FALL | 2017

PENN Medicine

PAIN

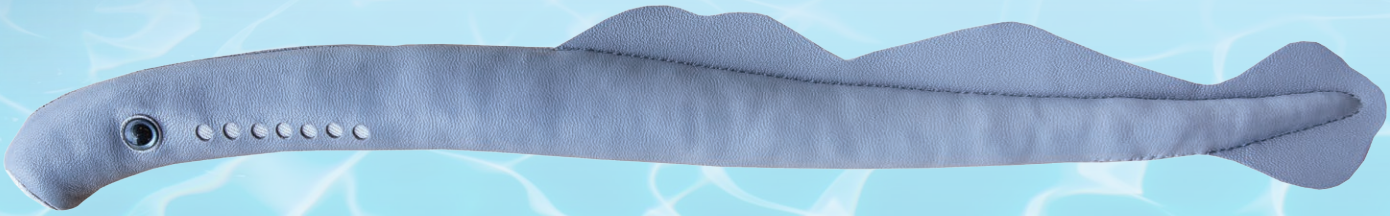
ADDRESSING THE OPIOID CRISIS AT ITS SOURCE

Symbiosis Inside Our Cells:
The Emergence of Mitochondrial Medicine

A Half-Century View of Health Economics

Neuroscience at the Arcade

The Power of Parasites



For nearly two years Casey Greene, PhD, has been working to change the culture of science with the help of a lamprey statue with magnetic mouthparts.

The parasitic sea creature is a prize in the Research Parasite Awards, for which Greene, an assistant professor of Pharmacology at the Perelman School of Medicine at the University of Pennsylvania, is the lead organizer. The awards are granted annually to two scientists, one junior and one established, for research that finds novel insights from reusing and analyzing other people's data.

The idea originated with a controversial editorial published in the *New England Journal of Medicine* in January 2016 about the promise and perceived perils of medical researchers reusing data they did not generate themselves. "There is concern among some front-line researchers that the system will be taken over by what some researchers have characterized as 'research parasites,'" wrote Editor in Chief Jeffrey Drazen, MD, and Deputy Editor Dan Longo, MD.

Greene was troubled by that characterization; he routinely reuses other people's data sets in his own lab developing algorithms to model biological systems. "The description of a research parasite sounded exactly like the description of a scientist," he said. And Greene was not alone in that displeasure.

ProPublica reported that "criticism was immediate, fierce, and widespread — probably more than for anything else the journal has done in many years." Amid that resounding backlash, Iddo Friedberg, PhD, a computational biologist at Iowa State University, tweeted, "I propose a new science award: 'The Research Parasite Award is given to those who used someone else's data to do some really cool sh*t.'" But he didn't really expect anyone to do it.

Nevertheless, Greene did it. The second annual Research Parasite awards will be granted in January 2018 at the Pacific Symposium on Biocomputing—and so will the first annual Research Symbiont awards.

Whimsical though the awards' concept may appear, Greene is serious about the meaning behind them. "We want a research ecosystem that celebrates and rewards those who contributed each component of a scientific discovery: Data generators for building and sharing data sets that can reveal something new, and those who analyze the data to derive insights from it," Greene said. "To tackle the tough problems that we face in medicine, we won't be able to do one without the others."

Look for information about both awards at ResearchParasite.com and ResearchSymbionts.com.

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Innovation, Tradition, and Collaboration

This issue marks the 30th anniversary of *Penn Medicine*. When the magazine launched in the fall of 1987, its inaugural editor, Marshall Ledger, articulated the idea that medicine at Penn may be best described as a balance between tradition and innovation. That idea has guided the magazine ever since. Earlier this year, in my first editor's note, I unwittingly echoed him—carrying the magazine's own tradition forward, even as new innovations continue to appear on these pages.

This magazine has changed quite a bit over three decades. There are the obvious visual things: Photos are larger and consistently colorful (black and white is strictly for historical stories now). And, of course, the scope of the medical enterprise at Penn has grown massively larger. Looking at the covers, the few redesigns are evident.

But there is one change that seems especially striking. In the early years, most of the magazine's covers featured a stylized portrait of one or two individual people. Later, illustrations and conceptual photos dominate. More than just a change in design trends, it symbolically captures the shift in emphasis from the individual might of the physician or principal investigator to a broader focus on the complex questions, challenges, and opportunities in medicine. More and more, medicine depends on collaboration to navigate the complexity of modern problems.

That is evident in the cover story of this issue, "Prevention at the Point of Pain" (page 12). Even without addressing all of the many dimensions of the opioid crisis in depth—such as social, criminal justice, and political factors—our take on the origins of the crisis with pain-medicine prescriptions and pain-management solutions is still complex and still requires many players in a coordinated response. From the subjectivity and variety of types of pain that require adequate treatment, to the science of pain, to the economic forces in health care that led to more frequent prescribing of opioids over the last two decades, building solutions to a comprehensive problem involves teams that cut across traditional disciplinary boundaries.

In "50 Years of the 'How' in Health Care" (page 28), we look at interdisciplinary collaboration as a means of handling complex challenges as its own topic, head-on. Through the Leonard Davis Institute of Health Economics, established half a century ago, and numerous other centers and collaborations, the act of cutting across

disciplinary boundaries to find complex solutions to complex problems has become second nature on the Penn campus. A consortium dealing with the complexities of the costs of precision cancer therapies is just one such example.

We're facing huge challenges in the world today, within medicine and outside of it. May you find inspiration in these pages that smart people, working together with diverse perspectives, can find the necessary nuanced and detailed solutions to multifaceted problems, for the next 30 years and far beyond. A balance of innovation, tradition, and collaboration may be the new description we carry forward. ▽

RE

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A Pivotal Milestone in Cancer Treatment

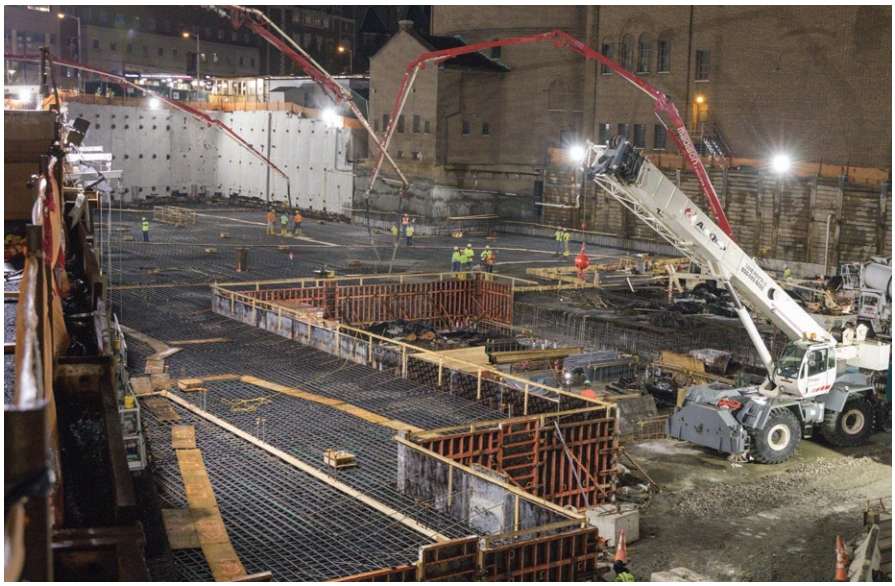
In a landmark decision this August, the U.S. Food and Drug Administration (FDA) approved the world's first personalized cellular therapy for cancer; it is also the first FDA-approved therapy based on gene transfer. Developed by the University of Pennsylvania and Children's Hospital of Philadelphia (CHOP), the chimeric antigen receptor (CAR) T-cell therapy will be sold by Novartis as Kymriah™ (tisagenlecleucel, formerly CTL019). The approval was granted for the treatment of patients up to 25 years of age with acute lymphoblastic leukemia that is refractory or in second or later relapse. Clinical trials of the therapy began at Penn's Abramson Cancer Center in 2010, in adult patients with chronic lymphocytic leukemia. After stunning results of the first three patients to receive the therapy were published, Penn entered into a global collaboration with Novartis in 2012 to further research, develop and commercialize CTL019 and other CAR-T cell therapies targeting different blood cancers and solid tumors.

Investigators hailed the FDA's approval as a game changer for the treatment of younger patients battling the aggressive blood cancer and a pivotal milestone in this new era of cellular therapies that treat cancer with a patient's own immune system.

A more in-depth look at the path toward this milestone and the future beyond it will appear in the next issue of *Penn Medicine*. For a look at the role of philanthropy in this achievement, see page 38 in this issue.

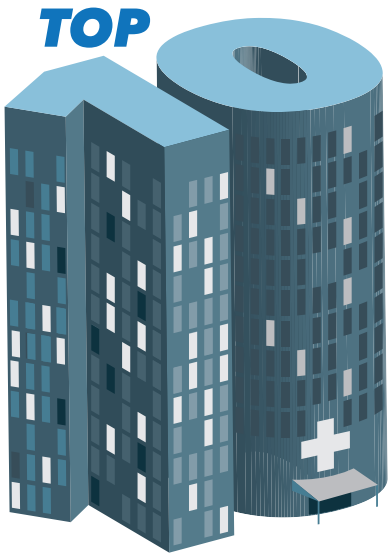
> "I think the cancer world is forever changed."
>
> —*Carl June, MD, the Richard W. Vague Professor in Immunotherapy in the department of Pathology and Laboratory Medicine and director of the Center for Cellular Immunotherapies in the Abramson Cancer Center, in the New York Times.*

A Solid Foundation



When completed in 2021, Penn Medicine's new inpatient facility, the Pavilion, will be a massive 1.5-billion square-foot facility with 500 private patient rooms and 47 operating rooms. It is already setting records and sitting on a solid foundation. Specifically, Penn Medicine set a Philadelphia construction record with a continuous pour of concrete over 14 hours for the Pavilion's construction at its site across the street from the Hospital of the University of Pennsylvania. The 6,540 cubic yards of concrete required 654 concrete trucks and the work of more than 120 construction crew members, site managers, and safety support personnel.

Watch at time-lapse video of the concrete pour at PennMedicine.org/magazine/fall17vs



Forbes Names Penn Medicine Among Top 10 Best Places to Work

Penn Medicine was named No. 7 on *Forbes* magazine's annual "Best Employers in America" list ranking mid-sized and large employers across the U.S. Other organizations listed in the top ten include Costco, Google, and REI, placing Penn Medicine among some of the most well-known and influential companies in the nation.

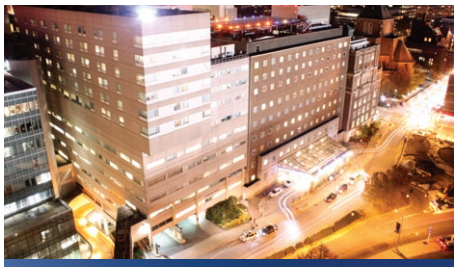
"We are extremely proud of the exceptional care we offer our patients, which is sustained by the commitment, compassion, and talent exhibited by every single person who works at Penn Medicine," said Ralph W. Muller, CEO of the University of Pennsylvania Health System. "Our staff is our greatest asset as we work together to continue our efforts as a health care leader."

Forbes partnered with research firm Statista, of Hamburg, Germany, to build its list of best employers. Statista's survey of 30,000 U.S. workers, asking them if they would recommend their organization to friends or family, was the most heavily weighted factor in determining the list.

The full list of *Forbes*' "Best Employers in America" is available at Forbes.com/best-employers.

Penn Medicine Hospitals Recognized on *U.S. News* Honor Roll

For the fourth year in a row, Penn Medicine hospitals ranked among the top 10 hospitals in the nation according to *U.S. News & World Report*. In its 2017-2018 annual survey, the magazine ranked the combined enterprise of the Hospital of the University of Pennsylvania (HUP) and Penn Presbyterian Medical Center (PPMC) as the 10th best hospital in the United States and as the No. 1 hospital in Pennsylvania, with additional top rankings in 11 clinical specialties. Of nearly 5,000 hospitals ranked, only 20 were selected for the Honor Roll, HUP/PPMC among them. Complete rankings as well as the *U.S. News & World Report* methodology can be found at www.usnews.com/besthospitals.



HUP/PPMC's Nationally Ranked Specialties

- Cancer
- Cardiology & Heart Surgery
- Diabetes & Endocrinology
- Ear, Nose & Throat (ENT)
- Gastroenterology & GI Surgery
- Geriatrics
- Nephrology
- Neurology & Neurosurgery
- Orthopedics (also for Pennsylvania Hospital)
- Pulmonology
- Urology

Honors & Awards

Jill M. Baren, MD, MBE'06

Professor, Emergency Medicine

John Marx Leadership Award

A renowned expert in emergency clinical trials, informed consent, and neurologic emergencies, Baren was recognized by the Society for Academic Emergency Medicine for exceptional contributions to emergency medicine through leadership.

David F. Dinges, PhD

Professor, Psychiatry; Chief, Sleep and Chronobiology

Nathaniel Kleitman Distinguished Service Award

The award from the American Academy of Sleep Medicine recognizes individuals dedicated to the sleep field who have made significant contributions in the areas of administration, public relations and government affairs.

Ronny Drapkin, MD, PhD

Associate Professor, Pathology in Obstetrics & Gynecology; Director, Ovarian Cancer Research Center

Rosalind Franklin Prize for Excellence in Ovarian Cancer Research

The prestigious award is from the Ovarian Cancer Research Fund Alliance in recognition of an individual's contributions to basic science, translational, or clinical research in ovarian cancer.

Ronald M. Fairman, MD, GME'84

Clyde F. Barker-William Maul Measey Professor, Surgery; Professor, Radiology; Chief, Vascular Surgery and Endovascular Therapy

Chair, Society for Vascular Surgery Foundation

Fairman served as the foundation's president last year. As chair, he will manage its highly competitive, peer-reviewed grant initiatives.

Irene Hurford, MD

Assistant Professor, Psychiatry

2017 Exemplary Psychiatrist Award

The National Alliance on Mental Illness honored Hurford for work that helps people at early stages of psychosis to manage their symptoms and achieve life goals, emphasizing recovery and resilience.

Carl June, MD

Richard W. Vague Professor, Pathology and Laboratory Medicine; Director, Center for Cellular Immunotherapy and Parker Institute for Cancer Immunotherapy

David A. Karnofsky Memorial Award

This honor from the American Society of Clinical Oncology goes to an oncologist who has made outstanding contributions to cancer research, diagnosis, and treatment.

Francis Marchlinski, MD'76, GME'81

Richard T. and Angela Clark President's Distinguished Professor of Medicine; Director, Electrophysiology

Heart Rhythm Society Distinguished Teacher Award

The international society recognized Marchlinski for educating colleagues and students for over 30 years, including providing vital information about his own clinical innovations in therapies for heart failure, atrial fibrillation, and ventricular tachycardia.

Emma A. Meagher, MD

Associate Professor, Medicine and Pharmacology; Vice Dean and Chief Clinical Research Officer; Senior Associate Vice Provost for Human Research

President, Association for Clinical and Translational Science (ACTS)

With a mission to advance research and education in clinical and translational science in order to improve human health, ACTS comprises 5,000 clinicians and researchers from 50 universities and medical centers nationwide.

Angela M. Mills, MD, GME'03

Associate Professor, Emergency Medicine

Arnold P. Gold Foundation Humanism in Medicine Award

Honored for compassionate, patient-centered care, by the Society for Academic Emergency Medicine, Mills serves as clinical mission leader for Emergency Medicine as the department's vice chair for clinical operations.

Jason H. Moore, PhD

Edward Rose Professor, Informatics; Director, Institute for Biomedical Informatics

Fellow, American Statistical Association

Moore's research focuses on developing and applying artificial intelligence and machine learning methods for uncovering complex patterns in biomedical big data.

Honors & Awards Continued

Benjamin L. Prosser, PhD

Assistant Professor, Physiology

Outstanding Early Career Investigator Award

The American Heart Association's Council on Basic Cardiovascular Sciences recognized Prosser for his research to date and a heart-failure discovery to improve the beating strength of heart cells by "softening" their internal cytoskeleton.

Ilene Rosen, MD'93, MSCE'06

Associate Professor, Clinical Medicine

President, American Academy of Sleep Medicine (AASM)

Rosen plans to help AASM members advance patient care and quality of life at a time when understanding of the role of sleep in care of cancer, neurological disorders, and more, is expanding.

Anil K. Rustgi, MD

Professor and Chief, Gastroenterology

2017 Julius Friedenwald Medal

This American Gastroenterological Association's highest lifetime honor recognizes contributions to all aspects of gastroenterology, including research, clinical medicine, education and service.

Felix W. Wehrli, PhD

Professor, Radiology

Gold Medal Award

The Society for Magnetic Resonance in Medicine honored Wehrli, whose research focuses on the conception, implementation and translation to the clinic of new quantitative imaging methods by MRI.

A Familiar Face Among Penn's Newest PIK Professors

Risa Lavizzo-Mourey, MD, MBA'86, returns to Penn's faculty Jan. 1, 2018 as the Robert Wood Johnson Foundation Population Health and Health Equity Professor with joint appointments in Medical Ethics and Health Policy in the Perelman School of Medicine, in Health Care Management in the Wharton School and in Family and Community Health in the School of Nursing. A world-renowned expert in health policy and geriatric medicine, Lavizzo-Mourey has served since 2003 as president and chief executive officer of the Robert Wood Johnson Foundation, and, for 15 years before that, as a distinguished professor and administrator at Penn.

Lavizzo-Mourey's new appointment will be as a Penn Integrates Knowledge (PIK) University Professor. PIK professorships are University-wide initiative to recruit exceptional faculty members whose research and teaching exemplify the integration of knowledge across disciplines and who are appointed in at least two schools at Penn.

Two new PIK Professors joined Penn Medicine in July. Jay Gottfried, MD, PhD, GME'01, a pioneer in research on the neuroscience of the sense of smell, is the Arthur H. Rubenstein University Professor, with joint faculty appointments in Neurology in the Perelman School of Medicine and in Psychology in the School of Arts and Sciences. Get to know computational neuroscientist Konrad Kording, PhD, on page 34.

In September, George Demiris, PhD, a leader in new technologies for e-health and home-based health care, was announced as the next new PIK Professor appointment; he will join Penn Medicine and Penn Nursing in 2018.

Jay Gottfried

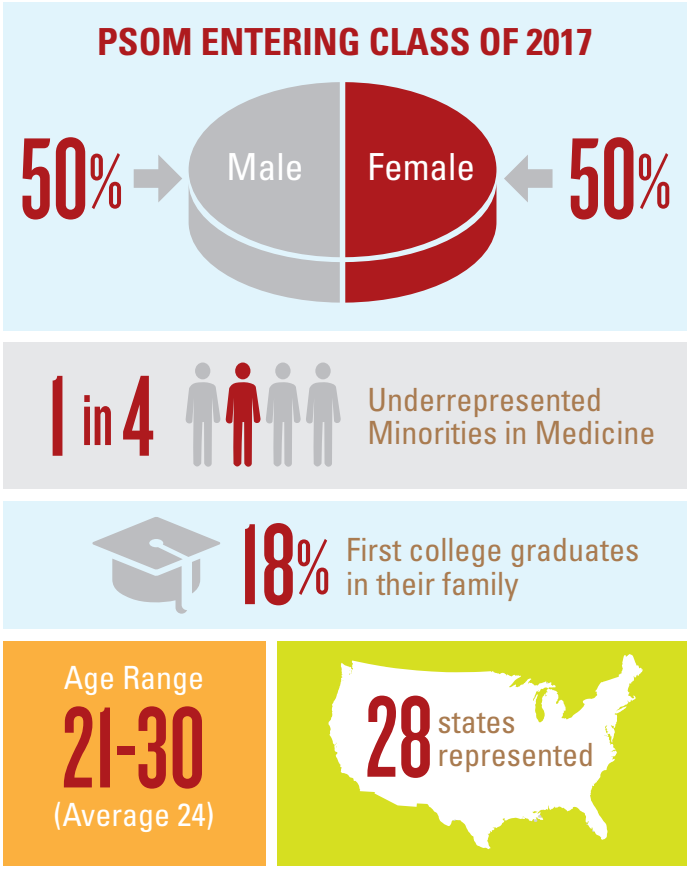
Konrad Kording

George Demiris

A Stethoscope, an Oath, and a Short White Coat

At the annual White Coat ceremony this August, 159 entering students received their first stethoscopes, recited the Hippocratic Oath, and donned their first short white coats. A bright and diverse group of medical students joined the ranks of the Perelman School of Medicine.

The school's oldest living alumnus, Joseph Schein, MD'41, like all physicians in attendance, stood with the entering class to recite the oath. Schein attended in support of his granddaughter, Yvette Schein, as she began her medical training. See more of their story on page 41.



Penn to Create Program for Asperger Syndrome Research

The Perelman School of Medicine will establish the Asperger Syndrome Program of Excellence (ASPE) with a $5.4 million gift from an anonymous donor. Led by Daniel J. Rader, MD, chair of Genetics, ASPE aims to energize the international research and clinical community by improving understanding of the genetic causes of Asperger syndrome (defined as autism spectrum disorder without intellectual disability). ASPE will take a two-pronged approach by conducting a pioneering family-based genetic study and simultaneously developing model systems to investigate specific mutations in genes found in earlier genome-wide association studies of autism spectrum disorders. Penn will host an international symposium for ASPE in the spring of 2018 to review early findings and stimulate new research avenues.

Mixing Metaphors and Methods

Highlights of recent Penn Medicine research, from innovations in hard-to-treat cancers to uncovering mysteries of the teenage brain

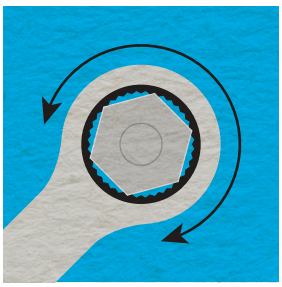
Retracing the Steps of Pancreatic Cancer Development Yields Early-Detection Blood Test

Researchers retraced the steps of how cells develop into pancreatic cancer and identified a signature footprint that could help diagnose this deadly cancer in an earlier stage. The team from Penn Medicine and the Mayo Clinic used a first-of-its-kind human-cell model of pancreatic cancer progression, initially described in 2013, for this study in which they genetically reprogrammed late-stage cancer cells into a stem-cell state. This enabled them to force the reprogrammed cells to progress to an early cancerous state, revealing secreted blood biomarkers of early-stage disease along the way. The findings were published in *Science Translational Medicine*. The researchers anticipate that health care providers will test for the presence and levels of these biomarkers in blood from pancreatic cancer patients and individuals with a high risk of developing pancreatic cancer.

Fuel for the Molecular Machinery of Memory

A metabolic enzyme "fuels" the machinery that controls which genes are expressed in the coordinated process of creating a memory, according to Penn Medicine research published in *Nature*. Forming memories involves restructuring of the synapse (the space between neurons), and that process relies on the coordinated expression of a group of memory genes. The addition of a chemical group, a process called acetylation, onto specific spots of the genome in neurons, opens up tightly-wound DNA to make genes involved in memory formation available to be "read," and eventually, for their encoded proteins to be made. The Penn researchers reported that a key metabolic enzyme, called acetyl-CoA synthetase 2, or ACSS2, works directly within the nucleus of neurons to turn genes on or off when new memories are being established. It binds to memory genes to directly regulate and fuel their acetylation, which is ultimately controlling spatial memory in mice. The researchers hope to apply this newfound memory path to prevent or even erase traumatic memories in people who suffer from post-traumatic stress disorder, by blocking ACSS2 in the hippocampus, a brain region that processes long-term memory.

A Ratchet Mechanism Untangles Distorted Proteins



The digital animation looks a bit like a sea creature climbing a rope: What it really shows is how a tangle-busting enzyme called Hsp104 processes a protein strand, stepwise in one direction, like a ratchet, with the enzyme's six subunits latching to the strand in sequence as it is pulled through the enzyme's central channel. The strand ultimately gets pulled out of the aggregate of a tangle of protein fibrils and can refold or be degraded. Researchers are interested in the therapeutic potential of this mechanism because misfolded proteins are the culprits behind amyotrophic lateral sclerosis (ALS), Alzheimer's disease, Parkinson's disease, and other neurodegenerative brain disorders. These distorted proteins are unable to perform their normal functions and clump together, causing devastating problems, and currently, there is no way to untangle the knotted mass of these proteins to treat disease. Hsp104 (heat shock protein 104), found in yeast, has been studied for its tangle-busting qualities for years. Researchers from Penn Medicine and the University of Michigan published the new study in *Science*; their up-close view of how Hsp104 works can enable better engineered molecules that could be used as therapeutics for neurodegenerative diseases.

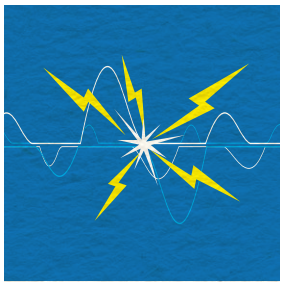
A Clarion Call for the Immune System to Fight Cancer

A clarion call that summons the immune system to deal a final blow to damaged cancer cells originates with surveillance proteins inside of those cells, according to Penn Medicine research published in *Nature*. These surveillance proteins typically detect foreign DNA from invaders such as viruses, but after DNA damage from cancer treatments such as chemotherapy and radiation, they can also find exposed DNA from the cell itself after pieces of it break off into micronuclei that are prone to rupture. The surveillance proteins then incite an immune response. Describing this mechanism helps to explain why immune cells arrive at tumors days after chemotherapy and radiation and not right away. The Penn team also found that this delay is the result of the tumor cells' progress through cell division; they conclude that changes in how fast or slow a cancer cell divides are an important consideration for cancer therapies that combine DNA damage and immunotherapy drugs known as checkpoint inhibitors.

Modules Mark Maturity in Adolescent Brains

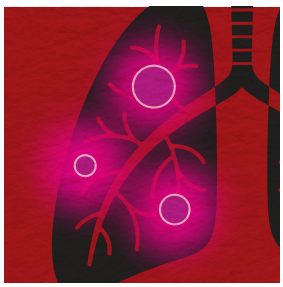
Distinct parts, called modules, in the brain, emerge during adolescence as part of a maturation process during which the brain also becomes more globally integrated, according to a study by University of Pennsylvania researchers, published in *Current Biology*. Modules are parts of a network that are tightly connected to each other, and less connected to other parts of the network. Modules are thought to support specialized brain functions like movement, sensation, vision, and more complicated tasks like executive function (the ability to control impulses, stay organized, and make decisions). The new evidence shows that the degree to which executive function develops during adolescence and young adulthood, depends in part on the degree to which these modules are present. The findings could lead to the identification of biomarkers of abnormal brain development that could predict a person's risk for psychosis and major mood disorders.

An Electric Pulse with DNA Vaccine for HPV-Related Head and Neck Cancer



Physicians used a special device to deliver a pulse of electricity to the area where antigens were injected in an effort to activate an immune response to human papillomavirus (HPV) subtype 16/18. The pulse stimulates the muscles and speeds the intake of the antigens. Penn Medicine researchers presenting at American Society of Clinical Oncology Annual Meeting this year reported success with this DNA-based vaccine delivered to patients who had already undergone therapy that was intended to be curative for head and neck cancer. HPV is an increasingly common cause of head and neck cancers—accounting for an estimated 70 percent of cases today. And 60 percent of cases are caused by the subtype HPV 16/18. When doctors followed up an average of 16 months after the DNA vaccine, 18 of the 22 patients showed elevated T cell activity that was specific to HPV 16/18. A multi-site trial is planned to test the vaccine in combination with drugs for patients with metastatic cancer.

Glowing Tumors Aid Precision Surgery



Making tumor cells glow from an injected, near-infrared contrast dye, is a bright idea in precision surgery. Penn researchers continue to publish surgical milestones from the use of this method, called intraoperative molecular imaging (IMI). One team from the Abramson Cancer Center, which published in *Annals of Surgery*, was able to identify and remove a greater number of cancerous nodules from 50 lung cancer patients when combining IMI with preoperative positron emission tomography (PET) scans. It was the first study to show the effectiveness of combining the techniques. A separate pilot study with 15 neurosurgery patients showed that IMI successfully lit up the benign brain tumors known as pituitary adenomas during removal surgery, allowing surgeons to identify tumor tissue. These tumors are the third most common brain tumor and can cause blindness and hormonal disorders. Over the past four years, Penn surgeons have performed more than 400 procedures using both nonspecific and targeted near infrared dyes in tumor types including lung, brain, bladder and breast.

A Brain Surgeon Finds a Sweet Hobby

Interview by Chiemela Ohanele *Photos by Graham Perry*

After scrubbing out of the OR, most surgeons don't trade their blue scrubs for a fresh white suit covering every inch from head to toe. But most surgeons aren't M. Sean Grady, MD, who uses that head-to-toe protection in pursuit of a sweet hobby. Outside of his work as chief of Neurosurgery at the Perelman School of Medicine, Grady is an amateur beekeeper who keeps bees and collects their honey in Chester County, Pa.

Chiemela Ohanele, a pre-medical student and biology major at the University of Pennsylvania, spoke with Grady about his beekeeping, his interest in ecology, and how these outside interests relate to his work as a surgeon.

What inspired you to start beekeeping?

I have been interested in beekeeping for many years. I never pursued it until about four years ago, when my daughter said that it is time to start doing instead of just talking. So she got me *Beekeeping for Dummies*, and that's what started it.

I like beekeeping for very practical reasons. As a neurosurgeon, I don't have a huge amount of free time. Beekeeping is not a huge time commitment. It's about an hour a week if you do it as a hobby. Secondly, I think the biology of bees is fascinating—from the workings of a beehive and how bees find nectar, to how they communicate with the rest of the beehive about where to go. Nobel prizes have been won for this. I am also an ecologically oriented person and beekeeping fits into that. Lastly, I get honey out of it.

Do you ever sell your honey or have you ever thought about creating an online market? Or do you mainly see your beekeeping as a hobby?

I see it primarily as a hobby. In fact, I just harvested honey yesterday from my four beehives and I probably got about seventy pounds of honey. So I could sell it, but generally I just give it away to family and friends.

Do you see any intersection between ecology and medicine?

I think ecology pushes me to think about what I can do to help our environment. I carry the same perspective in medicine. What kind of things can I do or what kind of influences can I exert on our medical environment? There may be some similarities there.

Do you think that beekeeping as a hobby can mitigate any of the effects of physician burnout?

Beekeeping is one of those activities that require a lot of focus. For example, when you open up a hive for inspection, you cannot disrupt the bees. Otherwise you might get seriously stung. So, you have to concentrate on what you're doing. I find this process meditative, and can take my mind away from things at work that I may have been dwelling on.

> "There is so much that is unknown about the brain, which means that there will never be a time in my career where I will not be a student."

See Grady's perspectives on his neurosurgery career in the extended online version, PennMedicine.org/magazine/bees

What is one piece of advice that you would give to anyone pursuing medicine and has a passion outside of medicine?

Medicine is an all-consuming passion—it is much more than a job. The problem is that this passion can be overwhelming sometimes. So, it is important to find some other intellectually engaging pursuit to balance that passion, so that your whole identity is not subsumed into this one thing.

You have to pick something that accommodates the type of schedule that you have as a doctor. While some physicians pick a career that gives them a lot a free time to pursue many activities, most surgeons don't have a lot of free time. You have to figure out something that can be done within that framework. You could be an artist, write, or even beekeep. Whatever you choose has to fit in with the kind of specialty you have chosen.

Chiemala Ohanele is a staff writer for Doctors Who Create, a website founded by Vidya Viswanathan, a third-year medical student at the Perelman School of Medicine. This story was produced as part of a partnership between *Penn Medicine* and Doctors Who Create, and is jointly published online.

PREVENTION AT THE POINT OF PAIN

By Mark Wolverton *Photos by Tommy Leonardi*

Penn Medicine clinicians and scientists are taking on the national opioid crisis where it began: the causes and treatment of pain.

The United States is in the grip of an opioid crisis. Drug overdoses, mostly from opioids, are now the leading cause of death for adults under 50, with an average death toll of 142 Americans each day drawing a comparison, by a presidential commission, to a "September 11 every three weeks."

In Philadelphia, Penn Medicine clinicians are on the front lines. The city has the third highest number of overdose fatalities in the U.S., according to the Centers for Disease Control and Prevention (CDC). "I've had shifts where I've treated multiple heroin overdoses," says M. Kit Delgado, MD, MS, an assistant professor of Emergency Medicine. His experience is borne out by the recent mayor's task force report noting an estimated 70,000 heroin users in the city. Yet often overlooked in media coverage about heroin addiction and drug-infested urban war zones is that the crisis largely originated not with the criminal underworld but in the office of the family doctor or dentist.

When he talks to patients about their heroin use after an overdose reversal, Delgado says, "the vast majority of them started after being exposed to prescription pain medication." People who picked up a relative's leftover pills to self-medicate, or who trusted their doctor to provide relief from chronic pain conditions such as back pain or arthritis, or from the pain of a routine surgical procedure, found themselves dependent, addicted, and sometimes dying—not because they started out looking to get high, but because something went badly awry when doctors were trying give proper care for pain.

National Institutes of Health Director Francis Collins, MD, PhD, and National Institute on Drug Abuse Director Nora Volkow, MD, recently wrote in the *New England Journal of Medicine* that "science is one of the strongest allies in resolving public health crises. Ending the opioid epidemic will not be any different." Penn Medicine's opioid task force has a number of efforts underway to help patients experiencing addiction, including smoother transitions into medical therapy for opioid

use disorder from the emergency department or from inpatient care for other conditions. At the same time, physicians, researchers, and primary care providers at Penn are using science to battle the opioid crisis from the other end, where it began: the causes and treatment of pain.

Tell Me Why It Hurts

It's a daunting challenge because of the very nature of pain. A fractured collarbone is just that, but pain isn't that straightforward. Unlike objective clinical measures like blood pressure, pain scales measure what patients report. And what one person experiences as excruciating, another might shrug off as mere temporary discomfort, like a quarterback spraining his ankle yet continuing to play in a championship game.

Another problem is that pain is maddeningly complex even at its most fundamental physiological and molecular level. Pain signals are transmitted through a large number of different ion channels and nerve endings via multiple mechanisms. Those different mechanisms also contribute to different sensations and perceptions. The inflammatory pain of arthritis isn't the same as a migraine headache, for example, because different mechanisms create each.

Doctors confront pain with a relatively limited set of treatment options. For major surgery, trauma, and cancer, the most powerful choice is opioids. For what's generally termed as "non-malignant chronic pain," choices are fuzzier. The usual non-addictive alternative to opioids is non-steroidal anti-inflammatory drugs (NSAIDs), familiar to everyone in over-the-counter forms such as Motrin, Advil, and Aleve. But as their name implies, NSAIDs are thought to be effective for inflammatory-based pain and virtually nothing else. And like all medications, they have side effects, including gastrointestinal irritation and bleeding, increased blood pressure, kidney problems, and even serious cardiovascular complications such as heart attack. For these reasons and others, NSAIDs simply aren't a choice for many patients.

Tilo Grosser, MD, a research associate professor of Pharmacology, whose research focuses mostly on NSAIDs and the mechanisms that drive their cardiovascular side effects, points out that just as NSAIDs should work best for inflammatory pain and not for other types, the same idea of specificity to certain types of pain applies to other pain drugs, including opioids. But the dearth of good research makes it difficult for doctors to know what drug works best for what type of pain. "That's why understanding the mechanisms that drive the pain process is so critically important," he says. "If we have a better handle on understanding what drives the pain process in a given patient, then we can target therapy for that individual patient much better."

But for too long, at least pharmacologically, the choice has been "basically opioids or NSAIDs," says Garret FitzGerald, MD, the Robert L. McNeil, Jr. Professor in Translational Medicine and Therapeutics. "There have been no new analgesics brought to market in 7 years." For clinicians, too often that leaves the easy choice of prescribing opioids.

Which, in part, led to the situation today: "The data are very clear that physicians as a group overprescribe opioids," notes Michael Ashburn, MD, a professor of Anesthesiology and Critical Care and director of the Penn Pain Medicine Center. "The U.S. makes up about 4.4 percent of the world's population, yet we use over 80 percent of the world's supply of opioids."

How It All Started

That prescribing opioids is easy doesn't fully explain the present crisis, but it contributes.

Beyond the ease of prescribing, a fundamental shift in attitudes over recent decades precipitated the explosive growth in U.S. opioid

Jeanmarie Perrone, MD is a founding member of Penn Medicine's task force to address the opioid crisis.

prescribing. In the 1980s, a handful of editorials in the medical literature sparked a movement, fueled at least in part by the pharmaceutical industry, to extrapolate end-of-life pain care to nonmalignant pain patients. The naïve notion was that "no one should suffer," says Martin Cheatle, PhD, an associate professor of Psychology in Psychiatry at the Penn Center for Studies of Addiction. Jeanmarie Perrone, MD, a professor of Emergency Medicine and director of Medical Toxicology, who is a founding member of Penn Medicine's opioid task force, traces the liberalization of opioid prescribing in the 1990s to a huge campaign to physicians misleading them to thinking that addiction was rare. For busy primary-care providers, Cheatle notes, the rising demand to treat more patients in less time made it all too easy to prescribe opioids routinely for even relatively minor pain complaints. It had become the automatic response, a routine practice, a one-size-fits-all solution.

The prescribing of opioids had, in fact, become so reflexive that it was enshrined in hospital computer systems. Delgado recalls, from a decade ago during his residency when electronic medical records at his hospital were new, "when you typed in the medication, for example Vicodin, the prepopulated number of tablets was 30 tablets. And so that's what was getting written. There was no thought as to what the patient actually needed."

Although the value of opioids for treating pain is well established and has never been at issue, their perceived value, both from the viewpoint of patients and too many doctors, has pushed aside other options, for physicians and patients alike.

Physicians report that managing patients' pain without opioids requires a lot of education. "A colleague of mine says that it takes 30 seconds to say yes and 30 minutes to say no," Cheatle says. Many patients believe that they should be completely pain-free, which is not a realistic prospect. But that belief leads patients to expect, for example, a prescription for Percocet instead of Tylenol, because they are convinced the strongest medication is best and anything available over the counter won't suffice.

"There's a spectrum here," says Garret FitzGerald. "If you're dying of cancer, you have a reasonable expectation that your pain should be managed, because frankly that is the dominant requirement, as opposed to, are you going to be addicted in 3 months' time? Because you probably won't be alive in 3 months' time. But is it a reasonable expectation that somebody who has a back strain or pulls their muscle playing football has a complete absence of pain? What's the tradeoff between relief of pain and risk?"

In managing that tradeoff, the question of whether opioids are even the best available choice is key.

Opioid drugs are so powerful because they work by switching off pain signaling in the central nervous system, Tilo Grosser explains. But for many types of pain, as for example in inflammatory processes, it may not be necessary to completely "switch off" the pain signal. "You may just be able to treat the source of the pain rather than shutting the pain transmission off through opioids."

A phenomenon by which opioids can transform acute pain into chronic pain is another factor contributing to the crisis. When a person recovering from injury or surgery is prescribed opioids, they're at risk for slipping into a downward spiral leading to physical dependence and sometimes addiction. Perrone, from Penn Medicine's opioid task force, cites the statistic that, once you've taken an opioid for even one day, there is a 6 percent risk of still being on an opioid medication by prescription a year later even if the original source of pain, such as an injury or surgery, is far in the rearview mirror. "There's no question that they have an attraction and a 'stickiness' rate that's certainly much higher than a normal pain reliever," she says.

Preventing that link from developing begins with the physician. Many national and local efforts to address the opioid crisis, including Penn's, focus on education of both patients and physicians to reduce initial opioid prescribing and thereby reduce the rate at which an instance of acute pain may transform into chronic pain.

There are many other things besides opioids and even non-opioid medications that can be effective for the treatment of pain, Michael Ashburn points out. Physical therapy, exercise, and psychological approaches such as cognitive-behavioral therapy (CBT) or even meditation, can be quite effective for many patients. Unfortunately, Ashburn says, "over the last 20 years, our ability to provide that care has actually worsened."

Ashburn is referring to the advent of managed care programs and insurance policies that disrupted a more balanced approach to pain treatment. He says the best pain care integrates several different pain treatment modalities. Physician care, mental health care, physical therapy, and other interventions are integrated with proper medication use—and the physician, psychologist, and physical therapist create that plan together after all have seen the patient. The plan can include everything from changing the patient's lifestyle by teaching them about their condition and how to self-manage their pain to the appropriate use of medications, preferably non-opioid—but only, Ashburn says, "rarely, in carefully selected patients, properly using opioids as part of the solution but not as *the* solution."

But because managed care and insurance company policies have fragmented such programs, Ashburn notes, "we've devolved to using opioids to treat pain. And that has caused significant harm to society."

Making Better Choices

As with Ashburn's emphasis on integrated pain care, most of the professionals who deal with the ravages of acute and chronic pain emphasize that alternative or complementary approaches that don't involve drugs at all, in addition to more research and better pain management education, are crucial to the solution.

Informed guidelines and protocols can help doctors be better stewards of opioids while helping patients get the pain care they need. With that goal in mind, the Penn opioid task force is developing a standardized approach for Penn Medicine clinicians to follow in treating pain, based on intensive study of electronic medical records to determine past prescribing patterns. Perrone points out that such investigations can tease out troublesome patterns of which overworked providers might not even be aware.

"It's all in the electronic medical record; we have tons of data," she says. And that data makes it possible to demonstrate extremes of prescribing to help doctors change their prescribing practices: If hard data indicate that a particular doctor might be prescribing opioids more frequently than his or her colleagues, it might inspire a bit more awareness

M. Kit Delgado, MD, MS, recalls that in the early days of electronic medical records, the default opioid prescription might be for as many as 30 pills. "There was no thought as to what the patient actually needed."

Michael Ashburn, MD, laments the loss of multidisciplinary, integrated pain care models.

and introspection. "I think one of the few ways that moves a physician's practice is provider feedback," she says.

The guidelines are being written for different factors based on direct experience, adjusting prescription amounts through patient surveys to learn exactly how many pills they actually used after a particular procedure. For example, Perrone notes that there was no standard answer to the question, "How many Percocet (if any) do you need after a procedure?" Delgado and Ashburn have partnered with Brian Sennett, MD'88, and Samir Mehta, MD, from the department of Orthopaedics for an initiative to answer that question among patients undergoing knee arthroscopies and other common orthopedic procedures. They aim to develop new prescribing protocols that better provide what patients actually need and reduce the excess number of opioid pills prescribed.

Reducing the supply of excess prescribed opioids is important not only for protecting the patient but those around them. Many patients with opioid use disorder began not as patients under treatment for pain, but simply because they happened upon some extra pills abandoned in the family medicine cabinet, or because a well-meaning friend offered them leftover pills to blunt the pain of a minor injury.

Efforts in recent years by the CDC and other agencies to promulgate physician guidelines for pain management are a step in the right direction. But without the resources to support alternatives, guidelines are only of limited value. Describing CDC guidelines to attempt CBT and physical therapy before considering opioid therapy as "common sense and good practice," Cheatle notes, there is a serious roadblock. "Access to these therapies is limited and reimbursement is poor or nonexistent," he says. "We just don't reimburse for cognitive medicine in this country. Unless

The Mirror Crisis: Chronic Pain

When acute traumatic or post-surgical pain becomes chronic, or when a patient is living with a chronic pain condition, the limited palette of available treatments becomes an even more critical issue. "The options that people have for chronic pain really are minimal and quite pathetic," says Garret FitzGerald. "Our approach to developing novel analgesics is like something out of the 19th century."

For the 100 million adults in the U.S. with chronic pain, that leaves a major unmet need. "We may have an opioid 'epidemic,' but we also have a pain epidemic," Martin Cheatle says. He points out that the annual cost of pain is 560 to 600 billion dollars, a huge sum in comparison to major diseases including heart disease and cancer.

Most of Cheatle's patients suffer with nonmalignant chronic pain. "They're the ones that have had layers and layers and layers of traumas, both physical and emotional," he says. "Pain patients in general feel fairly vilified, they don't feel that they're taken seriously, they don't feel that health care providers really listen to them, and I think there's pretty persuasive evidence that when pain goes from no pain to acute to chronic, it becomes a brain disease. It's not a symptom or a psychiatric disorder."

The result is a neglected flip side to the current crisis. Despite the clear dangers of opioid abuse, there are many chronic pain patients who need the medications and can handle them just fine. Some patients who are safely taking fairly low doses of opioids are seeing their prescriptions taken away because of widespread concern about abuse, Cheatle says. And new prescriptions are harder to obtain, even for those for whom opioids may be a part of the best treatment plan. "Now the pendulum has swung to the other side."

That can drive chronic pain patients to desperate and dangerous measures, such as turning to illicit alternatives when legitimate treatment is cut off. Kit Delgado recalls what he calls "a very common scenario": a back surgery patient from out of town who continued to have post-surgical pain. After her opioid prescription was discontinued and she was unable to wait four months for an appointment to a pain medicine clinic, she ultimately turned to heroin for pain control. "I agree that we need to be more careful stewards of opioids, especially for acute prescribing, but now we have this huge population of people who are dependent on these, and what we're seeing is the unintended consequences of acutely limiting prescriptions to these people and making it harder to get them," he says. "And because heroin is a lot cheaper than prescription opioids, people are unfortunately swapping one for the other, and we're seeing the devastating public health consequences right now."

Tilo Grosser, MD, and Garret FitzGerald, MD, have called for a major, multifaceted scientific initiative to better treat pain as part of the complex solution to the opioid crisis.

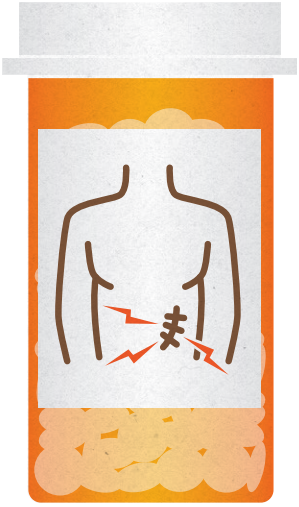
there's substance behind these recommendations, including policy changes and reimbursement changes, it's really not as effective as it could be." FitzGerald agrees, noting that while many promising strategies and research pathways exist, "there's precious little in the way of allocated budget to support this."

Getting Down To Business

The magnitude of the present crisis and the state of pain medicine led FitzGerald, along with Grosser and Clifford J. Woolf, to call for a major and multifaceted scientific initiative to identify better pain treatments in a *Science* article in March. Such a goal was also set out in a new report on the opioid crisis by a National Academies of Sciences committee, on which FitzGerald served.

FitzGerald compares the situation to AIDS in the 1980s, pointing out that more people now die every day of opioid abuse than died at AIDS at the peak of that crisis. More than a number, successfully confronting AIDS has required addressing a confluence of political, social, scientific, and criminal dimensions. FitzGerald contends that a similar broad-based campaign is critical for opioids. "What we don't have is a coordinated, strategic, well-financed initiative that reflects the importance of this crisis and the depth of investment that it demands."

In the *Science* article, the team suggests the establishment of a $10 billion research fund administered by the National Institutes of Health to pursue intensive research into the neurobiology of pain, the development of new drugs, and studying pain phenotypes (i.e., the varying responses of different individuals to medication).



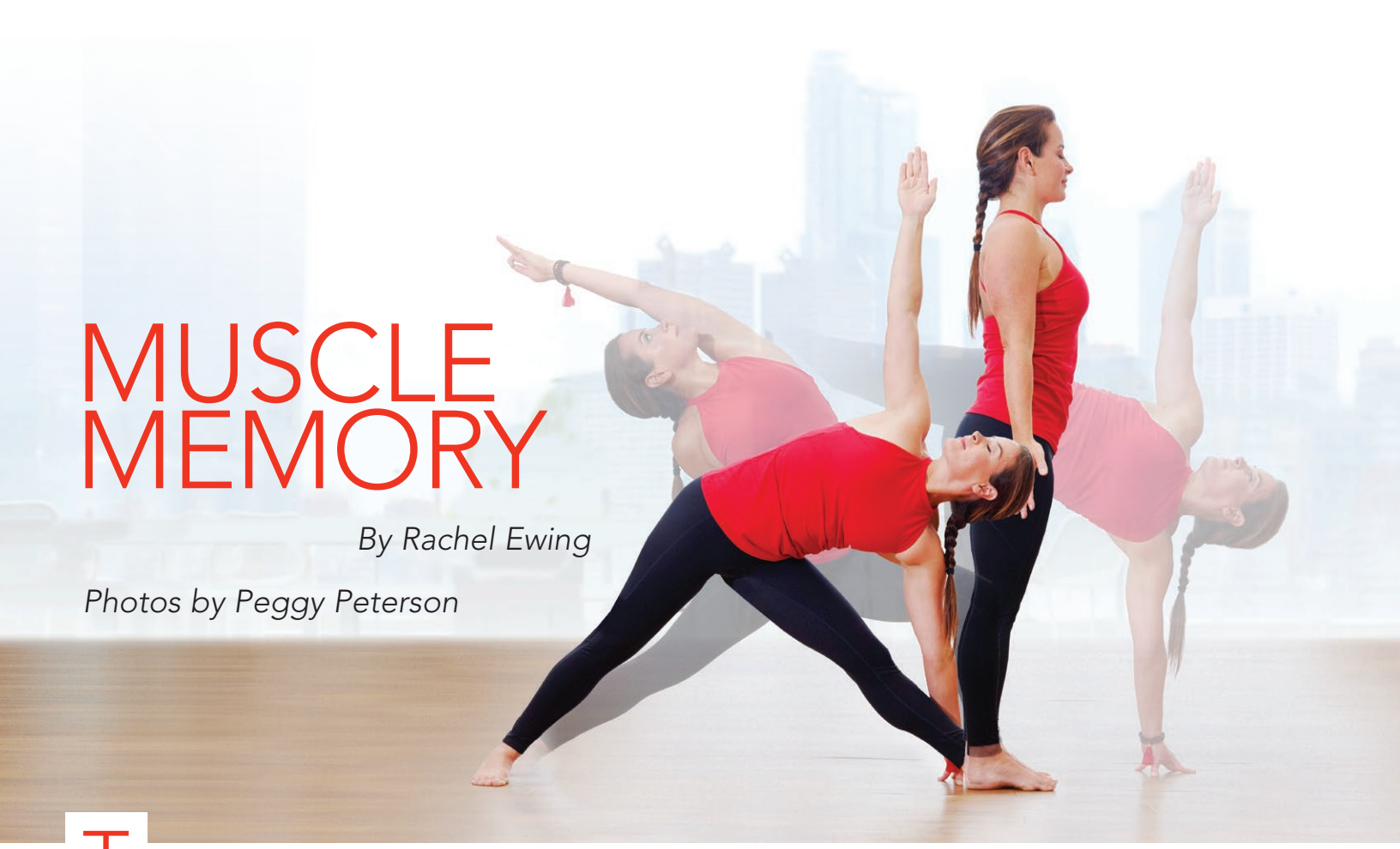
That amount is small in comparison to the expense of fighting AIDS, FitzGerald notes, but even the higher expenditures on AIDS ultimately cost far less than letting that crisis worsen with a less coordinated intervention. "And $10 billion would be a very cost effective investment if it got on top of this crisis."

FitzGerald finds plenty of agreement for the notion that the solution to the opioid crisis is not going to come solely from the trenches, the doctors seeing patients every day or treating overdoses in emergency rooms. "We need a top-down reformation and legislators, insurance companies, the pharmaceutical industry have to put their money where their mouth is," says Cheatle. "And until we do that, people are going to continue to suffer both from unremitting pain and from substance use disorders." FitzGerald also emphasizes the responsibility of the pharmaceutical industry, especially given its role in creating the crisis. "They have a real societal and moral obligation to invest in a solution, and that needs to be spelled out, I think."

That might sound like an uncomfortably political stance for doctors and scientists to take. But FitzGerald and his colleagues, working to achieve a better understanding of pain to help patients while averting the dangers of opioids, are unapologetic. "It is political. It *should* be political," says FitzGerald. "But the solution should be a completely ideologically independent one, because it's a bipartisan problem and it demands a bipartisan solution," he insists.

"It needs to be a national priority."

Read this story online with related links at PennMedicine.org/magazine/pain



MUSCLE MEMORY

By Rachel Ewing

Photos by Peggy Peterson

Take a deep breath in. As you breathe out, answer: What did your internal intercostal muscles do when you took that breath?

This isn't a common question in most yoga classes, but it is part of Yoganatomy at the Perelman School of Medicine, a yoga class that combines traditional yoga practice with reinforcement of lessons in gross anatomy. Yoganatomy is the first part of what will soon be a full suite of yoga instruction designed to complement classes spanning the full three-semester preclinical curriculum.

By mindfully moving and breathing with the body parts that earlier in the day they have learned about in lectures and examined up-close in donated cadavers in the lab, first-year medical students in Yoganatomy gain a deeper appreciation of these structures in a living body.

"The primary goal of Yoganatomy is to give the students an outlet to help them with their stress," said Nikki Robinson, the yoga instructor who developed and leads these classes. "Here's an hour when they're going to move, breathe, talk about things we learned in the anatomy lab, and then rest, so they're recharged to go about the rest of their day."

Robinson said "things *we* learned in lab" for a reason—and it wasn't just empathy with her students. Robinson was given permission to attend gross anatomy classes alongside Penn medical students last fall. She was introduced to Penn by Mitchell Lewis, DPhil, a professor of Biochemistry and Biophysics who audited gross anatomy himself some years ago—and still spends a few hours with students in the gross lab each year—out of interest in becoming a better-informed teacher of first-year students. After completing a full gross anatomy course this summer, Robinson is assisting in the lab at Penn this fall. "It is really important for me to be able to accurately reflect and represent what the students were taught," she said.

Yoganatomy runs in many ways as a typical yoga class, except for the parts that sound more like a gross anatomy study session.

When students are in plank pose—which is essentially holding the "up" position of a push-up—Robinson might say, "Now retract the scapula." Students are forced to think about the muscles connected to the scapula and to recall the distinction between protraction and retraction.

"I try to straddle keeping it really serious and medically accurate and just giving them something fun to do," Robinson said.

Medically Informed Yoga

The leader of the next yoga class in the sequence is an inversion of Robinson: Instead of a yoga instructor-turned-part-time-med-school-attendee, Sila Bal is a full-time medical student who became certified as a yoga instructor. Now a fifth-year MD/MPH student at Penn, Bal incorporates her knowledge of anatomy and physiology into teaching yoga.

Soon after she began teaching, Bal got to thinking, "Wouldn't it have been cool if when I was an MS1 or MS2, someone had gone through what is or isn't physiologically plausible that's taught in yoga classes?" Over the course of the last spring semester, Bal developed and taught multiple yoga lessons connected to topics in Mod 2, the preclinical learning block focused on organ systems and disease, and called them Medically Informed Yoga.

"I pick a paper from a reputable journal with trustworthy results and use that as a starting point for our discussions,"

Bal said. In connection with the brain and behavior module, she discusses a Penn Medicine study of depression published last fall (see below). The discussion spans the physiology of depression and physiological bases of the use of yoga in depression. "Depression has a lot of research behind it," she said. "For example, we know yoga stimulates the parasympathetic nervous system."

After a brief discussion, Bal leads the students through a 45-minute sequence of the asanas, or physical postures, that yoga teachers recommend for the organ system under discussion, to practice what they learned.

Creating Connection

The two yoga class sequences—Yoganatomy for first-semester medical students in gross anatomy, and Medically Informed Yoga for second- and third-semester medical students in Mod 2—arose independently by luck or chance last year. This year, the two programs are coming into alignment.

Bal and Robinson are working together to develop a coordinated curriculum of yoga classes to complement the full span of the three semesters of preclinical medical education that can be standardized and repeated in future years.

Already this year, yoga as a study enhancement is front and center for new students. During their orientation in August, new first-year medical students received an introduction to Yoganatomy and Medically Informed Yoga, and participated in a brief demo. Bal, Lewis, and Robinson all believe that all medical students can benefit from yoga

through integrating stress relief, exercise, and connection into their often high-stress learning experience.

The sessions last fall also lured more senior medical students—some of whom said that Robinson's Yoganatomy quizzes helped them study for board exams—as well as faculty and graduate students from other schools at Penn.

Medically Informed Yoga for Depression

Sudharsan Kriya Yoga is a breath-based meditation consisting of the breathing methods uiiayi and bhastrika, Om chanting, and a form of cyclical breathing called Sudarshan Kriya. It activates vagal afferents, improving autonomic function, neuroendocrine release, emotional processing, and social bonding.

In a randomized, controlled pilot study, led by Anup Sharma, MD, PhD, a Neuropsychiatry research fellow in Psychiatry at Penn, researchers found significant improvement in symptoms of depression and anxiety in medicated patients with major depressive disorder who participated in the breathing technique compared to medicated patients who did not partake. After two months, the yoga group cut its mean Hamilton Depression Rating Scale (HDRS) score by several points, while the control group showed no improvements. HDRS is the most widely used clinician-administered depression assessment that scores mood, interest in activities, energy, suicidal thoughts, and feelings of guilt, among other symptoms.

"With such a large portion of patients who do not fully respond to antidepressants, it's important we find new avenues that work best for each person to beat their depression," Sharma said when the study was published in the *Journal of Clinical Psychiatry* in November 2016. "Here, we have a promising, lower-cost therapy that could potentially serve as an effective, non-drug approach for patients battling this disease."

Neurophysiology of Sudharsan Kriya Yoga

Ujjayi: victorious breath
- Airway resistance → stimulation of somatosensory afferents in pharynx
- Increased vagal (parasympathetic) tone

Bhastrika: bellows breath
- Sympathetic activation and CNS excitation on EEG
- Activation of temporoparietal cortical areas

Om: the infinite
- Stimulation of Wernicke's area and the thalamus

Sudarshan Kriya: cyclical breathing with different rhythms
- Hyperventilation → sensorimotor cortex excitability and thalamic activation

Select Asanas that Benefit Depression
Savasana: Corpse Pose
Surya Namaskar A and B: Sun Salutations
Salamba Sarvangasana: Shoulder Stand
Paschimottanasana: Seated Forward Fold

Adapted in part from Medically Informed Yoga materials created by Sila Bal

OUR ELECTRIC SYMBIONTS AND THEIR REBEL CHAMPION

By David Steen Martin

Photos by Peggy Peterson

Long overlooked—or oversimplified— as primitive power plants in our cells, mitochondria are moving into the mainstream scientific limelight, thanks in large part to Douglas Wallace, PhD, the "world's biggest mitochondriac" who is galvanizing research on the Penn and CHOP campuses into the role of cellular energy in disease.

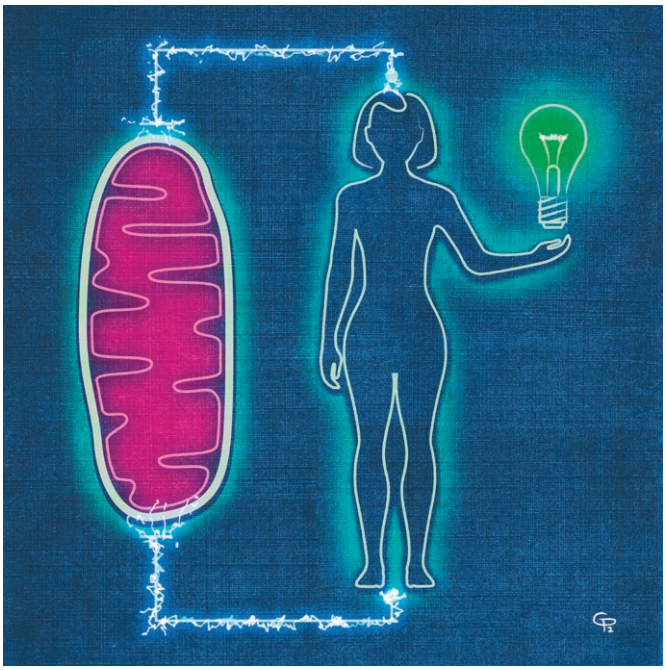
If you doubt the importance of energy to human health, Douglas Wallace, PhD, suggests you consider a cadaver. It may be anatomically perfect. It is just dead. Why? It lacks energy.

Wallace, a professor of Pathology and Laboratory Medicine at the Perelman School of Medicine at the University of Pennsylvania and director of the Center for Mitochondrial and Epigenomic Medicine at Children's Hospital of Philadelphia (CHOP), has spent the last five decades pushing medicine to look beyond the body's anatomy to focus on its energy.

"Western medicine is grounded in anatomy, which I call the anatomical paradigm of disease," Wallace said. If you have severe headaches, you see a neurologist. "But what if the problem is systemic, and the head is just more sensitive to that systemic defect than any other organ? Treating the head will not solve the problem."

Describing this conflict as "the conundrum created by mitochondrial disease," Wallace has focused his career on tiny structures inside our cells called mitochondria. Mitochondria convert oxygen we breathe and nutrients in our food to generate 90 percent of the energy in the human body. Biology textbooks have traditionally depicted mitochondria as primitive bean-shaped organelles in cells—simple power plants, churning out energy, but of little relevance to medicine. But this conventional wisdom is misguided, according to Wallace's pioneering research.

Wallace's work has not only permitted him to reconstruct the prehistory of our species, but has demonstrated that mitochondrial energetics impinges on virtually every aspect of medicine. Consequently, Wallace and his colleagues within the Center for Mitochondrial and Epigenomic Medicine collaborate with physicians and scientists across the medical landscape, both within Penn and CHOP and around the world.



These studies have demonstrated that mitochondria play a role in a wide spectrum of intractable diseases and conditions from autism, Parkinson's and Alzheimer's diseases to diabetes, obesity, and heart disease; as well as cancer and aging.

Ancient Bacteria

The story of how and why mitochondria came to be so crucial to our health begins two or three billion years ago, with a once-in-the-history-of-life event. This event was the formation of a symbiosis between two originally co-equal single-celled life forms, an oxidative bacterium that evolved into the mitochondria inside of all complex, non-bacterial cells, and an archaeon that would evolve to become the nucleus and everything else surrounding the mitochondria inside these cells. Without this singular episode in the history of life on Earth, there would be no plants, animals, or you.

The mitochondria brought to the partnership their unique ability to use newly abundant oxygen from the atmosphere

to extract chemical energy from carbohydrates that were consumed as food. Once established in their cellular symbiosis, the mitochondria proliferated inside the larger cell and collectively produced sufficient excess energy for the nucleus to increase the number and complexity of its genes. The increased genes permitted increased complexity of life.

The strength of this symbiotic relationship, powered by energy and driving all life processes, has been likened to Prometheus' mythical gift of fire.

"If mitochondria had not happened, nothing that you see out there would exist," Wallace said, waving a hand toward the panoramic view from a sixth-floor window at CHOP.

Given how much we depend on mitochondria, we know remarkably little about them. Mitochondria weren't even discovered until late in the 19th century. By the 1950s, scientists including Penn's Britton Chance, PhD, were probing the physical and electrical properties of mitochondria to understand their role in powering cells. Chance, a fellow and later director of Penn's Eldridge Reeves Johnson Foundation for Research in Medical Physics, was a pioneer in creating instruments to measure mitochondrial energetics. In a series of groundbreaking articles, six of them published in a single issue of the *Journal of Biological Chemistry* in 1955, Chance delineated the key aspects of how mitochondria produce energy, a process called oxidative phosphorylation (OXPHOS).

But it wasn't until the 1960s that researchers found that the mitochondria had their own DNA (mtDNA), retained from their origins as an independent life form. Around this time, the idea that mitochondria originated as ancient bacteria began to gain wider credence in science.

Wallace arrived at Yale as a graduate student in 1970 intent on studying mitochondrial genetics in the medical school's newly established department of Human Genetics. Though perceived as offbeat by those around him, Wallace's mitochondrial pursuit fit with his lifelong quest to answer three questions: "Who am I? Where did I come from? And why do I feel bad?" Wallace reasoned that because the mitochondria generated 90 percent of cellular energy they couldn't be trivial, and because the mitochondria had been recently found to have their own DNA, the mtDNA could mutate and cause disease. Moreover, the mtDNA was the only human DNA that could be purified at the time. So Wallace was able to begin studying human molecular genetics.

We now know that mtDNA includes the genes required to assemble enzymes essential to the primary energy-generating process, OXPHOS. The mitochondria continue to function as distinct living organisms inside our cells, carrying out the process of copying their mtDNA within the mitochondrion and using those genes to build OXPHOS proteins using their own mitochondria-specific ribosomes. But this distinctness is balanced with dependence. While the ancient ancestors of mitochondria had DNA that encompassed all of the genes necessary for a free-living bacterium, following the symbiosis, mitochondria lost many genes they no longer needed in the protective intracellular environment. Mitochondria also outsourced their anatomical genes to the nucleus. The mtDNA retained only the most critical genes for OXPHOS charge conduction. Thus, the mtDNA is the wiring diagram of the mitochondrial power plant, and human energy now requires interaction between genes in mtDNA and the nuclear DNA (nDNA). Unlike nDNA, in which each cell carries only two copies (one inherited from each parent), mtDNA has thousands of copies in every cell.

Without the singular episode in the history of life on Earth when two single-celled life forms became complex cells that included mitochondria, there would have been no plants and no animals, trilobites or human beings.

As a graduate student, Wallace split his time between the lab, where he began to define the rules of mtDNA genetics, and conversations with biophysicist Harold Morowitz, exploring theories about the fundamental physics of life. From these early days and for decades to come, Wallace encountered a scientific establishment that thought his focus on mitochondria was misguided. One early supervisor said to Wallace, "Why are you wasting your career on mitochondria? Mitochondria have nothing to do with medicine."

Uprooting the Pea Plant

The same biology textbooks that describe mitochondria as inert power plants typically introduce genetics with the story of the neat rules first set down by Augustinian monk Gregor Mendel in the mid-19th century. Mendel, the son of a struggling farmer, discovered the fundamental laws of genetics that govern inheritance of nDNA by studying pea plants in a small garden plot on his monastery's grounds in what is now the Czech Republic. By cross-breeding his plants over multiple generations, Mendel showed that for several inherited traits each parent passed along one copy of each gene to their offspring.

In the decades after he started working as a graduate student at Yale, Wallace's research uprooted the notion that all genetics followed Mendel's pea-plant ideal. Wallace not only described a completely different human genetic system, but went on to demonstrate that genetic defects in the mtDNA can play a fundamental role in disease (more on that below) and to show that ancient mtDNA variants permitted our ancestors to adapt to different environments to colonize the globe.

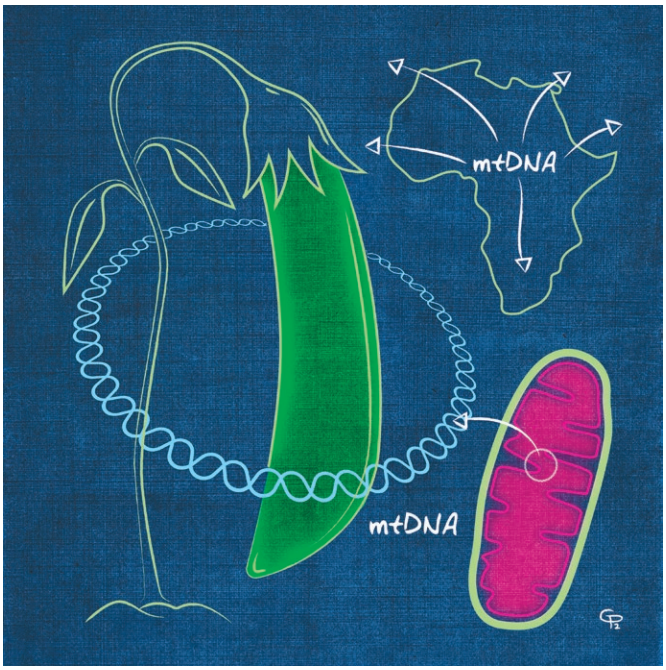
Though Mendel's model describes ordinary inheritance patterns of nDNA well—one copy of each gene inherited from each parent—Wallace showed that mtDNA is solely inherited from the mother, passed on through her oocyte (egg) at fertilization. Each cell has hundreds to thousands of mtDNAs, and the oocyte contains several hundred thousand mtDNAs. This means that mutations in mtDNA affect a living organism in a different kind of pattern. While a nuclear gene mutation can exist in three states: two normal, one normal and one mutant, and two mutant copies, by contrast, a mtDNA mutation can be present in a vast gradient of different percentages of the cell's mtDNA.

Wallace made an inductive leap from this insight to investigation and discoveries about human prehistory. Because the mtDNA is exclusively maternally inherited, it can only change over generations by the accumulation of sequential mutations along maternal lineages. Thus, the number of mtDNA sequence differences between any two individuals is proportional to the time since they shared a common female ancestor. By analyzing the mtDNA sequence differences between indigenous peoples from around the world, Wallace and associates determined the genetic relatedness of different people. By overlaying their genetic relationships with their geographic homeland, Wallace and colleagues were able to reconstruct the ancient origin and migration of peoples.

To do this work, Wallace and his team traveled around the globe getting samples of mtDNA. His favorite place was Siberia's Lake Baikal, an ancient body of water in a vast plain that harbors 20 percent of the world's fresh water. "It's an ocean of absolutely pure, crystal clear water, and it's thousands of feet deep," Wallace recalled. "It has its own seals. Its own fish. It's completely isolated."

Using mitochondria to reconstruct human migrations led Wallace to conclude that all human mtDNAs diverged from a single mtDNA in Africa about 200,000 years ago, a mtDNA that has been christened "mitochondrial Eve." After radiating in Africa for about 140,000 years, the descendants of only two mtDNA lineages left Africa about 65,000 years ago to colonize Eurasia. Of the numerous Eurasian mtDNA lineages, people from only five mtDNA lineages from Eurasia initially colonized the Americas.

The regional mtDNA lineages don't only represent chance mutations in mtDNA that are accumulated and inherited through maternal lines. Evolution is an ongoing process of selection in favor of mutations that offer some benefit to survival in an environment, as well as selection against mutations that cause harm. The major human lineages of mtDNA generally diverged from one another with the appearance of a mtDNA harboring a functional variant. This implies that these founder variants were advantageous in the environment in which they arose, and these variants became enriched by selection.



For Wallace, these insights into human prehistory and evolution are intricately connected with insights into mitochondria's role in health. Variations in mtDNA that were adaptive in one environment can be maladaptive in another environment. Consistent with this concept, mtDNA lineages

have been found to be associated with a wide range of metabolic and degenerative diseases, longevity, and cancer. But mtDNA mutations are far more directly implicated in certain rare diseases today—also thanks to Wallace's early insight.

Mitochondrial Medicine

The field of mitochondrial molecular medicine was founded in 1988 when Wallace and associates at Emory reported the first inherited pathogenic mtDNA mutation causing a hereditary disease, Leber Hereditary Optic Neuropathy (LHON). LHON is a form of acute-onset blindness that presents in the teens or twenties. Since this discovery, mutations in mtDNA have been linked to forms of deafness, neurodegeneration, stroke, seizures, dementia, heart disease, kidney problems, chronic fatigue, exercise intolerance, diabetes, gastrointestinal impairments, mood disorders, various cancers, and aging. Known inherited and acquired mitochondrial defects affect an estimated 1 in 4,300 people.

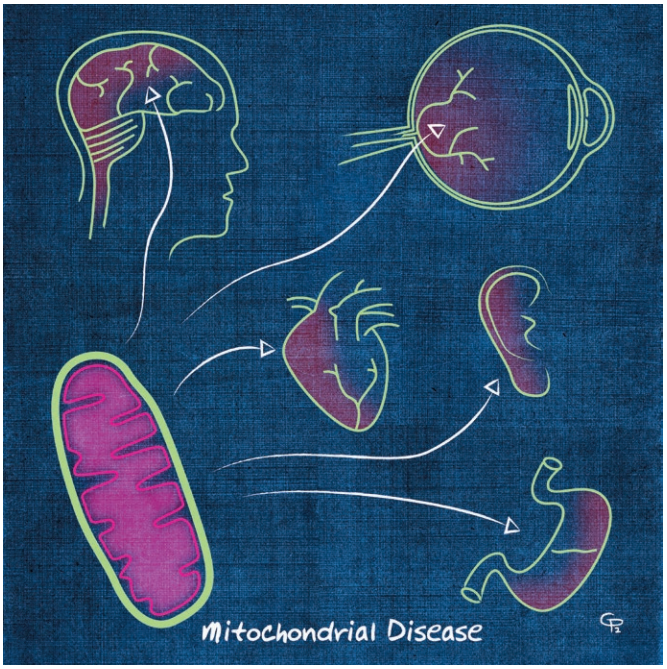
Mitochondrial genetic diseases today are increasingly recognized but clinically vexing. Like many rare diseases, they are often overlooked and misdiagnosed. Wallace's first patient was a woman with a bump on her back called a cervical lipoma, in addition to progressive dementia, heart disease, and gastrointestinal problems. She was receiving psychiatric care because doctors could not envision that a patient could have symptoms in so many different organs due to the same cause. Wallace found she had a mtDNA mutation. He has since seen many others like her with constellations of symptoms affecting multiple organs.

At CHOP, the Mitochondrial Medicine Frontier Program is one of a handful of centers worldwide specializing in mitochondrial disease. The program focuses on finding the underlying cause of a condition and finding the best treatments available, integrating clinical care across the spectrum of disease, and bridging clinical care with clinical research to improve outcomes. Mitochondrial dysfunction can damage any organ in the body and affect individuals from conception to old age.

> Wallace's research uprooted the notion that all genetics followed Mendel's pea-plant ideal.

"Patients typically have many symptoms progressively involving many organs," said Marni Falk, MD, the program's executive director, an associate professor of Pediatrics at the Perelman School of Medicine, and chair of the Scientific and Medical Advisory Board of the United Mitochondrial Disease Foundation. Falk was co-author of a consensus statement published in July in *Genetics in Medicine* on preventative guidelines for the management and care of people with mitochondrial disease. She also leads an active CHOP research group to gain better understanding of the causes, consequences, and novel therapeutic approaches for mitochondrial disease.

Current treatments are typically aimed at keeping these patients as healthy as possible through attentive clinical care, exercise, vitamins, and nutritional supplements, while avoiding medications known to be toxic to mitochondria. One actively discussed approach for eliminating harmful mtDNA mutations from being inherited in an embryo is a reproductive technique in which the nucleus from the oocyte or zygote of the mother is transferred into a donated egg from a woman with normal mtDNAs, from which the nucleus has been removed. A few such "three-parent babies" have been born, at least one of which had low levels of the harmful mtDNA; the controversial technique is one of the rare occasions when mitochondrial medical research has received popular attention. Recently, Falk served on a National Academy of Medicine panel weighing the ethical considerations of these techniques. In addition, gene therapy or stem cell therapy has potential to repair mutations in the mitochondria, and some pharmaceutical compounds are being studied that could promote mitochondrial health.



"There are a lot of therapies in the pipeline," Falk said. "I'm very hopeful we're going to reach the point where we have a series of approved therapies to choose from to target different manifestations and improve health across different subtypes of mitochondrial disease. I don't think it's a matter of 'if.' It's a matter of 'when.'"

But getting funding for mitochondrial research can be difficult, Wallace noted, even though understanding how to treat patients in rare mitochondrial diseases may lead to new approaches for treating a wide range of common diseases.

CARDIOVASCULAR INSTITUTE 'PLAYER-COACH' FOCUSED ON MITOCHONDRIA

Daniel P. Kelly, MD, the new director of the Penn Cardiovascular Institute, considers himself a player-coach, a researcher and team builder with ideas about the kind of collaboration that can crack some of medicine's most difficult challenges.

Breaking down barriers between disciplines and also between basic science and clinical research can open the door to breakthroughs in heart disease, diabetes, and cancer, Kelly said.

At the core of his approach is a focus on the mitochondria and energy production. The heart uses a lot of energy. People with heart failure are often unable to supply the heart with enough to function properly.

"If we could make the mitochondria more healthy, we might have one form of treatment for the global health problem of heart failure and sudden death," Kelly said.

Heart failure costs more than $30 billion in the U.S. alone and costs are projected to double over the next 20 years. Current treatments for heart failure aim to lower the energy needs of the heart, relieving some of the symptoms but often leaving patients with a poor quality of life. However, therapies aimed at improving cardiac mitochondrial energy transduction have not been developed.

Kelly's interest in this area was sparked by a rare genetic mitochondrial disease in children that could cause heart failure. He began studying it in his earliest research training as a young physician at Washington University in St. Louis.

"I was still seeing patients and still taking some call at night," Kelly said, recalling the long hours. "It was exhilarating but somewhat disorienting." As he worked late into the night on his research, shoulder-to-shoulder with graduate students, his beeper would go off with concerns about a patient.

"You know it's something you like doing if you find yourself spending a lot of hours doing it but don't count the hours," he said. "I learned that there is nothing quite like the thrill of discovery. Particularly if it could impact dread diseases of our time."

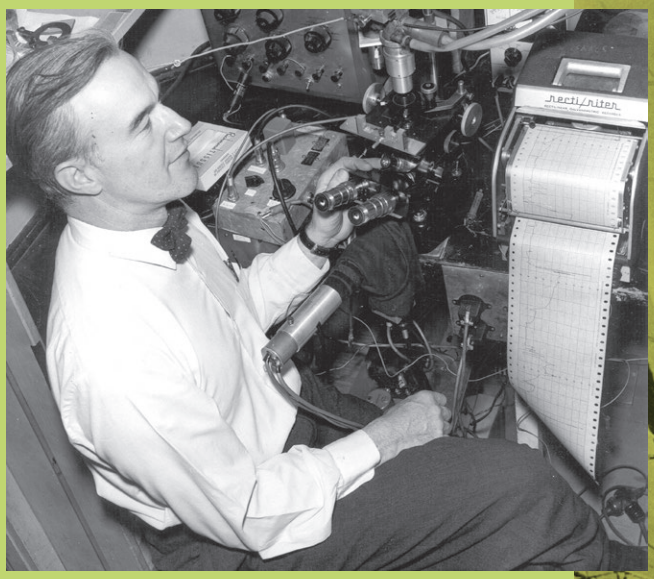
Kelly and his colleagues found the mitochondria in these young hearts had a genetic defect affecting an enzyme needed to break down fatty acids, a fuel source for mitochondria to provide usable energy the heart. When the children became ill with common viral diseases, the stress and fasting often precipitated heart failure due to energy starvation. The results were published in the *Proceedings of the National Academy of Sciences* in 1987.

Kelly began wondering if these rare mitochondrial diseases might offer insights into more common forms of heart disease, and his career changed course.

He was the founding director of the Center for Cardiovascular Research at Washington University and later the founding director of the Sanford Burnham Prebys Medical Discovery Institute at Lake Nona, Florida. There, he built a team focused on metabolism with a focus on diabetes and obesity and its cardiovascular complications.

Kelly said he considered Penn's concentration of talent focused on mitochondria, metabolism, and disease second to none worldwide, between Wallace at CHOP and Penn's Mitchell A. Lazar, MD, PhD, and the Institute for Diabetes, Obesity and Metabolism. He officially joined them in his new role at Penn in August.

"From our passion in understanding mitochondria in disease, we take broader views beyond the heart, across disciplinary boundaries," Kelly said. "This approach should lead to the assembly of 'out of the box' research teams across the Penn campus. Indeed, biomedical research is at a point where discoveries made by multidisciplinary groups are not only possible, but essential."



Among his many accomplishments, Britton Chance, PhD, was an Olympic gold medalist in sailing, a prolific inventor, and a first describer of the process by which mitochondria produce cellular energy.

"This is a new way of looking at the disease process," he said. "It has huge implications."

A better understanding of mitochondria, in Wallace's view, will change the way medicine understands health and disease. Traditional diagnoses focus on ailing organs. Heart disease originates in the heart, kidney disease in the kidney, Alzheimer's and Parkinson's diseases in the brain, and so on. To look at the body through Wallace's lens is to hold the opposite end of the binoculars. Numerous common diseases may be mitochondrial bioenergetic diseases with organ-specific symptoms. Heart disease can be an energy problem, not one due to an inherent problem in the structure of the heart.

Wallace and those who have joined him in the now burgeoning field of mitochondrial research, with their talk about "bioenergetics," sound more akin to practitioners of Eastern philosophy, with its concept of "vital energy" or "Qi." The term bioenergetics may have a mystical ring, but discoveries linking mitochondria, energy and disease are converging into an active area in science and coming fast.

"It All Goes Back to Britton Chance"

One afternoon this summer, J. Kevin Foskett, PhD, the Isaac Ott Professor of Physiology at Penn, was planning a week-long assay of 44,000 compounds, to see how they affect the flow of calcium ions to mitochondria in cancer cells. It's the first step of what he's hoping will be a cancer treatment that targets mitochondria.

Foskett has found mitochondria in cancer cells are addicted to calcium. Normal cells will slow down energy production when they don't have enough calcium. Under the same conditions, cancer cells continue to reproduce via mitosis, even though the lack of calcium limits the cells' ability to function.

"Cancer cells proceed into mitosis even though they're in a bioenergetics crisis and at the end of mitosis they kind of explode. What they call a mitotic catastrophe," Foskett said. Stopping the flow of calcium to the mitochondria could be a way to kill cancer cells while sparing normal cells.

Foskett's work is just one example of many across the Penn and CHOP campuses. More than 250 investigators participate in the CHOP/Penn Mitochondria Research Affinity Group led since 2008 by Marni Falk. Much of the ongoing work centers on the brain because this organ exerts such a high demand for energy that mitochondrial dysfunction is often evident there. The brain is only 2 or 3 percent of our body weight but expends 20 percent of its energy. Failure to deliver enough energy—the result of mitochondrial mutations—can result in neuropsychiatric disorders, Wallace argues. For example, his team reported a mtDNA mutation in 1993 that predisposes to Alzheimer's and Parkinson's diseases, and in August this year, Wallace's team reported that certain Eurasian mtDNA lineages are predisposed to autism spectrum disorders.

Efforts at Penn to understand the role of mitochondria in the brain span a number of areas and biological mechanisms. Erika Holzbaur, PhD, the William Maul Measey Professor of Physiology, is researching what happens to damaged mitochondria, a process called mitophagy. Her research could result in a better understanding of neurodegenerative disease, leading to new treatments. And James Eberwine, PhD, the Elmer Holmes Bobst Professor of Systems Pharmacology and Translational Therapeutics, is focusing on how mitochondria affect neuron function. The Eberwine lab has already developed a way to isolate and sequence single mitochondria from human neuronal cells, discovering a far greater diversity in

mtDNA in single cells than expected. Work in his lab could make it possible one day to create therapeutic mitochondria and offer new ways to treat mitochondrial disease.

After the brain, the next-biggest consumers of energy in the body are the heart and muscles. Daniel Kelly, MD, who joined Penn in August as director of Penn's Cardiovascular Institute, is focused on energy and heart disease, seeking ways to improve mitochondria to restore cardiac energy in heart failure patients. (See sidebar.) Kelly said the concentration of researchers at Penn and CHOP focused on mitochondria and bioenergetics is second to none in the world.

Foskett sees all this research on mitochondria as an extension of work at Penn that began almost a century ago.

> To look at the body through Wallace's lens is to hold the opposite end of the binoculars.

"It all goes back to Britton Chance," he said.

Chance was an inventor and innovator and Olympic gold medalist in sailing whose wide-ranging research spanned 70 years. He spent much of that time on bioenergetics, including his pioneering work that described how mitochondria generate energy through OXPHOS. He was still receiving research grants into his 90s.

"He was unbelievably vibrant, riding his bicycle down Hamilton walk to his research lab in his mid-90s," Falk said. "A fabulous person, brilliant scientist, dedicated educator, and inspiring role model." After Chance died in 2010, researchers traveled to Penn from all over the world to take part in a two-day memorial symposium to honor him.

Mitochondria Entering the Mainstream?

Wallace arrived at Penn and CHOP the year Chance died, and he is leading the next generation of work here on mitochondria. In addition to the role of mitochondria in disease, Wallace has taken aim at no less than the aging process itself. It's no accident the elderly often describe having a lack of energy, Wallace said. He argues that aging is the equivalent of a "metropolitan brownout" caused by mitochondria becoming weaker as mtDNA accumulates more mutations. The mutation rate of mtDNA is hundreds of times greater than that of nuclear DNA.

Wallace believes that accumulation of mutations in the mtDNA in our tissues with age progressively erodes mitochondrial bioenergetics and is the molecular basis of our aging clock. These accumulated mtDNA mutations may also exacerbate inherited partial mtDNA defects in mechanisms resulting in diseases with a delayed onset and progressive course.

This idea hasn't uprooted the mainstream understanding of aging yet, but Wallace is accustomed to challenging the status quo. For much of his career, the 70-year-old Wallace has worked in the face of naysayers who have considered his focus on mitochondria misguided and his findings irrelevant. "I've always been out in left field relative to the establishment," Wallace said.

Lately, the establishment has been paying attention. In recognition of his groundbreaking work, Wallace this year received the Dr. Paul Janssen Award for Biomedical Research and a Benjamin Franklin Medal in Life Sciences. Previous recipients of the Franklin Medal include Albert Einstein, Thomas Edison, Stephen Hawking, Marie Curie, Nikola Tesla and Max Planck. More than 100 Franklin Medal winners have also won the Nobel Prize.

As a token of recently won accolades, Wallace likes to wear a small, gold pin on the lapel of his sport coat. He received the medallion for winning the 2012 Gruber Prize for Genetics, the world's highest prize for genetics.

"I wear it because I have taken so much grief for trying to change the genetic paradigm," Wallace said.

As someone who describes himself as "the world's biggest mitochondriac," Wallace said he is heartened by the increasing attention mitochondria are receiving. A look at scientific literature since 1980 found a steep rise in papers focused on mitochondria. In fact, they now outnumber papers on the human genome.

As researchers look closer, they are finding mitochondria play a bigger role than previously thought possible. No longer dismissing them as static power plants, researchers have found mitochondria are able to move from one cell to another, and communicate within and across cells. Mitochondrial signaling is involved in the body's response to inflammation and viruses. One analysis by Wallace's research group even found mitochondria have the ability to regulate the expression of a large proportion of the genes in the human genome.

In defiance of his early supervisor's assumption that mitochondria were medically irrelevant, Wallace predicts research will find mitochondria play an ever larger role in health, eventually leading doctors to put energy and anatomy on equal footing. Once considered irrelevant himself, Wallace now sees a vanguard of mitochondria researchers reshaping medicine.

"We're going to change the way medicine is organized," Wallace said. ▽

What might the testing and treatment for diseases look like in the future if doctors took a bioenergetics-focused approach instead of an organ-centric view? Read this story online with related links, including one that answers that question, at PennMedicine.org/magazine/mito

50 YEARS OF THE "HOW" IN HEALTH CARE

By Christina Hernandez Sherwood

Established in 1967 to address the complexities of Medicare and Medicaid, the Leonard Davis Institute of Health Economics has had a lasting impact on national policy and on the strength and nature of interdisciplinary health inquiry at Penn.

They came from Penn Medicine and beyond—oncologists, economists, health care policy analysts, medical ethicists, lawyers, regulators, insurance and pharmaceutical executives and patient advocates—for a first-of-its-kind meeting to tackle a question that touches them all: What is the economic sustainability of precision cancer medicine?

Patients with cancer face not only the disease itself, but also the difficult choice of treatments from among the array on the market. These include precision cancer medicine, which uses a patient's own characteristics to fight cancer in an individualized approach. "[It] holds promise not just to cure their cancer, but to do so with the appeal of exactness," said Justin Bekelman, MD, an associate professor of Radiation Oncology, and Medical Ethics and Health Policy, at the Perelman School of Medicine. "That is so highly alluring that they're almost too good to give up." Yet as it stands now, he said, precision cancer therapies are expensive. And despite some high-profile successes, such as the personalized immune cellular therapy developed at Penn and recently approved by the FDA (see p. 3), precision therapies as an approach haven't proved more effective on average than traditional treatments.

Bekelman and Steven Joffe, MD, MPH, chief of the Division of Medical Ethics, lead the Gant Family Precision Cancer Medicine Consortium, established last year to help cancer patients, their providers, and insurers make informed care decisions by providing greater transparency on the price and effectiveness of precision cancer medicine. "[We] felt very strongly that bringing together people of diverse backgrounds, diverse scholarship, diverse experiences would lend a 'special sauce' that would help us drive toward sustainable solutions to the problem," Bekelman said.

While the topic the consortium addresses is decidedly modern, a collaboration of this nature, with stakeholders from academia, industry, and government convening to talk about costs, is an occurrence with a long history. That it happened at Penn is no accident. This conversation can trace its origins back a half century.

THE BEGINNING

President Lyndon B. Johnson signs into law the bill that will establish Medicare and Medicaid.

It was the mid-1960s when the health insurance magnate Leonard Davis picked up the phone and dialed the Wharton school. Davis and his wife, Sophie, had founded the Philadelphia-based Colonial Penn Group in 1963 to sell health insurance to people over 65. When he reached Wharton's dean, Davis said he was prepared to make a six-figure gift to the school to establish an institute focused on health economics. And then, as the story goes, the dean replied, "What's that?"

It wasn't an unreasonable question. As the infrastructure of Medicare and Medicaid was being built from the ground up, Americans were only beginning to address the complex questions of what this new health care structure should look like, and how it would balance accessibility, affordability and quality. Then a fringe interest within insurance, the field of health economics had only begun to stand on its own.

Despite the initial confusion, in 1967 the Leonard Davis Institute of Health Economics (LDI) opened its doors. As a link between University of Pennsylvania schools, convening faculty from medical, business, nursing, law, and other schools without sitting under any one of them, LDI was perfectly poised to address the interdisciplinary questions of health economics by sharing the expertise of leaders in these diverse areas. "The fact that economics and health care are so critically intertwined, I don't think was as generally appreciated at that time as Leonard Davis recognized it to be," said David Asch, MD, MBA'89, GME'87, who was LDI's executive director from 1998 to 2012 and now runs the Penn Medicine Center for Health Care Innovation. "This was prescient and important. It makes LDI one of the first programs in the country to recognize that."

Over the decades, this interdisciplinary inquiry into emerging questions germinated seeds that have bloomed across Penn's campus. LDI was instrumental in the creation of many research groups, departments, and centers that now populate Penn's health economics universe, such as Wharton's Health Care Management Department in 1968, the Division of General Internal Medicine in 1978, the Center for Health Incentives and Behavioral Economics in 2008, and the Department of Medical Ethics and Health Policy at the Perelman School in 2011, and more. "These groups now sit as satellites and operate independently from LDI but were developed with the LDI DNA embedded into them and remain interconnected through LDI," said Dan Polsky, PhD, MPP, who has been the institute's executive director since 2012.

"My work has been done with people in every other one of the ten schools of the university, other than Medicine and the Wharton School, where my appointments are," said J. Sanford Schwartz, MD'74, LDI's executive director from 1989-98, during a 50-year alumni panel this spring. "I think LDI has played a fundamental role in intellectual and academic enrichment of the whole campus."

By the time the Gant consortium held its capstone in-person meeting this past May, ready to take on the economics of precision cancer medicine, the stage had been set. Both Bekelman and Joffe are LDI senior fellows and, though not directly under the institute's umbrella, the consortium also has LDI's DNA embedded. It adheres to the

Leonard and Sophie Davis

institute's philosophy of seeking solutions to the problems of health economics by collaborating across boundaries. Consortium members debated questions including: What drives the cost of precision cancer drugs? Are all precision cancer drugs a home run, or are some base hits, if that? How does the United States handle precision cancer medicine in comparison to other countries? And, is cancer special?

"The topic area seems to me a perfect fit for the kind of work that LDI's mission sets out to do," Joffe said. "Without something like LDI at Penn, we wouldn't have had the depth and breadth of talent here to be able to do this at the same level."

IMPORTANT QUESTIONS ON THE NATIONAL STAGE

President Richard Nixon signs into law the bill encouraging the creation of HMOs.

Early on, LDI's work stretched outside Penn as well—all the way to Washington. During his time as a special assistant to President Richard Nixon, Robert Eilers, MBA, PhD, the institute's founding director and a Wharton insurance professor, helped develop national health insurance policies and health maintenance organizations. Eilers' work provided much of the basis for 1973's Health Maintenance Organization Act, which encouraged the creation of HMOs.

About a decade later, LDI had garnered enough clout to attract leading health services researchers and policymakers from across the country to a 1981 meeting. Attendees formed the Association for Health Services Research, which is now known as AcademyHealth, the world's leading professional society devoted to health policy.

By 1984, Leonard Davis had sold Colonial Penn and made philanthropy his full-time endeavor. He'd moved on to other causes, but continued to support LDI with annual gifts, and remained interested in its work. Near his New York City foundation office, Davis met for yearly lunches with Mark Pauly, PhD, the Wharton health care management and business economics professor who was the institute's executive director from 1984 to 1989. "We would talk a lot about [whether] people have the right to health care," Pauly said. "[Davis] thought they did and was, in a way, trying to do his small part to improve that when he was selling health insurance to the elderly. He had some money to devote philanthropically, which he was willing to do, but he wasn't just going to just throw it away. He wanted to pay attention to results."

Back at LDI, the end of Pauly's tenure was highlighted by a grant to serve as a Medicare Research Center, which entailed taking on Medicare assignments. Pauly convened a group of thinkers to tackle one such task: brainstorming alternative methods of physician payment. The final product, a book about the pros and cons of issues including capitation and salary, was released in 1991, but the physician payment question remains timely today, as does Pauly's earlier work on the individual mandate. "You do the research mostly because you find it interesting and you think it addresses potentially important problems," he said. "You set out the answers, and you wait for the questions."

Illustration by ImageThink

Conversations at the Gant consortium's in-person meeting spanned clinician, patient, drug industry, insurance industry, regulatory, and other perspectives.

Photo by Hoag Levins

Justin Bekelman, MD, speaks to members of the Gant Family Precision Cancer Medicine Consortium, which he co-leads with Steven Joffe, MD, MPH.

For its part, the Gant consortium has settled on one particular answer that is crucial to modern economic questions about precision cancer medicine: Cancer is special—at least, the world treats it that way. The unanswered questions that surround this answer are more complex: Why is the health care system willing to pay higher prices for cancer drugs than comparable medications? Is it ethical to treat cancer as special? "The [cancer] diagnosis is treated differently than other diagnoses," Bekelman said. "That informs how we think about the potential solutions to address the high pricing of these drugs."

CANCER AND THE COSTS OF SPECIAL TREATMENT

Is cancer "special" in terms of the public view and the value placed on potential treatment and cures? In one of the group's conversations leading up to its first in-person meeting, the multidisciplinary Gant Family Precision Cancer Medicine Consortium discussed whether cancer is treated differently from other diseases. Then it turned to the question of whether it *should* be treated differently.

The first answer is clear. Cancer is special. The many ways include the fear it evokes, the language used to describe it, and the level of research funding devoted to it. Multiple surveys indicate that people fear cancer more than almost any other condition. That fear may underlie the language used to describe initiatives to treat or cure cancer, such as "conquering this dread disease" in Nixon's 1971 "War on Cancer "or the current cancer "Moonshot" aimed at winning that war. Cancer, as described by oncologist Siddhartha Mukherjee, remains "The Emperor of All Maladies."

Both government and industry fund cancer research at levels disproportionately higher than the population disease burden, at least by conventional measures. Cancer accounted for 16 percent of all NIH funding ($5.6 billion) in 2013, and 25 percent of all medicines in clinical trials, according to a report published in the *Journal of the American Medical Association* in 2015.

However, cancer research is not uniformly overfunded relative to disease burden, but instead varies by individual cancer. In terms of National Cancer Institute funding, overfunded cancers include breast cancer, prostate cancer, and leukemia; underfunded cancers include bladder, esophageal, liver, oral, pancreatic, stomach, and uterine cancer. One member of the Gant consortium noted that cancers that carry stigma or can be connected to personal behavior such as smoking, tend to be underfunded.

Cancer is also potentially special in cost of care. Industry has been rewarded for its considerable investment in cancer drugs by prices that are high in absolute terms, as well as by conventional measures of value. By one such measure, the market seems to be willing to pay more for cancer drugs than for other drugs—on average more than twice as much for cancer drugs than for non-cancer drugs in the past decade, according to a recent review.

"Consumers seem to value avoiding a year of life lost to cancer more than a year of life lost to other diseases," one consortium member said. "If they fear some causes of death more than others, so be it."

But *should* we treat cancer differently? The "so be it" attitude toward cancer's exceptionalism is far from a settled consensus. The question of whether cancer *should* be

Photo by Hoag Levins

treated differently is much harder to answer than whether it already is. It raises ethical questions of how to allocate care and funding if some diseases are thought of as more deserving than others.

One group member posited that high prices for cancer drugs are a natural consequence of the free market: The public willingness to pay more for cancer drugs creates a market that bears higher prices. And one challenge, at least in the U.S., is that the third-party payer system obscures the public's view of the true costs of these drugs.

What does this all mean for precision medicine? One consortium member said that the "specialness" of cancer—lying at a scientific frontier of genomics and being well-funded for research—makes it a paradigm of a precision medicine disease. The affected population is large enough to allow for targeting smaller subgroups but small enough to allow for focused attention on a limited number of pathways.

And the potential for breakthrough treatments or cures also lies behind the considerable resources devoted to cancer research, as one consortium member pointed out, because cancer often lies at the cutting edge of science.

Thus, in addressing the economic sustainability of precision cancer medicine, the consortium's work may use the exceptionalism of cancer to understand issues that will arise in precision medicine for other conditions. In this work, paradoxically, the exceptional opens the door to the generalizable and—maybe—opens a window onto the future of precision medicine itself.

– Janet Weiner, PhD, MPH

A version of this article was originally published on the LDI HealthPolicy$ense blog. The blog is one of the ways that the Leonard Davis Institute of Health Economics disseminates its scholarly work to a wide array of stakeholders, including politicians and their staff and industry leaders.

ORGANIZING ACADEMIA, REACHING BEYOND

President Bill Clinton delivers his proposal for universal health insurance.

When Asch took LDI's helm in 1998, one of his first projects was to examine the policy questions related to testing women for the BRCA gene mutations that had been found to increase the risk of breast cancer. While life insurers wanted access to patients' BRCA results, consumer advocates worried this would lead to discrimination. Using actuarial modeling, the team determined that shielding BRCA results from insurers would not create a so-called "death spiral" that could threaten the companies' financial solvency.

It was the ideal interdisciplinary problem for both Asch, an internist focused on how health-related decisions are made, and for LDI itself. "We had a principle we followed when I was the director, which was that LDI would do the kinds of things that were hard for individuals, but easier for groups," he said. "One of the things LDI has always done is organize the academic community."

The institute was also expanding its education efforts, which started in 1973 with Penn's selection as an early site of the Robert Wood Johnson Foundation Clinical Scholars program. In 1999, LDI established its Summer Undergraduate Minority Research program to give college students the opportunity to work with research faculty. The project was dreamed up by Pauly, then deputy dean for Wharton's doctoral programs, and LDI's Deputy Director Joanne Levy, to create the minority candidates that universities were fighting over.

It was one of the last major LDI projects the Davises lived to see. Sophie and Leonard Davis died, within four months of each other, in 2000 and 2001 respectively. At the time of their deaths, the couple granted one last gift to the institute, a donation that brought their total support of LDI to more than $4 million.

The 1990s also brought change in LDI's approach to engaging with policy. In the years following President Clinton's controversial proposal for universal coverage, the national health care debate veered from policy into politics, and it became increasingly difficult to turn research into change. To reach a broader spectrum of stakeholders, including politicians and their staffs, and take advantage of the burgeoning internet, LDI began to disseminate its work in non-traditional ways. While LDI faculty focused on research, the institute hired a communications guru to relay its message. "You want to be academic and scholarly and rigorous," Asch said, "but you also want to be relevant and readable and actionable."

Soon LDI was publishing digital issue briefs that were indexed on MEDLINE and accessible to reporters. The institute launched its own magazine and digital media channels. "We ended up with our own, really one of the first, media presence aimed at communicating scholarship," Asch said, "not in a dumbed down way, but in a way that was understandable for relevant stakeholders."

The approach endures. Over the last year, to keep stakeholders and the public in the loop, LDI's blog has featured updates on the major topics discussed remotely by the Gant consortium in the run-up to its first in-person meeting in May. In the coming months, the consortium expects to publish its recommendations for policies around precision cancer medicine. "There's so much discussion and debate

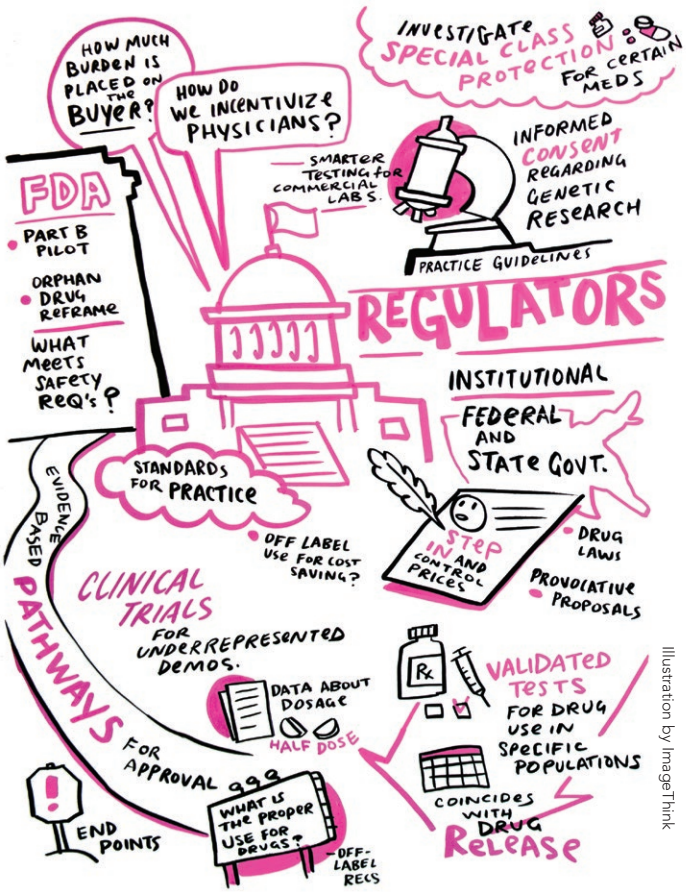


Illustration by ImageThink

about approaches to dealing with drug prices right now," Joffe said. "It gives us an opportunity with a really well thought-out set of ideas to put them in front of people who are looking for good ideas."

WORKING FOR EVIDENCE IN POLICY, VALUE IN CARE

President Barack Obama signs into law the Patient Protection and Affordable Care Act (ACA).

The passage of the ACA was perhaps the biggest health care policy moment since LDI's establishment. "That allowed us to spread our wings and realize we had an awful lot of knowledge we were sitting on," said Janet Weiner, PhD, MPH, LDI's associate director for health policy, who Asch hired in 1999 to communicate the institute's message. "It challenged us to get it out there in ways people could understand and, even further than that, to have an impact."

The institute published a four-part issue brief on various aspects of the ACA, including some of Pauly's decades-old work on the individual mandate. With Polsky as executive director, LDI's major drive was to inform the implementation of health insurance exchanges and individual insurance markets. "We've been very much connected to trying to understand the implementation of the Affordable Care Act," he said.

Alan Davis, who in 2001 took over his parents' foundation with his brother Michael, said LDI is moving in a direction he believes his father would have appreciated. "He was hopeful that through the research and public policy and public exposure a university can generate," Davis said, "[the institute] would move the health care agenda for the United States toward more accessible and affordable care."

When President Donald Trump assumed office this year with his party holding the majority in both chambers of Congress, the new politics and rapid pace of voting on health care legislation precipitated a drastic turn. On the train to Washington early on March 7, Polsky was feverishly reading the House Republicans' ACA replacement bill, which had been released the night before. Arriving at LDI's conference on health reform, which featured panels of market and coverage experts, Polsky was exhilarated, though not entirely comfortable. "We're positioned to present nonpartisan evidence and analysis rather than comment on the daily ups and downs of the political debate," he said.

Now, Polsky said, LDI has again shifted focus, advocating for the use of evidence and knowledge to inform evidence-based policy. "It wasn't something we had to advocate for [previously]," he said.

Today's political tumult makes LDI's work even more relevant, Weiner said. "In some ways, we are heading back to our roots of bringing people together," she said, with "more personal and deep contacts with policymakers who, at this point, are desperate to find non-partisan information they can rely on."

The work of the institute's 250 fellows, who are leading sessions at LDI's 50th anniversary symposium in October, reflects the larger shift of the public health care debate from policy to politics. While LDI's early work was on health care reform issues, such as insurance and finance, Polsky said the current political climate "has pushed more people into areas of health care where they can see impact on their work," he said. "Health care reform has become so politicized that we've seen more of our experts focus their efforts around trying to transform our health care delivery system toward value."

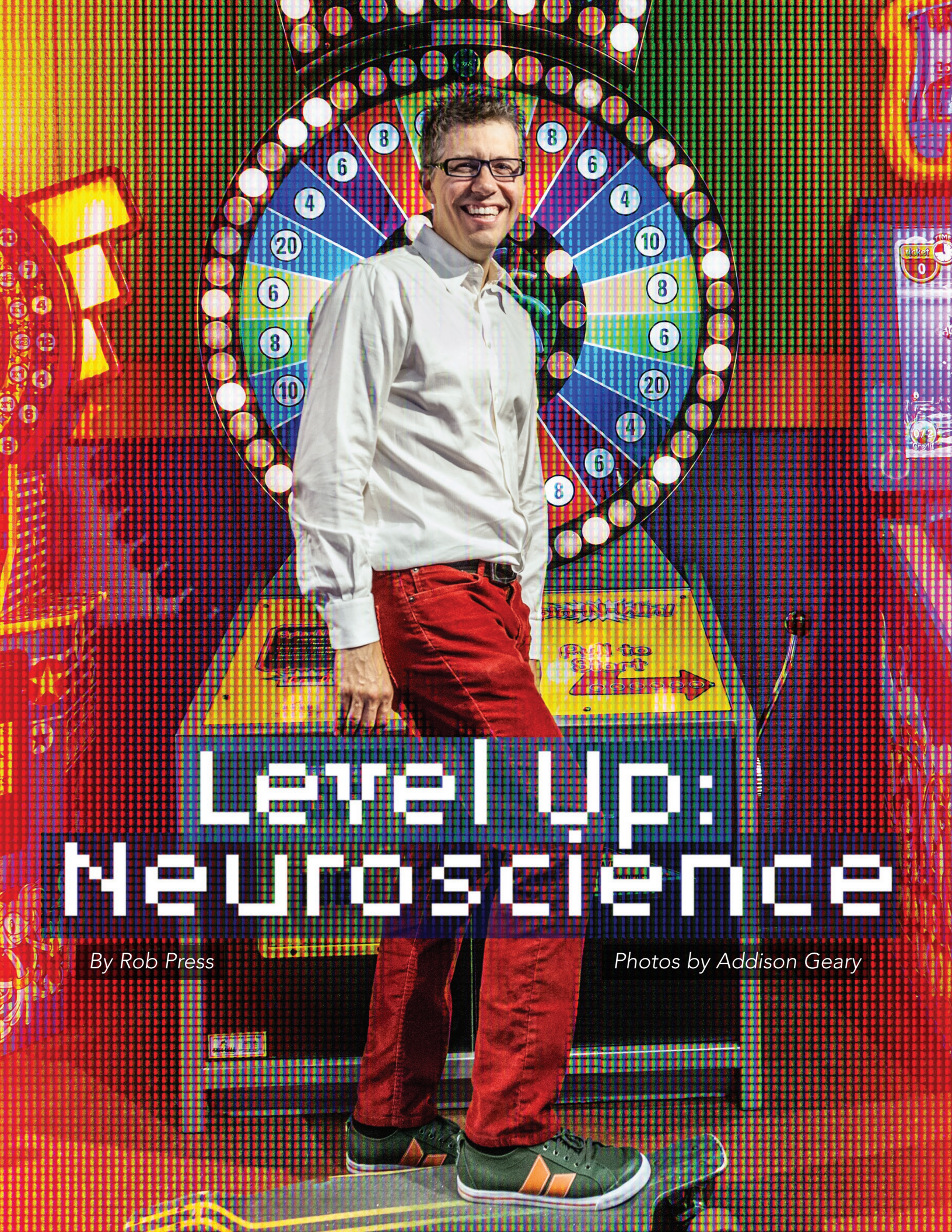
Photo by Hoag Levins

Dan Polsky, PhD, MPP

That emphasis is also evident in the aftermath of the Gant consortium's inaugural meeting. In addition to publishing recommendations, some participants might launch pilot projects to implement the ideas that came up through its discussions. The consortium's goal, like that of LDI, is to both propose solutions and help them find a place in the real world.

As for the institute's future, Polsky sees the potential for LDI to develop innovative solutions to emerging challenges. For example, senior fellows are now working together to tackle a variety of aspects of the opioid crisis and engage policy makers and stakeholders at the local, state, and national level. "LDI in the next 50 years should be known for its contribution to improved health and health care," he said. "The energy our experts are devoting to the opioid crisis offers hope that the epidemic will soon abate; our cross-disciplinary approach allows for new ways of solving difficult problems." ▽

Read this article online with related links, including links to ongoing coverage of the LDI 50th anniversary symposium held in October 2017, at PennMedicine.org/magazine/LDI50



Level Up: Neuroscience

By Rob Press

Photos by Addison Geary

Konrad Kording's ability to bridge gaps between seemingly disparate fields—utilizing data science to take new approaches to everything from brain science to prosthetics and robotics—makes him a smart pick as one of Penn's newest interdisciplinary PIK professors.

When Konrad Kording, PhD, rolled up to our interview on his skateboard, his fashionable glasses and red jeans were among the most obvious indicators that this was not your stereotypical Ivy League professor. Within a few minutes, he bounced a slew of ideas off of our photographer and challenged me to a pre-interview game of Guitar Hero. It set the tone quickly: His is a brain forever in need of stimulation, whether it comes in the form of an arcade game or, more commonly, through assessing data and drawing connections.

It's the latter that brought him to the University of Pennsylvania, where his ability to bridge gaps between seemingly disparate fields—utilizing data science to take new approaches to everything from brain science to robotics—will fit right in. Kording was hired earlier this year as a Penn Integrates Knowledge (PIK) University Professor with joint appointments in the Perelman School of Medicine's department of Neuroscience and the School of Engineering and Applied Science's department of Bioengineering.

For Kording, there's always another view to a given problem—and frequently, it involves stepping even further back to assess things in greater totality.

"The problem is: When we study complex systems like the brain or society, we don't know if what we conclude is really true," he said. "The problem is that if nobody ever tells us we are wrong about our theories, we may never fix that."

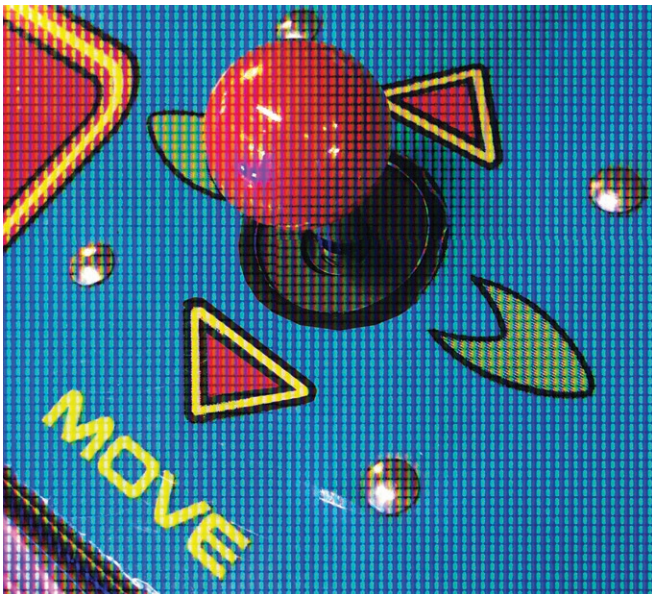
Recently, Kording decided to test whether we might be wrong about neuroscience and the human brain. How he went about it—and the things he ascertained about the very bedrock of neuroscientific study—made waves throughout the field.

That brings us to the venue of our interview: University Family Fun Center, a traditional video arcade just off of the University of Pennsylvania campus. Small and packed to bursting with games of all different types and eras, the arcade worked as a nexus for the myriad places Kording's neuroscientific questions can take us.

Take, for example, its out-of-order Ms. Pac-Man machine.

Wrong Like Donkey Kong

When Ms. Pac-Man was released in 1982, it was state-of-the-art. It ran on a Zilog Z80 microprocessor, which enjoyed (and in some circles, still enjoys) a heated rivalry with the MOS Technology 6502 microprocessor. In their heydays four decades ago, both were considered revolutionary. Compared to modern microprocessors, of course, they're



archaic—but for Kording and fellow study author Eric Jonas, that was part of the appeal. They were just complex enough to run something like Donkey Kong.

"The cool thing about Donkey Kong is we understand how it works," Kording said. "We understand how a microprocessor works."

So Kording and his team took an approach they'd typically use to study the human brain, with its 100 billion or so neurons, and applied it to the MOS Technology 6502 microprocessor, with its 3,510 transistors. The relative simplicity of the microprocessor allowed researchers to understand and manipulate the relationships between each of its many components, giving them absolute control over the entire system.

The idea is simple: If neuroscientists use these methods to investigate something as complex as the brain with the expectation that the results are useful and revelatory with regard to

the brain's function, it stands to reason that using these methods to investigate something comparatively simple that we already understand should yield results that are useful and revelatory with regard to the microprocessor's function.

But that's not at all how it played out.

They had hoped to apply the neuroscientific study of functional connectivity to the microprocessor. Functional connectivity is the process by which neuroscientists try and figure out which parts of the brain interact with which other parts of the brain at a given time or during a given behavior.

In the microprocessor, by controlling individual transistors and seeing how the other transistors react, they hoped to reveal the interconnected ways in which the transistors operate. What Kording and Jonas found, however, turned out to be "not very meaningful."

When they published their paper last year, it turned a lot of heads in the field of neuroscience. If scientists are using methods that don't fully work for the analysis of simple, linear systems, as their work suggested, then how meaningful can their inferences be when applying those methods to something as complex as the human brain?

"I think we have to have methods that are good enough to at least work on a pretty simple microprocessor," Kording said. "We're not asking questions about the brain. We're asking questions about the field."

The Ultimate Gap

In the next room over from the Ms. Pac-Man machine, among skeeball and other more conventional "games of skill," Kording lobbed basketball after basketball toward a hoop as the bright red countdown clock ticked closer to zero. He would be the first to tell you he isn't a very good shot, but what interests Kording is why more of us aren't worse.

Specifically, from his original field of movement science, Kording is interested in how the brain deals with uncertainty—the fact that you can't actually account for the exact position of your body during any given movement.

"You might believe there's never any uncertainty," he said. "You know where your hands are, no? But it turns out you don't. If you're looking at me, you aren't looking at your hands. If I give you a task with your hand—say to touch your knee or something—you will be a little wrong. Whenever we move, we have this level of uncertainty."

Consider this: Even the greatest basketball players in the world can't hit free throws with 100 percent accuracy. These are 15-foot shots taken at a complete standstill, with nobody trying to defend. It's not entirely unlike the hoop game in the arcade—yet even the very best only sink around nine out of ten shots. Given all the time in the world, even the most skilled professionals on the planet can't do it flawlessly every single time. That's uncertainty, in a nutshell. You can train to minimize it, but you can't eliminate it completely because it's inherent to our nervous and musculoskeletal systems.

You just don't notice it, because your brain masks it so well. That's where Kording comes in.

"A lot of my previous research has asked how the brain can be so good at this," he said. "Your brain's so good at it that you never even know it's a problem."

It's just one example of the complexity inherent to studying the brain: Unlike in Donkey Kong, where it's easy enough to discern hardware (the microprocessor itself) and software (the program the microprocessor is coded to run), figuring out where the hardware ends and the software begins in the brain is enormously complicated. Some parts of the field of neuroscience, according to Kording, say the

brain is built as a statistical machine. Others say it's just particularly great at learning. Piecing together where he and his lab actually fall on that continuum is one of the aims of their research.

It's what Kording referred to as "the ultimate gap" for his team to bridge. Neuroscience as a field has a reasonable understanding of how people are inclined to behave in given situations, and it has a reasonable understanding of the hardware—the nuts and bolts of the brain itself—but how that hardware actually gives rise to those behaviors is the question he's excited to take on through the use of data science.

Prosthetics with Precision

For Kording, understanding these intricate workings of the human brain is more than just an intellectual exercise. Piecing these things together could have a real and tremendous impact on the lives of disabled patients everywhere.

Let's go back to the arcade for a second: specifically, to the Guitar Hero machine where Kording and I performed admirably on Pat Benatar's "Hit Me with Your Best Shot." Guitar Hero is a game that requires a certain level of dexterity. Your fingers have to be in the right place at the right time, hundreds of times, over the course of a given song, as you compete to play it better than your opponent.

The human brain, of course, can learn how to build the connections and develop the speed necessary to play Guitar Hero almost flawlessly. Similarly, it would be almost trivial to build a robotic hand that, when programmed to do so, could play Guitar Hero with no mistakes whatsoever. It's drawing a direct connection between the two—creating a quick, precise, dexterous robotic prosthetic that responds perfectly to the human brain—that could change life forever for disabled individuals.

"There's a problem we've worked on a lot called decoding," Kording said. "You take the signals from the brain, and if you can figure out what the subject wants to do—if you can solve that problem—you can build prosthetic devices that you can steer with your thoughts."

If that sounds like science fiction to you, Kording doesn't necessarily disagree: He compared such a device to the one Luke Skywalker receives after losing his hand in "The Empire Strikes Back." It works seamlessly, imperceptibly, like a real human hand. But while science fiction typically shows us technology we could only dream of, Kording believes we're close to something like Skywalker's hand being a reality. Making sense of data recorded straight out of the brain and figuring out how they relate to behavior or intent opens the door to far more responsive prosthetics, robotics, and exoskeletons.

"At some level, we have these prosthetic devices," Kording said, pointing out examples like the BrainGate trials and a University of Pittsburgh experiment in which a monkey used a brain-controlled prosthetic device to feed itself. "They're just really slow and inefficient and imprecise."

The trick will be to perfect these devices. Rapid improvements in data collection should accelerate that process.

"My lab has discovered what we call Stevenson's Law, which is that the number of simultaneously recorded neurons doubles every seven years," Kording said, adding that our ability to collect such data is only accelerating.

Being able to use more electrodes to measure more neurons, predictably, means controlling quicker and more precise movement. According to Kording, one hundred times more electrodes could translate into movement that's ten times faster—or, at the very least, translate into movement along many axes, giving prosthetics new degrees of freedom.

Leveling Up

Kording's hopes for data science research at Penn venture well beyond just what we can learn about the brain: He wants to take a crack at accelerating the entire field of medicine.

"Medicine is a very high-dimensional optimization problem," he said. "Say I care about living healthily to an old age: At which point should I take which drugs? How should I change it as various diseases develop over time? This is a very complicated problem with lots of facets, and the world can only afford a relatively small number of randomized clinical trials every year. If we can develop ways of making progress at what helps and what doesn't help, without requiring randomized clinical trials, we can dramatically accelerate medicine."

When he talks about using data science to guide such seismic shifts in established fields, Kording doesn't appear to see these goals as lofty or infeasible so much as codes he has yet to crack—levels he has yet to beat.

Game on.

Listen to an audio interview excerpt and read this article online with related links at PennMedicine.org/magazine/kording

FDA APPROVED! How Philanthropy Made It Possible

The atrium of the Perelman Center was full of smiles and celebration as the Food and Drug Administration granted approval to Novartis of Kymriah™, Penn Medicine's chimeric antigen receptor (CAR) T cell therapy—the first of its kind— for pediatric and young adult leukemia. Developed by Penn's Carl June, MD, and his team, along with physicians from Children's Hospital of Philadelphia, philanthropy played an invaluable role in helping to launch this breakthrough work. June and members of his lab were recruited here through resources from the initial gift from Madlyn and Leonard Abramson establishing the Abramson Family Cancer Research Institute. As June's research progressed, Barbara and the late Edward Netter provided further essential funding through the Alliance for Cancer Gene Therapy to advance the immunotherapy clinical trials.

You're invited to become part of this historic journey to end cancer. To learn more, please contact Tricia Bruning at 215-898-0578 or tbruning@upenn.edu.

We are grateful for Penn Medicine's visionary donors who have supported endowed professorships.

With this funding, our scientists can continue the type of high-risk, high-reward research that leads to life-changing discoveries—and nowhere is this more evident than in our history-making work in developing CAR T therapy.

While many of these endowed chairs honor donors or memorialize family members, all of them promote the free flow of ideas that lead to breakthroughs and, ultimately, better health. Here, we share four of our endowed chair-holders and their benefactors who, together, are making a tremendous impact in the soaring field of immunotherapy.

Richard W. Vague Professor of Immunotherapy

From left: Donor Richard Vague with chairholder Carl H. June, MD

Barbara and Edward Netter Professor of Cancer Gene Therapy

From left: Donor Barbara Netter with chairholder Bruce L. Levine, PhD

Jodi Fisher Horowitz Professor in Leukemia Care Excellence

From left: Chair donors the late Jerome Fisher with his wife, Anne; chairholder David L. Porter, MD; grateful patient Doug Olson; and donors Lydia and George Weiss

Richard and Barbara Schiffrin President's Distinguished Professor

From left: Chairholder E. John Wherry, PhD, with donors Richard and Barbara Schiffrin

Ray Perelman: An Outstanding Penn Citizen Turns 100

August 22 marked the 100th birthday of noted Penn citizen and Center City resident Raymond G. Perelman, one of Philadelphia's most prominent businessmen and active philanthropists.

The son of Lithuanian immigrants, Perelman was born in Philadelphia in 1917. After attending Wharton and serving in the U.S. Air Force during World War II, he began his career at his family's American Paper Products Company, and later became a billionaire through savvy investments in steel manufacturing and other areas. A number of his children and grandchildren have attended Penn, including his son, Ronald, an active University philanthropist.

In 2011, Ray Perelman and his late wife, Ruth, made a $225 million naming gift for the **Raymond and Ruth Perelman School of Medicine**, which stands as the University's largest gift ever. Additional philanthropy includes $25 million to help build the Perelman Center for Advanced Medicine, Penn's state-of-the-art outpatient facility. The couple endowed a professorship—the first to support a full-time clinician in internal medicine. For his extraordinary works at Penn, Ray, a Penn Medicine trustee from 2002-2012, has received many accolades, including Penn's Medal for Distinguished Achievement. The University also granted him an honorary Doctor of Laws in 2014.

Ray Perelman has championed organizations throughout Philadelphia, including the National Museum of American Jewish History, the Philadelphia Museum of Art, Perelman Day School, and the Kimmel Center for the Performing Arts.

And so we honor Ray's contributions, salute his longevity, and thank him for his continued devotion to Penn Medicine.

Penn Medicine Builds Toward a Healthier City

With a birds-eye view of the construction site and the Philadelphia skyline beyond, the city and region's future was in sight at the Hospital of the University of Pennsylvania's groundbreaking. Philadelphia Mayor James Kenney congratulated Penn leadership on the $1.5-billion inpatient tower, the Pavilion, and called the May celebration a "banner" day for the city.

"The University and its health system are a critical part of the city's DNA, our identity, and our workforce," said Mayor Kenney, shining a spotlight on the Pavilion's importance to not just Penn Medicine's patients, but to the health of the entire region.

Naming opportunities for the Pavilion are available. To learn more, please contact Kim Grube at (215) 898-0578.

Send your progress notes and photos to:
Donor Relations
Penn Medicine Development and Alumni Relations
3535 Market Street, Suite 750
Philadelphia, PA 19104-3309
medalum@dev.upenn.edu

1970s

Ronald B. May, MD'73, has been appointed chair of the North Carolina State Commission for Public Health by Governor Roy Cooper. He is vice president of medical affairs for CarolinaEast Health System.

Jerald Winakur, MD'73, is author of a new book of poems, *Human Voices Wake Us*, published in the Literature and Medicine series by Kent State University Press. The book is a treatise on the importance of self-reflection and connection f or physicians and patients at risk of dissatisfaction and burnout.

Eric Mitchell, MD'74, GME'79, has joined the medical board and been appointed medical director of AGRiMED Industries, a national medical cannabis organization dedicated to enriching the lives of patients. He is a practicing orthopaedic surgeon and sports medicine physician, and a retired colonel in the U.S. Army.

Jack A. Elias, BA'72, MD'76, was named the inaugural Senior Vice President for Health Affairs at Brown University. Elias takes on this role in addition to his positions as dean of Medicine and

Biological Sciences and professor of Biology and Medicine. Elias will now oversee the newly constituted Brown Institute for Translational Sciences and Brown Biomedical Innovations Inc., which fosters entrepreneurial biomedical activities, and he will provide leadership in clinical, research and teaching activities involving Brown's clinical faculty and affiliated hospital system partners.

Mark E. Lowe, MD, PhD'77 has been named vice chair of clinical affairs and strategic planning of the department of Pediatrics and a professor Pediatrics at Washington University School of Medicine in St. Louis. He comes from the University of Pittsburgh School of Medicine, where he was a vice chair, an interim chair and a professor of Pediatrics.

1980s

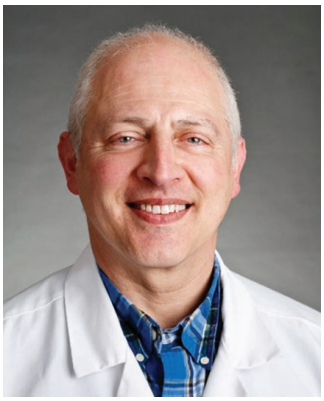
Michael S. Nussbaum, MD'81, has been appointed chair of Surgery at the Virginia Tech Carilion School of Medicine. He was an endowed professor and chief of the division of General Surgery at the University of Florida College of Medicine-Jacksonville. He will also serve as chair of Surgery for Carilion Clinic.

Nicholas A. Dinubile, MD, GME'82, has joined the National Tennis Health & Wellness Task Force. In addition to his private practice with Premier Orthopaedics, he has been a longtime member of the teaching faculty at the Perelman School of Medicine, and is chairman of Orthopaedic Surgery at Delaware County Memorial Hospital.

Scott Boden, BA'82, MD'86, was appointed chief medical advisor of Juvent. He is a tenured professor of Orthopaedic Surgery at the Emory University School of Medicine and serves as the director of the Emory Orthopaedics & Spine Center.

Gary Koretzky, MD'84, PhD'84, has been appointed vice dean, focused on academic integration at Cornell University and Weill Cornell Medicine. He was recruited to Weill Cornell Medicine in 2013 as dean of the Weill Cornell Graduate School of Medical Sciences and vice dean of Research.

Jack A. Pasquale, MD, GME'85, was awarded the 2017 ASPEN Distinguished Nutrition Support Physician Service Award by the American Society for Parenteral and Enteral Nutrition. Pasquale



has been a practicing physician for over 30 years and has lectured extensively on nutrition, nationally and internationally.

James A. Underberg, MD'86, was elected president of the National Lipid Association. He is a clinical assistant professor of Medicine at the New York University School of Medicine in the divisions of General Internal Medicine & Endocrinology. He is also the director of the Bellevue Hospital Lipid Clinic and a member of the Center of Prevention of Cardiovascular Disease at NYU.

Joel Fuhrman, MD'88, has written a new book, *Fast Food Genocide* (HarperOne), published in October 2017. The book addresses how poor nutrition has had a deleterious effect on populations. Fuhrman has a nutritional medicine practice in Hunterdon County, N.J., and is president of the Nutritional Research Foundation.

John Duncan McCallum, III, MD'89, has joined the new Connecticut Orthopaedic Institute at MidState Medical Center.

1990s

James M. Musser, MD, PhD, GME'91, was named president-elect of the Federation of American Societies for Experimental Biology for 2017-2018. He will serve as the federation's president for 2018-2019 and for three years as a member of its executive committee. Musser is chair of the department of Pathology and Genomic Medicine at Houston Methodist Hospital.

Natalie Sacks, MD'96, GME'02, has been appointed to the board of directors of Zymeworks, a clinical-stage biopharmaceutical company dedicated to the discovery, development, and commercialization of next-generation multifunctional biotherapeutics. She has served as the chief medical officer of Aduro Biotech since September 2016. She is also an assistant clinical professor of Medicine in the division of Hematology/Oncology at the University of California, San Francisco.

Derrell Dejuan Porter, MD'97, MBA'98, has been appointed senior vice president and global commercial jead at Atara Bio-

therapeutics. Prior to joining Atara, he was a vice president with Gilead Sciences. Porter currently serves on the board of directors for Biosortia Pharmaceuticals.

Anil Vachani, MD, GME'99, PhD'11, has been appointed to the medical advisory committee of OncoCyte Corporation, a developer of novel, non-invasive blood-based tests to aid in the early detection of cancer. He is a

pulmonologist and director of the Lung Nodule Program. He also serves as an assistant professor of Medicine at the Hospital of the University of Pennsylvania and the Veteran's Administration Medical Center.

2000s

Gregory L. Beatty, PhD'00, MD'04, GME'10, has been appointed to the Pancreatic Cancer Action Network Scientific and Medical Advisory Board for a three-year term. He is an assistant professor of Medicine at the Perelman School of Medicine.

David Brooks, MD, PhD, GME'00, has been appointed senior vice president of clinical development for Eleven Biotherapeutics, Inc., a late-stage clinical oncology company advancing a broad pipeline of novel product candidates based on its Targeted Protein Therapeutics platform. He joined Eleven Biotherapeutics from Deciphera Pharmaceuticals, where he served as vice president of clinical research and translational medicine.

C. Charles Fikry, MD'04, MBA'04, has been appointed executive vice president of Pharmaceutical Product Development Laboratories. He joined PPD from Quest Diagnostics, where he served most recently as vice president and general manager for oncology and companion diagnostics.

Alexander Kutikov, MD, GME'08, has been appointed the new chief of the division of Urologic Oncology at Fox Chase Cancer Center. He joined the department of Surgical Oncology at Fox Chase in 2010 after completing a Society of Urologic Oncology fellowship at the center.

OBITUARIES

1940s

Alan Fulton Scott, MD'43, a family physician; Aug. 10. He completed his undergraduate degree at Wake Forest College and completed his medical degree at the University of Pennsylvania. His residency was at Fitzgerald Mercy Hospital in Upper Darby, Pa. In January of 1943, he was inducted into the U.S. Army as a First Lieutenant and entered the 292nd Field Artillery Observation Battalion. He became captain in the United States Army Medical Corps and served in Europe until the end of the war. He had a family practice in Salisbury, N.C.

James Francis Hammill, MD'48, a neurologist; June 21. Hammill attended medical school with GI funding after service in the enlisted Army Reserve, then rejoined the Army after medical school to serve in the Medical Corps. His military service included service in the Korean War, working as chief of Neurology at the Walter Reed Army Medical Center, and a stint in the office of the surgeon general. He retired from the Army in 1957 with the rank of lieutenant colonel, and joined the medical faculty of Columbia University that year. He was honored by Columbia for his compassionate and humane care of patients and for being a role model for medical students and colleagues. He retired from Columbia in 1992 as professor emeritus.

William J. Williams, MD'49 GME'53, a retired dean and professor at SUNY Upstate Medical University; Nov. 4. During World War II and the Korean War, he served in the U.S. Navy. He worked at SUNY Upstate Medical University for 33 years. As dean of the College of Medicine (1991-1992 and 2002-2004), he oversaw a college with more than 600 students and 480 faculty.

1950s

John T. Carpenter, Jr., BA'48, MD'52, an obstetrician and gynecologist; May 5. After graduating from medical school at Penn and completing an internship at Pennsylvania Hospital, Carpenter served as an Army medical officer in Germany for two years. Back in the Philadelphia area, he became known as an innovator in childbirth management and was one of the first area physicians to permit fathers in the delivery room. He established natural delivery birthing rooms and allowed mother-baby bonding in the hospital and early discharge from the medical center before these became standard practice. For 30 years ending in the mid-1990s, Carpenter was a member of Penn's medical faculty. From 1958 until his retirement in 1997, he maintained a solo ob-gyn practice in Bryn Mawr, Pa.

Herbert L. Needleman, MD'52, GME'56, a pediatrician and psychiatrist; July 18. Born in

Schein Family Shines

Photo by Daniel Burke

Yvette Schein, one of the 159 new medical students at the Perelman School of Medicine this fall, had a distinguished guest sitting in the front row when she received her first white coat. Her grandfather, 102-year-old Joseph Schein, MD'41, is Penn's oldest living medical alumnus.

"I wish my late wife, Yvette's grandmother, could also be here to see this today," Joseph Schein said.

When Schein first met Selma Snyderman, BA'37, MD'40, he was a first-year medical student, and the pair had immediate chemistry—literally, as they were introduced for tutoring in the subject. Schein, a humanities graduate from Princeton, was struggling, so one of his medical classmates, a Penn alumnus, suggested Snyderman. The classmate had seen Snyderman overtake him as an undergraduate because she was such a chemistry whiz that she began medical school after three years. Snyderman helped Schein catch up in science. "Then we found chemistry of a different kind, and ended up getting married my third year," he said.

Snyderman went on to have a distinguished career as a pediatrician and scientist, for more than 50 years on the faculty at NYU. She was a pioneer in the treatment of inborn errors of metabolism such as PKU and the previously fatal disorder, maple syrup urine disease. She was the recipient of Penn Medicine's Distinguished Graduate Award in 2004. Her two sons with Joseph Schein (whose own distinguished career was in pathology and psychiatry) are also physicians. Snyderman passed away in 2012. Now, Yvette continues in the family tradition.

"My grandmother was a trailblazer for women in medicine," Yvette said. "She was one of only four women in her class in medical school, and I am so proud to follow in her footsteps."

Philadelphia, he completed his undergraduate degree at Muhlenberg College. He served in the Army and the Army Reserve, attaining the rank of captain. He was internationally renowned for his pioneering work demonstrating the negative effects of low level lead exposure on childhood development and behavior. His landmark 1972 paper in the *New England Journal of Medicine* showed that low-income, mostly black children in Philadelphia had lead levels five times higher than suburban, mostly white children. In 1979, he demonstrated that even low levels of lead exposure had a measurable impact on cognitive development. Needleman was founding chairman of the Committee of Responsibility (COR) to Save War-Burned and War-Injured Vietnamese Children from 1966 until the Vietnam War's end in 1975. During that time, COR brought about 200 Vietnamese children to the U.S. for treatment of war injuries and helped 300 more get treatment in Vietnam. Needleman received numerous awards, including the Heinz Award in the Environment.

Albert I. Winegrad, BA'49, MD'52, emeritus professor of Medicine; July 20. Winegrad was the Ware Professor of Medicine and director of the Cox Institute of Diabetes Research at Penn. He was a past vice president of the American Diabetes Association and winner of the 1986 Banting Medal for his pioneering work in diabetic neuropathy. He joined Penn in 1957 as an associate instructor of Endocrinology. In 1960, he became assistant professor and in 1966, he became associate professor. He was named professor of Medicine in the Cox Institute in 1970. In 1992, he retired and became emeritus professor of Medicine.

Julio Noguera, MD, GME'54, an otorhinolaryngologist; March 30. After graduation from the University of Maryland Medical School, Noguera trained in otolaryngology at the University of Pennsylvania. He completed his residency in otolaryngology/head and neck surgery at Temple University Hospital. From 1955 to 1957, he served as a captain in the Army Medical Corps. Upon discharge, he established a practice in Asbury Park, N.J. From 1960 to 1985, he was director of the section of Otolaryngology in the surgical department of what is now Jersey Shore University Medical Center. He started the center's practice of head and neck surgery. Noguera retired in 1990.

Liebe S. Diamond, MD'55, GME'60, a pediatric orthopaedic surgeon; May 17. Born in Baltimore, with a rare condition called constricted ring syndrome which resulted in the loss of several fingers and toes in utero, she underwent more than two dozen surgical procedures on her hands and feet by age 13. She began her undergraduate studies at Smith

College at age 16 and went on to complete her medical degree at the University of Pennsylvania. She completed a pediatrics internship and surgical residency at Sinai Hospital in Baltimore. After working briefly as a pediatrician, she returned to Penn and in 1955 obtained a degree in Orthopaedics, then was the first female resident and chief resident at the Hospital of the University of Pennsylvania in 1957, in Orthopaedic Surgery. She established a solo practice in the early 1960s, specializing in the care and treatment of children with hand and limb deformities, and was professor of orthopaedic surgery at the University of Maryland Medical School from 1961 to 1996.

David Kuhl, MD'55, GME'58, a nuclear medicine pioneer; May 28. Kuhl was an internationally known pioneer in positron emission tomography. He earned a bachelor's degree from Temple University and then a medical degree from the University of Pennsylvania, where he also completed his residency. He joined Penn's faculty in 1958 as assistant instructor and resident of Medical Radiology. He became a professor of Radiology in 1970. He later worked at UCLA (1976-86) and as division chief at the University of Michigan (1986-2011). Radioactive tracer and tomography techniques he developed enabled the creation of drugs targeted to the earliest stages of degenerative brain disease. Kuhl was a founding member of the Society of Nuclear Medicine.

Samuel H. Tucker, MD'56, GME'60, a pediatric neurologist; April 7. Raised in Chestnut Hill, he was a graduate of Phillips Exeter Academy in New Hampshire and Princeton University. He served in the U.S. Naval Reserves, retiring with the rank of captain. He retired in 2000 after 38 years as a pediatric neurologist at the Children's Hospital of Philadelphia.

Emily Meginnity Seydel, MD'57, a pediatrician; Aug. 12. A trailblazing woman, she completed her undergraduate degree at Bryn Mawr College and her medical degree at the University of Pennsylvania. She was a pediatrician who worked in schools and treatment facilities for troubled children, and later was a partner in her own practice.

Mary Catherine (Susy) Glick, PhD'58, professor emerita of pediatric research at the University of Pennsylvania; March 6. After earning her PhD in microbiology, Glick was initially hired at Penn as a Woodward Fellow at the William Pepper Laboratory of Clinical Medicine. She became professor of therapeutic research in 1965. Glick pioneered the field of terminal glycosylation of membrane glycoconjugates and their role in disease, specifically neuroblastoma and cystic fibrosis. In 1996, she retired and became professor emerita of pediatric research.

Richardson B. Glidden, MD'59, GME'63, an obstetrician and gynecologist; July 21. He graduated from Franklin and Marshall College. He served in the United States Army National Guard and United States Army in Germany during the Korean War. After earning his medical degree from the University of Pennsylvania, he practiced obstetrics and gynecology in Dover, Del. for twenty years.

H. Ralph Schumacher, Jr., MD'59, rheumatology pioneer; July 30. A fundamental force in the field of rheumatology internationally, Schumacher was a professor emeritus and former acting chief of Rheumatology at the University of Pennsylvania School of Medicine and section chief of Rheumatology at the Philadelphia VA Medical Center. Born in Montreal in 1932, Schumacher served for two years after his medical training as a staff physician and only rheumatologist in the U.S. Air Force. He joined the Penn faculty in 1967

and steadily rose to rank of full professor in 1979. A quintessential physician-scientist, he explored with state-of-the art laboratory techniques many questions that emerged from his astute clinical observations. His work led to many major advances in both the understanding of the pathophysiology of inflammatory arthritis and the treatment of these complex disorders. A memorial service at Penn is planned.

2000s

Amy J. Reed, MD'05, PhD'02, GME'11, an anesthesiologist and patient-safety advocate; May 24. She completed her undergraduate

degree at Pennsylvania State University. She worked as an anesthesiologist in Boston. In 2013, upon being diagnosed with uterine fibroids, she underwent a hysterectomy performed with an electric morcellator. In a post-surgery biopsy, it was shown that an undiagnosed malignancy, leiomyo-

sarcoma, had been spread and aggravated by the device. She and her husband, Hooman Noorchashm, BA'92, PhD'01, MD'02, GME'11, became patient-safety advocates devoted to exposing the risks and banning the morcellator, successfully convincing the FDA to study the device and warn against its usage in almost all cases. "It is a statistical certainty that the public health battle she won for women will save the hundreds, if not thousands, of families from the oncological catastrophe to which she fell," Noorchashm said.

Jessica Panzer, MD'06, PhD'06, a pediatric neurologist and scientist; May 13. Panzer was attending physician and assistant professor of Neurology and Pediatrics at Children's Hospital of Philadelphia and the Perelman School of Medicine. She received her undergraduate degree from Cornell University in Ithaca, N.Y. In the MD/PhD program at Penn, she received a predoctoral medical student fellowship from the Howard Hughes Medical Institute. She earned a PhD in Neuroscience working in the laboratory of Rita Balice-Gordon, PhD. Panzer was a pioneer in developing *in vivo* imaging of neuromuscular synapotogenesis in zebrafish. She was one of the few pediatric movement disorders subspecialists in the country, as well as one of the few pediatric physician scientists with expertise in autoimmune etiologies of the CNS in children. Her primary research focus related to NMDA receptor encephalitis.

FACULTY

Arthur Auerbach, BA'47, MD, faculty member in Psychiatry; Feb. 13. Auerbach served as a lieutenant in the U.S. Navy and joined the Penn faculty as an instructor of Psychiatry in 1961. He was president of the Society for Psychotherapy Research from 1983-1984.

John T. Carpenter, Jr., MD. See Class of 1952.

Mary Catherine (Susy) Glick, PhD. See Class of 1958.

Jessica Panzer, MD, PhD. See Class of 2006.

H. Ralph Schumacher, Jr., MD. See class of 1959.

Bayard T. Storey, PhD, emeritus professor of Obstetrics and Gynecology; June 4. Storey was a renowned researcher whose work provided a foundation for the analysis of specific forms of male infertility, the development of techniques for the evaluation of sperm function and the generation of new approaches to conception. He also was an expert on sperm glycolysis and mitochondrial function. Storey earned his bachelor's degree from Harvard in 1952, his master's degree from MIT in 1955 and his PhD from Harvard in 1958. He worked at Rohm and Haas before joining Penn in 1965, where he held faculty roles in the departments of Biophysics and Biochemistry, Obstetrics and Gynecology, Physiology and Physical Biochemistry.

Albert I. Winegrad, MD. See class of 1952.

Paying it Forward: The Perfect Gift for Future Generations of Medical Students

In preparing for her 2017 retirement, Lorraine M. Giordano, BA'74, MD'85, GME'88, decided to update her estate plans, and, in the process, homed in on what was important to her.

"My years at Penn Med prepared me well for a profession from which I've derived great satisfaction and pride," she said. "Thanks in part to some scholarship funding, I was fortunate to graduate without much debt, giving me peace of mind and a head start on a stable financial future. So I knew that I wanted to pay it forward and support future students in a similar way."

Since graduation, she has been making annual contributions to Penn Medicine. She decided to include a bequest in her will for Penn Medicine, which will help fund student scholarships in the same way that another alumnus funded her scholarship 35 years ago. "I am proof that even modest contributions can make a significant impact. You don't have to be a billionaire to give a gift to Penn that will make an everlasting difference in a person's life," she said. After almost three decades of practice, Giordano has recently retired as assistant professor of emergency medicine with an expertise in forensic medicine at New York City's Mount Sinai Hospital system.

Throughout Giordano's career, teaching students, residents, nurses and physician colleagues was an important focus. "Giving back through a financial legacy can be compared to teaching," she said. "Sharing knowledge at the bedside and in the classroom benefits not only today's patient but future generations of students and patients. Providing a bequest to support medical education felt right because it too rolls forward."

Adding a bequest to your will is a wonderful and easy way to supplement the generous support you provide during your lifetime. Planned giving is often described as the final piece of a philanthropic puzzle. Figuring out how this important puzzle piece can work best for you, your family, and your philanthropic goals is what we do best. Speak with us to learn more about giving options. Contact Christine S. Ewan, JD, executive director of Planned Giving, at 215- 898-9486 or cewan@upenn.edu.

For more information, please visit our website at: www.plannedgiving.med.upenn.edu.

Guiding and Connecting with Tomorrow's Global Health Leaders

By Johanna Harvey

Rosa Chemwey Ndiema, MBChB, MMEd, has years of bedside experience as a gynecologist in her native Kenya, and aspires to have an even greater impact on the health of her community. Ndeima hopes to put Kenya on the path to virtual elimination of pediatric HIV through research on how to better involve community leaders to prevent mother-to-child transmission.

And that brought her to Philadelphia for mentorship and training in clinical research from renowned physicians and researchers in the Perelman School of Medicine.

Ndeima was one of five scholars from three different African countries (Kenya, Botswana, and Tanzania) visiting Penn for a month-long fellowship this summer as part of the Afya Bora Consortium (ABC). ABC is a partnership between four

Rosa Chemwey Ndiema (center), with Namrata Narain (left), director of PSOM Research Financial Operations, who is also a trainer for ABC workshops in Africa, and Megan Doherty (right), administrative director of the Center for Global Health

U.S.-based universities, including Penn, and five African universities to offer African global health leaders practical skills and training not typically available to them.

"ABC is about both leadership and research, and, most importantly, how to join the two together to improve the quality of care back at home," Ndiema said.

Typically, ABC scholars come together throughout the year for one to two weeks at a time in various locations across Africa. But this year, Penn was the first U.S.-based institution to host ABC fellows, presenting both the fellows and Penn faculty with the opportunity for unique and fruitful collaborations. During their time at Penn, ABC fellows had the opportunity

Emerging African health leaders including Mooketsi Molefi (left), had the opportunity to network with African health leaders who are on the Penn Medicine faculty, including Kojo Elenitoba-Johnson, MD (right).

to take courses and work with mentors on topics such as clinical epidemiology, biostatistics, translational research, and clinical trials.

"Our main goal was to provide ABC fellows with the advantage of learning from our faculty here at Penn, but we knew that faculty would also learn a lot from the fellows," said Glen Gaulton, PhD, vice dean and director of the Penn Center for Global Health. "It was really remarkable that in just a few short weeks the fellows opened the eyes of our faculty and staff about the constraints they face to practicing medicine and conducting research in a resource-limited setting. They have their own innovative solutions to today's health care challenges and our team can learn just as much from the fellows as they learn from faculty here at Penn."

Mooketsi Molefi, MBChB, MSc, from the department of Family Medicine and Public Health at the University of Botswana, highlighted the value of his mentoring relationship with Penn biostatistician Alisa Stephen, PhD. "She was exactly the person I needed to help me fill the biostatic gap in my research project," he said. "We've established such a great relationship over these past few weeks; I know we will continue to work together even after I leave Philadelphia." Molefi's project is focused on evaluating the quality of life for patients with HIV-associated meningitis in Botswana in order to improve treatment methods and life expectancy.

The ABC program at Penn is one of many examples of how the Center for Global Health is working to foster opportunities for collaboration at Penn from around the world, and just a snapshot of the dynamic and growing field of global health, especially in academic medicine.

"As the world gets smaller, thanks to improved communication, travel, and social media interconnectivity, the awareness of health disparities only grows larger," Gaulton said. "We want to create an environment at Penn that supports students, staff, and faculty who have a passion for global health and translate that passion into strong in-country collaborations, ultimately helping our partners develop practical solutions to their health priorities."

Established in 2015, the center's mission is to improve health equity worldwide through enhanced public health awareness and access to care, discovery, and outcomes based research, and comprehensive educational programs grounded in partnerships like ABC.

"We know that by coming together, we can make the biggest impact," Gaulton said.

To learn more about the Penn Center for Global Health visit http://www.med.upenn.edu/globalhealth/

More online

Training the Eye of the Beholder

By Rob Press

Sometimes, the intersections of art and science are subtle. They're represented by the physician whose musical background helps him develop a new listening device, or the artist whose anatomical drawings aid medical research centuries beyond his death. Sometimes, however, those intersections are far more direct—such as with the work of Jaclyn Gurwin, MD'15, and Gil Binenbaum, MD'02, MSCE'09, GME'06, who have drawn connections between ophthalmological observational skills and the training one would receive in art observation, description, and interpretation.

The idea was simple: Take some number of medical students and bring them to the museum instead of the morgue, give them courses in art observation, and see how well they respond when presented with clinical images yet again, especially compared with those students who haven't taken the same art observation courses.

If you're unfamiliar or uncomfortable with how art and science can mingle to produce something clinically beneficial, it's a study premise that might seem far-fetched—but it didn't seem that way to Gurwin, an ophthalmology resident at Penn, in part because she'd already seen the benefits of art education on a medical career firsthand.

"Having studied fine arts myself and having witnessed its impact on my medical training, I knew art observation training would be a beneficial practice in medical school," she said. "Observing and describing are skills that are taught very well in fine arts training, and so it seemed promising to utilize their teachings and apply it to medicine."

Gurwin and Binenbaum's findings, published in the journal *Ophthalmology* in September: The medical students who've dabbled in art just do better.

It's a glimpse at how non-clinical training can and does make for a more well-prepared medical professional. Not only does art observation training improve med students' abilities to recognize visual cues, it also improves their ability to describe those cues.

Take a closer look at what Gurwin and Binenbaum's study can teach us in the full version of this story online. **Visit: PennMedicine.org/magazine/artvision**

Audio Extra: Arcade Neuroscience

Listen in on more of the interview with neuroscientist Konrad Kording with the multimedia extra available online. **Visit: PennMedicine.org/magazine/kording**

In the Winter Issue:

When cancer runs in a family, tragedy is compounded. But now, so is hope. The world's first center devoted to the study of BRCA-related cancers, the Basser Center for BRCA at the Abramson Cancer Center, has made remarkable progress in only five years.

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In Philadelphia, the city with the third-highest number of overdose fatalities in the country, Penn Medicine clinicians are on the front lines of the opioid crisis. While helping people who already misuse opioid drugs is one part of the solution, so is getting to the source. Physicians, researchers, and primary care providers at Penn are using science to battle the opioid crisis from where it began: the causes and treatment of pain.

See more on page 12.