bayır and Kagan have collaborated with Pitt’s Sally Wenzel and others (seven labs in all, mostly from Pitt) to better understand “the reason” for ferroptosis—exactly what biomolecular line is crossed, how that signal is communicated within and between cells, which molecules pull the trigger, and how. Combining clinical observations

City,” adds Kagan. “It would be a shame for us not to understand this process.”

Imagine a body has one of those smash-into-a-truck kind of impacts. In the aftermath, immune cells activate and rush in to help, and the brain is bombarded. Soon, what were once healthy neighboring cells start going down, too—collateral damage.

The road to hell is paved with good intentions, as Kagan likes to say.

Bayır explains that, in order to both treat and monitor this flood of cell-slaughtering inflammation, doctors surgically place a catheter in the brain to siphon excess cerebrospinal fluid out. As a fellow, Bayır saw this fluid, which was just going straight to the garbage, for its worth and began examining it more closely.

“I was doing measurements for a long time,” she recalls. “Dr. Kagan taught me that there’s a difference between measurements and research. It’s very important to understand the difference, and it takes time,

especially for MDs in training.”

Back then, Kagan adds, Bayır was doing the double duty of a rising physician-scientist. “She came [into the lab] from the pediatric ICU in her blue scrubs,” he tells me. He recalls when Pat Kochanek, who’s now professor and vice chair of critical care medicine, first introduced her as a new fellow who wanted to study redox—a chemical reaction in which one substance is oxidized and another is reduced. Redox had long been among Kagan’s areas of expertise.

Bayır began to notice a pattern: Within

like what’s in corn oil. But in ferroptosis the enzyme suddenly betrays its usual mission and oxidizes a specific subgroup of cell-membrane molecules called PEs instead.

“We’d been fantasizing a lot about this,” recalls Kagan. They mentioned it to Wenzel, professor of medicine at Pitt and director of the Asthma Institute at UPMC. And she told them that actually, oxygenated PE may play a role in asthma. They quickly figured out that their areas of study shared some interesting molecules in common.

“And so, in our parallel universes, we even-

and the enzyme that uses GSH is inactive, this complex comes together, which changes LOX’s behavior. And then: death (for cells, at least).

The team hypothesizes that, with these complexes flooding cells along airways, hell breaks loose. Epithelial barriers deteriorate, and tissues become sitting ducks for viruses, pollutants, and all manner of toxins. And probably, immune pathways spur into action, as well. Many of these ideas were first tested by Ivet Bahar, professor and chair of computational and systems biology, and her team using computational modeling.

Wenzel has examined samples from people who’ve died of asthma attacks, and found LOX/PEBP1 in their airways. She’s found it in living patients with severe asthma, as well, and also correlated its levels to those of a biomarker of disease severity, exhaled nitric oxide. The biomarker and LOX/PEBP1 had “one of the strongest relationships I could possibly imagine,” she says.

The same complex showed up when Bayır examined cells from a model of traumatic brain injury, as well as when the team examined models of kidney failure, which is also believed to be a result of ferroptosis. Striking images of the complex, captured by Claudette St. Croix, a PhD associate professor of cell biology, ran in the team’s paper in *Cell* in October 2017.

Wenzel cautions that there’s work to do. Still to come is confirmation of the significance of what they’re finding—but the data are thus far very encouraging. If the hypothesis holds together, it could mean a lot for patients with severe asthma. As of now, the only therapies available for serious asthma attacks are albuterol inhalers and oral steroids. She adds that asthma tends to run in families—and her preliminary data suggest some people may have susceptibility to this destructive complex written into their genetics.

“We may have the chance to treat an asthma exacerbation in a way that’s way, way, way different from anything that has ever been done before,” she says.

The team is now searching for molecules that can target the LOX/PEBP1 complex. The LOX inhibitors currently on the market can’t

“We may have the chance to treat an asthma exacerbation in a way that’s way, way, way different from anything that has ever been done before.”

the first week after a patient’s injury, levels of GSH progressively decreased—a sign that oxidation was on the rise. (Recall that GSH is the same antioxidant that would later figure into the discovery of ferroptosis.) But the tools at the team’s disposal couldn’t explain what was being oxidized or what exactly that signaling process was.

So, for the next 10 years, Bayır and Kagan worked to develop a new technology that could reveal what was happening. “It’s really kind of like looking for a needle in a haystack. That’s what we had to overcome,” in addition to waiting for mass spectrometry technology to catch up to them, says Kagan.

Using a technique they named mass spectrometry-based redox lipidomics, they identified the products of ferroptosis and sussed out which molecules initiated the signal that causes cells to die. They published their findings in two papers in *Nature Chemical Biology* (both e-published in November 2016).

Normally, LOX oxidizes free fatty acids,

usually found each other,” Wenzel explains in a separate interview.

Wenzel, a translational researcher, is an international leader in asthma; the condition is another kind of hell that begins in good intentions.

Say a body comes into contact with pollen. That body will do its best to stop the allergen in its tracks by drowning it in mucus, and by restricting airways so that the pollen can’t get through. But unfortunately, then, neither can air.

In 2011, *PNAS* had published Wenzel’s findings on the pathways for mucus production in people with severe asthma. And wouldn’t you know: One of the key molecules was LOX.

The Pitt Med colleagues found evidence that in severe asthma, LOX was abandoning its script, too; instead of keeping cellular proliferation in check, like it’s supposed to, LOX sticks to a protein called PEBP1.

It’s much more complicated than this, but in short: When cellular GSH levels are low

do the job, so new ones must be developed from scratch. A laboratory at the University of California, Santa Cruz, is collaborating, and other potential partners have expressed interest as their investigations gain steam in this wholly new area of drug discovery.

In acute radiation syndrome, at first, a body finds itself in gastrointestinal misery. Then a calm sets in—for a time. The latent phase passes, followed by what's known as manifest illness; and depending on the level of exposure, that "manifestation" can mean utter "devastation" for cells throughout the body, potentially to fatal effect.

Some of this damage, particularly in the gut, appears to be caused by ferroptosis. Bayır explains that she and her colleagues believe this intestinal damage triggers a cascade of health complications that lead to sepsis, a deadly syndrome. "If we can stop that process and get the body to repair, rather than systematically destroy those cells, we might save the victims of devastating dirty bomb attacks," she says.

Pitt is one of four centers funded by the National Institutes of Health to prepare for such events. The Pitt Center for Medical Countermeasures Against Radiation is directed by Joel Greenberger, professor and chair of radiation oncology. Within the center, Bayır leads a project aimed specifically at stockpiling therapies to stem ferroptosis in the fast-dividing cells of the gut and bone marrow in the event of a nuclear attack.

The good news is that in this particular cell-death program, time is on a body's side. Ferroptosis isn't the initial crash and smash of electrons, but rather a reaction to it. Relevant therapies could be administered a few days after an attack and still save lives. The team is excited about their progress thus far.

Two weeks before their big *Cell* paper came out, that same journal published a review paper on ferroptosis that Bayır and Kagan wrote, along with 16 other attendees of an invitation-only meeting called the Cold Spring Harbor Symposium. The paper outlines what is known about this cell death pathway, tools for its study, and areas of promise for the future: Alzheimer's, Huntington's, Parkinson's, cancer, stroke, intracerebral hemorrhage, traumatic brain

injury, ischemia-reperfusion injury, kidney degeneration, and even heat stress in plants. Pitt has projects along several of these lines—many irons in the ferroptosis fire. (A follow-up meeting is planned for November.)

One of the main challenges in studying ferroptosis is that there is no direct biomarker for it. Bayır and Kagan's redox lipidomics technology yields the closest thing to it—but the technique is slow going. "It's not high throughput. We cannot today immediately implement it into clinics," says Kagan. "But it will be done."

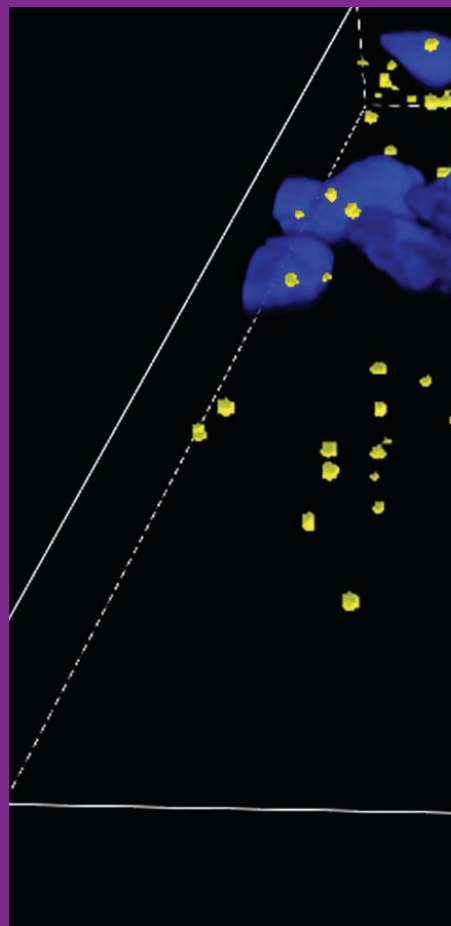
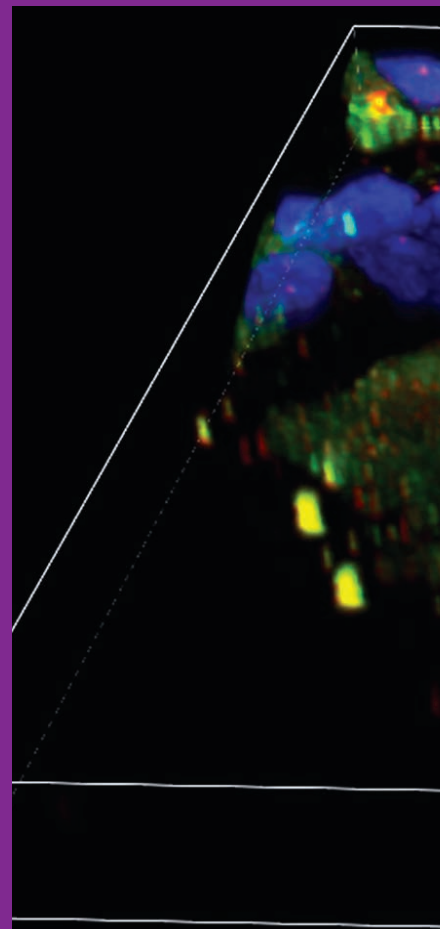
Institutions around the world are lining up to collaborate with the Pitt group and their unique technological capability. Meanwhile, Bayır and Kagan are working to break up their own monopoly. A new international laboratory for navigational redox lipidomics, to be based in Moscow, is in the works. "Pitt will of course play a major role," says Kagan, who will act as a consulting director from afar.

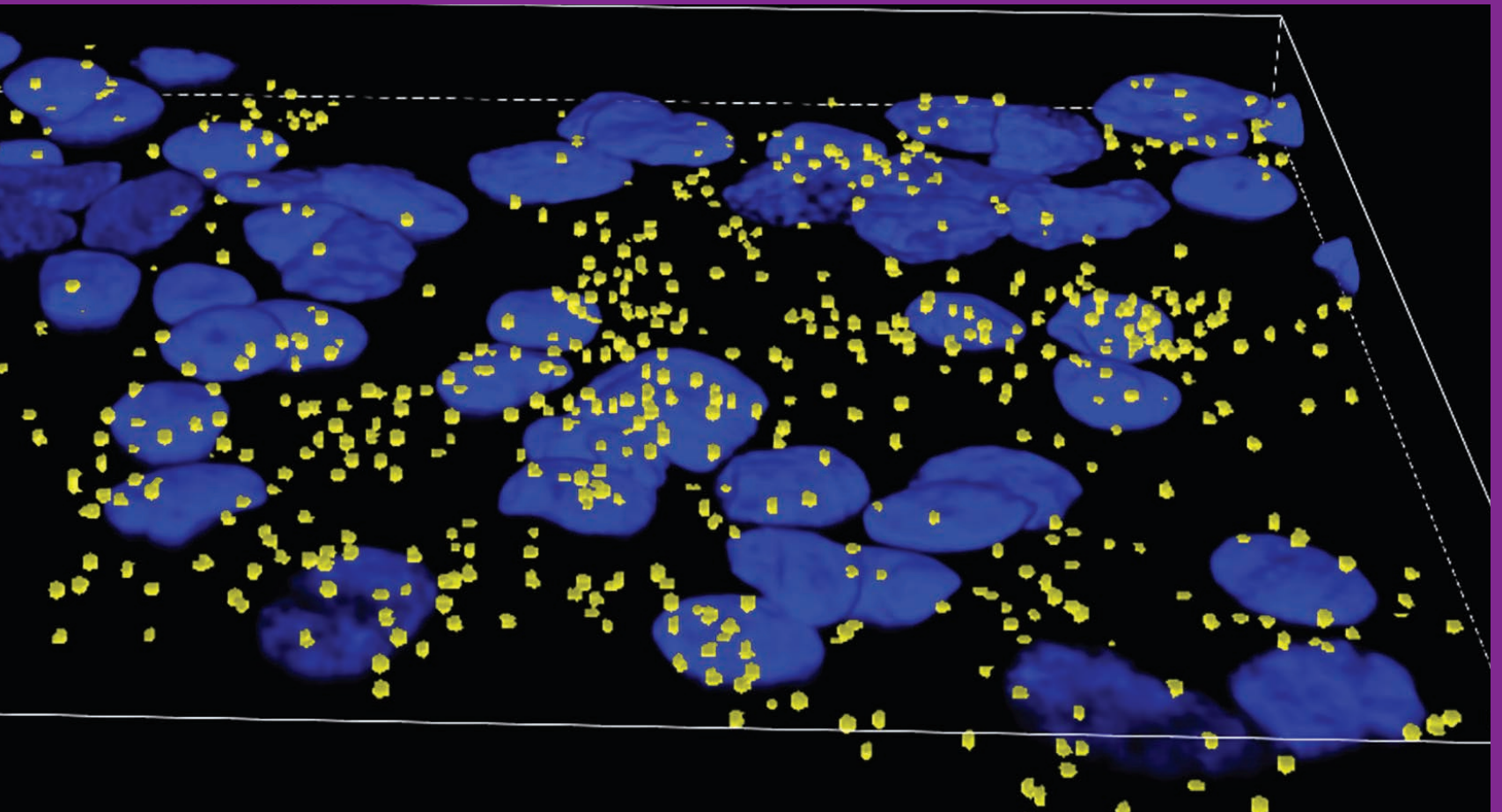
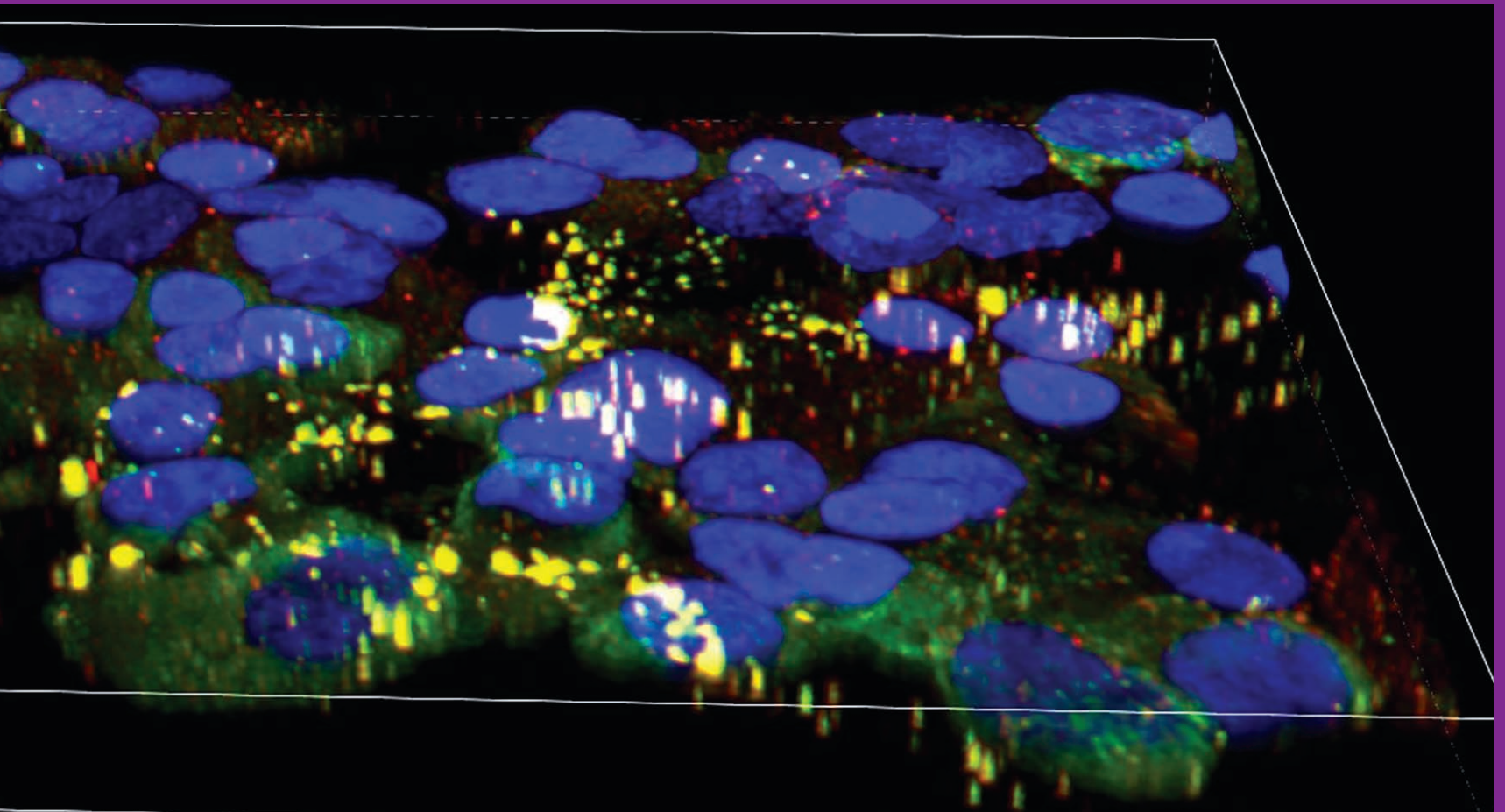
Why Moscow? For a lot of reasons, he says. Lomonosov Moscow State University, his alma mater, is the scholarly home of his longtime collaborator and friend Yury Vladimirov, who is developing another possible new way to detect ferroptosis. In fact, several other labs in that city are piecing together new tools for this fast-dividing field of study, Kagan notes. He adds that once the new facility opens, so will additional opportunities for mentoring, which has long been a passion of his. Many rising Russian scientists have come to Pitt to work in his lab.

Here in Pittsburgh, a soon-to-be-launched Neuroscience Institute at Children's Hospital, directed by Bayır, will be central to this new partnership. In time, the Pitt team's bicontinental efforts could grow to a global ferroptosis force to be reckoned with.

"There will be people recruited not only from Russia, but also Europe, Germany, and Portugal," Kagan says. "It will be very international and interdisciplinary. That's what science is all about."

When he presents at conferences, Kagan uses a slide with pictures of his happy American home of 26 years. Pittsburgh, he likes to mention, is also home to 446 bridges. And now the Iron City is building yet another new byway to the broader world. ■





In the epithelial cells (nuclei in blue) within the airways of patients with severe asthma, Wenzel found the LOX/PEBP1 complex (yellow and green). She then compared its abundance to levels of a biomarker for asthma severity—exhaled nitric oxide—in the patients and found “one of the strongest relationships I could possibly imagine,” she says.

STICKING IT



ABOVE: The hand of Sarah Nelmes, a dairymaid. Edward Jenner used the pus from her cowpox lesions to inoculate his gardener's son against smallpox.

TO DISEASE

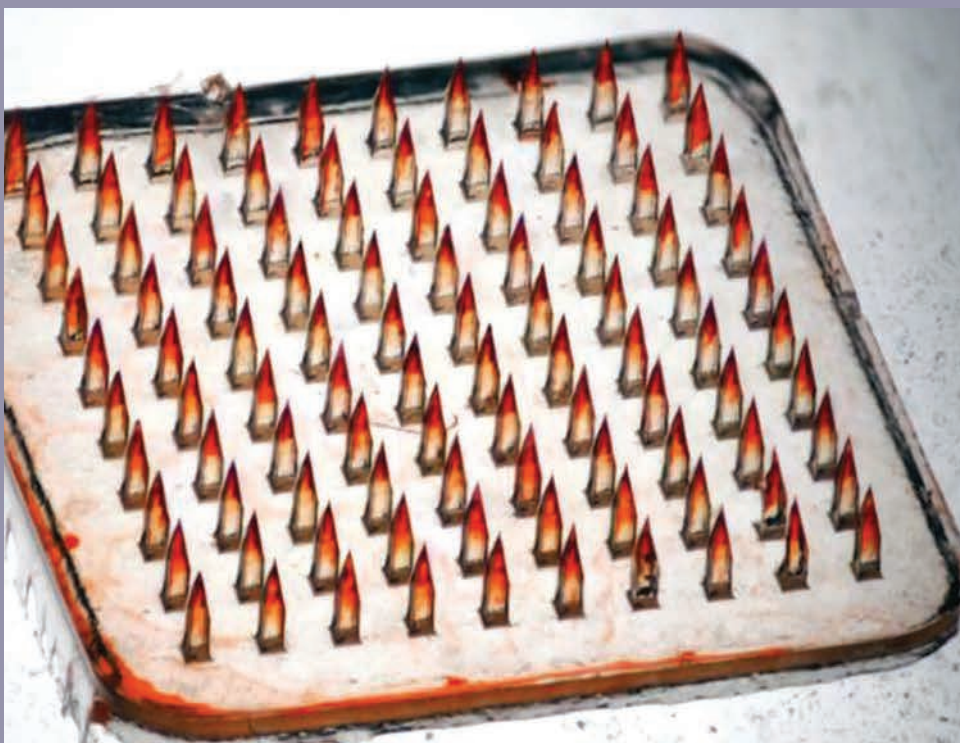
A BUNCH OF LITTLE NEEDLES CAN STIMULATE
THE IMMUNE SYSTEM | BY GAVIN JENKINS



Smallpox was once called the scourge of mankind. The disease's origin is unknown, but its existence can be traced to 10,000 BCE in northeastern Africa. During the 18th century, 400,000 Europeans died annually because of smallpox. In England, where a 13-year-old orphan named Edward Jenner was an apprentice to a surgeon and apothecary, the disease was also known as the “speckled monster” because of the resulting skin condition—sores filled with opaque fluid.

As an apprentice, Jenner once overheard a dairymaid say, “I shall never have smallpox for I have had cowpox. I shall never have an ugly pockmarked face.”

IMAGE COURTESY NATIONAL LIBRARY OF MEDICINE



Microneedle arrays are fingertip-size patches that deliver drugs right to the skin. The needles can contain multiple adjuvants that stimulate the skin's immune response.

COURTESY FALO LAB

For centuries, it had been common knowledge that smallpox survivors became immune to the disease; and because of this, many doctors inoculated people by removing smallpox scabs or pus from an infected person, then rubbing that onto the arm of someone who was uninfected. This was called variolation. The method worked fairly well for people inoculated in this manner; only up to 2 percent died from smallpox. Yet, they were likely to pass on a severe case of the disease to someone else.

Jenner never forgot what the dairymaid had said. Years later, as a physician, he decided to research his theory that the pus in cowpox blisters protected people from smallpox.

In 1796, Jenner removed cowpox scabs from the hands of a milkmaid named Sarah Nelmes and rubbed them onto the arms of James Phipps, his gardener's 8-year-old son. Phipps came down with a fever, but no lesions. Later, Jenner injected the boy with smallpox, but the child never developed the disease. He repeated the test, and Phipps remained in good health. Jenner successfully tested 23 other patients this way and published his findings. His results were debated in England until 1840, when the government banned variolation and provided free vaccinations using cowpox, which was deemed much safer.

To vaccinate patients, doctors scratched a person's arm with a cowpox-covered needle;

this method continued into the 20th century. Smallpox was officially declared eradicated in 1980, but some people who grew up during the first half of the 1900s may have a scar on their arm from when they were vaccinated with a needle scratch.

These scratch vaccinations were pretty effective, but far from perfect. Doctors couldn't scratch the same way twice, which meant they couldn't guarantee they'd deliver the same amount of vaccine each time. Vaccinations need to be reproducible. In time, intramuscular injections became popular; but Louis Faló, an MD/PhD and chair of the University of Pittsburgh's Department of Dermatology, notes these miss the skin completely. Unlike skin, muscle does not directly elicit an immune response. So, at the cellular level, intramuscular injections are only modestly successful compared to smallpox vaccinations of the early 20th century.

Inspired by the history of scratch vaccinations, seven years ago, Faló began researching microneedle array technology, which delivers medicine through the skin.

Our skin isn't just keeping our insides from spilling onto the sidewalk. It's our biggest organ, and our first line of defense against viruses and other pathogens we come across.

"The control of the body's entire immune response can probably be achieved by manip-

ulating the skin," Faló says. "I have always tried to manipulate immunity by manipulating skin immunity."

In 2016, with Andrea Gambotto, MD associate professor of surgery and member of the Center for Vaccine Research, Faló coauthored a study using microneedles to deliver a vaccine for the Zika virus. Mice showed immunity against Zika six weeks after immunization when the vaccine was delivered with microneedles. Today, the vaccine is still in preclinical testing, and Gambotto and Faló continue to develop novel vaccination strategies using microneedles.

And now Faló's work has led to what is probably the world's first study examining the effectiveness of microneedles on skin cancer.

A phase I clinical trial is testing proper dosages for patients with cutaneous T-cell lymphoma. It's still early in the process, but if microneedle therapy pans out, it could change how skin cancer is treated. No more operations. No chemotherapy injections. Just a Band-Aid covering a fingertip-size patch with tiny medication-infused needles.

Microneedles, Faló says, are better than intradermal injections, which introduce a drug to the dermis (the thick layer of "living tissue" under the epidermis, the outer skin layer). Intradermal injections are hard to reproduce. Microneedles, on the other hand,



deliver the same results each time, and they inject medicine directly to both the dermis and epidermis.

The immune system is more efficient in the skin than in other tissues. Faló has found that immunizations delivered directly to the skin result in stronger and longer-lasting immunizations than those delivered below the skin or into muscle.

Faló grew up in Greensburg, Pa., and attended Pitt as an undergrad before going to Harvard Medical School, where he also served on the faculty. He was drawn to dermatology because of the skin's adaptability. He's fascinated by how it responds to trauma, heat, cold, infection, and sunlight.

"In terms of immune responses," Faló says, "it is truly sentinel, guarding against and identifying any invading organism, tuning the body's systemic immune response to neutralize that specific attack."

Faló, whose inventions have led to a number of patents, has cofounded a company devoted to developing new therapies for skin cancer, including microneedles.

Research on microneedles began in the mid-1990s, when microfabrication technology facilitated their manufacture. The research was led by three isolated efforts operating in parallel at the Georgia Institute of Technology, Becton Dickinson (a medical technology company), and Alza Corporation (a pharmaceutical company).

Last year, Mark Prausnitz at Georgia Tech published the results of a phase I trial for a self-administered influenza vaccine using microneedles. Georgia Tech is also developing microneedle patches for polio, measles, and rubella vaccinations, notes Prausnitz.

There are a few different types of microneedles. For his research, Faló uses dissolvable microneedles. In this variety, a drug is mixed with the patch's structure, and then the needles disintegrate in the skin's aqueous environment.

Microneedles can be mass produced at a low cost, shipped in bulk, and stored at room temperature. The technology could eliminate the need for cold chain distribution, which is a series of stages of uninterrupted refrigeration, from production to storage.

The cold chain costs \$13.4 billion a year

Mellon University. A micro-milling expert, Ozdoganlar built a machine for Pitt with diamond-tooled tips that cut precise angles for microscale molds.

One June afternoon, Pitt's Geza Erdos, a PhD and assistant professor of dermatology, and Oleg Akilov, MD/PhD and director of the Cutaneous Lymphoma Program and Extracorporeal Photopheresis Unit, show off the narrow area where the microneedles are made. Akilov slides open an unassuming counter drawer. It's full of tiny, white patches that could eliminate melanoma-plagued cells. Akilov picks up a patch with two fingers and presses it against his forearm.

"It feels like Velcro," he says.

Joseph Lane (not his real name), who participated in the clinical trial, agrees that the patches feel like Velcro, and he insists they don't hurt when inserted. "But you can definitely feel it being pushed in," he says.

Lane, a lecturer at Pitt, was diagnosed with folliculotropic mycosis fungoides in 2009. With this disease, the body is the site of a traffic jam of sorts; but instead of cars, it's T cells that get waylaid. "They get confused about where to go because of how they're made," Lane says. "So they go to my hair follicles."

Lane gets cancerous lesions; they can appear wherever he has hair. He has itchy,

Lane says the disease has been manageable since he finished the microneedles trial earlier this year. "If I could freeze it like this, I would," he says of his condition.

globally, and vaccines sometimes expire or denature before reaching children in need, especially those in remote regions of developing countries. The World Health Organization reports that more than 50 percent of vaccines are wasted each year.

Faló's team makes microneedles in a small, narrow lab across the hall from his office on the 11th floor of the Thomas E. Starzl Biomedical Science Tower. Seven years ago, when Faló decided to see if the technology could work with skin cancer, he asked O. Burak Ozdoganlar for help. Ozdoganlar is the Ver Planck Endowed Professor of Mechanical Engineering and associate director of the Engineering Research Accelerator at Carnegie

red patches of skin on his hands, forearms, legs, and lower back. He says the disease has been manageable since he finished the microneedles trial earlier this year.

"If I could freeze it like this, I would," he says of his condition.

"I could live with this the rest of my life."

Lane has participated in a few trials at Pitt, and each time, Akilov explains why he thinks the study could help him. "He's a funny guy," Lane says of Akilov. "And he's really good at talking to me and saying why the studies make sense" for him.

Akilov grew up in Yekaterinburg, Russia. At Ural State Medical Academy, he was in awe of how much one of his professors

could learn about a person from examining the skin. Akilov embraced the notion that experienced dermatologists could have powers akin to palm reading. They could tell you a patient's profession, diet, and how much time had been spent in the sun. This passion led him to immunology, and before Faló hired him at Pitt, Akilov served as a postdoc at the University of Notre Dame and as a research instructor at Harvard.

During the lab tour in June, Akilov hands me a fingertip-size microneedle patch. To make microneedles, he explains, they pour carboxymethyl cellulose into the molds, insert them into a centrifuge, and then pop them out. The needles are shaped like tiny Washington Monuments. Faló and his team experimented with the shape of the needles before landing on this structure. At first, the team built them like tiny pyramids, but Akilov says those didn't deliver the drugs effectively because they were too wide.

"You want to have a maximum volume achieved in a reasonable, geometric structure that will pierce the skin," Erdos adds.

"Two thousand bucks," Erdos adds.

Later, Faló guesses each patch costs about two cents to make.

The lab has three unofficial team members in Faló's children: Isabella, 15, and 18-year-old twins, Dominick and Gabriel. (During their summers, between wrestling, soccer, football, and lacrosse practices, they've helped with microneedle development.) Akilov says other members of the team turn to Faló for fatherly counsel.

"When he gives you a piece of advice," Akilov says, "be sure to print it and laminate it, because that is going to be your instructions for how to live for the next couple years."

When doctors administer chemotherapies through an IV or injection, they destroy rapidly dividing cells faster than other cells. But then the toxins flow throughout the body, producing the side effects of hair loss, nausea, and fatigue.

Faló believes microneedles can deliver a lower dose of doxorubicin straight to squa-

that the microneedles missed. There are two benefits to this. One is obvious: This kills skin cancer in the patient. In addition—similar to a vaccination—immune memory is developed. The T cells can mount a response if the disease metastasizes or if a new skin cancer forms.

"You don't have to go through the whole process of stimulating a new immune response again," Faló says. "The T cells are already there, waiting for [cancer] to come again."

This element of the response is crucial, Faló explains, because researchers interested in developing cancer vaccines struggle to find common antigens. It's not like the flu, where there's one antigen, one protein, and everyone is immunized against that protein. Tumors have multiple antigens, and there is an individualization to them. Your squamous cell carcinoma or basal cell carcinoma might look very different from mine, antigenically speaking.

In this regard, treating skin cancer with microneedles is personalized medicine, says Faló.

Akilov embraced the notion that experienced dermatologists could have powers akin to palm reading. Just by examining the skin, they could tell you the patient's profession, diet, and how much time had been spent in the sun.

The shape permits the needles to hold multiple drugs. One therapy can be in the tip, while one or two more can be stored in the shaft. Faló and his team are experimenting with doxorubicin, a chemotherapeutic, in the tip and, in the shaft, one or two adjuvants (i.e., artificially made molecules that stimulate and improve immune response by imitating the types of danger created by bacteria or viruses). Microneedles are easily broken, and that's the point. (Sorry about the pun.) Once they are inserted into the skin, they break off and dissolve, releasing medicine.

Holding the patch with two fingers, I accidentally snap it in half, and Akilov and Erdos laugh.

"Oh my God, now we're going to charge you," Akilov says.

mous cell carcinomas, basal cell carcinomas, and cutaneous lymphomas. The drug's high concentration to one area would cut down on, and possibly prevent, negative side effects.

"It enters cancer cells in the skin where it is delivered and essentially doesn't go anywhere else," Faló says. For example, Lane did not experience side effects from the microneedle therapy.

So: It's not possible to hit every single tumor cell with doxorubicin, and even if you could, that would not be enough to stop cancer. You've got to exploit the immune response. That's how Faló's microneedles operate.

After the microneedles release doxorubicin, the dying cancer cells let loose antigens for the immune cells to pick up. The immune response should wipe out the cancer cells

"I don't need [to find] an antigen to immunize you against cancer," he says. "I'm using your tumor. It's got the right antigen. It's yours. It's your tumor serving as the source of antigen for your immunization—all because of the reaction started by the chemotherapeutic in the patch that was delivered to the cancer."

Microneedles might not be there yet, but Faló says that the field is gaining momentum. And his team also is devoted to reversing autoimmunity with microneedles. In this context, microneedles are a tool for introducing changes to the microenvironment. Down the road, he envisions help for patients with psoriasis, eczema, and contact dermatitis (like poison ivy).

"It's a remarkable tool," Faló says. ■

SURGERY IN SPACE: SOMEBODY NEEDS
TO FIGURE IT OUT | BY ELLEN KRUCZEK

REALLY OUT THERE

Where does humanity push its limits? You might think deep space travel or maybe medical interventions capable of bringing us back from the brink of death. Sandip Panesar, an MD pursuing a postdoctoral research fellowship in the University of Pittsburgh Department of Neurological Surgery this year, thinks both. He uses his role as a researcher to work on, as he says, “weird papers.” The physician was interested in neurosurgery in space, but found that even the basics of general surgery in that context were not laid out. So he published a review in the *British Journal of Surgery* in June to explore the potential issues and solutions a surgeon might encounter. He says, “The thing is, nobody knows anything about [surgery in space]. What I was trying to do, the whole point of the article, was try to open up a discussion.”

When astronauts need medical attention on the International Space Station, they are sent back to Earth. However, if SpaceX, NASA, and other organizations realize a human mission to Mars, interventions will need to happen in space.

Panesar’s review highlighted the well-known effects of prolonged time in orbit on the human body. We know that astronauts are vulnerable to a loss of bone and muscle mass, plasma, red blood cells, and immune function. We weren’t built for low gravity, recycled air, or being stuck in enclosed spaces 24/7—or whatever the length of a day would be in a shuttle hurtling away from here. (At least a solar day on Mars is about the same as it is on Earth.)

Floating entrails, cramped quarters, no FedEx . . . How will we take care of seriously injured people when they’re millions of miles from here?

MARS IMAGE COURTESY NASA

A long-term Mars mission would expose astronauts to more radiation, as well. In space, people experience an increase of fluids to the head and mental strain; they also up their odds of getting cancer.

Panesar explored medical crises that astronauts are most likely to encounter, notably blunt trauma. He frames surgery within that context, tackling the limits of the current protocols for trauma care. Some issues don't have easy answers. For example, bottled oxygen is in every hospital emergency department, but it would create an enormous fire hazard in a closed shuttle. Regardless, Panesar sees space flight medicine as an inevitable, rather than an accessory, field. Panesar, who recently accepted a fellowship at Stanford University with Pitt Med fellow alum Juan Fernandez-Miranda (Fel '10), is now tackling the limits of neurosurgery in space.

When asked why his interest led him to address bodies celestial, he says, "Don't we all have that sort of interest? If someone said, *Do you want to go to space?* what would you do?"

SAVING BUZZ

Let's say that while making repairs on his way to Mars, flight engineer Bluford Buzz gets hit in the abdomen by a loose piece of machinery. Lucky for him, his suit didn't break and depressurize. Unlucky for him, he's 13 million miles from Earth. How would his treatment differ in space versus on Earth?

Scenario: Buzz might have internal bleeding from his injury.

On Earth: To look for free fluid in the abdomen, a doctor uses sonograms to check for where fluid may be gathering. This technique is called FAST.

Problem: The doctor might not be sure where to look for free fluid in Buzz. Fluid disperses differently in microgravity and might not collect in expected areas.

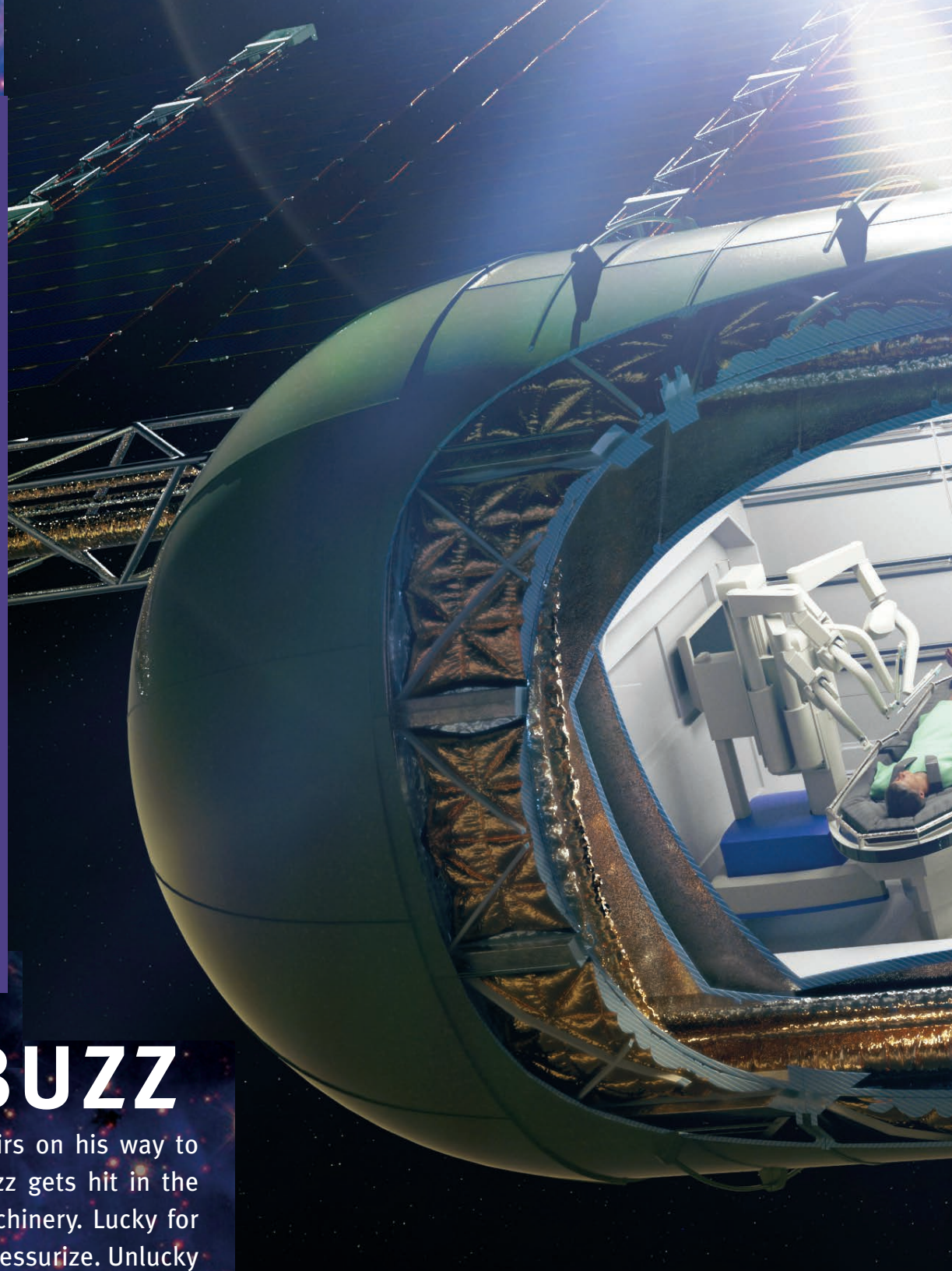
Solution: Researchers are exploring 3-D FAST approaches that could be effective in microgravity.

Scenario: Buzz might experience depressed airway muscle function or hypoventilate.

On Earth: Intubation is sometimes used to protect an airway and keep patients breathing.

Problem: Buzz is more likely to need intubation in space, as microgravity strains the cardiovascular system and, in turn, the respiratory system. Yet, microgravity also draws fluid to the face, so Buzz will have facial swelling. This makes intubation more difficult.

Solution: New methods could help. The i-gel, for example, which is used internationally and which Pittsburgh EMS will be adopting, creates an upper passageway guide for more complex intubation.





Both the physician and the patient are strapped down in this imagined trauma pod.

ILLUSTRATION BY T. TRAPP/PLANVIS
COURTESY JOHN WILEY AND SONS PUBLISHERS

Scenario: Buzz's doc needs specialized equipment to treat him.

On Earth: In developed countries at least, surgeons have access to vast hospital resources. They're also able to receive shipments.

Problem: NASA estimates it costs \$10,000 to send a pound into orbit, so the Mars mission has packed light. There are no delivery trucks headed into deep space toward Buzz.

Solution: Onboard 3-D printers make the necessary tools for Buzz's procedure. He'll need a lot of fluids, so do-it-yourself saline mixes could do the trick—just add sterilized water.

Scenario: Buzz is bleeding heavily.

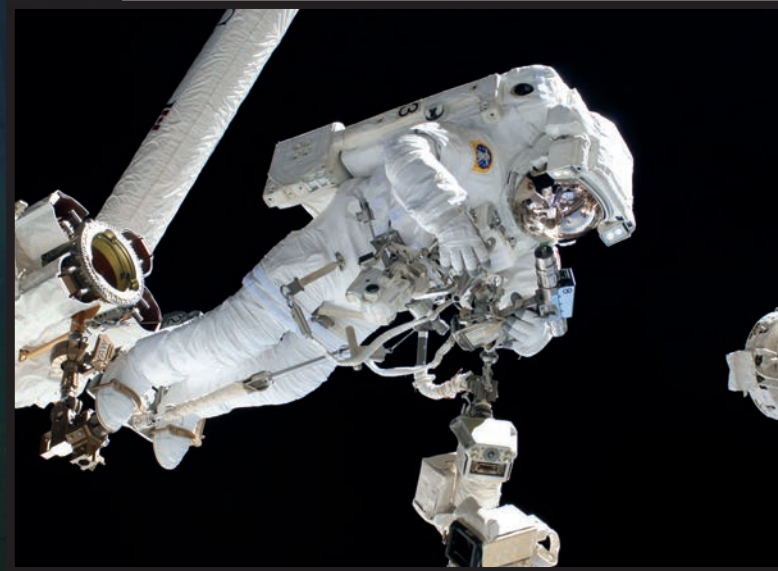
On Earth: During surgery, blood is contained in the body or falls to the ground, where it's mopped up.

Problem: In microgravity, Buzz's blood separates into droplets. His blood (and intestines!) would be free-floating, creating more problems for Buzz and a biohazard on the shuttle.

Solution: His space surgeon might be able to use a sealing system to keep Buzz's insides, well, inside. James Antaki is developing hermetic sealing for spaceflight and the military. Antaki is a Pitt PhD adjunct professor of surgery and bioengineering who recently joined Cornell University.

Consider the gravity of the situation if a space walk were to go wrong. **BELOW:** European Space Agency astronaut Luca Parmitano has some idea. In 2013, an equipment malfunction caused his helmet to fill with water.

IMAGE COURTESY NASA/JOHNSON



Scenario: Not enough space in space.

On Earth: A surgeon uses an operating room to hold patients and surgical materials.

Problem: The cramped shuttle would not be able to dedicate cubic footage to anything like what a typical OR requires. Further, neither Buzz nor the surgical materials would be contained in microgravity.

Solution: A trauma pod, like one being developed at SRI International, could strap down and contain Buzz and required materials. It would also create a specialized, compact area for procedures.

Scenario: Buzz's doctor isn't sure what's wrong with him.

On Earth: The hospital has many specialist physicians and resources for critical care. If needed, they can also do telemedicine consults.

Problem: Radio waves take 13 or more minutes to reach Mars, and that limits the usefulness of specialists calling in during an emergency.

Solution: An emergency medicine physician with combat surgery experience would have a wide enough skill set to stabilize Buzz. For other surgeries, autonomous robotic surgical arms could fill some expertise gaps. This technology is still under development for critical care, but fully autonomous bots already perform dental implants in China. ■



Lawyers Alan Meisel and Mark Nordenberg, former Pitt chancellor, c. 1994

GOOD ENDINGS:

LEGAL SCHOLAR ALAN MEISEL
ON OUR LAST DAYS

BY ROBYN K. COGGINS

Alan Meisel, a JD, has spent a career engrossed in a topic people typically shy away from—death. The professor emeritus of law and psychiatry at the University of Pittsburgh retired this June. He is a national authority on the case law that outlines physician responsibility and patient rights involved in choosing to end one's life.

Appropriately, he's also one of the founders of Pitt's multidisciplinary Center for Bioethics and Health Law, which began as the Center for Medical Ethics in 1984.

"The area was so active that [when] you picked up The New York Times every morning, there would be an article on the front page about some ethical issue in medicine," he says of that time.

For decades, Meisel and Ken Schaffner (a PhD philosopher who went back to get his MD with Pitt Med's Class of '86 and is now Distinguished University Professor Emeritus of History and Philosophy of Science), codirected the center. Since 2016, the center has been directed by Lisa Parker, professor of human genetics, who's a philosopher (and a Pitt PhD graduate, A&S '90) known for her work on ethical issues surrounding informed consent and genetic research.

Meisel's rise as a young scholar accelerated in 1982, when he was invited to join the staff of the President's Commission for the Study of

Ethical Problems in Medicine and Biomedical and Behavioral Research—a group charged with reporting on current ethical subjects. That led to Meisel working on the commission's report, Deciding to Forego Life-Sustaining Treatment, in 1982.

His subsequent legal tome, The Right to Die: The Law of End-of-Life Decisionmaking, was first published in 1989 and is still updated twice a year by his coauthors, Kathy Cerminara (LAW '87) and Thaddeus Pope, to reflect the ever-changing legal analyses for these thorny issues. At nearly 1,500 pages, it is considered the authoritative source for legal precedents relevant to end-of-life decisions.

Can, and should, doctors actively help their patients die?

Today, six states and the District of Columbia allow physician aid in dying, with bills in the legislature or court decisions pending in several others. (Bills in Pennsylvania have failed to come to a vote.) There have been many court cases over the last few decades that grapple with this difficult issue: Can, and should, doctors actively help their patients die?

Such challenging questions are common fodder for debates within Pitt's bioethics center. Here, Meisel shared some insights from 50 years of probing tough questions about end-of-life decisions.

Why is law such an important part of medicine and medical ethics?

It's very difficult to analyze bioethics issues in the United States in the last 30 years without paying attention to legal aspects of the same issues. So, they really are overlapping, complementary disciplines.

One of the subjects you study has been in the news a lot recently, so let's start with that: What is death with dignity?

[First of all,] I don't like the term "death with dignity," because I don't think it conveys very much at all. I talk about "actively aiding patients in dying." Many physicians still

have a very, very hard time accepting the idea of actively aiding

patients to die—so-called death with dignity. Although, I do think that there is increasing acceptance of it.

[End-of-life approaches such as] palliative care have been, of course, a tremendous development. It's helped so many people. But, it's also proved to be a major barrier to the acceptance of physicians of aid in dying.

How so?

Because [some] palliative care docs think that everybody can die painlessly—that they can medicate the pain away. And that's not always true.

In addition, pain is not even the major concern of most people at the end of life: If you look at the surveys in Oregon and Washington where [physician aid in dying is



Meisel

legal and] the state department of health does a report on this every year, you find that the major reason that people seek medication to end their life is not pain, but loss of independence, loss of ability to control their lives and do the things they want to do that they find meaningful.

And I think that doctors like to say they're afraid of the slippery slope—that if we legalize aid in dying, we will eventually get to involuntary euthanasia. My feeling is, there isn't anything we do that doesn't have some risk of being taken to the extreme. But, we've been pretty good at drawing lines that would allow people to engage in certain practices and not go any further.

Bring [the practice of aid in dying] out in the open and regulate it.

Do you get a sense physicians generally feel like these laws for revoking care or making end-of-life decisions are clear now?

Clearer, yeah. The current generation of physicians grew up with these practices. Whereas, when they were first being estab-

lished between '75 and '90, you had a generation or two of doctors for whom this was all new, it was changing.

What are some of the newest ethical concerns in end-of-life care?

[In addition to] the adoption of death with dignity laws, another area has been so-called futile treatment.

Whereas the whole right-to-die movement was kicked off by patients or their families wishing to refuse treatment, the futility cases involve patients and families *demanding* treatment from doctors who believe that it's futile to provide it. That had a fair amount of momentum for a while, but there's not been a lot of litigation in that area in recent years. It may be because they get settled at the bedside level or the hospital level, and they just never make it into the legal annals.

What would you say to physicians who feel uneasy about the aid-in-dying movement?

My position is, doctors have been aiding patients in dying in the United States legally since the Karen Quinlan case in 1976. [That was a landmark suit in which Quinlan's parents petitioned to remove comatose Karen from artificial respiration after a devastating accident; doctors refused, and the Quinlans took their case to the New Jersey Supreme Court and won.]

They've been doing it by withholding treatment, by withdrawing treatment at the patient's request—or at the request of a family member who has the legal authority to speak for the patient who can no longer speak for himself.

Physician aid in dying [as a movement] is saying, *There are certain patients who are near death, [but] who are not being kept alive by any medical treatment that you could withhold or withdraw. All we're doing is providing them with the means to end their life, the same as the patients from whom you could withdraw treatment. They deserve the same humane treatment. (I use treatment in the nonmedical sense there.) And that can be done by providing them, at their request, with medication.*

What about in cases where the person can't make that request?

Here, if you want to err on the safe side, let's say the patient has to be competent to do it. Let's see how that works. If we want to expand it later, we can.

I think that probably the laws in the states where it has been legalized have one major flaw, and that is for patients who are going to suffer from dementia. The laws require that you be terminally ill [and] within six months of death. Well, people who are demented, by the time they're six months from death, no longer have the capacity to make these kinds of decisions on their own. So, we need to be able to figure out some way to provide aid in dying for them, as well. And my feeling is you do that through an advance directive. You either specify that when you reach a certain point, you would like to have a lethal dose of medication, or when you reach a certain point, that you authorize your family members to decide whether or not to do that.

It sounds like you and colleagues [in medicine] have some pretty interesting conversations.

Yeah. Sometimes it's like, *Okay, we'll have to agree to disagree on this one. . . .*

But one of the reasons that I have no desire to leave Pittsburgh, especially as I get older, is because of the great medical care here.

ESQUIRING MINDS

Though Alan Meisel is stepping back from his work at Pitt, he will continue to direct the Master of Studies in Law program, which he says could be a boon to physicians seeking more knowledge of the law. "Part of my portfolio is dreaming up new online legal education programs for nonlawyers," he says. "There are so many people that have jobs that are affected by law in one way or another, who need to know something about law and don't need a law degree." —RKC

TAKE TWO

THE PHYSICIAN'S RESPONSE

ROBERT ARNOLD ON GOOD ENDINGS

Known to collaborate as well as disagree, Alan Meisel and Robert M. Arnold—associate director of the Center for Bioethics and Health Law—have worked together on end-of-life ethics and training at Pitt for years. Arnold, an MD, is a Distinguished Service Professor of Medicine, director of the Section of Palliative Care and Medical Ethics, and director of the Institute for Doctor-Patient Communication at Pitt. He is a recipient of the Patricia Price Browne Award, as well as other honors recognizing his lifetime achievements in palliative care. We asked him to weigh in on debates about death.

What kind of legacy is Alan Meisel leaving behind?

Alan basically started a field. He's a scholar in this space, and his book is the reference for all others. Starting a center for bioethics and running it for 30 years is a humongous accomplishment. In some ways, you could tie the birth of palliative care to the work that Alan did.

How does a lawyer like him approach end-of-life issues differently than a physician like you?

Lawyers are logical and rational. For those of us who are physicians, the degree to which emotions are important, and the degree to which people make decisions [based on them], matters.

Bioethics [—and law—] often is about the worst-case scenarios. In medicine, you work to try to avoid the worst-case scenario.

Meisel suggested that some doctors think they can do more than is realistic to help someone at the end of life—say, relieve all people's pain.

I think that some of the push for physician aid in dying has to do with the fact that you

can't always relieve all of a patient's pain. We should be honest about what we can and what we can't do.

While I think he's right, I still think that's the exception rather than the rule. And so the question is, How much time and energy should we spend on the cases when we can't relieve all of someone's pain, and what are the options then?

I would like us to spend a lot more time training clinicians to promote good quality of life for seriously ill patients and develop

“For those of us who are physicians, the degree to which emotions are important, and the degree to which people make decisions [based on them], matters.”

public policies that have this focus, rather than letting the conversation be dominated by physician aid in dying.

What about so-called “futile treatment,” which is just starting to become a legal issue?

Well it's not really a new controversy [in medicine], but there is this issue: How do you define treatment that's futile? Do doctors have to offer treatment that they think is futile? How do you figure that out? Who gets to decide if things are futile?

It doesn't happen as much as we think it happens, because we always remember the worst cases, right? We should spend at least as much time thinking about what we could do to try to help people not get stuck in that fight.

That is, often, patients will say things like, “We want everything done.” My response would be to say, “Oh, tell me what you mean by everything.” Because often people say they want everything done, but they don't have any idea what

that means.

So rather than get into a debate regarding futility, I find that by communicating better, you can resolve the issue.



Arnold

What's your reaction to the legal actions in California and elsewhere regarding death with dignity?

I think that it's clearly the case that physician aid in dying is going to happen in America. The question, it seems to me as a physician, is, How do we develop good policies? [And] how do we collect data so that we know we are doing as good a job as possible

for dying patients?

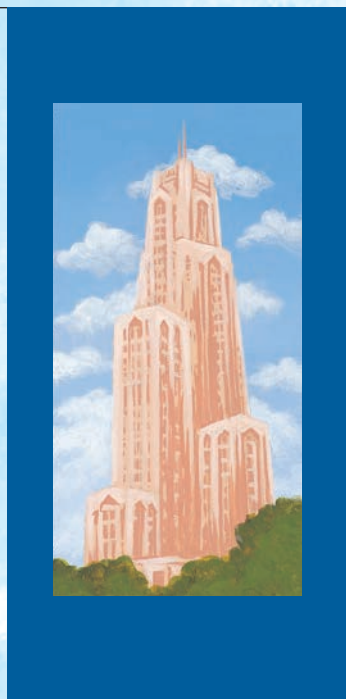
It's sad that the medical profession is basically taking a hands-off position to this. Because, when 20 percent of the [country's] population has access to aid in dying, it seems to me you can't take a hands-off position. We need to make sure that we're paying attention to the dying, and we're training doctors so that they can deal with these very difficult issues.

What's on the horizon for end-of-life issues from your perspective?

Changes are going to continue to occur. The issue now is about the use of opiates: How do you come up with good opiate [pain relief] policies for people who have serious life-limiting illnesses, given the rise in opiate abuse? Another example is how to deal with marijuana. As health care delivery changes, we need to think about how social and health care policies affect the care of seriously ill patients.

I see Pitt scholars continuing Alan's legacy for the foreseeable future. —RKC

Both conversations have been edited for clarity and length.



CLASS NOTES

'60s

While building his plastic surgery career, **Henry Shimizu** (Plastic Surgery Resident '62) also chaired the Japanese Canadian Redress Foundation for 13 years—an organization whose work, he says, restores “Japanese Canadian communities which had been destroyed by the federal government.” Shimizu retired from medical practice in 1999, but he continues to raise awareness about the internment of people of Japanese ancestry in Canada during World War II. (Born in British Columbia, Shimizu was interned in the New Denver camp from 1942 to 1946.) Shimizu has painted internment scenes that have been exhibited at university galleries and collected in his memoir, *Images of Internment* (Ti-Jean Press). For his life of service in medicine and to the community, Shimizu was awarded the Order of Canada. Last year, the National Association of Japanese Canadians honored him at a lunch marking 75 years since the internment of Japanese Canadians.



Shimizu

'70s

Michael Handler (MD '79) holds the McMurry-Seebaum Chair in Pediatric Neurosurgery at the Children's



Handler

Hospital of Colorado and the University of Colorado. As associate surgeon-in-chief for the former, he juggles administrative and clinical duties; yet, at the end of the day, he says, his main focus is “taking care of the kids.” Handler specializes in pediatric brain tumor and epilepsy surgeries, as well as operations for fetal closure of spina bifida. While he notes it can be difficult emotionally to work in fetal medicine, Handler nevertheless finds the work invigorating. He also serves as treasurer for the International Society for Pediatric Neurosurgery, and recently hosted their 45th annual meeting in Denver. He was also on the organizing committee for the 2018 International Symposium on Pediatric Neuro-Oncology.



Dean Levine with the Brents

'80s

The 2018 School of Medicine Diploma Day wasn't just another day at the office for **David A. Brent** (Psychiatry Resident '82, Psychiatry Fellow '85), who holds Pitt's Endowed Chair in Suicide Studies and serves as a professor of psychiatry, pediatrics, epidemiology, and clinical and translational science. He got to “hood” his son **Jacob Brent** (MD '18) during the graduation ceremony. “It's a wonderful moment, because Jacob has worked for so long and so hard, and now he's on

the threshold of what we think is going to be a terrific career,” says the proud dad. Jacob also received the Matthew Eric Piraino Award for Excellence in Infectious Disease and the John B. Reinhart, MD, Award for Pediatrics and Child Psychiatry. He will soon begin a triple board residency in child and adult psychiatry and pediatrics at Pitt.

Jorge Reyes (Transplantation Fellow '89), professor and chief of the Division of Transplant Surgery at the University of Washington, remembers how Thomas Starzl's office “always smelled like pizza,” thanks to a Pizza Hut on the first floor. Reyes, who served on the Pitt Med faculty until he left for Seattle in 2004, recalls what it was like to work with Starzl: “We were always learning, always cutting edge.” His latest research addresses factors associated with mortality within 24 hours of liver transplantation; he has also compared outcomes for end-stage liver disease patients receiving organs from living versus deceased donors.



Reyes

Katherine Wisner (Pediatrics Resident '81, Child Psychiatry Resident '85) is the Norman and Helen Asher Professor of Psychiatry and Behavioral Sciences, as well as professor of obstetrics and gynecology at Northwestern University. She directs the Asher Center for the Study and Treatment of Depressive Disorders and is principal investigator on a NICHD grant to study medication management for mothers with depression. In 2017, she published the results of a randomized controlled trial (conducted here while on the Pitt faculty) that revealed telephone-based depression care management was therapeutic for postpartum women with a history of childhood sexual abuse. Wisner received the American Psychiatric Association's Annual Award for Outstanding Research last year. “Pregnant women get sick, and sick women get pregnant,” she says. “I am committed to providing effective treatment to this neglected population—the mothers of our next generation.”



Wisner

'90s

Scott Hultman (MD '90) is director of the newly relaunched Johns Hopkins Burn Center, professor of plastic and reconstructive surgery, and vice chair of strategic development for its Department of Plastic and Reconstructive Surgery. He joined Hopkins this summer after being recruited by former Pitt Med surgery professor Andy Lee. Hultman says he combines his training in general surgery, critical care, and plastic surgery to provide “the complete arc of care for burn patients.”

On a personal note: Last year, Hultman completed a double century, a 200-mile race—the New Bern MS

Cycling Classic. And he's a huge U2 fan (he likes to sneak their lyrics into the titles of his papers).

'00s

In January, **J. Nadine Gracia** (MD '02, Pediatrics Resident '05) joined Trust for America's Health, a D.C.-based public health advocacy organization, as its executive vice president and chief operating officer. She says advocacy allows her to influence the development of U.S. health policy. Under the Obama administration, Gracia served as deputy assistant secretary for minority health and director of the Office of Minority Health at the U.S. Department of Health and Human Services, where she worked to implement the Affordable Care Act. Gracia returned to Pitt Med this April to speak with students taking the Changing Science, Changing Society elective. "I reminded them," she says, "that for as much as you try to plan your next steps, it is important to be open, flexible, and prepared."

Earlier this year, **Seth Hawkins** (Emergency Medicine Resident '03) published the medical textbook *Wilderness EMS*. The assistant professor of emergency medicine at Wake Forest University also co-launched the monthly podcast *RAW Medicine* (that's Remote, Austere, and Wilderness). He serves as the medical director of Burke County EMS, supervising the oldest wilderness EMS team in North Carolina. The Carolina Wilderness EMS Externship, which Hawkins founded in 2011, was recognized this year with the Society for Academic Emergency Medicine's Innovation in Medical Education Award.

Carolyn Rogers-Vizena (MD '07), an attending physician in plastic surgery at Boston Children's Hospital and assistant professor of surgery at Harvard University, has had a busy 2018. Her clinical practice in Boston spans numerous pediatric plastic surgery procedures, primarily cleft lip and palate and adolescent breast surgeries. She also researches simulation in plastic surgery and was recently awarded a National Endowment for Plastic Surgery grant to further study cleft lip simulation. In addition to her responsibilities in Boston, Rogers-Vizena carries her expertise abroad, most recently returning from a trip to Beirut with the Global Smile Foundation. In Lebanon, Rogers-Vizena hosted a workshop to help local clinicians expand their cleft lip and palate services; she remained after the training to provide free operations to kids in need, mostly Syrian refugees. "It was humbling," she says, to hear the stories of her patients.

—Rachel Mennies and Maureen Passmore

WE KNEW YOU WHEN: INNA BELFER

Inna Belfer was a Pitt associate professor of anesthesiology and human genetics when a May 2014 National Institutes of Health announcement got her attention: Evaluation of all biomedical research grant applications would soon be expanded to include consideration of sex as a biological variable (SABV).

For an MD/PhD whose own research laid the groundwork for the relevance of sex as a variable in pain, an opportunity to help promote that policy throughout academic medicine was too good to pass up. Today, Belfer serves as the NIH's scientific lead for implementation of the SABV policy in the Office of Research on Women's Health (ORWH).

"At least in pain, everyone knows that differences in sex are fundamental and have to be considered in our work to develop treatments for painkillers," says Belfer, "because they work very differently in men and women."

Despite her full-time NIH appointment, Belfer, who formerly directed the molecular epidemiology of pain program at the Pittsburgh Center for Pain Research, still managed to coauthor a dozen papers in 2017, detailing findings from research she was pursuing when she left Pitt, including a clinical trial testing a novel treatment for post-mastectomy pain and investigations into the mechanisms of pain sensitivity in sickle cell disease.

Belfer has stepped into this role at the NIH as the national conversation around sex and gender gains new prominence. As part of her position, she helps inform NIH funding priorities; she also founded the NIH Scientific Interest Group on Sex and Gender in Health and Disease, of which she now serves as chair. To promote greater participation in such conversations, she's developing an online course on the topic, with modules on immunology, mental health, and urology, among others.

"We shape the science," says Belfer, who serves as the ORWH liaison with the FDA, as well as with initiatives and agencies within the NIH, including those that support the career development of women scientists. "I make sure that important science will be done by the best labs and the best scientists." —Sharon Tregaskis



Belfer

MAA SAYS, "COME ON OVER!"

van Shulman (MD '72) has done surgery in Nicaragua, El Salvador, Mongolia, the Philippines, and Kenya—and that's an incomplete list of countries. In April, the voluntary assistant professor of surgery at UCLA returned to Pitt Med to speak to the Global Health Interest Group, addressing students who share his wanderlust. He talked about sustainable medicine—providing care abroad while teaching community members skills and medical knowledge. "It's one thing to do a case," he says, but "more importantly, can I give that knowledge to someone else?" (Shulman, an award-winning teacher, has also stacked up honors as a virtuoso performer and conductor. He is the music director of the Los Angeles Doctors Symphony Orchestra.)

Cardiologist **Michael Hess** knows something about teaching. A professor emeritus at Virginia Commonwealth University, Hess (MD '68, Intern '69, Res '70) was inspired by the late Jack D. Myers, famed Pitt chair of medicine. "I was [one of Myers's] last chief residents. Jack always demanded that you teach at the bedside, and I never lost that," he says. Hess "jumped at" a chance to visit Pitt in December; while here, he spoke



Shulman conducting

ANNE NEWMAN MARCH ON

BY KRISTIN BUNDY

Baby Boomers have long been known as one of the largest generations, and now they are living longer and healthier than any generation before, says Anne Newman (MD '82, Res '85, Fel '87), the newly appointed clinical director of the Aging Institute of UPMC and the University of Pittsburgh. She is a Boomer herself.

"We're going through an aging revolution," says Newman. (Apropos for the generation known for anti-war protests and civil rights rallies.)

"The 65-year-old today is a healthier person than a 65-year-old was 30 years ago," Newman explains. Could it be because of lifestyle changes? The availability of medications? Better care? "Big picture—we're looking at people who are older now and questioning if there's a different phenomenon than there was before, and what it means to clinical practice."

Historically, aging studies focused on understanding risk factors for premature death, physical disability, and dementia, which are really important, Newman says. But now there's a shift toward understanding the flip side—the absence of disease—and how older people can stay healthy for as long

as possible.

Newman, Distinguished Professor of Epidemiology and professor of medicine, as well as clinical and translational science, has been studying the aging process for more than 30 years at Pitt. Her interest in the elderly population began when she was a student at Pitt Med. Learning how all of the bodily systems interacted in the sickest, most complicated cases challenged and intrigued her. Geriatrics is "internal medicine—plus," she says.

As principal investigator on a myriad of aging studies, Newman has tracked thousands of participants for up to three decades, yielding an extensive body of research. In 2014, she published a landmark study demonstrating what many physicians had previously only assumed: Walking is indeed protective against the loss of mobility in the elderly. Last year she reported in *JAMA* on rates of disability and pharmaceutical use in 90-year-olds who

had been followed since they were in their mid-60s. This year's publication highlights include a paper identifying cardiovascular biomarkers and physiologic indicators associated with mortality—information that could be used to develop new drugs or other therapies to "alter the trajectory of aging."

Through her clinical directorship at the Aging Institute—a newly created position—she is working alongside institute director Toren Finkel, a basic scientist, to guide promising animal research toward clinical studies. As she and Finkel move forward, they're "drawing on the collective wisdom of many researchers here at Pitt," she says. That wisdom pertains to prevention, social environments, rehabilitation science, nursing, and basic science, notes Newman. "All of these aspects are important to the Aging Institute to address what it means to be healthy as you age."

Ultimately, they hope to unearth what Newman calls "the holy grail of biomarkers"—the ability to measure substances in the blood to determine how old somebody is. "We've not had good ways of measuring that besides knowing someone's birthday," she notes.

Newman says her own research has influenced how she approaches aging, motivating her to make regular trips to the gym. She loathes the anti-aging industry that is so formidable in the United States. "I think it's really important not to think of aging as a war to be waged but rather a process to be shepherd." ■



RIC EVANS

Newman with a portrait of her maternal grandmother, who lived to the age of 92.

Continued from previous page

with cardiology fellows and offered feedback on their "highly impressive" research.

The Medical Alumni Association (MAA) loves having alumni back to campus. This year also brought **Matthew E. Fink** (MD '76) presenting a grand rounds lecture to the neurology department, **Deborah Gilboa** (MD '00) speaking at a family health conference, and **Mary-Elizabeth Patti** (Res '88) sharing research on mediators of metabolic disease risk.

Next time you're planning a trip to Pittsburgh, check maa.pitt.edu for upcoming events or consider giving the MAA (medalum@medschool.pitt.edu) a heads-up. The invitation is open! —Keith Gillogly

MEDICAL ALUMNI ASSOCIATION WWW.MAA.PITT.EDU

CHARLENE DEZZUTTI

JUNE 18, 1964–MARCH 15, 2018

In 1986, an infection changed Charlene Dezzutti's career trajectory. She had been studying veterinary pathology at Ohio State University when she learned that a favorite uncle had been diagnosed with AIDS. After sitting vigil with him in a Pittsburgh hospital, she went back to grad school and added viral immunology to her studies. While she earned her PhD, her uncle got healthier. (He is still one of the longest surviving participants in the Pitt Men's Study on the natural history of HIV/AIDS.)



Dezzutti

Since graduation—and in her nearly 30 years of HIV research—Dezzutti made significant contributions in preclinical HIV prevention trials and preclinical product testing. She spent 13 years at the Centers for Disease Control and Prevention and then moved back to her hometown in 2005 to join Magee-Womens Research Institute (MWRI), Pitt Med, and eventually Pitt's Graduate School of Public Health.

For the past two years, Dezzutti served as the principal investigator of the Microbicide Trials Network Laboratory Center, in which she oversaw product evaluation and pharmacodynamics studies in her own laboratory and six others. Her studies included examining HIV-infection susceptibility of tissue in the presence of contraceptive hormones. Before that, she held leadership roles in federally funded trials and in trials funded by the Bill and Melinda Gates Foundation.

Dezzutti died of a sudden, aggressive cancer at the age of 53. Friend and colleague Sharon Hillier, Pitt professor of obstetrics, gynecology, and reproductive sciences, says: "The loss of Charlene has left a big hole in our world. In our office and lab, we miss her smile, her infectious laugh, and her unwavering commitment to the search for HIV prevention options that are safe and effective."

—Kristin Bundy

FRANK SESSOMS

OCT. 24, 1947–JULY 22, 2018

A graduate of Meharry Medical College who returned to his native Pittsburgh for an internship and residency, Frank Sessoms (Res '77) ran a private practice in East Liberty, specializing in pain management, for more than 40 years. "He touched a lot of lives," former patient and friend Ralph Watson told the *New Pittsburgh Courier*. "He never hesitated to write a check, and he mentored a lot of people."

Among those Sessoms mentored was David Hicks, a Pitt undergraduate and student officer for the Student National Medical Association chapter for Pitt pre-meds in the late 1990s. Paula Davis, now head of the University's Office of Health Sciences Diversity, urged the aspiring physician to ask Sessoms for help funding travel to a conference. Sessoms was a mentor for Gateway Medical Society and allowed countless pre-med students to shadow him in his practice.

At Sessoms's clinic, Hicks recalls, R&B

played on the office sound system, and the walls were lined with photos: Sessoms with celebrities, Sessoms at local jazz clubs, Sessoms clad in the dapper suits for which he was known. The bulk of their brief appointment was devoted to an impromptu career advising session. "I could tell in five minutes he cared about me, my career development," says Hicks, now deputy health officer for Jefferson County, Alabama.



Sessoms

The undergrad left with a \$1,000 pledge from Sessoms for Hicks's student group trip to attend the conference—and a dedication to pursuing the life of service the older physician exemplified.

"There weren't many people itching to go into the community where he worked to provide medical care," says Hicks.

"I imagine kids coming up through that neighborhood, they saw that their doctor was a black man with a style to his presentation. That's a powerful image."

—Sharon Tregaskis

IN MEMORIAM

'40s

AVERY D. WEISMAN
RES '41
JAN. 2, 2017

RICHARD A. NELSON
MD '42
JAN. 26, 2017

JOHN F. COCHRAN
MD '48
MAY 14, 2018

'50s
CHARLES L. ADAMS
MD '53
JUNE 18, 2018

DONALD I. COPE
MD '53
APRIL 23, 2018

WILLIAM J. WALTER
MD '54
JUNE 24, 2018

ROBERT E. MCMILLEN
MD '56
APRIL 14, 2018

EDWIN J. WHITMAN
MD '56
MAY 29, 2018

WILLIAM R. MCWHIRTER
RES '59, '65
APRIL 30, 2018

'60s
ROBERT W. HARTNETT
MD '61
MAY 26, 2018

ROBERT SCOTT FURMAN
MD '62
APRIL 29, 2018

JUERGEN HOMANN
RES '63
MAY 5, 2018

FRANK A. YARUSSI
MD '63
MAY 25, 2018

RICHARD W. DODDS
MD '64
FEB. 19, 2018

JOHN R. RUBY
MD '64
APRIL 18, 2018

STANLEY L. KAMPNER
RES '69
OCT. 31, 2017

'70s

THOMAS L. ANTKOWIAK
MD '71
APRIL 18, 2018

SHAWKI N. HABIB
RES '73, FEL '75
MAY 25, 2018

CHARLES A. HENDERSON
MD '73
MAY 6, 2018

CAROL J. WHITE
MD '77
JUNE 21, 2018

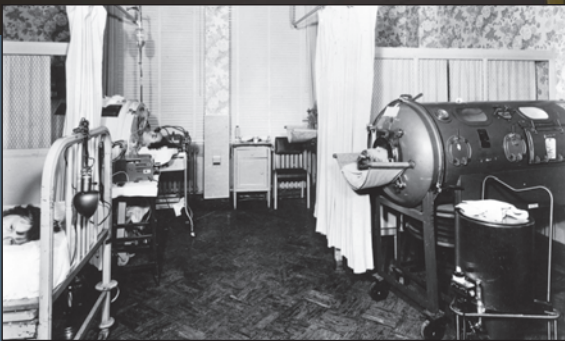
JAMES BUTREM WEBER
MD '78
JUNE 2, 2018

BENJAMIN T. GRAVATT
MD '79
APRIL 28, 2018

'90s

ANDREW MICHAEL PACOS
RES '90
JUNE 3, 2018

FACULTY
CHESTER B. HOLLINGER JR.
FEL '91
MAR. 4, 2018



From 1951 to 1954, before the Salk vaccine, polio caused 65,000 cases of paralysis in the United States.

INSPIRATION, EXPIRATION

In the lobby of the Pitt Public Health building is a sobering public service announcement of sorts: an iron lung, about 8 feet long, cordoned off in front of a window overlooking the former site of Children's Hospital of Pittsburgh. In the '40s and '50s, hospitals around the world tended to thousands of patients in these devices, which used negative pressure to draw air into their lungs. Children and young adults paralyzed by severe polio typically spent weeks inside them; some didn't survive.

This April, nearly 63 years to the day after the announcement was made that the killed poliovirus vaccine developed by Pitt's Jonas Salk and his research team was a success, the iron lung debuted as a new permanent display. Don Burke, dean of the Graduate School of Public Health and associate vice chancellor for global health, had wanted one for years before he finally tracked it down with help from Salk's son, Peter Salk, a part-time Pitt professor of infectious diseases and microbiology. The Salk Institute for Biological Studies in La Jolla, San Diego, Calif., donated the device. "It's such a potent symbol of what happens when you don't have vaccines and preventives," says Burke. "Because of a vaccine, this kind of requirement disappeared." —*Elaine Vitone*

CALENDAR

FOR ALUMNI & FRIENDS

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

PITT HEALTH ACADEMY ATLANTA SEPTEMBER 13

The Ritz-Carlton, Atlanta, Ga.
hsalumni.pitt.edu/event/Atlanta2018

MEDICAL ALUMNI WEEKEND 2018 OCTOBER 5–6

Reunion Classes:

1958

1963, 1968,

1973, 1978,

1983, 1988,

1993, 1998,

2003, 2008,

2013

maa.pitt.edu/reunion

HOMECOMING WEEKEND OCTOBER 5–6

alumni.pitt.edu/news-events/homecoming-2018/

SCIENCE 2018 OCTOBER 17–19

Alumni Hall and Wyndham Pittsburgh
University Center
science2018.pitt.edu

2019 WINTER ACADEMY FEBRUARY 15

The Ritz-Carlton, Naples, Fla.
hsalumni.pitt.edu/event/WA2018

To find out what else is happening
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ANDREY POPOV/GETTY IMAGES



Soothe saying



FOR REAL! TWEEN SCIENCE

Remember the time when you were biking and you absolutely wiped out? You ended up with an asphalt-bitten scraped knee simmering in the sun. Maybe you rubbed it or held it in pain. That's not a far cry from your mom kissing a boo-boo. And it turns out there's a scientific explanation behind our instinct to alleviate pain with a gentle touch.

After that initial *ouch!*, you know that duller, annoying throbbing that sticks around? Sometimes your nervous system can lower that after-pain. If you get enough sensory signaling from elsewhere—like caresses or a cold pack (think touch or temperature)—that can override the pain transmission before it even reaches the brain.

Researchers aren't sure why. Some think it might be because the nonpain signals are traveling on faster neurons than the painful ones!

Your mind can help, too. Any soothing—a gentle touch, a kind word—can put your limbic forebrain (which deals with emotions) in gear, sending signals to the midbrain (which is right near the start of your spine). Neurons in the midbrain can lower pain signals so you don't feel so overwhelmed by them.

So, there are at least two systems in your body that take the sting out. Talk about painkillers! —Ellen Kruczek

Thanks to Ajay Wasan, MD vice chair for pain medicine at Pitt and UPMC, for helping us out with his soothing words.

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

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DON'T SNOOZE ON REUNION WEEKEND

Okay, so maybe just the thought of all-nighters during med school or training makes your eyelids droop. But trust us—you don't want to miss **Medical Alumni Weekend on October 5–6**. Come see Scaife Hall's new fifth-floor coffee shop, Morning Grounds, and other perks of the first phase of Pitt Med's refreshing renovations.

On Saturday morning, the new documentary on Thomas Starzl (pictured) will be screened in good old Scaife LR5 and LR6. (We're hoping those lecture halls weren't the sites of too many naps.)

For more information on Medical Alumni Weekend, visit maa.pitt.edu/reunion.