WINTER | 2017

PENN Medicine

THE CANCER VISIONARY

PETER NOWELL'S LASTING LEGACY

Guam's Elusive Medical Mystery Could Hold the Secrets to Alzheimer's

Tweet, Yelp, Heal: Penn Medicine Harnesses Social Media for Health

Choose Your Adventure

This issue of *Penn Medicine* encompasses journeys far and wide by alumni and faculty of the Perelman School of Medicine at the University of Pennsylvania. Just as many beloved fantasy novels map out the lay of the land before readers venture into a new world, "The Prep" this winter shows the landscape of the pages ahead.

Philadelphia
Home to the University of Pennsylvania, and to the Philadelphia chromosome ***p. 10***

Guam
The island home to the mysterious disease known as lytico-bodig ***p. 22***

Bethesda, Md.
Home to the National Institutes of Health, where William Eaton, BA'59, MD'64, PhD'67, has spent his nearly half-century-long career ***p. 30***

Beyond the Map
Penn Medicine's new Center for Digital Health explores the digital realms of social media to connect individuals' online activity to their health. ***p. 16***

Also in this issue:

Los Angeles
Penn doctoral student Brett Beaulieu-Jones accepted an Emmy award in October 2016 for his work on software used in the entertainment industry. ***p. 8***

Basel, Switzerland
Headquarters of Roche Pharmaceuticals, where John Reed, MD'86, PhD'86, GME'89, works. Reed's work on identifying the role of a key cancer gene began during his MD-PhD studies with the late Peter Nowell, MD'52. ***p. 10***

San Diego
UC San Diego researcher W.C. Wiederholt, MD, was principal investigator on a series of NIH grants to study lytico-bodig from 1997-2007 in collaboration with Penn investigators. ***p. 16***

Papua New Guinea
Home to the disease kuru, spread through consuming infectious tissue, a mechanism briefly considered to explain lytico-bodig. ***p. 16***

Vietnam
Seeking to avoid involvement in the U.S. military during the war here contributed to Eaton's decision to skip his medical internship; he served through the U.S. Public Health Service after earning his PhD in 1967 instead. ***p. 30***

Cambridge, U.K.
Eaton studied at the Medical Research Council Laboratory of Molecular Biology for a summer during medical school, among scientists who had six Nobel prizes in total. ***p. 30***

Chernogolovka, Russia
"Why don't you work on a hard question, like protein folding?" This question, asked of Eaton at a conference here, set him on a new direction in his research. Eaton was earlier briefly involved in anti-Soviet spying as an exchange student in Berlin. ***p. 30***

DEPARTMENTS

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News & Announcements

Princeton HealthCare System to Join Penn Medicine

In December, the Executive Committee of the University of Pennsylvania Board of Trustees approved plans for Princeton HealthCare System (PHCS) to become a part of the University of Pennsylvania Health System (UPHS). The agreement is contingent upon agreed upon closing conditions, including final approval by state and federal authorities. Founded in 1919 and located 40 miles northeast of Philadelphia, PHCS is a 429-bed integrated health care system that serves more than 1.3 million people. PHCS has earned both regional and national accolades for high quality care. PHCS announced in June 2015 that it would begin evaluating partnership opportunities to ensure its continued success in the future and in July of 2016, executed a Letter of Intent with UPHS. The move to join Penn Medicine comes following PHCS officials' consideration of 17 potential partners.

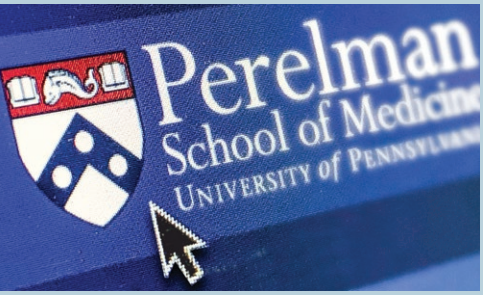
"We are proud of this exciting opportunity to combine Princeton HealthCare's strong reputation for providing excellent care in the community with Penn Medicine's strengths as a national leader in complex and specialty care," said Ralph W. Muller, CEO of UPHS.

J. Larry Jameson, MD, PhD, Reappointed

Penn President Amy Gutmann and Provost Vincent Price announced in January that J. Larry Jameson, MD, PhD, has been reappointed executive vice president of the University of Pennsylvania for the Health System and dean of the Perelman School of Medicine. The reappointment will run through June 30, 2023 and is subject to approval by the Board of Trustees. It follows a review of his first term by a consultative committee appointed by Gutmann and Price.

The committee found especially notable the comprehensive, inclusive and far-reaching strategic plan, developed with Jameson's strong leadership and support. It also noted two overarching accomplishments that merit special mention: his abiding sense of University citizenship and his full embrace of the multi-dimensional and integrated mission of Penn Medicine.

"We agree with the committee's conclusion that Dean Jameson's first term was one of significant accomplishment," Gutmann said. "The Perelman School and Penn Medicine have seen impressive and continued progress under his leadership."



Perelman School to Offer Online Master of Health Care Innovation Degree

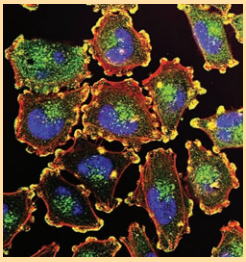
A new Master of Health Care Innovation (MHCI) degree from the Perelman School of Medicine will be the University of Pennsylvania's first online master's program. The program will recruit working health care professionals worldwide interested in health policy, behavioral economics, and operations management. The MHCI is designed for mid-career health care professionals and housed in the department of Medical Ethics and Health Policy. It will draw its faculty primarily from the Perelman School, with additional members coming from the Wharton School, School of Law, and School of Nursing.

Research Countdown

800 **patients at 20 medical centers** enrolled in the largest study to date of the rare inflammatory condition sarcoidosis, yet many critical questions remained unanswered. Penn's first mobile app developed with Apple's ResearchKit framework has the potential to enroll many more sarcoidosis patients across the world, and to collect a broad array of data from their iPhones.

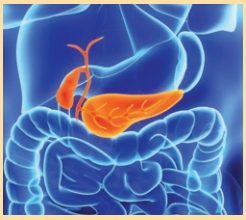
50 **years ago, the Leonard Davis Institute of Health Economics** at Penn (LDI) was established to fill critical gaps in evidence about health policy and management in the aftermath of the establishment of Medicare and Medicaid. As major health policies come up for debate in the U.S. Congress, LDI's expertise is as critical as ever. Follow anniversary updates at http://ldi.upenn.edu/50at50 and #PennLDI50.

30 **to 40 percent of melanoma** cases are estimated to arise from a nevus, or mole composed of non-cancerous cells at the skin surface. A Penn-led study recently identified a genetic biomarker to distinguish nevus from melanoma, which could be part of standard dermatology practice in as little as one to two years.

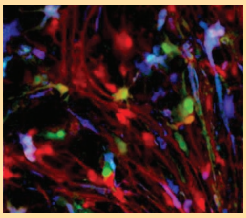


$20 **offered as a financial incentive**, whether as a payment, charitable donation, or both, helped older adults increase their walking activity compared to a randomized control group, in a Penn study published in the *American Journal of Preventive Medicine.*

6 **Penn teams** with diverse, interrelated expertise will collaborate in the new Human Pancreas Analysis Program, the newest program in the Human Islet Research Network funded by the National Institute of Diabetes and Digestive and Kidney Diseases. The program is focused on procuring and phenotyping pancreatic tissues from individuals with or at risk for Type 1 diabetes, Type 2 diabetes, or other types of pancreatic islet dysfunction characterized by changes in beta cell mass.



5 **known brain cell types**—oligodendrocytes, microglia, neurons, endothelial cells, and astrocytes—were identified growing after three weeks, the first time live adult human neurons were grown and studied in culture. The Penn study identified the cells' patterns of gene expression. The cells came from patients ranging in age from their twenties to sixties, showing the potential of this system for use in human aging studies.



Method to Heal Wounds Without Scars Pioneered through Penn Research

Doctors have found a way to manipulate wounds to heal as regenerated skin rather than scar tissue. The method involves transforming the most common type of cells found in wounds into fat cells—something that was previously thought to be impossible in humans.

"Essentially, we can manipulate wound healing so that it leads to skin regeneration rather than scarring," said George Cotsarelis, MD'87, the chair of the department of Dermatology and the Milton Bixler Hartzell Professor of Dermatology at Penn, and the principal investigator of the project. "The secret is to regenerate hair follicles first. After that, the fat will regenerate in response to the signals from those follicles."

The Cotsarelis lab previously discovered factors necessary for the formation of hair follicles. The new study, published online in *Science* Jan. 5, showed hair and fat develop separately but not independently, and identified additional factors produced by the regenerating hair follicle that convert the surrounding myofibroblasts (skin cells involved in healing wounds) to regenerate as fat cells (adipocytes) instead of forming a scar.

"[Global academics] encompasses everything in our view, from climate change to global health and global finance. What do you do in a world where states seem to have less and less power? Those are *global* questions."

—Ezekiel Emanuel, MD, PhD, vice provost for global initiatives at the University of Pennsylvania and chair of the department of Medical Ethics and Health Policy in the Perelman School of Medicine, in a Q&A with the *Chronicle of Higher Education.*

"We must reconcile the seemingly conflicting hallmarks of the medical profession: our dedication to first do no harm and our lifelong commitment to learn, improve, and evolve."

—Neha Vapiwala, MD'01, vice chair of education and advisory dean at the Perelman School of Medicine, about teaching about mistakes.

"As my peers watched, I cajoled, reasoned, and pleaded with each of my 'patients.' Each task proved harder than I expected and humbled me."

—Jason Han, MS4, about training with standardized patients at the Perelman School of Medicine to practice handling clinical scenarios, including medical errors.

Vapiwala and Han wrote companion pieces for the *Philadelphia Inquirer* about learning to handle medical errors, from the perspective of the medical educator and of a medical student who was once a patient harmed by physician error.

New Leaders Connect Penn Schools

There is something unusual about the newest associate dean for Graduate Education and director of Biomedical Graduate Studies (BGS) in the Perelman School of Medicine: Her primary faculty appointment is in another school.

Kelly Jordan-Sciutto, PhD, chair and professor of Pathology at Penn's School of Dental Medicine, took on this new role Feb. 1, but she has long been highly active in graduate education in biomedical sciences at Penn. Housed within the Perelman School, BGS draws approximately a quarter of its faculty from other schools at Penn, including Dental Medicine, Veterinary Medicine, Nursing, Arts and Sciences, and Engineering and Applied Science. Jordan-Sciutto's appointment represents "a truly unique opportunity to further strengthen connections across programs, Schools and the University," Jonathan Epstein, MD, executive vice dean and chief scientific officer of the Perelman School, said in his announcement to the faculty, in which he also thanked Michael P. Nusbaum, PhD, for his nearly four years of service preceding Jordan-Sciutto in this role.

"I'm excited to continue to advance Mike Nusbaum's leadership in areas such as increasing diversity among our student body, keeping our graduate program on the cutting edge to create the next generation of leaders in all fields of science, and supporting students' career development including alternative career trajectories and alumni networking," Jordan-Sciutto said. "And as I pursue my own plans for the future, I look forward to working with all of the BGS faculty to help our students reach their scientific potential."

Kelly Jordan-Sciutto

The new role of associate dean for research integration in the Perelman School of Medicine will simultaneously advance the cause of cross-school discovery on another front. Louis J. Soslowsky, PhD, the Fairhill Professor of Orthopaedic Surgery in the Perelman School and a professor of Bioengineering in the School of Engineering and Applied Science, was appointed to this position in January to address and strategize on increasingly important collaborative opportunities across campus.

Honors & Awards

J. Larry Jameson, MD, PhD

Executive Vice President, University of Pennsylvania for the Health System; Dean, Perelman School of Medicine

John Phillips Memorial Award from the American College of Physicians

This award is bestowed for outstanding, lifetime work in clinical medicine which has been innovative and/or had a regional or national impact. Jameson has identified the genetic basis of more than a dozen different hormonal disorders. As a leader at Penn Medicine, Jameson has championed pioneering translational research, access to advanced clinical care, innovation in medical education, and diversity as a means to catalyze discovery and societal impact.

James D. Lewis, MD'91, MSCE'98

Professor, Gastroenterology and Epidemiology, Perelman School of Medicine

2016 Achievement in Inflammatory Bowel Disease (IBD) Clinical Science award *from the Crohn's and Colitis Foundation of America (CCFA)*

Lewis was nominated by the medical and research community for his exceptional dedication to the field of IBD. Lewis, who is also a senior scholar in the Center for Clinical Epidemiology and Biostatistics, is among few researchers leading NIH-funded clinical trials for novel therapeutic strategies for IBD. Lewis is also the lead scientist behind CCFA's IBD Plexus, which aims to be the largest IBD research and information exchange platform ever developed.

Yvonne J. Paterson, PhD

Professor, Microbiology, Perelman School of Medicine

Fellow, National Academy of Inventors

Election to fellow status recognizes academic inventors named on U.S. patents who have "demonstrated a prolific spirit of innovation in creating or facilitating outstanding inventions that have made a tangible impact on quality of life, economic development, and the welfare of society." Paterson works to harness the body's immune system to provide protection against, and find cures for, cancer. She has been issued 32 U.S. patents and numerous foreign patents. Read more in *Penn Medicine*, Fall 2016, "A Citizen of the University."

Malek Kamoun, MD, PhD

Professor, Pathology and Laboratory Medicine, Hospital of the University of Pennsylvania; Director, Clinical Immunology and Histocompatibility Laboratory, Perelman School of Medicine

2016 American Society for Histocompatibility and Immunogenetics (ASHI) Distinguished Scientist Award

This award honors a scientist who has contributed significantly to the field of immunogenetics and/or transplant immunobiology and who is also an ASHI member. Kamoun is a past president of ASHI, an international society dedicated to the science, education, and application of immunogenetics and transplant immunology.

Susan J. Mandel, MD, MPH

Professor, Diabetes, Endocrinology and Metabolism, Perelman School of Medicine; Director, Clinical Endocrinology and Diabetes, University of Pennsylvania Health System

President-elect of the Endocrine Society

Mandel's clinical and research interests include the use of sonography in the evaluation of patients with thyroid nodules, the novel introduction of I-123 imaging in differentiated thyroid cancer, and thyroid disease during pregnancy. Over the course of her nearly 30-year career, Mandel established the model for thyroid nodule evaluative services and she was one of the first endocrinologists to teach neck ultrasound to endocrine practitioners.

Lawrence N. Shulman, MD

Professor, Hematology-Oncology, Perelman School of Medicine; Deputy Director for Clinical Services, Abramson Cancer Center

Chair of the Commission on Cancer of the American College of Surgeons

Shulman aims to expand the Commission's role in enhancing overall cancer-care quality in the United States, reinforce its relationship with its accredited hospital programs, and reduce cancer health disparities.

"There are proven steps we can take to address these disparities, such as promoting greater use of screening tests, enhancing access to care, improving the quality of that care, providing more dietary and lifestyle education, and increasing participation in clinical trials," he said.

Catch Up on More News

More Penn Medicine news is available online. Recent highlights:

"Sniff Test" May Be Useful in Diagnosing Early Alzheimer's Disease

Most Primary Care Doctors "Strongly Endorse" Key Elements of the Affordable Care Act

New Zika Vaccine Candidate Protects Mice and Monkeys with a Single Dose

Fat Shaming Linked to Greater Health Risks

Bundled-Payments Model Cut Joint Replacement Costs By More than 20 Percent

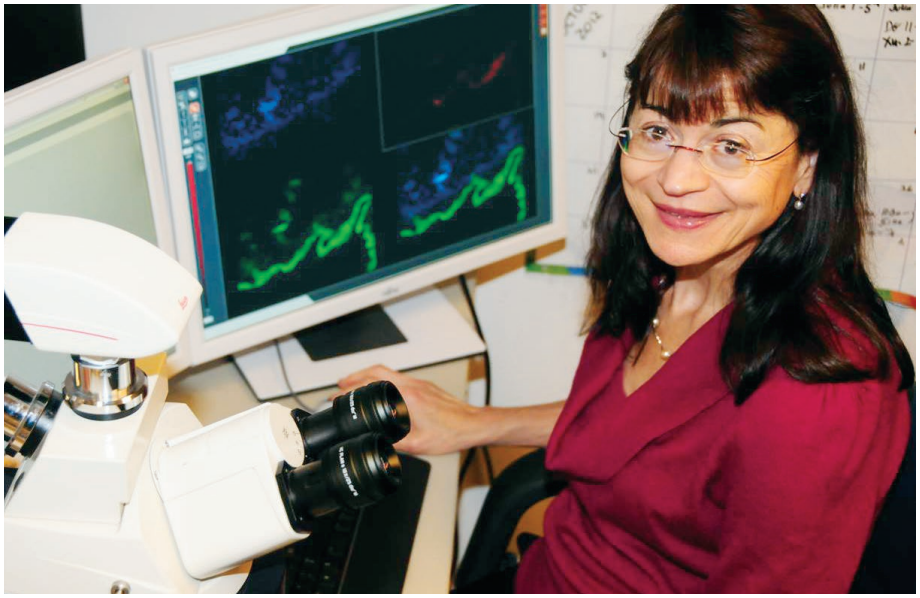
Predictive Analytics: Harnessing Powerful Technology to Improve Patient Care

Some Patients Grow Wary of Opioids as Epidemic Looms

Find all of the stories in Vital Signs and links to the above news items and more at PennMedicine.org/magazine/winter17vs

"I realized this was the worst orthopedic problem I had ever seen, and there was no one working on it."

—Frederick Kaplan, MD, Isaac & Rose Nassau Professor of Orthopaedic Molecular Medicine at the Perelman School of Medicine, in a CNN story, recalling the start of his interest in the rare bone-overgrowth disorder fibrodysplasia ossificans progressiva (FOP) more than 30 years ago. Kaplan (GME'81) and colleagues discovered the genetic mutation that causes FOP in 2006 and continue to seek treatments. Kaplan will be awarded the Perelman School's Distinguished Graduate Award in 2017.



Millar's List

Sarah Millar, PhD, the Albert M. Kligman Endowed Professor and vice chair for basic science research in Dermatology at the Perelman School of Medicine at the University of Pennsylvania, always considered herself a feminist and mentored younger women from early on in her career. But, until a few years ago, she was heavily focused on pursuing her own research to earn tenure, and spent her personal time on raising her family—not actively working to make the system more equitable for women in academic medicine.

"But now I'm a full professor, I have tenure, my kids are almost grown up, and so I have time to think about it a little bit," Millar said.

Beginning in 2012, Millar convened a group of colleagues to meet informally and discuss areas where they felt they could make progress. They created a list of priorities to address barriers to gender equality:

- An on-site daycare for the medical campus
- Greater transparency about faculty salaries and research space allocation
- Greater consideration of unconscious or implicit biases

List in hand and with support of Dean J. Larry Jameson, MD, PhD, Millar and colleagues from across Penn got to work. Millar chaired a task force to find vendors for a new on-site childcare facility, projected to open in January 2019. The Office of Inclusion and Diversity released aggregate data about faculty salaries and, for the first time, about research space, broken down by gender and type of faculty role. And Millar spearheaded efforts to address implicit biases by pushing for greater consideration of qualified women for awards and promotions, and she co-organized a symposium about gender bias in academic publishing in April 2016 with Anh Le, DDS, PhD, chair of Oral and Maxillofacial Surgery at Penn's School of Dental Medicine.

"It's actually a relatively easy to issue to address because there is a pipeline," Millar said. Half of medical students and doctoral students in biological sciences are women, and women are hired to tenure-track positions at the assistant professor level in healthy numbers. However, as women move further up the ranks their progress is impeded; there are fewer women in more senior levels. "It's much more feasible to address the issues underlying this imbalance once you recognize their existence."

For these efforts, Millar was awarded the 2016 FOCUS Award for the Advancement of Women in Medicine.

Public Libraries Go Beyond Books—to Public Health

Libraries routinely help patrons secure basic human needs that are fundamental to health. The Free Library of Philadelphia's Edible Alphabet Program, for example, offers English language, cooking, and life skills instruction for refugees, and other programs address needs such as housing, food, employment, and health care. A Penn team conducted interviews with Philadelphia residents and library staff and analyzed ten of The Free Library's largest programs to reach these conclusions, reported in the journal *Health Affairs*.

The team also found that library staff reported feeling under-prepared and stressed by the profound health and social needs of many library patrons. This finding led to "The Healthy Library Initiative" partnership between Penn and Philadelphia's public library system, in which Penn advisors collaborated with librarians to integrate evidence-based public health programming in a library setting.

"Public libraries are a critically needed and trusted lifeline for many vulnerable citizens," said Carolyn Cannuscio, ScD, director of research at Penn's Center for Public Health Initiatives and an assistant professor in Family Medicine and Community Health at the Perelman School of Medicine.

The connection between Penn's medical enterprise and the Free Library of Philadelphia is not a new one. The Free Library and the Hospital of the University of the Pennsylvania were both founded by William Pepper, Jr., a Penn provost who earned his medical degree at Penn in 1864.

LETTERS

Blame Profit-Driven Systems

I was fascinated by "The Impact of Poverty on Health Care" by Dr. Richard Cooper, printed in the *Penn Medicine* Fall 2016 issue. I agree that poverty in our country is a major healthcare cost driver. But Dr. Cooper says not one word about the number one cost driver, the private for-profit health insurance industry, which spends millions if not trillions on advertising, dividends, buying each other out, corporate bonuses, and concocting hundreds of confusing plans (aka "products"). Medicare has none of those costs. Further, this capitalistic complexity carries massive additional costs for providers in the form of endless delays and mistakes, endless paperwork and endless befuddlement. I ran a practice for twenty years and I can tell you that dealing with hundreds of plans is a big overhead item.

Throw it all out! Medicare for all would not be perfect, but it would result in drastic cost decreases, drastic coverage increases, and lowering the toll of preventable deaths. But an entrenched health insurance industry will never let that happen. What a moral tragedy.

Speaking of waste, how many billions is Big Pharma spending on patient-directed advertising so they can go tell their doctor what to prescribe? This is illegal in most other "developed" countries. If patients have to do that, they should go to another doctor.

John K. Herpel, MD, GME'77

No Proof of Capitalism's Villainy

I object to the extensive posthumous quoting of Dr. Richard Cooper's book.

All Dr. Cooper has shown is that there is an association of ill health and extra medical expenses with poverty. He has in no way proven cause and effect.

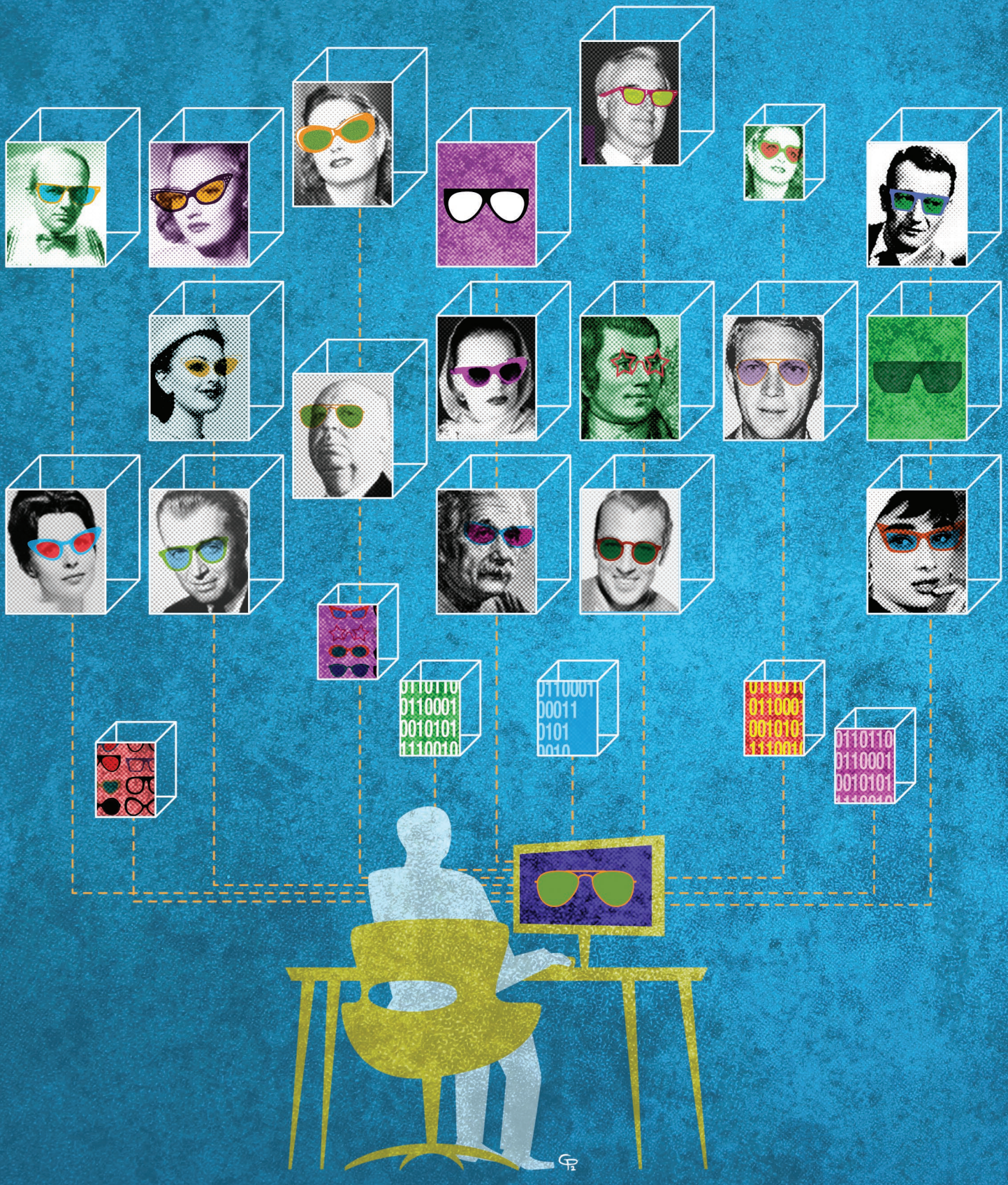
In our pro-socialist world, big government proponents such as Dr. Cooper are always patted on the back for "proving" that the capitalist system is injurious to the population.

Benjamin D. Bernstein, MD, GME'78

Editor's note:
To share thoughts about any of the articles in this issue, please send letters to rachel.ewing@uphs.upenn.edu.

HOLLYWOOD INFORMATICS STAR SHINES AT PENN MEDICINE

By Paul Foster



It started with a pair of sunglasses.

In the spring of 2012, Brett Beaulieu-Jones was preparing to enter the doctoral program in genomics and computational biology at the Perelman School of Medicine when a friend, Jeffrey Impey, asked if he was up for a project. Impey had seen a pair of sunglasses in a movie and, wanting to get himself a pair, did what everyone does and did some online digging. Surprisingly, he found nothing. These days, though, when you can't find something on the internet, generally what you find instead is an opportunity.

The quest for those sunglasses led the pair, with a third friend, Alex Loverde, to foray into the logistics of movie and television production, where Beaulieu-Jones applied the computational skills that are now helping him glean fresh insights from health data. In his doctoral studies, he is training computers to analyze huge samples of patient data. Through machine learning—helping the computers get better at the analysis on their own—Beaulieu-Jones hopes his team can more easily find disease subtypes in patients just by looking at the data in electronic medical health records.

At the opposite end of the technology spectrum are the methods still in common use in Hollywood just a few years ago. While researching the movie and television industry, Beaulieu-Jones and his friends learned that production designers were still using binders to keep track of *everything* on set. They worked for the next few years to build Synconset, a company that developed software aimed at improving collaboration among production teams, an especially important feature as productions often include hundreds of people working in different locations—not great for a binder.

The Synconset team also developed an app that could receive a screenplay and perform a breakdown, turning the script into metadata. The metadata is used by crews to determine how many costumes will be needed, which characters should be wearing what costumes for which shots to maintain continuity, the consistency of design between shots for a scene, and so on. A hit out of the gates, the software was expanded to include props, makeup, hair, locations, and set decorations.

Beaulieu-Jones said the company grew organically, spread by word of mouth, and now, after a relatively short period of time, Synconset is used by half of all television and film productions. The effect they've had in Hollywood hasn't gone unnoticed, either. In October 2016, the Synconset team flew to Los Angeles to accept a Primetime Engineering Emmy Award.

"I think we were the youngest group to win an Engineering Emmy," Beaulieu-Jones said. "We were the only winners there who all brought their parents."

Meanwhile, back at Penn, Beaulieu-Jones isn't as involved in Synconset as he used to be. Instead, he's now using his technical know-how to help make the most of the digital mountains of data we collect each day.

"Synconset has helped me learn how to build and manage large databases in complicated workflows," he said. "Electronic medical records struck me as an area where there's a huge amount of data, but due to the realities of the clinic, the data is complicated and noisy and we aren't fully utilizing it for research yet."

Jeffrey Impey, Alex Loverde, and Brett Bealieu-Jones

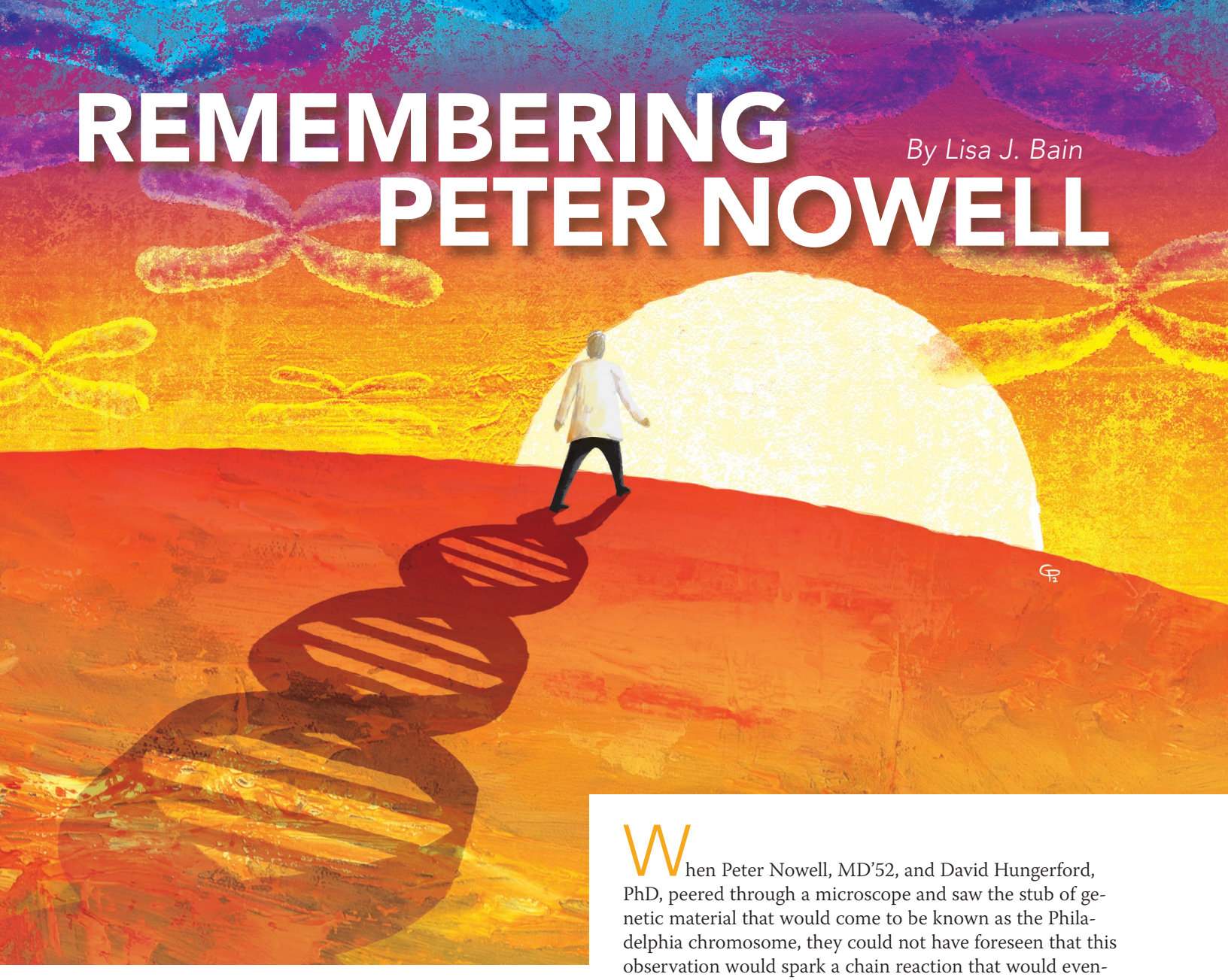
Beaulieu-Jones and team are studying how machine learning can potentially help diagnose patients with metabolic syndrome, a cluster of symptoms that places them at risk of diabetes or cardiovascular disorders, through the health data collected while they are treated at Penn. Patients come in for a variety of reasons, and doctors are focused on treating the priorities. So Beaulieu-Jones wants to develop the system to automatically analyze the many points of data collected and predict future issues a patient could face, ultimately allowing a physician to intervene earlier.

Digesting the amount of data created at Penn and accurately predicting future diagnoses isn't possible for humans to do on their own, according Beaulieu-Jones, but thanks to enormous advancements in technology and a clever team from a broad, and unexpected, range of backgrounds, it's becoming a reality.

This article was originally published on the Penn Medicine News Blog. To read a series of posts about big data at Penn Medicine published in January, visit http://bit.ly/PMbigdata

REMEMBERING PETER NOWELL

By Lisa J. Bain



The Big-Thinking Penn Scientist Best Known for Discovering the Philadelphia Chromosome Pioneered Concepts Underlying Precision Medicine and Championed Education at All Levels

When Peter Nowell, MD'52, and David Hungerford, PhD, peered through a microscope and saw the stub of genetic material that would come to be known as the Philadelphia chromosome, they could not have foreseen that this observation would spark a chain reaction that would eventually enable the development of targeted and personalized cancer treatments. Yet friends and colleagues point to myriad factors that allowed Nowell to make some of the most important biomedical discoveries of the 20th century: He was smart, a true genius by some accounts; he loved basic science and was devoted to defining the principles that would lead to better therapies; he was humble and nurtured the careers of students and other scientists; and his thinking was not limited by existing dogma.

"He always said that we made the boxes, biology did not," said his long-time collaborator Jonni Moore, PhD, a professor of Pathology and Laboratory Medicine in the Perelman School of Medicine at the University of Pennsylvania. "And that was totally the way he approached science—always thinking outside the box, always open to new ideas and new approaches."

Nowell died Dec. 26, 2016 at age 88. With the exception of two years at the U.S. Naval Radiological Defense Laboratory after his training in Pathology at Presbyterian Hospital (GME'56), he spent his entire career at the Perelman School of Medicine. A recipient of numerous international honors including the Lasker Award in 1998 and the Benjamin

Franklin Medal in Life Science in 2010, he served at Penn as chair of Pathology and Laboratory Medicine from 1967 to 1973 and was the first director of what is now the Abramson Cancer Center. His far-reaching scientific legacy lives on through the fond memories of his professional peers and the lasting impact of his ideas that suffuse the medical landscape today.

Fundamental Discoveries Transform Cancer Therapy

The 1960 discovery of the Philadelphia chromosome—an abnormality initially seen only in the cancerous white blood cells of patients with chronic myelogenous leukemia (CML)—provided the first evidence that cancer was a genetic disease, and set off a chain of research that defined a new era for cancer care. Ten years later, Janet Rowley, MD, at the University of Chicago showed that the Philadelphia chromosome came about when part of chromosome 9 broke off and reattached itself to chromosome 22. Subsequently, Nora Heisterkamp, PhD, at the National Cancer Institute showed that the translocation resulted in the fusion of two genes known as *BCR* and *ABL*; and Owen Witte, MD, at UCLA showed that the *BCR-ABL* fusion gene produced a type of enzyme called a kinase that caused cancer cells to proliferate. Brian Druker, MD, of Oregon Health and Science University used this knowledge to study an inhibitor of the kinase, later called Gleevec, which became the first small molecule targeted therapy for cancer. The drug has made CML a manageable chronic disease for the approximately 5,000 U.S. patients newly diagnosed each year, saving these lives and others with related forms of leukemia, and transforming cancer treatment.

Following the discovery of the Philadelphia chromosome, scientists worldwide went on to document different kinds of mutations driving virtually every human cancer that has been studied.

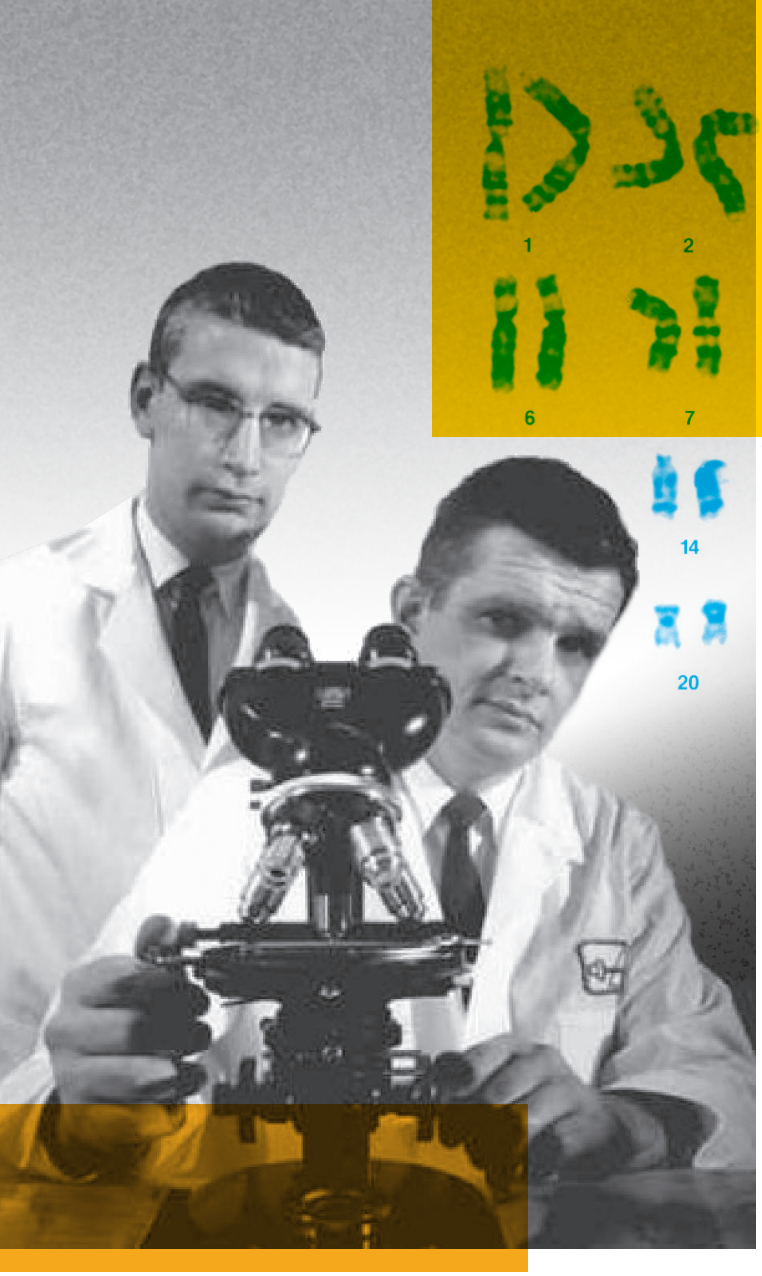
Meanwhile, Nowell made other important discoveries. He showed that a plant substance called phytohemagglutinin stimulated lymphocytes to divide, a tool that launched a new era in the field of immunology.

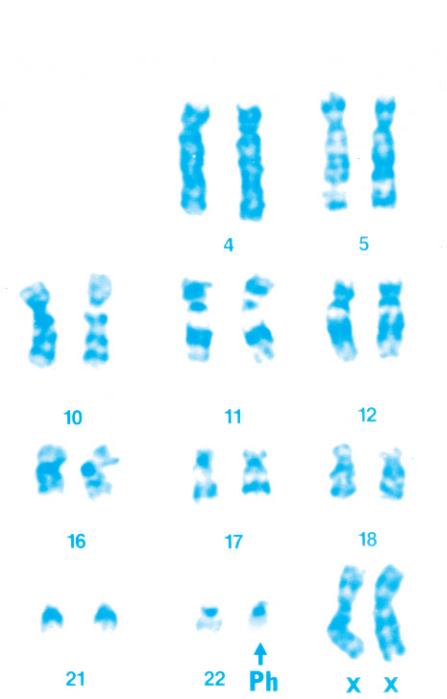
He also made an observation that transformed a generation's thinking about cancer genetics: By looking at the cells of patients multiple times over the course of their disease, he realized that additional changes in the genes accrued over time. In 1976 he published a "thought paper" in the journal *Science* describing his hypothesis that defined the concepts known as clonal evolution and tumor heterogeneity. He proposed that most tumors arise from a single genetically mutated cell, that cancer cells are prone to additional mutations over time, and that those additional mutations will persist and evolve if they enable continued tumor survival and growth. He went on to suggest the need for cancer therapies targeted to the genetic cause of an individual's disease. The paper presented no data.

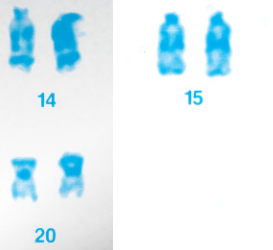
"It was incredibly prescient for him to come up with that hypothesis based on limited data," said David Roth, MD, PhD, the Simon Flexner Professor and chair of Pathology and Laboratory Medicine. "It was almost like magic."

But, of course, it was more than magic. "He used to always say that one of the most important things was to observe and then to actually take the time to think about what you observed and try and apply it," said Jennifer Morrissette, PhD, an assistant professor of Clinical Pathology and Laboratory Medicine at the Perelman School and clinical director of the Center for Personalized Diagnostics. "He said one of the best things about the department of Pathology was that the pathologists would do their work and then walk around campus, particularly around the Biopond, and talk about what they thought about patterns they were seeing, the importance of different findings; constantly saying things out loud and talking about them with colleagues who would challenge you."

Moore agreed that Nowell was a man of his time. "He was a true scientist in the sense that he always looked at the big picture and wanted to ask important, very big questions that led to very important discoveries," she said. "A scientist can't do that today. Our system is not set up to allow people to ask the big questions." In 1986, Nowell received an outstanding investigator award from the NIH, a 10-year grant







that required no specific aims. "The NIH, in its infinite wisdom, knew that he was a gifted scientist and that their investment in him would be rewarded," Moore said.

The Ripple Effect

Like drops in a vast pool of water, the discovery of the Philadelphia chromosome and Nowell's theory of clonal evolution rippled outwards and continue to do so to this day. Mark Greene, MD, PhD, now the John W. Eckman Professor of Medical Science in Pathology and Laboratory Medicine, was recruited to Penn by Nowell and then-Pathology Chair Leonard Jarrett, MD, in 1986. Although Nowell worked at the cellular level and Greene at the molecular level, the two scientists were close colleagues and talked almost every day. And both made central discoveries that have led to promising new cancer therapies. (See "Targeted Therapies for Breast Cancer," p.13)

Kojo Elenitoba-Johnson, MD, who holds the Peter C. Nowell MD endowed professorship and directs the Center for Personalized Diagnostics at Penn Medicine, said that many scientists have built their stellar careers on Nowell's fundamental observation of the Philadelphia chromosome: "The entire universe of understanding that acquired genetic mutations drive sporadic cancer emanated from that work." Elenitoba-Johnson also noted that virtually everything Nowell predicted in his seminal paper on clonal evolution has also turned out to be true, including the fact that cancer cells acquire secondary alterations, among them metabolic alterations, that allow them to adapt, grow, and proliferate under oxygen-poor conditions while sacrificing efficiency of energy generation for production of cell mass. Nowell also predicted interactions with the immune system and envisioned a critical role for immunotherapy as an strategy to combat cancer long before the field matured. (See "Exploiting the Immune System to Target Cancer," p.14)

The emergence of precision medicine—targeting treatments to an individual patient's mechanism of disease—owes a debt to Nowell's insights. "The field of precision medicine is bigger than cancer, but it really started in cancer, so not only is the Center for Personalized Diagnostics a direct outgrowth of Peter's work but so is precision medicine in general," Roth said. "Peter's work started that whole line of thinking." (For an in-depth look at the Center for Personalized Diagnostics and the Penn Center for Precision Medicine, which Roth directs, see "One Size Does Not Fit All," *Penn Medicine* Summer 2016.)

Educator and Enabler

To Nowell, education was paramount. One of his many sayings Moore recalled was, "We have to remember we're a medical *school* primarily." He felt that the people he trained were his real legacy, she said, even beyond his scientific discoveries. In his lab, there was also no hierarchy. "Everyone was respected for their role in the project and he well understood the concept of team science, well before team science was talked about," she said. Moreover, his commitment to education and training was not restricted to the Penn students, postdocs, and fellows who passed through his lab.

He also led courses for elementary and high school students, aiming to cultivate their love for science, Moore recalled.

According to John Reed, MD'86, PhD'86, GME'89, who worked in Nowell's lab as an MD-PhD student, Nowell spent as much time training his students how to express themselves in writing as he did on scientific methods. Reed recalled how after completing research for his PhD thesis, he spent weeks writing what he thought was a brilliant manuscript that would impress Nowell. "Rather, he handed me a copy of Strunk & White's book, *The Elements of Style,* and instructed me to read it, then tell him whether I still wanted him to read my draft manuscript. The next day, after reading the book, I sheepishly returned to Peter's office and retrieved my manuscript, realizing that it was horribly flawed." Reed and Nowell ultimately published more than 30 papers together. "Each time, we would spend hours debating how to construct particular sentences or phrase ideas succinctly," Reed said. "That experience was more important in preparing me for a career as a scientist than any experimental technologies I mastered."

"I definitely won the training lottery," Moore said. It was not easy to be a woman scientist with a family when she

FROM PHILADELPHIA *(Chromosome)* TO THE WORLD *(of Modern Precision Therapies)*

Peter Nowell was renowned for his ability to see the big picture. His visionary 1976 *Science* paper predicting that cancer cells evolve and accumulate adaptive genetic changes over time was not only correct, but laid the groundwork for modern approaches to precision medicine. When Nowell peered into his microscope nearly 60 years ago and saw the Philadelphia chromosome for the first time, could he have envisioned how far that discovery and other discoveries built on his ideas would someday reach?

TARGETED THERAPIES FOR BREAST CANCER

"Peter Nowell was the major reason I came to Penn, because we worked on similar problems of the evolution of malignant cells," said Mark Greene, MD, PhD. "However, my lab is much more atomic and molecular than his was; and we deal with principles of designing therapies."

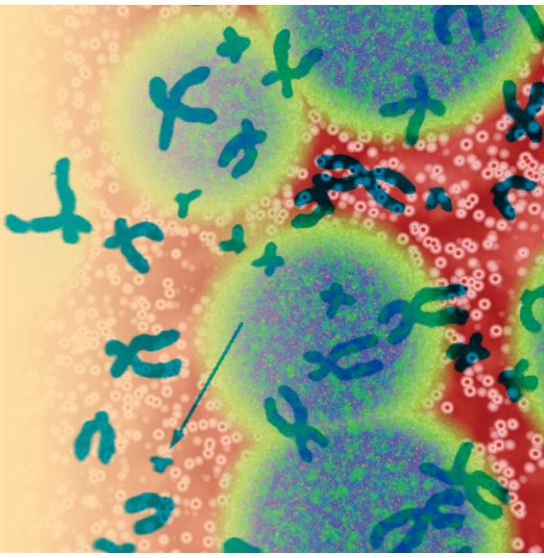
Greene's work over the past 30 years has helped transform the treatment of breast cancer, achieving the translation of fundamental discoveries about the genetic basis of cancer into more effective therapies that was always Nowell's ultimate goal. In 1985, Greene's lab showed that antibodies directed against a protein called HER2 inhibited the growth of tumors driven by an oncogene called *HER2/neu*. This discovery led to development of Herceptin, the first targeted therapy for HER2-positive breast cancer, a particular aggressive form of breast cancer that is found in about 20-30 percent of cases. Approved by the FDA in 1998, Herceptin is thought to have saved many thousands of lives worldwide.

Greene's lab has gone on to develop small molecule inhibitors of HER2, which have the advantage of oral delivery, in comparison to antibody-based treatments that are delivered by intravenous injection. Small molecules may also be able to penetrate more deeply into a tumor and are potentially easier and cheaper to manufacture. Since *HER2* is also overexpressed in other types of cancer, these small molecule inhibitors may further expand the universe of targeted therapies.

NEW CLASS OF DRUGS FOR BLOOD CANCERS

In 2016, the Food and Drug Administration granted accelerated approval to a drug called venetoclax for the treatment of chronic lymphocytic leukemia. Several more drugs in its class are in development and clinical trials for the treatment of hematologic cancers. These drugs target a protein called Bcl-2 and related molecules produced by genes that, like the Philadelphia chromosome, result from a translocation event. The 14:18 chromosome fusion that creates the *Bcl-2* gene is now known to be the most common cytogenetic abnormality in cancers of the blood.

In the mid-1980s, Nowell's lab, in collaboration with Carlo Croce, MD, then at Penn and now chair of Cancer Biology at Ohio State, were the first to discover the *Bcl-2* gene in lymphoma cells from nearly all patients with Hodgkins lymphoma. Shortly thereafter, John Reed, MD, PhD, (now at Roche) joined Nowell's lab as an MD-PhD student and set out to determine how *Bcl-2* causes cancer. Over the next few years, Reed and his colleagues showed that Bcl-2 increased the formation of tumors in mouse cells, that blocking the *Bcl-2* gene's expression in cells could suppress tumor formation, and that the Bcl-2 protein is necessary for cell survival in both healthy cells and cancer cells. Reed's team went on to show the *Bcl-2* gene could switch leukemia cells from being chemosensitive to chemoresistant, and finally that synthetic DNA molecules that shut off *Bcl-2* expression could convert chemoresistance to chemosensitivity in lymphoma—bringing the potential for today's class of drug candidates within reach.



joined Nowell's lab as a postdoc in the '80s, but "if it was late in the day, he would say to me 'please go home and be with your children,'" Moore said. "You would never have found anyone saying that back then, but that's the way he lived because his family was really primary in his life." That support extended to her growth as a scientist. She recalled a time when Nowell was invited to speak at a prestigious meeting of ten of the world's leaders in the field of leukemia and lymphomas. As the parent of a special-needs child, Nowell rarely traveled, preferring to stay at home and help care for his eldest daughter, Sharon, who had severe disabilities from cerebral palsy. "He called them up and said, 'I'm sending Jonni Moore, who is a postdoc in my lab, because I won't come,'" Moore said. "I can promise you that they probably didn't want me, but they weren't going to tell him that." She attended—and held her own as the only woman at the event and a postdoc at that. The meeting helped her make connections important for the rest of her career, she said.

After her postdoc, Moore went on to collaborate with Nowell for 20 years in a specialty he had made possible. (See "Cell-Basd Analyses Fuel Precision Medicine," p.15) He encouraged her early on to find her own voice and establish independent scientific credentials, even advising her not to put his name on her papers. "You don't want people to say 'somebody in Peter Nowell's lab,'" she recalled him saying. "And that was a very important piece of advice. Now, people know I trained with him but they never assume I accomplished what I did because of him."

Elenitoba-Johnson, who joined the Penn faculty in 2015, never worked with Nowell himself but felt his influence after meeting him once in 2005. "He was very humble, inspiring, and insightful in his questions regarding my work, and also forward thinking in ways that I hadn't even considered." Then early in his faculty career, Elenitoba-Johnson was studying the signaling consequences of *NPM-ALK*, a fusion gene occurring in the most common form of pediatric T-cell lymphoma, and had started to investigate unanticipated consequences of expression of the fusion gene using mass spectrometry. Nowell suggested that in addition to signals that turned on growth promoting genes as a result of excessive activity of the protein, it was also likely that other pathways were switched off, and that it was the combination of these two signals that contributed to a tumor's aggressive growth. "It was not his area, but he was able to see beyond a few technicalities and say, 'here's what's going to be important,'" Elenitoba-Johnson said.

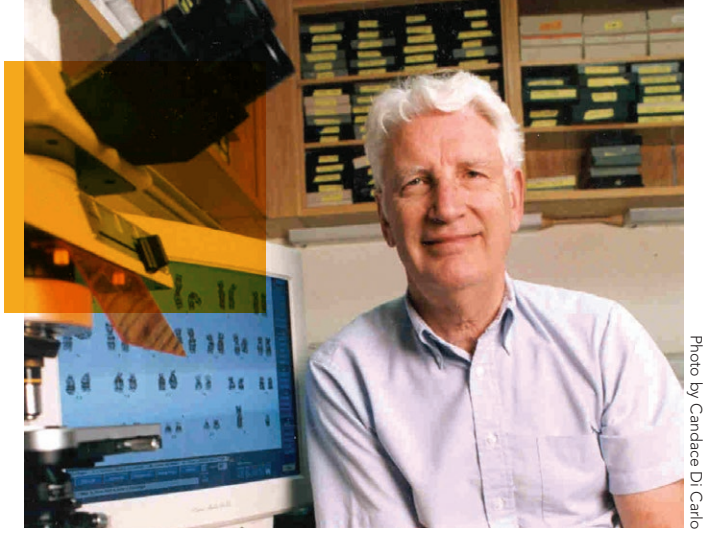


Photo by Candace Di Carlo

It is a testament to his impact that Elenitoba-Johnson and Roth, who knew Nowell only later in his life, as well as people who worked by Nowell's side for many years like Reed, Moore, and Morrissette, can all trace much of their success back to Nowell. "He was an extraordinary man," Greene said. "I've worked with Nobel laureates, but he was the most extraordinary of them all because of his total commitment to defining basic principles that would lead to better therapeutic opportunities. He was one of the believers that great science leads to great discoveries. He was a real hero."

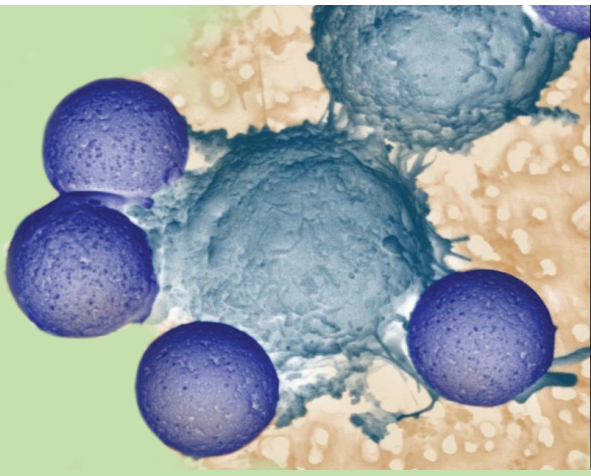
Read this story online with related links at PennMedicine.org/magazine/nowell

EXPLOITING THE IMMUNE SYSTEM TO TARGET CANCER

In Nowell's seminal paper on clonal evolution, he predicted not only that cancer cells undergo stepwise, sequential mutations to adapt to their environment, but also that those changes could be exploited to develop immunotherapies for cancer. Since then, scientists at Penn's Abramson Cancer Center (ACC) have pioneered a variety of approaches that marshal the body's immune system to kill cancer. One of the most promising, and one that provides an ultra personalized approach, is CAR T-cell therapy.

Chimeric antigen receptor (CAR) T cells are engineered from a patient's own immune cells to target the specific proteins expressed on their cancer cells. T cells isolated from the patient's blood are modified in the laboratory to recognize the cell-surface proteins of interest and are then reinfused into the patient, where it is hoped they will go on attack against tumors.

Carl June, MD, the Richard W. Vague Professor of Immunotherapy at Penn, directs the ACC's Center for Cellular Immunotherapies. In 2010, his team—including David Porter, MD, and Bruce Levine, PhD—used CAR T cells to treat three patients with advanced chronic lymphocytic leukemia; two experienced complete remissions of their disease and a third had a partial response. As of 2017, several hundred patients—both adults and children—have received investigational treatments using CAR T cells for other cancers. The first two trial participants who went into remission remain well, six and a half years later. "In only a few years, we have generated significant achievements that have moved the field of personalized cellular therapies forward, opening clinical trials to test these treatments not only for patients with blood cancers, but also those with solid tumors," June said.

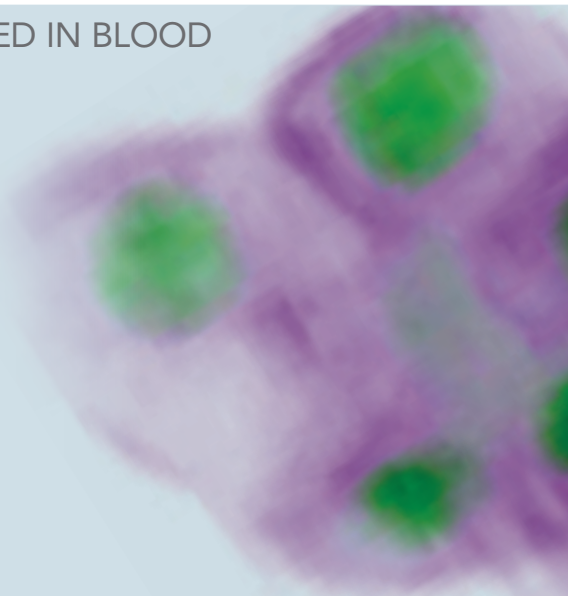


"FULLER SPECTRUM OF CLONAL EVOLUTION" DETECTED IN BLOOD

Nowell's early insights into tumors' clonal evolution laid the groundwork for today's targeted therapies, but determining which of the many new targeted therapies is most likely to work requires genotyping a tumor. This is usually done using tissue samples obtained from biopsy or surgical removal. But tissue is often unavailable, making genotyping and monitoring of clonal evolution challenging, said Erica Carpenter, PhD'09, MBA, director of the Circulating Tumor Material Center at Penn Medicine. Carpenter's lab is using a relatively new method that requires only a simple blood draw to collect circulating tumor DNA or live circulating cells shed from tumors.

Carpenter calls it a "liquid biopsy," noting that it is essentially non-invasive when incorporated into routine blood draws. Her lab recently demonstrated the power of the technique by studying a group of 102 patients with non-small-cell lung cancer. While tissue was only available for half of the patients, blood was obtained from all of them. Using ultra-deep sequencing techniques, Carpenter's team identified one or more mutations in 86 of the 102 patients, including many mutations for which targeted therapies are available.

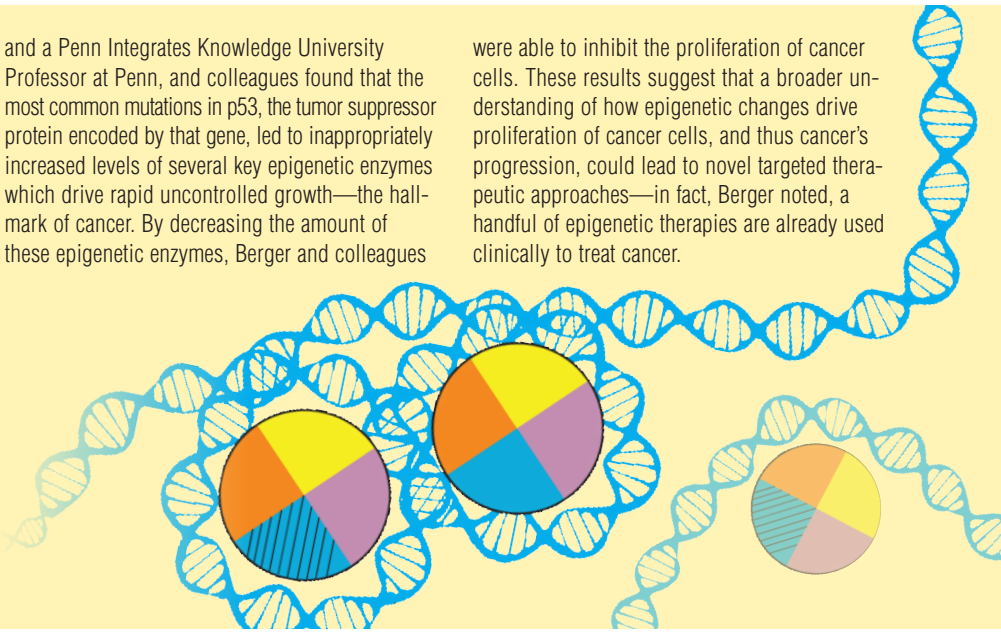
Testing the blood at multiple time points to monitor disease progression, response to therapy, and clonal evolution was also possible given the ease of drawing blood, Carpenter said. In addition, she said sampling from the blood may be more likely to show the full genetic spectrum of a patient's disease from both primary and metastatic sites. "In other words, a fuller spectrum of clonal evolution."



EPIGENETICS AND CANCER

In Nowell's landmark 1976 *Science* paper, he predicted that each malignancy might have to be considered as "an individual therapeutic problem." Subsequent work has confirmed that tumors are highly heterogeneous, not just due to differences in genes themselves, but also due to chemical modifications to proteins that regulate the expression of genes—epigenetic changes. Recent insights from DNA sequencing of patient tumors across numerous cancers have led to a new view of cancer as arising from complex interplay between gene mutations and an altered epigenome.

For example, in the lab of Penn Epigenetics Institute Co-Director Shelley Berger, PhD, researchers have identified epigenetic changes due to a famous gene called *TP53*, which is the mutated in a remarkable 50 percent of human cancers. Berger, the Daniel S. Och University Professor and a Penn Integrates Knowledge University Professor at Penn, and colleagues found that the most common mutations in p53, the tumor suppressor protein encoded by that gene, led to inappropriately increased levels of several key epigenetic enzymes which drive rapid uncontrolled growth—the hallmark of cancer. By decreasing the amount of these epigenetic enzymes, Berger and colleagues were able to inhibit the proliferation of cancer cells. These results suggest that a broader understanding of how epigenetic changes drive proliferation of cancer cells, and thus cancer's progression, could lead to novel targeted therapeutic approaches—in fact, Berger noted, a handful of epigenetic therapies are already used clinically to treat cancer.

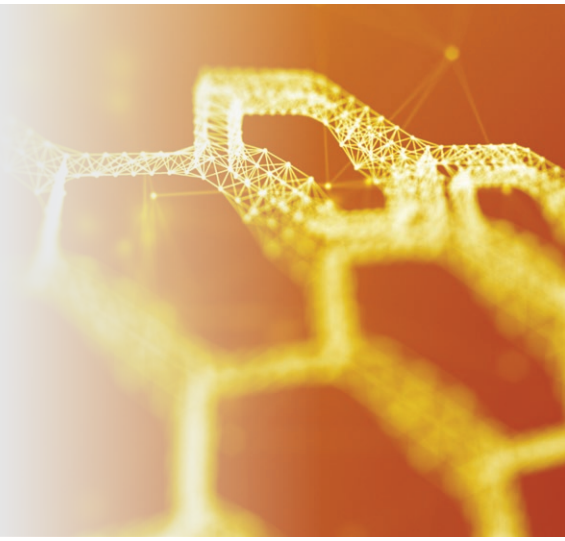


CELL-BASED ANALYSES FUEL PRECISION MEDICINE

At Penn's Flow Cytometry and Cell Sorting Resource Laboratory, Jonni Moore, PhD, oversees an instrument that she describes as the cutting edge of cell-based analytics: A 48-color flow cytometer, the only one outside of the National Institutes of Health. The instrument provides an additional tool to explore cytomics—the molecular analysis of cellular systems—to analyze cells across multiple dimensions. Cytomics was pioneered by the late Carleton Stewart, PhD, who came to Penn as Nowell's first postdoctoral fellow in 1966.

"We wouldn't have that instrument here if Peter hadn't encouraged me and others early on that looking at the genomic level is important, but looking at the cell-based level is really where the rubber meets the road," Moore said, because even more important than what gene is expressed are the effects that expression has on the cell. "It is at the level of the cell that we find the integration of genetic, proteomic and environmental causes of disease," she said.

Cytomics has fueled the development of precision medicine by enabling physicians to apply advanced computational algorithms to identify signature biomarkers of disease status from cell samples. By providing actionable information for diagnosis, disease progression, and treatment response, Moore said, this information allows physicians to make patient-specific decisions.



Emergency physician and social media research pioneer Raina Merchant, MD, MSHP'09, was recently named associate vice president for the University of Pennsylvania Health System and director of Penn's Center for Digital Health.

Tweet, Yelp, Heal

By Carole Bernstein *Photos by Tommy Leonardi*

An Innovative Penn Team Believes Tracking Patients' Digital Footprints on Social Media Could Transform the Future of Personalized Medicine

In Facebook posts, Tweets, Instagram photos, and other social media, we continually leave clues about ourselves. Our words and images tell about our friends, families, and children; our business trips and where we vacationed, how we celebrated the holidays, what parties we attended; recent illnesses, political views, what we find funny or thought-provoking. We even say what we ate for breakfast or what movie we watched last night. And on popular sites like Yelp and TripAdvisor, we report detailed personal experiences with businesses, health care facilities, restaurants, and hotels.

We're leaving a digital trail that leads to who we are and how we live our lives.

Advertisers and marketers have been hot on that digital trail for a number of years now, trying to find out as much as they can about our behavior in order to target their products and services. Could similar techniques be used to help patients and doctors better understand health and disease, and to improve medical care?

That's the intriguing question posed by Raina Merchant, MD, MSHP'09, and her interdisciplinary team at the Penn Center for Digital Health.

The Center for Digital Health initially launched in 2013 as the Social Media and Health Innovation Lab. It is associated with the Penn Medicine Center for Health Care Innovation in partnership with the Leonard Davis Institute of Health Economics. Merchant, the center's director, is an assistant professor of Emergency Medicine with secondary appointments in General Internal Medicine and Anesthesia and Critical Care.

Merchant runs the group like a startup, and she encourages studies of the connections between social media use, technology, and health with a broad, unique perspective, according to Elissa Klinger, the center's assistant director. Though social media and digital media are trendy topics, the lab is taking a long view of what it can achieve. They are already marking successes along the traditional metrics of research productivity, including grant awards from the National Institutes of Health and publications in high-impact journals. But they hope that, just as social media itself has transformed our social connectivity, their research will be a transformative force in the future of personalized medicine.

Mining the "Social Mediome"

In ongoing studies, Merchant and her team are comparing individuals' social media posts with their electronic medical records to discover patterns in how people with already-diagnosed disorders talk about their lives online. "Our focus is on how we can learn by listening to patients through digital means," she says.

The center refers to the research as "the social mediome," which Merchant describes as a way of collectively describing people or groups based on their digital data merged with their health record data. The "–ome" suffix, she explains, is to suggest its place among the other –omes currently being explored under the umbrella of precision medicine: "the genome, the microbiome, the metabolome, the proteome." (For more on this idea, see sidebar, "The 'Social Mediome': Comparable to the Human Genome?")

Just as researchers need patients' consent to sample and study their genomes, the team needs to get permission to collect and analyze social media data to study their health. A landmark finding of the Social Media and Health Innovation Lab was that this consent could, in fact, be obtained, and on a significant scale. In 2015, the team reported in a *BMJ Quality & Safety* paper that over 1,000 patients in the Penn Medicine health system had agreed to donate their Facebook data along with access to their electronic health record. More than 4,800 participants have now signed on, and the team is studying Twitter and Instagram activity as well. Some of the study participants the lab has recruited have even allowed access to their Google search histories.

"Most people do allow us to look in these ways for research purposes. That in itself is an interesting finding, because there's so much attention being paid to privacy. And rightfully so," notes David Asch, MD, MBA'89, GME'87, a Penn professor of Medicine, Medical Ethics and Health Policy,

Raina Merchant, MD, MSHP'09, and David Asch, MD, MBA'89, GME'87, collaborate on research on the "social mediome" to understand and improve health, on using online reviews to improve hospital quality, and more.

and executive director of the Center for Health Care Innovation, of which Merchant's lab is a part. Asch is a co-founder of the lab with Kevin Mahoney, executive vice president and chief administrative officer for the University of Pennsylvania Health System.

When patients are concerned about privacy, this must be respected, Asch acknowledges. He points out, though, that some people find therapeutic value in blogging about a journey through cancer treatment, for example, or they discuss their health problems on Facebook or Twitter, "which is about as un-private as it gets."

Now that they have permission to collect data, the team is in an exploratory phase where they are thinking about ways to make sense of all that information. Some intriguing connections have already come to light.

For example, people who are documented in their health record as being overweight have a common theme in their Facebook activity. You might guess it's food, but it isn't. It's being sedentary. "They're all about relaxing and chilling out," Asch says. Another finding involves patients with hypertension: They tend to post about their families, which, Asch says, the team found surprising, despite the standard joke about your kids giving you high blood pressure.

In looking at patients with depression, the team has in fact found more topics overtly related to sadness than in people without this disorder. But according to Merchant, there may be other words and phrases linked to depression which are not as obvious. "This work has really been enabled by collaborating with computer scientists at Penn who have expertise in natural language processing, deep learning, and mental health" like Lyle Ungar, PhD of Penn Engineering, Merchant says.

A new area for the team is studying social media to trace language changes that may be associated with Alzheimer's or other types of cognitive decline. For this effort, they are partnering with Penn Memory Center Co-Director Jason Karlawish, MD, a Penn professor of Geriatric Medicine, Medical Ethics and Health Policy, and Neurology.

"If there's one organ that is uniquely tied to technology, and where the use of technology is affected early, it's the brain," Karlawish notes. A person's use of social media could become a way to detect if they are experiencing changes in brain function.

He says that based on existing research into cognitive decline, one might see the affected person's writing become less syntactically complex, and shorter overall. Another change might be that the individual simply posts on social media less and less as their condition worsens.

Merchant says the plan is to study the posts of caregivers as well as patients. Karlawish explains that the team will track changes in the emotional tone of caregivers' social media. Such changes could signal the onset of the anxiety and depression that often plague people caring for family members with cognitive decline.

Of the collaboration, Karlawish comments that Merchant reaches "way outside the comfort zone of things she's studied," which he says is a "great testament" to her skills as a researcher.

Your Social Media Health Dashboard

An ultimate goal of collecting and analyzing all of this information is to provide useful reports to both patients and providers, which could be used in a preventive or diagnostic way. Such a report could become a standard part of the annual primary care visit.

"We don't envision that we need to know that patient X posted on Facebook," Merchant clarifies. "That would be overwhelming. Or that they liked something on Facebook."

Instead, she says, the idea is that the doctor would look at a dashboard summary of what someone's posts had been about over the past six months or so, perhaps along with the sites they'd visited and the questions they'd asked on Google. Merchant points out that this could jumpstart and add to the conversation between doctor and patient that typically begins, "So, what brings you in today?"

Such a report could spark conversations that truly address patient-generated data and not just data that patients fill out on forms during a clinical visit, Klinger notes. It could also promote shared decision-making between patient and provider. "Providers don't have a lot of time to

engage with patients, to go through very detailed discussions about their social and behavioral lives," Klinger says. "Hopefully, these kinds of tools might help."

The team is weighing ways that empowering patients with specific knowledge about how social media relates to health could offer further benefits. For example, preliminary findings by other researchers suggest that people who are not depressed tend to post photos with more vibrant colors and fewer muted hues compared to those who are depressed. Could patients and their loved ones someday benefit from learning about such trends from their physicians? "This work suggests that changes in image filters or treatments could suggest changes in mental health and signal to an individuals' network potential decline or need for a check-in," Merchant says.

In December of last year, Merchant became one of the eight inaugural recipients of an accelerator grant from the Penn Center for Precision Medicine Accelerator Fund. Her project is titled "Precision Medicine and Digital Media: Exploring Applications for Clinical Care."

"We received that funding—which we're really excited about—to think about how do we move beyond just the prediction to the clinical applications." She says the focus will be on figuring out how to give social media analyses back—in an easily digestible form—to patients and providers, and discover whether they find that information useful and actionable. The team also plans to use the grant to explore more ways to recruit and connect with patients through existing Penn health system portals.

Could Yelp Reviews Help to Improve Hospital Quality?

"Let's say you're a patient and you have a really great experience with your hospital stay," Merchant says. "You might, ten years ago, have sent a letter to the department or the provider." Same with a really negative experience, she says. You wouldn't have any way to broadcast that letter so that other patients, or your friends, or your neighbors, could know about your experience. And you wouldn't know what happened with that letter. Today's online reviews have made that a whole different ball game.

In addition to her social mediome research, Merchant has been studying online reviews as a way of listening to patients to discover what really matters to them. What makes people post things in the first place, or to say the experience was a one-star versus a five-star?

The "Social Mediome": Comparable to the Human Genome?

"Social mediome" is the term used by experts in the Penn Center for Digital Health to describe the study of how people's social media activity may yield clues about their health. Asch notes that the "–ome" suffix is an echo of "genome." Could their work yield information similar to investigating the human genome, which has brought us revolutionary diagnostic and therapeutic tools?

"I think there are lots of parallels," Asch says. He asserts that like the genome, the social mediome may reveal an enormous amount of information about individual health and disease. "And the social mediome is observable in ways that are actually easier than the genome," he points out. All that is required is the individual's permission, which can be obtained remotely without a visit to a medical facility.

One key difference, Asch says, is that while someone's genetic makeup may cause them to develop a disease, their use of social media doesn't. "We don't actually think there's something about tweets, for example, that causes heart attacks or cancer." While there is good reason to believe the genome mediates health and disease, the social mediome is merely a marker for it—one Asch says may turn out to be "incredibly predictive."

An individual's social mediome could be used almost like a screening test in preventive care. For example, if we know that "people who tweet about X also tend to have a higher incidence of depression, obesity, hypertension," or other conditions, we and our doctors could be better attuned to the need for disease-specific preventive efforts. Asch theorizes that the social mediome might also someday be used therapeutically to correct behavioral errors the way gene therapy is used to correct harmful genetic mutations.

"I don't know if any of this would work—it's sort of new frontier stuff—but you could imagine [for example] for people who have misconceptions about the risks of heart disease, you could communicate back the truth, that cigarettes are bad for you." Social media is bi-directional, he says. We can tweet at someone and send messages to them.

The messages could be sent from one's physician, or from a social network, which he says have already been shown to be useful in the area of health. Perhaps, he suggests, they could be harnessed to create support groups for people with cancer, or give people advice on healthy eating.

"Human behavior sits on the final common pathway between health and disease."

However incongruous we may find the connection between our spur-of-the-moment, even humorous, social media posts and the researcher's realm of useful health information, Asch points out that there is a vital pathway connecting them: "No matter how much we might have a biomedical view of disease, for so many conditions human behavior sits on the final common pathway between health and disease."

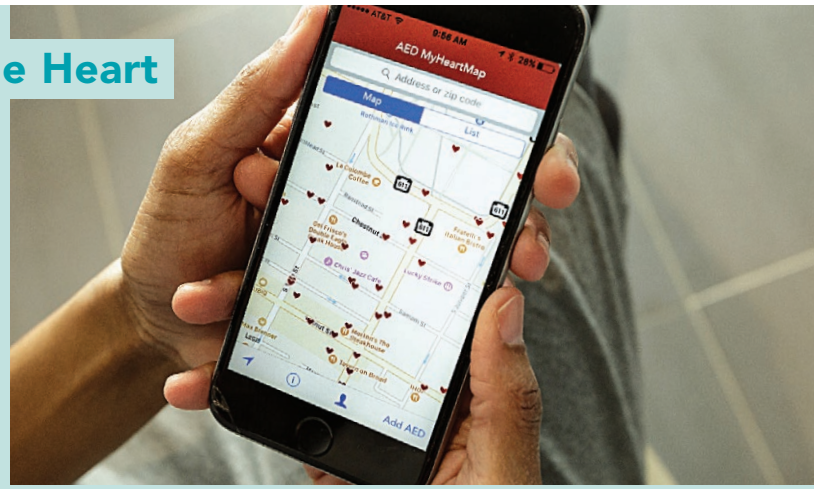
He cites examples of widespread risky behaviors such as people failing to take prescribed lifesaving medicine, or not bothering to use the seatbelts provided in their cars. Regardless of the genes you're born with, it's behavior that can often make the difference between health and disease, life and death.

She is well aware that Yelp reviews aren't perfect: "They aren't validated, and there are all these caveats… but we think there's a really important opportunity to learn from patients through these channels." For example, she points out, in Yelp reviews individuals volunteer unscripted information rather than responding to canned survey questions like those patients receive through Press Ganey surveys following doctors' appointments and hospital stays.

Merchant and Asch recently studied 16,000 Yelp posts about U.S. hospitals and compared them to HCAHPS (Hospital Consumer Assessment of Healthcare Providers and Systems), the traditional government-based survey related to hospital quality that is sent to patients. The team found that people on Yelp talk about all the areas that HCAHPS asks about, but also plenty of areas that it doesn't ask about. The twelve areas they counted include the cost of the visit, insurance and billing issues, ancillary testing, amenities, the compassion of the staff, the quality of nursing, and more. The results were published in *Health Affairs* in April 2016. Merchant, Asch, and Kevin Volpp, MD'98, PhD'98, a professor of Medicine and Health Care Management in the Wharton School, also published about the potential value of online reviews in *JAMA* in December 2016 as "Learning by Listening—Improving Health Care in the Era of Yelp."

One aspect of the Yelp study that Merchant finds intriguing is the ability to hear from caregivers who may contribute to online reviews themselves, although they are never included in the standardized surveys sent to patients. Merchant believes they are incredibly important. "They're often the ones who will remember the most about the experience, because they weren't under the influence of pain medications, they weren't in pain, they weren't as afraid or nervous,

Using Crowdsourcing to Restart the Heart



Even before the founding of the Penn Social Media and Health Innovation Lab, ideas were spinning in Merchant's brain about how digital technology could be used to improve health care.

"I was excited by this problem that AEDs, or defibrillators, are these lifesaving devices that are located all over the place in public locations, and yet no one knows exactly where all of them are," she says. (You've probably walked past many of these devices without noticing them, in shopping malls, gyms, airports, casinos, recreation centers, and other locations.)

An emergency medicine physician, Merchant points out that these devices can flip the odds of survival after sudden cardiac arrest from less than two percent to better than one in two. The devices are equipped with audio instructions for non-medical professionals, she notes. "You open the device and it starts talking to you and tells you how to use it."

"AEDs are an essential part of the 'chain of survival' that's necessary to save cardiac arrest victims," Merchant noted in a 2012 Penn Medicine press release. "Despite thousands of [devices] in the community, our results show they are usually not readily available during cardiac arrests. Without an AED, the minutes bystanders spend waiting for paramedics to arrive could mean the difference between life and death."

Thus the MyHeartMap Challenge, which Merchant launched in 2012 to improve awareness of, and access to, these lifesaving portable devices. She partnered with people across Penn, including at Wharton, and several different schools of design and others to address the challenge of finding these devices so people could use them.

The team developed a mobile app and promoted a contest using crowdsourcing. The contest offered $10,000 to whoever could find, photograph, and supply the location of the most AEDs in Philadelphia County over a six-week period. Participants submitted the required data via the project website or mobile app.

The challenge garnered widespread media coverage including NPR, CNN, the *Wall Street Journal*, and many local Philadelphia news outlets. The university's "Frankly Penn" blog ran a story at the time that described the contest in a nutshell: "Want to Win $10,000 and Save Lives By Using Your Cell Phone?"

The contest resulted in submissions of thousands of AED locations in Philadelphia, which were then validated and mapped by the team. "Before, there were close to 50 devices which were catalogued in the city, [but] we found over 1,400 of them. We were able to validate 99 percent of these devices, and we created a mobile app that people can use to report [where they found additional] devices and to locate them in an emergency."

The MyHeartMap team continues to accept electronic submissions of AED locations toward the implementation of a nationwide database.

Visit http://maps.myheartmap.org to see or submit AED locations near you.

Merchant, at center right, collaborates with Center for Digital Health team members (L to R) Jesse Goldshear, MPH, Elissa Klinger, Emily Seltzer, MPH, Jeremy Asch, and Remi Gurak. A broad range of disciplines, including medicine, design, engineering, and business, contribute to the team's innovations.

or all these emotions that you go through as a patient," she says. "But we don't traditionally ask them about their experience."

Leading in Precision Medicine

Not every emergency medicine physician branches out to take on social media and digital health analysis. Merchant may be the first. Her unorthodox foray into social media and digital health research owes its origins to the MyHeartMap Challenge, a project built on her expertise caring for and studying patients who've suffered from cardiac arrest. Merchant directed this innovative crowdsourcing project at Penn in 2012, aiming to raise public awareness and access to automated external defibrillators (AEDs) to boost survival from this leading killer. (See sidebar, "Using Crowdsourcing to Restart the Heart.")

"We experimented with using social media in different ways for the contest," she says. "That got me really excited about understanding more about how networks work, how to access people, how people share information, and their motivations." She also was inspired to think about other ways to use social media for good.

Merchant was recognized by the Robert Wood Johnson Foundation in 2012 as one of ten young investigators "likely to have a significant impact on the future of health and healthcare in the U.S."

Asch characterizes her as "brilliant, charismatic, high-energy, and fun." Klinger describes her as "extremely innovative."

All three believe that a key strength of the Penn Center for Digital Health is the diversity of the team—spanning from the Perelman School of Medicine and the Wharton School to the School of Design, School of Engineering and Applied Science, and Annenberg School for Communication—and from emeritus faculty to Penn undergraduates. (There were even two high school students who came on board to help last summer: "They were amazing," Merchant says.) Asch credits the union of different intellectual viewpoints largely to Merchant's vision and leadership.

The team's work is intimately connected with health outcomes for Penn Medicine patients as well, according to Mahoney, the Health System executive vice president who cofounded the group with Asch in 2013. "The center is an important initiative for the health system as we focus on how new technologies and platforms can enhance our ability to understand and improve individual and population health behaviors and outcomes, as well as improve health care management and operations," he says.

Both Merchant and Asch note that Penn is largely unique in its work on social media and individual health. "To the best of our knowledge, Penn is the only place really building a social mediome, where we are [collecting] digital footprints to validate or compare with data from your health records," Merchant says. Asch agrees and adds, "I think it'll be even more exciting as the field expands… Because of the uniqueness of the center, [it's] beginning to *define* the field of social media, digital media, and health."

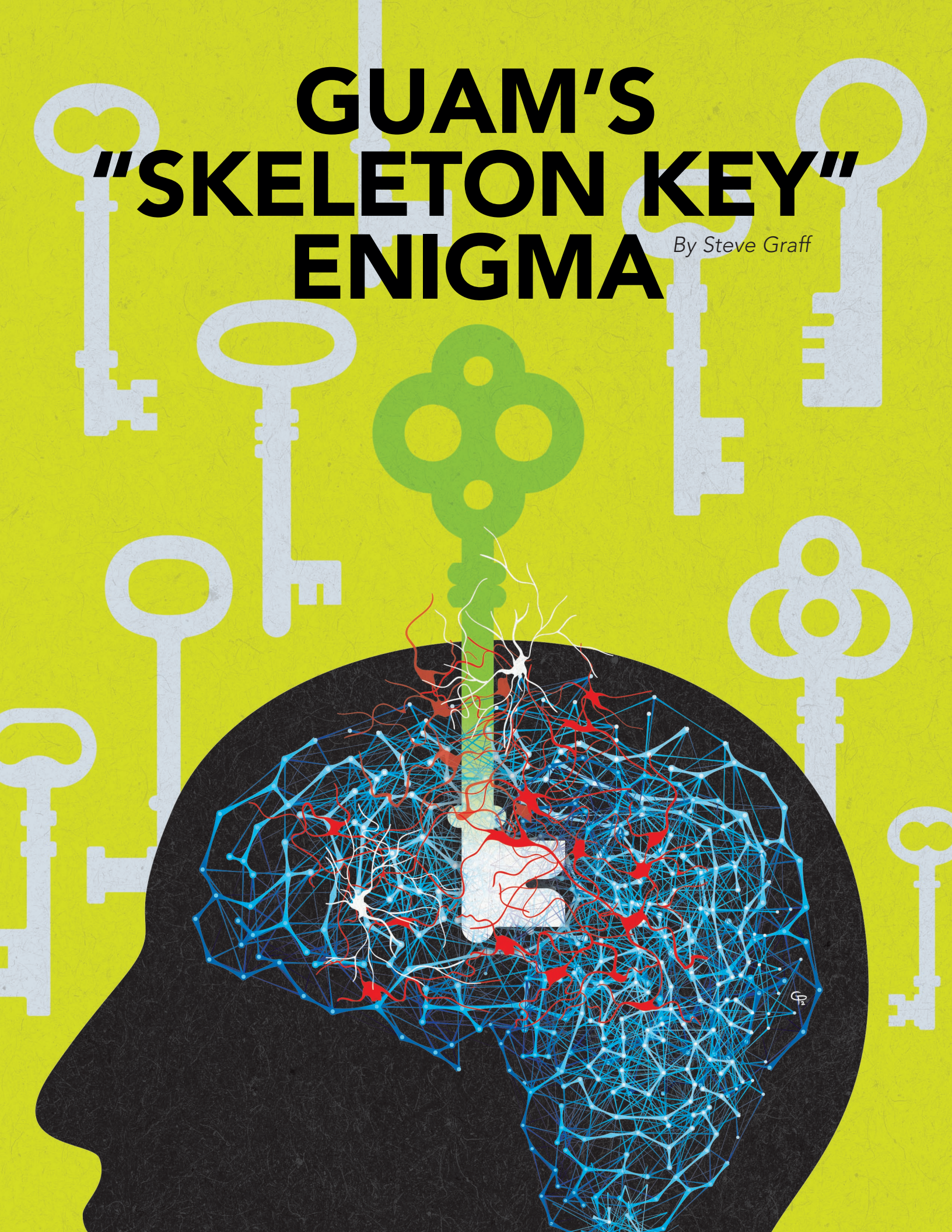
According to Klinger, the center's research cuts through the "buzz" around Big Data and predictive analytics "to start to make sense of this data in a research-oriented, knowledge-generation way."

For Merchant, the lab's research is in keeping with the nationwide focus on precision medicine as transforming the future of health care. "The precision medicine initiative really calls for being able to collect data that's more personalized, and that includes mobile data, online data," she says. "And we want to be part of the group that cracks this: that figures out what promise this data may hold."

Read this story online with related links at PennMedicine.org/magazine/digitalhealth2017

GUAM'S "SKELETON KEY" ENIGMA

By Steve Graff



A Tiny South Pacific Island's Rare Neurodegenerative Disease Sent Researchers on a Decades-long Hunt for Answers that Could Unlock Alzheimer's and More

UMATAC, GUAM— On a hillside along a steel blue ocean cove here at the southern tip of the South Pacific island sits a cemetery. It's small but hard to miss from the road that winds around the water's edge and through this sleepy, centuries-old village. The 50 or so white tombstones—many adorned with colored Mary and Jesus statues and tall crosses, all facing the water—shine bright on the half-manicured, lush, green grounds. Palm trees and flowered shrubs sway in the wind while sounds of the sea fill the air. Fake flowers and wreaths lean up against some of the chipped graves, deteriorated by harsh rains and harsher sun.

It's a serene place to mourn locals who have passed, but also a solemn reminder of the town's plight. Many buried at Umatac Cemetery in the decades following World War II died of a debilitating, rare neurological disease that has yet to be fully explained, and that has since nearly vanished from existence as mysteriously as it appeared. Sharing many of the characteristics of Parkinson's and Alzheimer's disease, and amyotrophic lateral sclerosis (ALS), lytico-bodig is a complex medical mystery that has captivated but befuddled scientists for more than half a century.

Though folklore suggests the disease has been around much longer—two centuries even—the first official reports come from 1904. International attention came to lytico-bodig after the United States took back Guam from the Japanese more than 40 years later, when an American neurologist stationed here picked up on the disease's emergence among the Chamorro people who are native to Guam. By the mid-1950s, it was a full-blown epidemic on an island of 60,000, afflicting people at a rate 100 times greater than similar neurodegenerative diseases did in other parts of the world. And Umatac bore the brunt of it.

The search to understand lytico-bodig since then has been a continual source of frustration, with no shortage of etiological hypotheses: genetics, the cycad tree, metals, prions, algae, the water, bats, a virus, a parasite, some combination of these. None has been proven as a definitive cause.

Instead, investigators found only "decades of dead ends," said Gerard D. Schellenberg, PhD, a professor of Pathology and Laboratory Medicine in the Perelman School of Medicine (PSOM) at the University of Pennsylvania, who studied the disease and the potential mutations behind it.

Even as the number of cases dwindled, researchers have flocked to the island to try to crack the case—not just to help the locals, but because they believe it's a skeleton key, a neurological Rosetta stone.

"If we could solve Guam disease at some point, it would help with these other neurodegenerative disorders," Schellenberg said, though with skepticism. "Or, it may be the other way around."

Photo by Victor Consaga

Umatac Cemetery: Nearly half of the population of 600 in this village perished from a mysterious neurodegenerative disease at its peak in the 1950s.

A Treasured Island

Decades before John Q. Trojanowski, MD, PhD, a professor of Geriatric Medicine and Gerontology in the PSOM and director of Penn's Center for Neurodegenerative Research, studied lytico-bodig or even heard of it, he found himself on Guam, a tropical, coral reef island in the Pacific Ocean—a speck on the world map 8,000 miles west of Philadelphia and no bigger than Harrisburg, Pa. He was just four years old.

His father, then a captain in the U.S. Air Force, was stationed here as America worked to build up its military installations after the war. Some of Trojanowski's earliest recollections are of the 30-day boat ride he and his parents took to Guam, with small snapshot memories he has managed to

Photo by Peggy Peterson

Virginia M.-Y. Lee, PhD, and John Q. Trojanowski, MD, PhD, began studying Guam's lytico-bodig disease in 1996. It has led them to new approaches to Alzheimer's disease.

hold onto: fish jumping out of the water, his mother's hysteria when she could not find him after he locked himself in a bathroom while playing.

By the time Trojanowski and his parents arrived in 1950, the disease was on the rise. The Chamorro people call it lytico-bodig (*lytico* from the Spanish word *paralytico* meaning weakness and *bodig* from the Chamorro word for listlessness), but in 1961 researchers assigned a formal scientific name which reflects its connections to other vexing neurological diseases, amyotrophic lateral sclerosis-parkinsonism-dementia, or ALS/PDC.

Trojanowski did not learn about the disease until he reached medical school at Tufts University in Boston in the mid-1970s. He worried then that he had been exposed to something during his short time here. He hadn't, he decided, since it was primarily found in Chamorro people. The disease left his mind until it intersected decades later with his research on Alzheimer's—which he would find shared molecular similarities, in addition to some symptomatic ones, with lytico-bodig.

The symptoms plaguing Guam residents in the second half of the 20th century included tremors, paralysis of the arms and legs, missed memories, and bouts of dementia. The afflicted were typically over 50, though reports of patients as young as 15 exist. Technically, lytico-bodig represents two different diseases: Patients with lytico present with ALS-like symptoms that usually appear first, while bodig patients have symptoms resembling Parkinson's disease with occasional dementia. Some patients suffer from all those maladies.

Severe deterioration of the body and mind can start within just a year of diagnosis, doctors and families have said. Patients eventually become bedridden, relying on families for care, and succumb from the inability to swallow and breathe on their own. Being a full-time caregiver for sick relatives is part of the culture on Guam, where it's not

Photo by Victor Consaga

Lucy Cruz cared for her dying mother with lytico-bodig. Nearly every house on her street in Umatac had someone with the disease at one time, she said.

uncommon that extended families already live together.

"When she was first diagnosed, it was more her repeating herself, along with dementia," said Lucy Cruz, an Umatac resident who left her job as a pediatric nurse in 1998 to care for her mother, who lived four years with the disease. "She only remembered things from the past and what was happening right [then]. Twitching of the hands; she was unstable," she said. "Eventually, she lost her speech and swallowing mechanisms. That was right before she died."

Cruz also has uncles, aunts, and a grandfather who died from lytico-bodig, all buried in the Umatac Cemetery, a few hundred yards from her house and theirs. Most everyone on her street had someone in their home suffering from the disease at one time, she lamented.

During the 1950s, local Navy doctors and off-island researchers, including Leonard T. Kurland, MD, a young neurologist from the National Institute of Mental Health and Mayo Clinic, took note of the disproportionate numbers of sufferers in Umatac, one of the island's poorest and most isolated communities. The disease struck people all over the island, but nearly half of those living in the village of about 600 perished from the disease at its peak in the 1950s. Overall, the incidence rate among the Chamorro was 50 to 100 times that of the global average for ALS during this time, Kurland and colleagues reported in 1954 in a *Neurology* paper.

That same year, Kurland stressed the importance of the village and the island in the *U.S. Armed Forces Medical Journal*. It's a geographic isolate, making it, theoretically, easier to home in on what's causing neurological disease, here and elsewhere. The National Institutes of Health (NIH) was convinced. A year later, it established a research center on the island that ignited the great search.

Lytico-bodig was now the number one cause of death among Chamorro people.

Batty Ideas

In the decades before Trojanowski developed a research interest in lytico-bodig as a faculty member at Penn in the 1990s, several theories had already surfaced. A familial link was clear, meaning a genetic factor was possible. But Filipino immigrants who moved to the island also developed the disease, so many researchers surmised the cause was more of a shared environmental exposure rather than a genetic disposition.

Scientists turned to the Chamorro diet in 1960s for perhaps the most well-known of theories: the seeds of the cycad (*Cycas circinalis*), a prehistoric, palm-like tree that's nearly extinct on the island. Chamorros harvested these baseball-sized seeds to make flour—known as *fadang* locally—for tortillas or as a thickener for soups, but only after soaking them in water for days to rid them of toxins. Locals knew they were poisonous to animals and people if not properly handled, with reports dating back centuries of people becoming violently ill after ingestion, some with brain damage. Kurland, working under the NIH center, and a visiting anthropologist named Marjorie Whiting marked the seeds as the culprit for lytico-bodig.

However, no one could reproduce a connection between cycad seeds and lytico-bodig in the lab. Consumption never drove animals to acquire the actual disease, and their brains never showed the unique set of neurofibrillary tangles that Kurland discovered a few years before. (Those tangles, a surprising finding at the time that further linked lytico-bodig to Alzheimer's and ALS, were later key to Trojanowski's involvement with the disease.)

By the late 1970s, after six NIH conferences on the cycad theory, it mostly faded away, only to be resurrected in the mid-1980s with a fresh clue. Peter Spencer, MD, then director of the Institute of Neurotoxicology at the Albert Einstein College of Medicine, reported in *Science* that feeding cynomolgus monkeys large amounts of β-N-methylamino-L-alanine (BMAA), one of the main toxins released by the cycad seed, affected their motor neurons. Scientists eyed the finding

> Researchers have flocked to the island to try to crack the case—not just to help the locals, but because they believe it's a skeleton key, a neurological Rosetta stone.

with criticism because a person would have to eat hundreds of pounds of *fadang* in a week to show the effects seen in the monkey. Also, because Chamorros washed the seeds, only small amounts of BMAA would have been left behind.

"It seems unlikely that these low levels could cause the delayed and widespread neurofibrillary degeneration of nerve cells observed in amyotrophic lateral sclerosis and the parkinsonism-dementia complex of Guam," Mark W. Duncan, PhD, a neurologist at the National Institute of Neurological Disorders and Stroke, and colleagues concluded in a 1990 *Neurology* study.

Other theories materialized amid the early cycad suggestions.

In 1976, Carleton Gajdusek, MD, received the Nobel Prize in medicine for his work on kuru, an infectious neurodegenerative disease (and happened to share the prize that year with Baruch Samuel Blumberg, MD, a Penn undergraduate alumnus who later became a professor of Medicine and Anthropology at PSOM). Gajdusek showed that kuru was transmitted through cannibalism in Papua New Guinea. That research prompted him to suggest that lytico-bodig may be another form of transmissible spongiform encephalopathy. Perhaps Chamorros were consuming infected tissue.

However, studies couldn't support Gajdusek's idea. Monkeys fed infected tissue never acquired lytico-bodig, so he abandoned the theory in 1982. He and others also suggested that low levels of calcium and magnesium concentrations in the

Timeline of Lytico-bodig

1904 **First official reports of lytico-bodig**

1940s Navy doctors and American neurologist Leonard T. Kurland, MD, begin to note the disproportionate impact of lytico-bodig disease in Umatac

1950 John Trojanowski spends a year on Guam as a young child

1954 **Lytico-bodig among Chamorro people is found to occur at 50 to 100 times the global rate of ALS and is the leading cause of death**

1955 NIH establishes a research center on Guam

1960s Consumption of cycad seeds suspected as cause of lytico-bodig

1970s Cycad hypothesis largely fades away by the end of the decade

1976 Consuming infected tissue suspected as cause of lytico-bodig

1982 Metal contamination hypothesis emerges

1983 Following decline in lytico-bodig cases, NIH closes its Guam research center

1985 **Lytico-bodig rate has declined to be near-comparable with mainland U.S. rate of ALS**

1987 Cycad hypothesis is resurrected with a controversial monkey study in *Science*

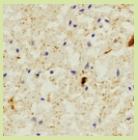
1991 Trojanowski and Lee discover tau tangles in Alzheimer's disease

1996 Trojanowski and Lee meet Schellenberg and begin to collaborate on lytico-bodig

1997 NIA awards a major grant to study lytico-bodig via interactions between aging, genetics, and environment

2003 **Report of demographic changes on Guam correlates with the near-disappearance of lytico-bodig disease**

2005 Trojanowski and Lee begin studying microtubule stabilizing drugs in a mouse model of tau disease they developed



2007 NIA grant for multi-institution group studying lytico-bodig aging, genetics, and environment, ends

2013 Schellenberg publishes his last paper on lytico-bodig (unless "something new comes up")

2016 Applying lessons from lytico-bodig to models of Alzheimer's and other tauopathies, Trojanowski and Lee show that the microtubule stabilizing drug dictyostatin has promise

2017 **Lytico-bodig remains an unsolved mystery**

soil and water caused an excess absorption of aluminum. Aluminum seemed a reasonable culprit because, in the 1970s, it had emerged as a possible cause of Alzheimer's. However, a closer look at the soil and water in Umatac and other parts of Guam didn't reveal any abnormal levels, studies showed. That theory, too, fell to the wayside.

A new cycad hypothesis came up in the early 2000s, this one from Paul Allan Cox, PhD, the director of the Institute for Ethnomedicine in Wyoming, and the late Oliver Sacks, MD, a neurologist and author of *The Island of the Colorblind*, an oft-cited travelogue of his island-hopping experiences in the Pacific. They blamed the fruit bat, a delicacy on Guam that locals call *fanihi*, near extinction today in large part because of its consumption. The bat, which fed on the seeds, "bioaccumulated" BMAA in its fat tissue to levels that could cause motor weakness and other neurocognitive deficiencies if consumed over long periods of time, the researchers reported in monkey studies published in *Neurology*. The decline of the bat population also paralleled the decline of the disease, they said.

The hypothesis grabbed people's attention but hit a nerve in the scientific community. Cox's assay techniques, cycad sampling and use of museum bats, were questioned by many scientists, and follow-up studies never backed up the findings.

"I didn't ever really believe the cycad story," Trojanowski said. "It was never compelling to me. It's good entertainment, but not science."

John Steele, MD, a neurologist who studied lytico-bodig for nearly 30 years on Guam, shared that doubt. "They invested years and years of very intense study, yet nothing came of that," said Steele, who was a co-author on the 1990 *Neurology* paper questioning the neurotoxicity in monkeys, and a self-described friend of Cox. "I don't believe it."

Steele, a Canadian who made a name for himself studying progressive supranuclear palsy, another rare neurological disease that shares many of the traits of lytico-bodig, arrived on Guam in 1983, after the NIH had closed the doors on its research center here following a significant decline in the incidence of cases and a lack of any breakthroughs. Steele split his time as a neurologist at the Veterans Affairs Medical Center and the Navy Hospital. The decline of lytico-bodig cases complicated the search for its cause, but helped firm up the belief that the disease wasn't genetic—or at least not solely genetic, Steele said. Purely genetic diseases don't just stick around for a single generation.

Ambitious and passionate, Steele stayed with it, studying and treating patients, teaming up with researchers from different fields along the way, and pursuing his own investigations of a novel detail: markings on the eye seemingly left by a parasite (See sidebar: "Keeping an Eye on the Disease"). He lived in Umatac for 10 of his years on Guam, where he would often find himself sitting on the graves at the cemetery to reflect, looking out over the water, hoping something would click or reveal itself.

"You'd think it would have been very easy to have come up with the reason, the cause for such a localized disease

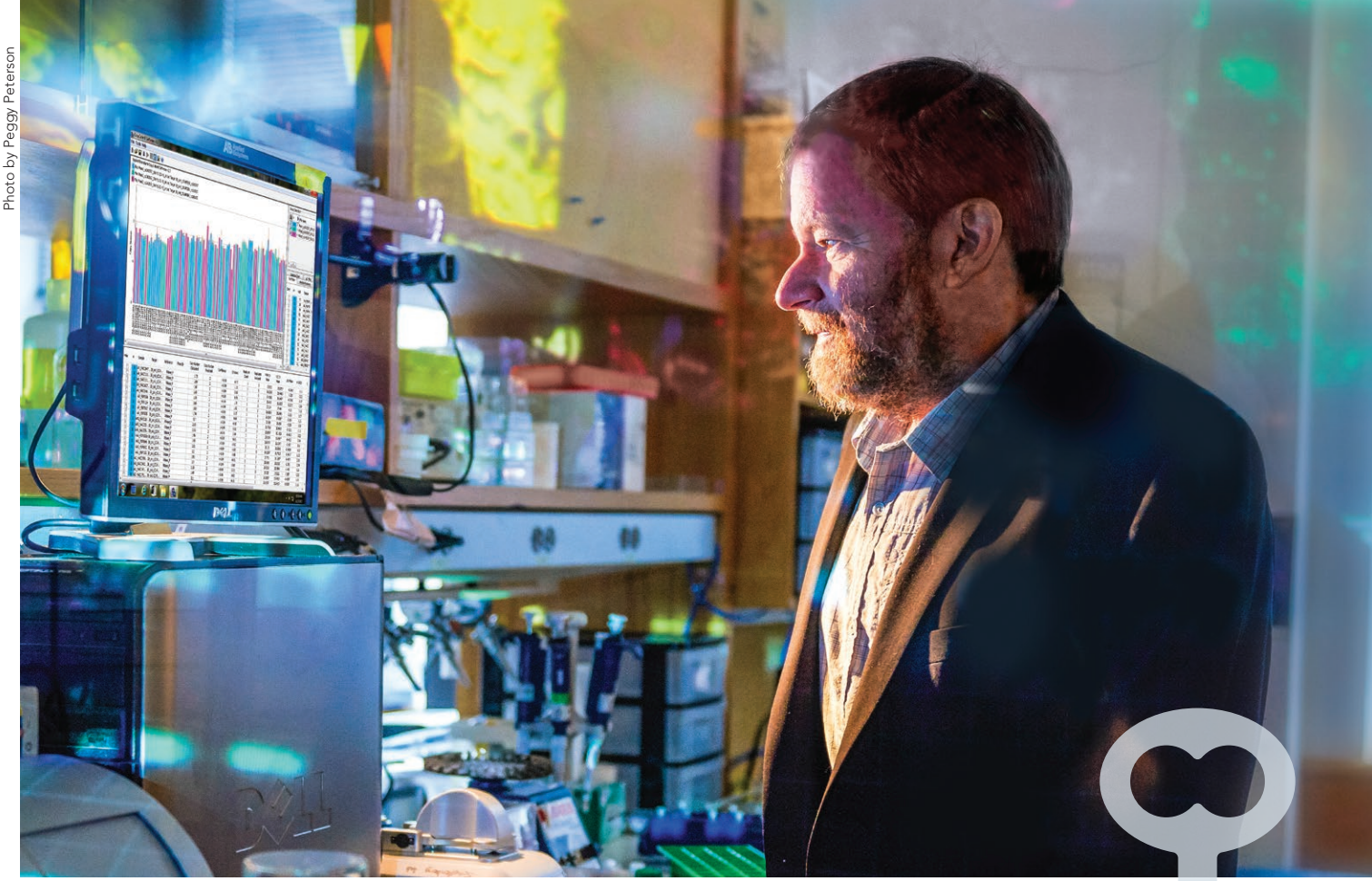


Photo by Peggy Peterson

"If we could solve Guam disease at some point, it would help with these other neurodegenerative disorders," said Gerard Schellenberg, PhD. "Or, it may be the other way around."

confined to Guam, and pretty much confined to Chamorros," Steele said. "But that wasn't the case."

Over all this time, there was no consensus among the Chamorro people, either. Verena Keck, PhD, of the University of Heidelberg in Germany, noted in her book, *The Search for A Cause: An Anthropological Perspective on a Neurological Disease in Guam, Western Pacific,* that many locals were re-interpreting theories such as overall poor eating habits, not one seed, or "bad blood" from interfamilial marriages. Others pointed to military waste or a locally infamous and vengeful Spanish Catholic priest. Legend has it, in the 1700s, a family stole mangoes from a tree outside of his Umatac church, and as a consequence, he put a curse of fatal paralysis on that family and its descendants.

Untangling a Disease

Halfway across the world at Penn in the 1990s, Trojanowski joined the search for the "skeleton key" that might unlock the secrets of both lytico-bodig and other, more common neurodegenerative diseases, with his life and lab partner, Virginia M.-Y. Lee, PhD, a professor of Pathology and Laboratory Medicine at PSOM and director at its Center for Neurodegenerative Disease Research. As Alzheimer's researchers, their focus was on neurofibrillary tangles formed by abnormal versions of proteins called tau that clump together within nerve cells and their processes, a discovery the pair made in 1991.

Tau tangles are hallmarks of Alzheimer's disease and an underlying feature in both lytico and bodig that Trojanowski, Lee, and others believed could reveal clues to its cause. One of lytico-bodig's distinctions rests in the topography of its tangles: They are more prominent in the spinal cord compared to other diseases. Otherwise, the brain of a lytico-bodig patient is remarkably similar to the brain of an Alzheimer's patient.

"It was intriguing because it was dominantly a tauopathy, a neurodegenerative disease in which tau pathology is the main underlying brain abnormality," Lee said. And the correlation between the tau tangles and cognitive deficiencies closely mimicked Alzheimer's disease. "So, this was an opportunity to study a pure tau disease and its impact on the nervous system."

A key collaboration in that study began in 1996 when Trojanowski and Lee met Schellenberg for the first time at a medical conference at another researcher's poster presentation on lytico-bodig. "John walked up, and we started talking about genetics," recalled Schellenberg, who was on faculty at the University of Washington at the time. They all decided to team up to study lytico-bodig shortly thereafter and have worked together in collaborative studies of neurodegenerative tauopathies continuously ever since. It's how Schellenberg ended up coming to Penn in 2008.

The three were named co-investigators on a grant awarded to researchers across the country in 1997 by the National Institute on Aging (NIA) of the NIH. After a lull in NIH support for lytico-bodig following the closure of the Guam research center, the grant represented a renewed investment in the disease. It would last 10 years and add up to

nearly $20 million. Collaborators on the project also included the principal investigator W.C. Wiederholt, MD, and Douglas Galasko, MD, from the University of California, San Diego, and Ulla-Katrina Craig, DrPH, from the University of Guam.

Some interaction between aging, genetics, and the environment served as the driving hypothesis for this grant. By this time in the late '90s, scientists could depend on more advanced genetic technology to help answer these questions. While Trojanowski and Lee worked in Philadelphia to investigate the pathogenesis and development of neurofibrillary tangles, Schellenberg, in Washington, focused on the genetics of tau proteins and the interaction of genetic and environmental risk factors in disease.

Trojanowski and Lee led studies showing that many of the abnormal proteins in other neurological diseases existed

Photo by Peggy Peterson

Though lytico-bodig has virtually disappeared from Guam, Schellenberg still has samples and data. "If something new comes up, I'll find a way to pursue it," he said.

in lytico-bodig patients in addition to tau, including Aβ in Alzheimer-like amyloid plaques, alpha-synuclein that Lee and Trojanowski showed were the building blocks of Parkinson's disease Lewy bodies, and TDP-43 inclusions that Lee and Trojanowski discovered are the pathological brain signatures of frontotemporal degeneration and ALS.

Finding the misfolded protein TDP-43 made the disease unique and important, in part because it helped better distinguish the disease. Some asymptomatic Chamorros in their 30s and 40s and many over the age of 50 had some variation of tangles in their brains. This group, however, had little or no TDP-43 pathology prior to age 70, the Penn team found in studies of control subjects, while patients with lytico-bodig did. Pathological TDP-43 might therefore reflect a more specific disease process, the authors concluded in a 2007 *Acta Neuropathologica* paper.

Trojanowski and Lee further spurred what seemed to be a tantalizing approach to therapies. They first engineered a mouse with spinal cord tangles and motor weakness to model lytico-bodig, a feat in itself published in the journal *Neuron*, as the first authentic model of the disease. Then they successfully offset the spinal cord tau pathology for the first time by using paclitaxel, a known cancer compound that functions as a "microtubule stabilizing" drug. That proof-of-principle led to other animal models and investigations with the drug in studies of Alzheimer's and other diseases involving misfolded tau.

Trojanowski and Lee then discovered a more brain penetrant and therapeutically effective microtubule stabilizing drug for the treatment of Alzheimer's, lytico-bodig, and related tauopathies, called epothilone D. Remarkably, the drug slowed tau buildup in the brain, helped improve cognition due to the build-up of tau tangles, and reduced nerve dysfunction in mice, several of the team's studies showed.

But this, too, became another dead end in the search for answers to lytico-bodig: Despite epothilone D's promise, the drug was shelved in 2013 when Bristol-Myers Squibb, the drug's maker, shifted its focus away from Alzheimer's. Trojanowski considered that act an abandonment of one of the most promising drugs that mitigates tau pathology in mouse models of Alzheimer-like and lytico-bodig-like tau pathology and neurodegeneration.

Meanwhile, Schellenberg's risk-factor subproject on the NIA grant led him down a breadcrumb trail from genes to environmental exposures and back to genetics.

He and his colleagues found that variants in the tau gene known as *MAPT* contributed to a higher risk of developing lytico-bodig, but they weren't dominant mutations. That meant if it the variants were to blame, they needed help to trigger the disease, like an environmental factor.

Schellenberg was surprised to find that consumption of *fadang*, the flour of the cycad seed, did show up as a risk factor in epidemiological studies. But that didn't necessarily mean the consumption contributed to the disease, he noted. It might just correlate with a more rural lifestyle.

"The problem is that when you say environmental risk factor, the first thing that comes to mind is that people are eating a toxin," Schellenberg said. "It could also mean that you are consuming something protective. A [different] diet perhaps protects you against the lytico-bodig on Guam. You may be looking for something rare that disappeared, or something that has now become common that protects."

The concurrent demographic shifts on Guam and changes in the disease rate made it challenging to find answers based on environmental exposures. Cases of lytico-bodig peaked in the 1950s, right around the time the island started to become more westernized, and slowly declined thereafter. Save for a peak in bodig cases in the 1990s, by the mid-2000s, the disease pretty much disappeared altogether. By then, Guam looked more like mainland America with amenities, restaurants, grocery stores, construction, and more. People changed the way they ate and lived, re-

Keeping an Eye on the Disease

In a nursing home in Michigan lies John Samuel Terry, a World War II veteran stationed on Guam in 1945, now 93 and severely disabled with symptoms of advanced Parkinson's. His daughter Rebecca Lawlor, a nurse, believes he might instead have lytico-bodig.

"It will immeasurably advance our knowledge if he does," Canadian neurologist and long-time Guam resident John Steele, MD, wrote to Lawlor in an email in the fall of 2016.

That email came shortly before Terry's appointment with an ophthalmologist to determine if he had a pigment, a scar really, on his retina, that a Navy doctor first spotted in the 1970s in lytico-bodig patients. With its meandering crisscross pattern, it resembled the handiwork of a botfly's parasitic larvae, which migrate to the eye through the blood via infected mosquitoes or other biting insects. Steele teamed up with neurophthalmologist Terry Cox, MD, in the mid-1980s to pursue the phenomenon, which they called linear pigment retinal epitheliopathy (LPRE).

What exactly left the markings is unclear because no parasites were ever found in examinations, but reports from Cox and Steele showed a link between LPRE and the disease.

There is a precedent for a connection between retinal disease and brain disease. The eye is part of the nervous system, and damaging it can lead to neuroinflammation, which is a common thread among many neurodegenerative diseases, said Joshua Dunaief, MD, PhD, a professor of Ophthalmology at Penn's Scheie Eye Institute. A fleeting parasitic infection in the eye could trigger a lasting immune response. "So regardless of what the neuroinflammation was initiated by, once it's rolling and raging, the mechanisms lead to neurodegeneration," Dunaief said.

But at Terry's ophthalmology appointment, no retinal pigmentation could be found. His disease is likely Parkinson's. Now 82 and mostly retired, Steele waits. Only an autopsy upon Terry's death, which his daughter consented to, will officially rule lytico-bodig out. In 2015, right after he published his last LPRE paper in the journal *Movement Disorders*, Steele packed up his apartment overlooking Agana Bay and left Guam.

"My interest and passion about the whole disease will continue," Steele said. "It does seem, though, it may be a mystery that is never understood."

searchers from the NIA grant noted in a 2003 paper in the *American Journal of Epidemiology*. And that made the epidemiological studies a virtual dead end.

Into Obscurity

When the NIA grant ended in 2007, Daniel Perl, MD, who studied the disease for decades and is now at the Uniformed Services University of the Health Sciences in Bethesda, Md., said the NIH urged him to keep lytico-bodig specimens intact so they could be made available to investigators in the future. Today, he said, some of the rare and limited samples he's held onto are with four different research groups, and three of these projects have full or partial NIH support.

Details are scarce, but Perl, along with Galasko, who is still at UCSD, plan to start up a new investigation, which is not funded by the NIH, analyzing mRNA expression for genetic mutations in frozen brain samples. This, and Cox's continued studies on BMAA, are among the few projects still investigating lytico-bodig.

Schellenberg's last paper on lytico-bodig was published in *JAMA Neurology* in 2013, five years after the grant ended. While lytico-bodig afflicted mainly Chamorro people, cases of a very similar disease on the Kii Peninsula in Japan and in Western New Guinea had scientists linking them together, though several studies have muddied that water, including Schellenberg's.

A mutation known as *C9orf72*, linked to ALS in Western populations, was found to be the driver of disease in the Japanese cases; however, Schellenberg and colleagues found no such mutation in Chamorro patients. They concluded that the mutation wasn't the cause of lytico-bodig.

"So that was the last thing," Schellenberg said. "I have samples, all sorts of information. If something new comes up, I'll find a way to pursue it."

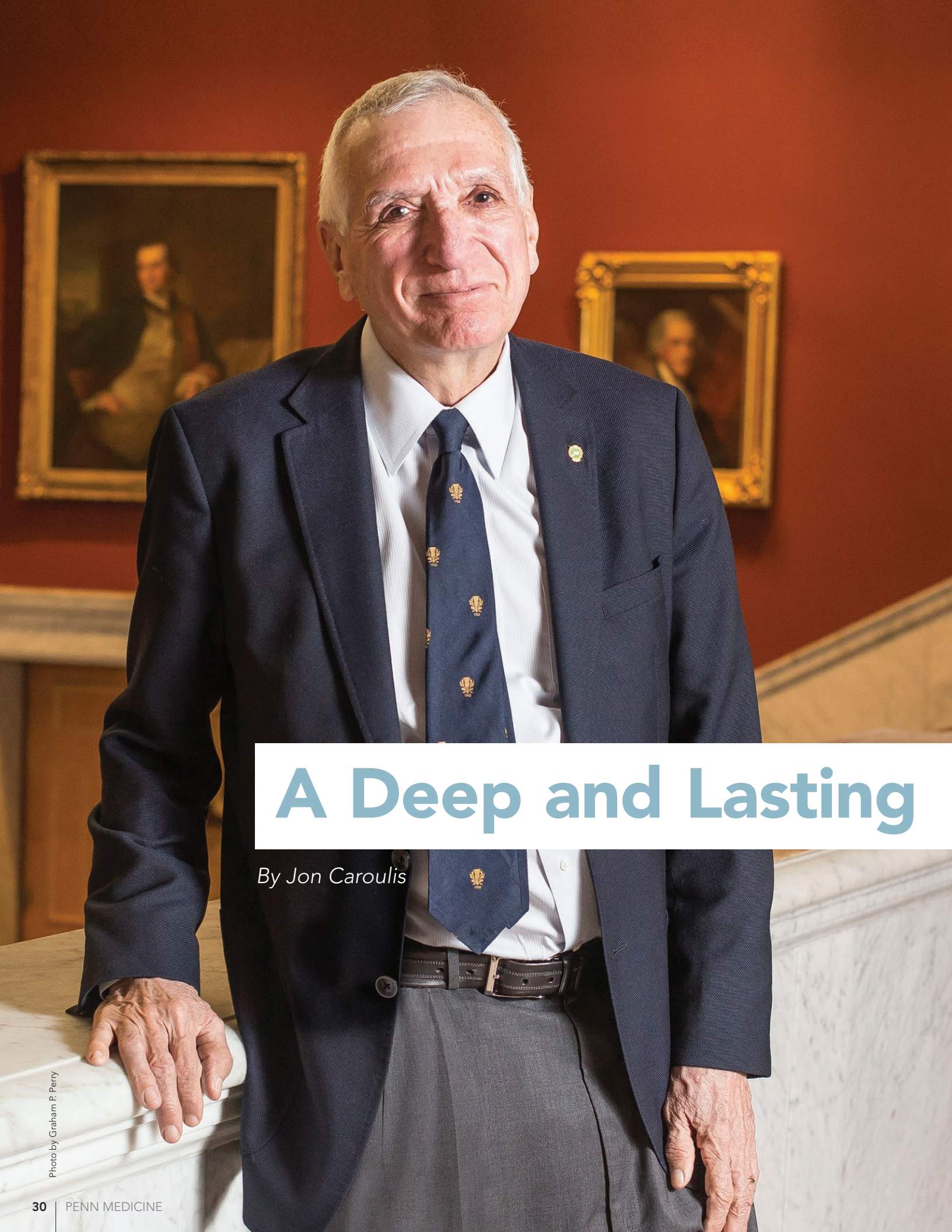
As lytico-bodig fades into relative obscurity on Guam, the onetime epidemic lingers in the memory of the generations old enough to remember and mourn those buried at the Umatac Cemetery and others like it across the island. And it endures in the form of its continuing influence on research into similar diseases.

Trojanowski and Lee revived their work with microtubule stabilizing compounds after the grant ended but with another drug, dictyostatin, and a focus on Alzheimer's and other tauopathies, like progressive supranuclear palsy. A 2016 study in *Acta Neuropathologica Communications* showed that dictyostatin mirrored many of the promising results found with the related, abandoned drug epothilone D in the mouse model of lytico-bodig. That finding reinforced the power and potential of microtubule stabilizing drugs to treat tau diseases, the authors said.

"Guam contributed to new ideas for therapies to treat Alzheimer's," Trojanowski said. "But I don't see a path forward for lytico-bodig. Its time has come and gone. Time to move onto the next challenges."

Steve Graff is the former assistant director of strategic communications in the department of Communications at Penn Medicine. He moved to Guam in the summer of 2016 and currently works as a freelance writer and an environmental scientist on the island.

Read this story online with related links, including the author's behind-the-scenes look at reporting on lytico-bodig while living on Guam, at PennMedicine.org/magazine/guam.



A Deep and Lasting

By Jon Caroulis

Photo by Graham P. Perry

After Nearly a Half Century at the National Institutes of Health, William Eaton Continues to Make Biophysical Breakthroughs

Passion for Science

It was the fall of 1967. The war in Vietnam was escalating. The University of Pennsylvania's medical school dean Samuel Gurin, PhD, had told William Eaton, BA'59, MD'64, PhD'67, that if he did not take an internship that it was unlikely he'd be drafted into the armed forces, and that he could continue a career in basic research after graduation from medical school without interruption.

The dean was wrong.

Eaton received his draft notice, but learned he could fulfill his military obligation by joining the U.S. Public Health Service as a medical officer. He landed a research position at the National Institutes of Health (NIH) in Bethesda, Md. Now approaching the 50th anniversary of his arrival, Eaton is still there as an NIH Distinguished Investigator.

Eaton has enjoyed a prodigious career buffeted by lucky breaks—from landing in his dream job as a basic scientist instead of at the Vietnam warfront, to carrying out research alongside a gaggle of Nobelists thanks to a well-timed airmail letter—and distinguished by important insights on the physical properties of the molecules of life and disease. And at 78, he has no plans of stopping.

"When I left Penn for the NIH—a relatively unknown federal research institution at the time to my fellow chemical physics graduate students—they felt sorry for me since I was not headed for academia," Eaton recalled. "It did not take long before they started to envy my position as a basic researcher in what I believe is arguably the greatest research institution in the U.S."

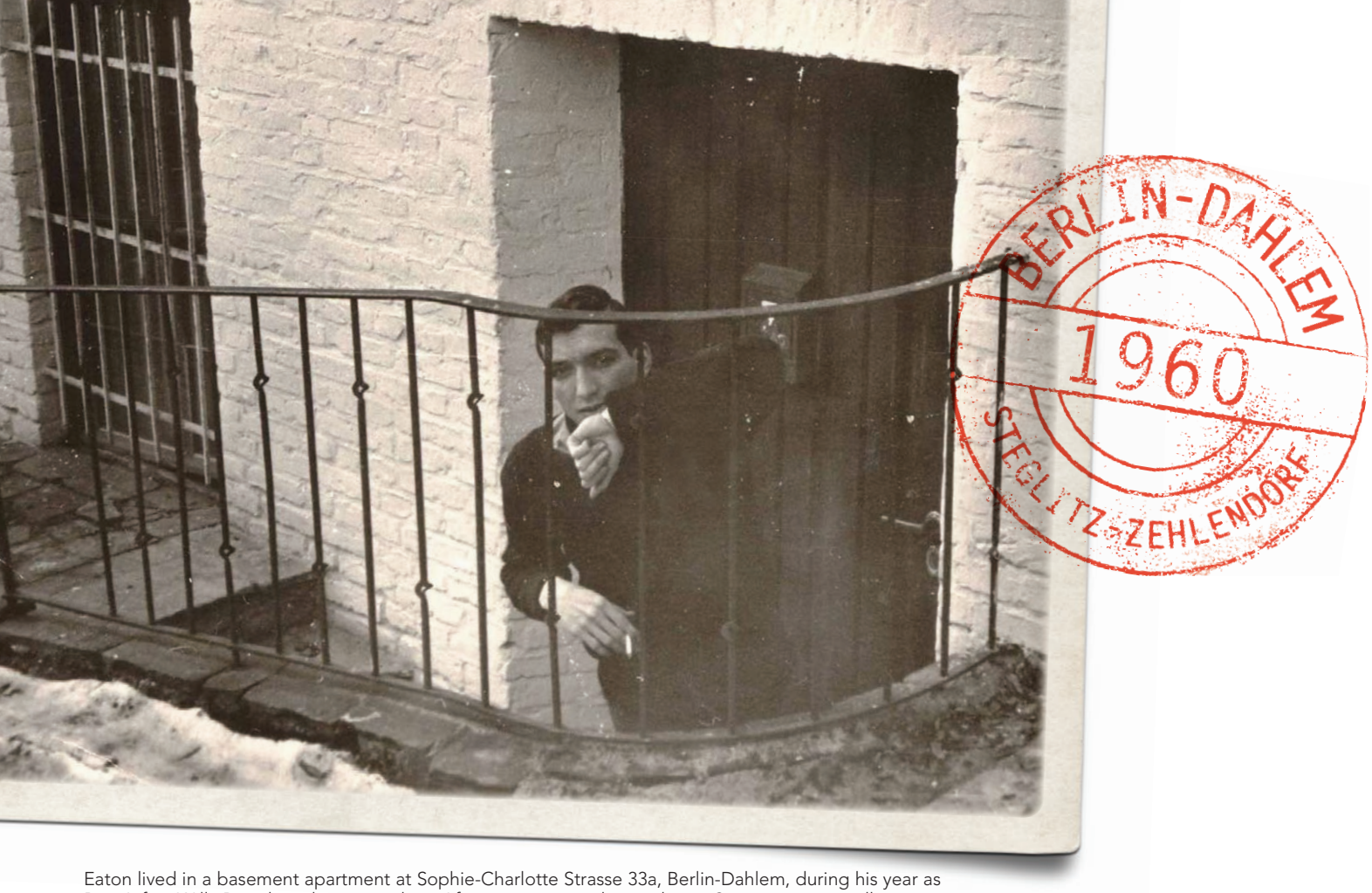
He has served for the past 30 years as chief of the Laboratory of Chemical Physics, the major biophysical science laboratory at NIH, where he has made important discoveries on the molecular basis of sickle cell anemia and the folding of proteins. These research accomplishments have been recognized by his election to the National Academy of Sciences and many prestigious awards, including the Perelman School of Medicine's Distinguished Graduate Award in 2014. Since 1986, Eaton has been the scientific director of the NIH's Intramural Aids Targeted Anti-viral program (IATAP), taking time away from his own research to oversee a significant part of NIH's basic research on the human immunodeficiency virus (HIV) and recruiting scientists to come to the NIH to work on HIV structural biology.

In West Philadelphia, Born and Raised

Eaton grew up not far from the Penn campus within a family of Penn graduates. Family members who are also Penn alumni include his mother—who Eaton said might have been the first woman to earn a graduate degree from Penn in the classics, and whose intellectual inclinations Eaton cited as a major influence—his brother, sister, and a daughter. (His wife, Gertrude, BA'59, MA'62, PhD'72, whom he met as an undergraduate, as well as both of Gertrude's siblings, also graduated from Penn. So did her parents; her father, Thomas D. McBride, BA'24, JD'27, later an inspiration to Eaton as a man who earned success through hard work, was a legendary trial lawyer, Pennsylvania attorney general and state Supreme Court justice, whose *pro bono* defense of eight teachers accused of communist activities put a halt to the McCarthy hearings in Philadelphia.)

Eaton's interest in science did not begin by playing with chemistry sets, but when he was 11 he did conduct a chemistry "experiment." An adventurous friend whose father owned a pharmacy enlisted Eaton to collaborate on building a bomb from chemicals found in the store. On an empty lot at 44th and Locust Streets, Eaton and his friend packed a Campbell's soup can with potassium nitrate and sulfur and inserted a fuse to ignite the incendiary. It worked, causing an explosion big enough for the police and fire departments to investigate, but the culprits escaped undetected.

Though Eaton had always wanted to be a doctor and was thrilled to be accepted into medical school at Penn, early in his educational career he decided he might want to pursue research. His interest was sparked by his work as an



Eaton lived in a basement apartment at Sophie-Charlotte Strasse 33a, Berlin-Dahlem, during his year as Penn's first Willy Brandt exchange student. After getting mixed up with anti-Soviet counterintelligence in December 1959, he said, "I spent the last six months in that apartment scared."

undergraduate with the research group of famous electrochemist and professor John O'Mara Bockris, PhD, DSc.

"They had no access to computers, and I was recommended by the math department as someone who could perform calculations reliably," Eaton recalled.

Global Intrigue

After graduating with a degree in chemistry and an interest in using the methods of physics and physical chemistry in research, Eaton was the first recipient of the Willy Brandt exchange fellowship between Penn and the Free University of Berlin, which provided him with an opportunity to study in Germany for a year before beginning medical school—taking a brief, unplanned turn as a Cold War spy along the way.

In December 1959, a year and a half before construction of the Berlin Wall began, Eaton and two friends crossed over to East Berlin to inquire at the Soviet embassy about getting visas to visit the Soviet Union. He was met there by the embassy's cultural secretary, whose parting comment after a friendly discussion was, "Mr. Eaton, perhaps we can meet again sometime." A month later, the cultural secretary telephoned Eaton requesting a book about Abraham Lincoln, and the two arranged a meeting in a West Berlin café. Once Eaton disclosed the contact to a close friend who worked as a Russian language specialist with the U.S. Army, he became wrapped up in covert activities. The U.S. Army Counter Intelligence Corps (CIC) asked him to report as much as he could remember about each of his several subsequent meetings with the cultural secretary who, he was told, was a member of the KGB.

In retrospect, Eaton came to believe that the secretary was testing to see if he was a candidate for defection, while the CIC sought to understand the Soviets' recruitment tactics. He gave a full accounting of all of his experiences to the FBI, sitting in a car at 37th and Spruce streets, upon his return to Philadelphia. He still hopes to someday see a transcript of that interview, which arrived largely redacted and marked "SECRET" in response to his Freedom of Information Act requests after the Cold War's end.

(Not to be outdone, the second Willy Brandt exchange fellow who went to Berlin from Penn after Eaton, Marvin W. Makinen BA'61, MD'67, was arrested for spying in the Soviet Union and was imprisoned in Russia for two years.)

When he started pursuing his medical degree, Eaton received several opportunities to carry out basic research, one of which brought him back to Europe.

Though Eaton stayed at Penn for the summer after his first year to work on muscle biochemistry with Robert E. Davies, PhD, his second summer brought him into contact with a larger group of scientific luminaries overseas, thanks to a terse but career-defining communication. He went to work at the Medical Research Council Laboratory of Molecular Biology in Cambridge, U.K., with Sydney Brenner, MBBCh, DPhil, one of the founders of molecular biology.

"I'd heard Sydney give a lecture [at the Federating meeting] in Atlantic City on the genetic code, which was simply

spellbinding," Eaton recalled in 2009 profile in *Proceedings of the National Academy of Sciences* (*PNAS*). "I wrote a letter asking if I could come to work with him. His response was characteristically Sydney, a thin aerogram that read:

'Dear Bill, Come if you like. Sydney'"

And so Eaton worked on purifying an enzyme involved in protein biosynthesis for a summer in the company of scientists who had six Nobel prizes among them: Brenner, Fred Sanger (two prizes), John Kendrew, and Francis Crick, in addition to Max Perutz, the head of the Laboratory of Molecular Biology.

"Listening to Sydney and Francis discuss and define the major outstanding problems of modern biology at coffee, lunch and afternoon tea in the canteen was a great experience," Eaton told *PNAS*. "That summer convinced me that I wanted to do research full-time as a career."

Biophysical Insights into Cell Sickling

Eaton was among the earliest Penn alumni to earn a PhD and an MD from the University. He credits Robin M. Hochstrasser, his PhD thesis supervisor, who also became a close friend, as the most important faculty member at Penn for igniting his initial interest in a science career into much more. "Robin's brilliance, charisma and encouragement turned that [interest] into a deep and lasting passion for science, which I retain to this day," he said.

Working with Hochstrasser, Eaton developed microscope techniques to make optical absorption measurements in polarized light on very small, single crystals of proteins including myoglobin, which carries oxygen in muscles, and hemoglobin, which carries it in blood.

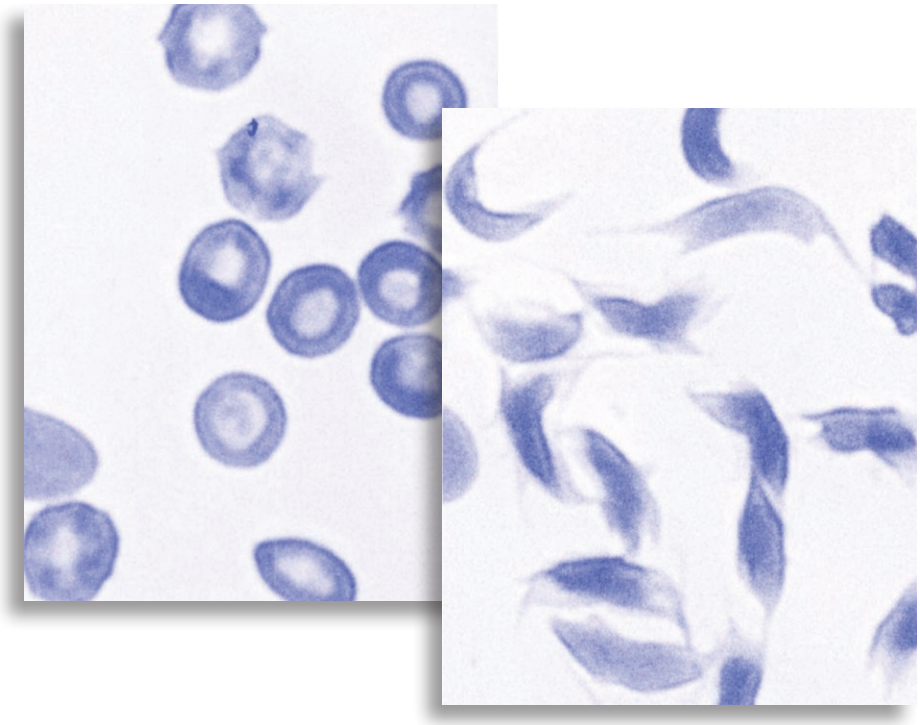
The application of these techniques made it possible for Eaton to use his medical and scientific abilities together to make significant discoveries in sickle cell anemia, which was emerging in the early 1970s as a "hot" area of research in both hematology and biochemistry. A large investment by the NIH and the creation of the Sickle Cell Disease Branch in the National Heart Institute to distribute the funds in grants and contracts to universities partially fueled this surge in interest.

Sickle cell anemia is a hereditary disease that results in chronic damage to multiple organs and acute episodes of pain so severe that they are called "sickle cell crises." In the U.S., it is considered an "orphan disease" because there are only about 100,000 patients, almost all of African descent. However, many millions are afflicted worldwide, primarily in Africa, but also in the Middle East, the Mediterranean, and India. The disease is caused by the formation of fibers when red blood cells unload oxygen in the small vessels of the tissues. The hemoglobin fibers distort and stiffen the cells into a fixed shape resembling a shepherd's sickle, instead of the round, squishy healthy cells that can squeeze through narrow vessels. The less-flexible sickled cells getting stuck and occluding vessels is the root cause of the disease.

"I knew of an experiment on the optical properties of single sickled cells in polarized light, which was given the wrong interpretation by a prominent sickle cell researcher at the time," Eaton said. "This was a subject that I knew well because of my PhD thesis research."

Shortly thereafter, he learned of work by Perutz and John Finch, PhD, at the Laboratory of Molecular Biology which proposed a structure for the sickle hemoglobin fiber.

With a postdoc, James Hofrichter, PhD, Eaton carried out model-building studies based on their optical experiments on the orientation of the hemoglobin molecule. The pair determined from their model building that the Perutz/Finch structure could not be correct. Eaton wrote a letter to Perutz, pointing out their mistake. In response, Perutz invited Eaton to show why he was wrong in a presentation at the Royal Society of London in January, 1973—the major meeting on hemoglobin of the era—with all travel expenses paid by Perutz.



"Bill's lecture on the optical properties of the sickle hemoglobin fiber was brash, ebullient and brilliant," said H. Franklin Bunn, MD'61, a professor of medicine at Harvard Medical School and recipient of the 2003 Distinguished Graduate Award, who first met Eaton at that Royal Society gathering. "From that day on he has remained in the top echelon of biomedical research."

John Hopfield, PhD, the Howard A. Prior Professor of Molecular Biology, Emeritus, at Princeton University, also

met Eaton during this time. "I still remember his clarity of thought, both in his writings and in his lecture presentations, where he was clear not just about what he knew, but also refreshingly frank about what he did not know," Hopfield recalled.

His presentation was so well-received at the meeting that it motivated Eaton to devote his career full-time to learning how the sickle cell fibers form, and he went on to do so—with some time instead focused on protein folding—at the NIH.

Working with Hofrichter and Philip Ross, PhD, Eaton's key discovery was that there is a marked delay period before the appearance of fibers, and that the delay time is enormously sensitive to the sickle hemoglobin concentration. He immediately recognized that these highly unusual kinetics could explain and predict numerous aspects of the disease.

Factors which decrease the delay time before cells sickle, or that increase the time blood cells spend in transit, make the disease worse because they increase the likelihood that the blood cells sickle while passing through the narrowest

Years after Eaton (right) completed his studies at Penn, his thesis advisor, chemist Robin Hochstrasser, PhD (left), regularly traveled to attend the Eaton family's annual Christmas Eve parties. The gentleman at center also travels regularly to visit homes on Christmas Eve.

vessels, he realized. Conversely, increasing the delay time before sickling or shortening the transit time can benefit patients. This idea suggested that therapies that decrease sickle hemoglobin concentration by a small amount would allow more cells to escape the small vessels before fibers form.

"I was absolutely thrilled when I found that out," Eaton said. "You don't get too many chances in science to make a real discovery."

The only drug for treating sickle cell disease that is approved by the Food and Drug Administration, hydroxyurea, works by precisely this mechanism.

Several years later, working with Hofrichter and postdoc Frank Ferrone, PhD, who had then recently completed his PhD with Hopfield and is now a professor of physics at Drexel University, Eaton and colleagues revealed a new kind of mechanism to explain the unusual sickle hemoglobin kinetics. Not only do hemoglobin fibers aggregate into polymers as a first step toward stiffening the cells, but the polymers themselves induce the formation of new polymers on their surfaces.

"It explained how so many polymers could form so rapidly, and was a process that was previously unknown in the realm of biological polymerization," Ferrone wrote for *Scientific American* in 2013, remarking on the new adoption of an equivalent mechanism to explain the aggregation kinetics of the peptide that causes Alzheimer's disease.

After learning that there had been little progress in finding additional drugs after the approval of hydroxyurea in 1998, Eaton returned to work on sickle cell anemia about 10 years ago. His current research uses a drug-screening method initially developed by a former postdoctoral fellow, Jeffrey F. Smith, PhD. (Before working with Eaton, Smith received undergraduate degrees in business and chemical engineering, a master's degree in bioengineering, and an MBA at Penn, and did so in only four years and one summer with an A in every course but one. In order to attract Smith to his lab, Eaton sponsored his graduate studies at the University of Cambridge through an NIH partnership program.)

Hard Problems and Lasting Legacies

"Why don't you start working on a 'hard' problem, like protein folding?" Peter Wolynes, PhD, a renowned scientist and the leading theorist in the protein folding field, asked Eaton in 1991 at a meeting on protein dynamics in Chernogolovka, near Moscow, organized by the Soviet and U.S. academies. That question launched a new chapter in Eaton's professional life. Though Eaton regards his work on the kinetics of sickle fiber formation to be his most significant achievement, he has received more recognition and awards for his work on protein folding.

Protein folding is a process by which a chain of amino acids assembles from a myriad of random structures into a distinct three-dimensional structure that is necessary for the protein to perform its biological function. Understanding the physics of protein folding is essential for understanding protein misfolding that leads to aggregation, the cause of many diseases, including Alzheimer's disease, type II diabetes and Parkinson's disease.

Eaton used an experiment he learned of from Penn biophysicist Heinrich Roder, PhD, using a laser pulse to initiate the folding of a protein and monitoring the process with a high-precision spectrometer developed in Eaton's own lab. The experiment allowed Eaton to observe the early events in the folding of the protein cytochrome c, dramatically improving the time resolution of kinetic studies in this field from the millisecond to the nanosecond time scale and launching what has come to be known as the "fast folding field."

Photo by Graham P. Perry

Eaton met his wife, Gertrude McBride, at the Fisher Fine Arts building at Penn, then the University Library. Both the Eaton and McBride families contain numerous Penn alumni.

More recently, Eaton pioneered the application of fluorescence measurements on single protein molecules to study the fastest events of crossing the energy barrier between folded and unfolded states. Both advances now play a critical role in scientists' evolving understanding of how proteins fold.

Eaton's efforts are additionally having a powerful and lasting impact through his work in building the Laboratory of Chemical Physics and his "good citizen" job as scientific director of the IATAP, funding and recruiting NIH scientists to study the basic science of AIDS. The laboratory is reputed as one of the best groups of biophysical scientists anywhere, according to Eaton, and the AIDS program is now a model for new special granting programs within NIH in areas such as bioterrorism and translational research.

"Exercising the extraordinary scientific taste that resulted in his own research success, Bill Eaton has built an intramural grant program supporting an outstanding group of scientists who study the structural and cellular biology of HIV/AIDS," said Michael Gottesman, MD, the scientific director of NIH. "Bill is one of the pillars of a powerful basic science research program at NIH that has helped move basic biomedical research forward."

In addition to his election to the National Academy of Sciences, Eaton's many honors include The Max Delbruck Prize in Biological Physics from the American Physical Society; the Founders Award of the Biophysical Society; the Neurath Award of the Protein Society; The John Scott Award of the City of Philadelphia; the Humboldt Research Award for Senior Scientists; the 2015 Penn Chemistry Distinguished Alumni Award; election to the American Academy of Arts and Sciences and to the Accademia Nazionale dei Lincei of Rome; and in 2016, an honorary doctorate from the Free University of Berlin sponsored by its physics department.

Now that his daughter, Helen Eaton, a Penn graduate (BA'93) and Juilliard-trained violist, is settled in Philadelphia with her family as chief executive officer of the Settlement Music School, Eaton makes frequent visits to Philadelphia and calls himself "a born-again Philadelphian."

Though he has no interest in retirement, Eaton acknowledges he has slowed down a little and no longer works late into the night—"only" about 60 hours per week.

"There is no reason for me to retire," he said, "since I have nothing that I would like to do every day more than research." ▽

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

Highest Honors:

A Special Celebration of Endowed Professorships at Penn Medicine

More than 300 guests came to the Hyatt at The Bellevue for Penn Medicine's **December Endowed Professorships** dinner, celebrating the extraordinary achievements that endowed professorships can make possible. Chairholders were presented with their endowed chair medals and certificates, and all guests received a copy of the *Endowed Professorships* book, a handsome blue and gold volume that includes profiles of each endowed chair and lists its chairholders.

The centerpiece of the evening was a conversation with **Penn President Amy Gutmann, PhD**, and panelists **Michael Parmacek, MD; E. John Wherry, PhD; Donita Brady, PhD; Shelley Berger, PhD; and Ezekiel Emanuel, MD, PhD**—all endowed chairholders.

The panelists provided compelling testimony on the power of academic medicine and how endowed professorships have shaped their lives and deepened the impact of their careers.

"Endowed professorships hold a special place in academic medicine," explained Perelman School Dean J. Larry Jameson, MD, PhD. "We are proud to offer this evening as tribute to our donors, the individuals after whom these endowed chairs are named, and the distinguished faculty members who hold them." ▽

Snapshots of Recently Appointed Endowed Chairs

Lerman and Glick

Caryn Lerman, PhD, the vice dean for Strategic Initiatives for the Perelman School of Medicine, celebrated her appointment as the **John H. Glick, MD Professor in Cancer Research** in October 2016. The Glick Professorship in Cancer Research was made possible through the generosity of numerous philanthropic partners, and honors John Glick, MD, the Madlyn and Leonard Abramson Professor of Clinical Oncology and former director of the Abramson Cancer Center (ACC).

E. John Wherry, PhD, was named the inaugural **Richard and Barbara Schiffrin President's Distinguished Professor**. He serves as co-director of the recently-launched Parker Institute for Cancer Immunotherapy at Penn and has led Penn Medicine's Institute for Immunology since 2012. The chair was established through the generous support of Richard and Barbara Schiffrin, who are powerful advocates for disease research at Penn Medicine and the Abramson Cancer Center. They are also members of the ACC Director's Leadership Council.

Wherry with the Schiffrins

Mauck with Dean Jameson

Robert L. Mauck, PhD, is the inaugural **Mary Black Ralston Professor for Education and Research in Orthopaedic Surgery**. He is also director of the McKay Orthopaedic Research Laboratory and co-director of the Translational Musculoskeletal Research Center at the Philadelphia VA Medical Center. The Ralston Chair was made possible through a bequest by Edgar Ralston, MD—chair of the department of Orthopaedic Surgery from 1960 to 1977—to honor his wife, Mary, a longtime volunteer at the Hospital of the University of Pennsylvania.

James Wilson, MD, PhD, director of the Gene Therapy Program at Penn Medicine, is the inaugural **Rose H. Weiss Orphan Disease Center Director's Professor**. The Weiss chair was made possible by George Weiss, a Wharton graduate of the Class of 1965, in honor of his late mother, Rose. Weiss helped found the Orphan Disease Center at Penn in 2011. Its mission is to improve the quality of life of those afflicted with rare diseases—defined as a single disease affecting 200,000 or fewer people in the U.S.—and ensure that patients worldwide have access to the latest novel therapies.

Weiss and Wilson at Penn's Orphan Disease Center

Legendary Names Live On Through Endowed Professorships

As this issue of *Penn Medicine* marks the passing of Peter Nowell, MD'52, we celebrate some endowed professorships created to honor Perelman School of Medicine luminaries.

Established in 2015 by faculty and many long-time supporters of the Abramson Cancer Center and the department of Pathology and Laboratory Medicine, the **Peter C. Nowell, MD Professorship** honors this groundbreaking physician-scientist and first director of the Abramson Cancer Center. Nowell was named the Gaylord P. and Mary Louise Harnwell Professor in 1990, a position he held until his retirement in 2006.

In addition to holding the Nowell Professorship, **Kojo S.J. Elenitoba-Johnson, MD**, is director of Penn Medicine's Center for Personalized Diagnostics and director of Precision and Computational Diagnostics in Pathology and Laboratory Medicine. His research focuses on the pathogenesis of malignant lymphomas and biomarker discovery using genomics and proteomics.

The Penn community mourned the loss of Nowell on Dec. 26, 2016, and held a memorial service on March 1, 2017.

Drs. Mark Greene, Kojo Elenitoba-Johnson, David Roth, and Dean Jameson with the late Dr. Peter Nowell

The **Jonathan E. Rhoads Professorship of Surgery** was established in 1978 through the contributions of colleagues, friends, and grateful patients of Rhoads, honoring his more than 50 years of distinguished contributions as physician, scientist, educator, scholar, and chair of Surgery at Penn Medicine. Rhoads is credited with numerous medical advances, including early exploration into the use of antibiotics and the development of intravenous hyperalimentation.

Current Rhoads chairholder **Douglas Fraker, MD**, vice chair of research and chief of Endocrine and Oncologic Surgery, has pioneered isolated liver perfusion and intraperitoneal photodynamic therapy, and is one of the most accomplished clinical endocrine surgeons in the U.S.

The **Edward Rose, MD and Elizabeth Kirk Rose, MD Professorship** celebrates two of the Perelman School's most distinguished alumni and physicians. Edward Rose, MD'21, became known worldwide for the diagnosis and treatment of disorders of the thyroid gland; prior to joining the Perelman School faculty, Elizabeth Kirk Rose, MD'26, headed the division of Maternal and Child Health at the Philadelphia Department of Public Health.

Current Rose chairholder **Jason H. Moore, PhD**, the senior associate dean for Informatics, leads an active NIH-funded research program focused on the development of artificial intelligence and machine learning algorithms for the analysis of complex biomedical data.

The **Benjamin Rush Professorship of Biochemistry** honors a signer of the Declaration of Independence, treasurer of the National Mint, president of both the American Society for the Abolition of Slavery and the Philadelphia Medical Society, and a founder of the College of Physicians of Philadelphia. In 1769, Rush was named professor of Chemistry, and 20 years later he succeeded Perelman School founder John Morgan, MD, as chairman of Theory and Practice of Medicine. The professorship was created in 1910 through through an anonymous bequest.

Current Rush chairholder **A. Joshua Wand, PhD**, studies applications of nuclear magnetic resonance spectroscopy to fundamental problems in biophysics and biochemistry and develops novel approaches to drug design and discovery.

The **Stuart and Emily Mudd Professorship of Human Behavior & Reproduction** was established in 1975 through a bequest from longtime Penn Microbiology Department Chair Stuart Mudd, MD, as a tribute to his wife, Emily, who was the first woman to be named a full professor at the Perelman School of Medicine and a pioneer in the fields of marriage counseling and family studies.

Current Mudd chairholder **Karl Rickels, MD**, founded both the Mood and Anxiety Disorders Section in Psychiatry and in the division of Human Behavior and Reproduction in Obstetrics and Gynecology at Penn.

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1960s

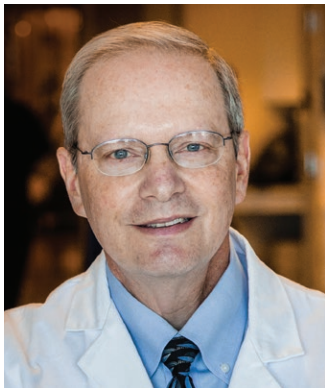
Moritz Ziegler, MD, GME'69, GME'77 was awarded the William E. Ladd Medal, the highest award granted by the Surgical Section, American Academy of Pediatrics, in October 2016. Ziegler retired in 2010 from Children's Hospital Colorado and now resides in Cincinnati. He was previously a faculty member at Penn, Cincinnati Children's Hospital, and Boston Children's Hospital.

1970s

Yale E. Goldman, MD'75, PhD'75, has been appointed co-director at the newly established Science and Technology Center for Engineering Mechanobiology at Penn, funded by a $24 million grant over a five-year period from the National Science Foundation. Goldman is a professor of Physiology and of Biochemistry and Molecular Biophysics in the Perelman School of Medicine, and a professor of Mechanical Engineering and Applied Mechanics in Penn Engineering.

1980s

Robert M. Wachter, BA'79, MD'83, has been appointed chair of the department of Medicine at the University of California San Francisco School of Medicine. He will also become the Holly Smith Distinguished Professor in Science and Medicine. He already holds the Lynne and Marc Benioff Endowed Chair in Hospital Medicine.



Andrew A. Ziskind, MD'84, has been named the new senior vice president of academic strategy on the executive team of Premier, a leading healthcare improvement company. He is an interventional cardiologist who, before joining Premier, was the managing director for healthcare transformation at Huron and a partner at Accenture.

Richard Eric Besser, MD'86, moderated a panel of Penn scientists and leaders celebrating the official launch of Penn's participation in the Sean Parker Institute for Cancer Immunotherapy in October 2016. He serves as chief health and medical editor at ABC News.

1990s

Julie A. Gubernick, BA'86, MD'90, has been elected president of the Pennsylvania Radiological Society, a chapter of the American College of Radiology. She serves as chief of Radiology at Einstein Medical Center Montgomery.

Niraj M. Desai, MD'92, GME'02, is leading a pilot study at Johns Hopkins University to test transplanting kidneys from deceased donors with hepatitis C into recipients who don't already have the virus. The research seeks to provide more organs, even infected ones which require the recipient to take hepatitis C medications, to those on the nation's long transplant waiting list. Desai is an assistant professor of Surgery at Johns Hopkins.

Valerie Weil, MD'91, GME'94, has been appointed chief operating officer at University of the Sciences. She previously served as associate dean for Finance,

Humanitarian Aid Leader Takes New Philanthropic Role

Rajiv Shah, MD'02, becomes the 13th president of the Rockefeller Foundation March 1, succeeding former Penn President Judith Rodin, PhD. Shah, who served on the foundation's Board of Trustees since 2015, will be the first-ever Indian-American to serve as its president. The Rockefeller Foundation is a philanthropic organization that for more than a century has worked to promote the well-being of humanity throughout the world. The foundation pursues this mission through dual goals of advancing inclusive economies that expand opportunities, and of building resilience to help people and communities prepare for and recover from acute shocks and chronic stresses.

For Shah, the seed of his involvement in global aid was planted early. He was raised outside of Detroit, and, during childhood, had several opportunities to travel to India. During one trip, his uncle drove him through a slum where he observed "excruciating poverty" like he had never seen before, he recalled in a 2013 interview with *Wharton* magazine. (He earned a master's degree in Health Economics from Wharton in 2005.) "I remember seeing these other kids that were kind of like me but didn't have shoes and were walking around in open sewage, and were living in these huts with no floors," he said. "I just was blown away and felt like anyone who had the opportunity should really work to end that kind of extreme human deprivation and suffering."

Shah's extensive CV includes service as chief scientist and undersecretary for research, education and economics at the United States Department of Agriculture and a number of leadership roles at the Bill & Melinda Gates Foundation and the International Financing Facility for Immunization.

Shah is widely acclaimed for his work as the administrator of the United States Agency for International Development (USAID), from his appointment by President Obama in 2009 through 2015. During his leadership of USAID, Shah led responses to major humanitarian crises, including the earthquake in Haiti in 2010 and the Ebola outbreak in West Africa in 2014. Shah secured bipartisan support to advance work across the globe to end extreme poverty. In 2014, Shah established the United States Global Development Lab which brings together public and private sector partners to develop innovative solutions to a wide array of international challenges including water, health, food security, nutrition, energy and climate change. When Shah left USAID in 2015, he founded Latitude Capital, a private equity firm focused on power and infrastructure projects in Africa and Asia.

He told the *New York Times* that his experience cultivating public-private partnerships aligns with the foundation's recent strategies. "I've seen what's possible when people come together," he told the newspaper. "We were able to save tens of thousands, if not millions, of lives."

Administration, and Operations at Cooper Medical School of Rowan University.

David B. Agus, MD'91, has been appointed to the Board of Directors of CrossChx, a healthcare technology company developing ways for patients to connect and share information about their health. He is a professor of Medicine at the Keck School of Medicine and of Engineering at the Viterbi School of Engineering at the University of Southern California.

Harold I. Feldman, MD, GME'91, HOM'99, has been appointed president of the American College of Epidemiology. In addition, he will become editor-in-chief of the *American Journal of Kidney Diseases*. He currently serves as the George S. Pepper Professor of Public Health and Preventive Medicine and the chair of the department of Biostatistics and Epidemiology at the Perelman School.

Robert John Pignolo, BA'85, MD, PhD'93, has been appointed to lead the new division of Geriatric Medicine and Gerontology in the Department of Medicine

at the Mayo Clinic, which will include more than 50 geriatricians. He also will serve as director of the Translation and Pharmacology Program at the Robert and Arlene Kogod Center on Aging.

Elizabeth Robinson Henry, MD'94, has been appointed to the Board of Directors of The Raritan Valley Community College Foundation. She is the founder of Dr. Liz Consulting and a fellow of the American Academy of Pediatrics. She was a partner at the New Brunswick Pediatric Group for 16 years.

Barbara E. Troupin, MD'95, MBA'95, has been appointed chief medical officer and vice president of Clinical Development at Aquinox Pharmaceuticals, a clinical-stage pharmaceutical company discovering and developing targeted therapeutics in disease areas of inflammation and immuno-oncology. She most recently served as senior vice president and chief medical officer at Apricus Bioscience.

Rebecca A. Baum, MD'96, was appointed chief of the division of Developmental and Behavioral

Pediatrics at Nationwide Children's Hospital. Baum is an associate professor of Pediatrics at The Ohio State University and assistant professor of Pediatrics at the Ohio University Heritage College of Osteopathic Medicine.

Marc Gorelick, MD, MSCE'96, will take the role of president and chief operating officer of Children's Hospitals and Clinics Minnesota in March. Prior to this appointment, Gorelick was chief operating officer and executive vice president of Children's Hospital of Wisconsin.

Adam D. Cohen, MD'98, GME'02, is the lead author of a new study on two new treatments for immunoglobulin light-chain amyloidosis, which were presented at the 58th Annual American Society of Hematology Meeting and Exposition. Cohen is an assistant professor of Medicine in Hematology-Oncology and director of Myeloma Immunotherapy at the Hospital of the University of Pennsylvania.

2000s

Sam Jackson, MD'00, MBA'00, was named chief medical officer of Alkahest Inc., a biotechnology company focused on neurodegenerative diseases and other age-related conditions. Jackson will lead the translational and clinical development activities at Alkahest.

Raegan McDonald-Mosley, MD'04, MPH, was selected as one of the "Power 100" most inspiring African-Americans in 2016 by *Ebony* magazine. McDonald-Mosley is chief medical officer of Planned Parenthood Federation of America and a vocal proponent of reproductive rights.

Jonathan J. Hogan, MD'07, GME'10, has been named a member of the new Scientific Advisory Board for Variant Pharmaceuticals, an emerging specialty pharmaceutical company developing drugs for rare diseases. He is the clinical director of the Penn Glomerular Disease Center and an assistant professor in Nephrology at the Hospital of the University of Pennsylvania.

Caroline A. Banks, MD'08, has joined Massachusetts Eye and Ear, where she specializes in the treatment of facial nerve disorders, aesthetic facial surgery, and facial reconstruction. She is also a member of Massachusetts Eye and ear Facial Nerve Center, where she focuses on the medical and surgical treatment of facial paralysis and Bell's Palsy.

Dave A. Chokshi, MD'09, was appointed to President Obama's National Advisory Group on

Prevention, Health Promotion, and Integrative and Public Health. Chokshi is a clinical assistant professor of Population Health and Medicine at the NYU School of Medicine.

Raina Merchant, MD, MSHP'09, was appointed associate vice president for the University of Pennsylvania Health System and director of Penn's Center for Digital Health. The newly created center evolved from Penn Medicine's Social Media Laboratory, led by Merchant since 2013. See "Tweet, Yelp, Heal," p. 16.

2010s

Eric Ojerholm, MD'12, led a new research effort which has found that neutrophil-to-lymphocyte ratio is not effective in predicting the overall survival of patients with muscle-invasive bladder cancer. The study was published in Cancer in October 2016. Ojerholm is a resident physician in Radiation Oncology in the Perelman School.

David C. Fajgenbaum, MD'13, MBA'15, will serve as principal investigator for ACCELERATE, a patient-driven registry dedicated to empowering patients with Castleman Disease to contribute

their medical information in order to advance the knowledge of the disease. ACCELERATE was launched by a partnership between Janssen, the University of Pennsylvania, and the Castleman Disease Collaborative Network, of which Fajgenbaum is co-founder and executive director.

Charlene Wong, MD, MSHP'15, will join Duke University in the Duke-Margolis Center for Health Policy Research and the Duke Clinical Research Institute. An adolescent medicine physician and health policy researcher, Wong completed a Robert Wood Johnson Foundation Clinical Fellowship and a fellowship in Adolescent Medicine at Penn and Children's Hospital of Philadelphia.

OBITUARIES

1940s

Stanley Spoont, MD'48, Delray Beach, Fla., a retired physician; Nov. 22, 2016. Born in South Philadelphia, he worked as the Philadelphia Flyers' first team physician from 1966 to 1974. He then moved his practice to Punta Gorda, Florida. In 1980, he became the physician for the Key Largo-based The Ocean Reef Club before retiring in 1986. He served in the Navy as a lieutenant from 1954 through 1956, and was on the faculty of Penn's School of Medicine.

William Lander, MD'49, Villanova, Pa., a family physician; Jan. 6, 2017. Described as an "old-school family physician" known for his compassion and his signature bow tie, Lander was an internist based at Bryn Mawr Hospital in Bryn Mawr, Pa., where he maintained a family practice from 1953 until his death. During the Korean Conflict, Lander served in the U.S. Navy as a lieutenant and was stationed with the First Marine Division on the front line at the Chosin Reservoir. Lander was active with the Montgomery County Medical Society, and he served as president of the Pennsylvania Medical Society in 1990. For 25 years ending in the 1990s, Lander was the resident physician at Haverford College.

1950s

Peter Nowell, MD'52, GME'56, HON'10. See "Remembering Peter Nowell," p. 10.

Frank S. Jannotta, MD'55, Tucson, Az., a retired pathologist; May 20, 2016. After graduating cum laude from Williams College he entered Penn's medical school and completed his medical training at Presbyterian Hospital in Philadelphia and Jackson Memorial Hospital in Miami. He also served for two years as a medical officer (LT MC USNR) in the U.S. Navy. Initially licensed in Florida, he spent the majority of his 37-year medical career at The George Washington University Medical Center, department of Pathology, in Washington, DC. He was board certified in anatomic pathology, clinical pathology, and neuropathology. After retiring in 1993, he spent several years as visiting professor of Pathology at the University Medical Center, University of Arizona. He was also a life-long student of music, an accomplished pianist, and a would-be linguist, studying Japanese, Italian, Latin, Polish, and German languages in his spare time.

1960s

Charles R. Koch, MD'60, a psychiatrist, Philadelphia; Jan. 11, 2017. Koch was a clinical professor of psychiatry at Penn and associate psychiatrist-in-chief at the Children's Hospital of Philadelphia for many years. He joined Penn as a fellow in the division of child psychiatry in 1964 and became an associate professor in 1972. He left in 1995, but returned in 1997 as a clinical associate professor, and held that position until 2005. He also held positions including director of the child and family mental health component for Hall-Mercer Community Mental Health/Mental Retardation Center in Philadelphia and medical director of the Delaware Guidance Service in Wilmington, De.

Norig "Skip" Ellison, MD'61, GME'70, West Chester, Pa., retired professor of Anesthesiology at the University of Pennsylvania. Born in Philadelphia as the youngest of four siblings, Ellison earned a full scholarship to Lafayette College, where he played football and earned a degree in chemistry. He completed his medical internship at Tripler Army Hospital in Honolulu, undertook a general practice residency at Walson Army Hospital at Fort Dix, N.J., and was deployed by the US Army to Vietnam. He earned the Bronze Star Medal for meritorious achievement in ground operations against hostile forces, the highest honor bestowed on a medical military officer. He retired from the military as a Major in in 1967. Ellison began his nearly 40-year career at Penn that year, when he began his residency in anesthesia under the mentorship of Dr. Robert Dripps, a legend in the field. Ellison rose through the ranks to full professor and ran the department of Anesthesia as acting chair in 1987-88, then served as vice chair from 1989-2001. He was a prolific researcher and writer, in addition to his full-time practice and teaching. He published textbooks and scholarly medical writings and served as the editor of numerous prestigious medical journals. He served as president of the Pennsylvania Society of Anesthesiologists in 1982-83 and the American Society of Anesthesiologists in 1995-96.

Allen D. Roses, MD'67, a clinical neurologist; Sept. 30, 2016. He was the Jefferson-Pilot Corporation Professor of Neurobiology at Duke University School of Medicine, chief of the division of Neurology at Duke University Medical Center, and founding director of the Joseph and Kathleen Bryan Alzheimer's Disease Research Center. He served as senior vice president of research and development at GlaxoWellcome (now GlaxoSmithKline) and owned Zinfandel Pharmaceuticals. He is world-renowned for his work on identifying two genes that put people over 65 at higher risk for Alzheimer's disease. He served as a doctor, and later captain, in the Air Force in Vietnam.

1970s

Mark Josephson, MD, GME'75, a renowned cardiologist recognized internationally as the "father of cardiac electrophysiology;" Jan. 11, 2017. He was the Herman Dana Professor of Medicine at Harvard Medical School and Beth Israel Deaconess Medical Center (BIDMC) and previously chief of Cardiology at the University of Pennsylvania School of Medicine from 1981-1992. During his tenure at Penn beginning in 1978, Josephson pioneered intracardiac recording

techniques that enabled a series of landmark studies defining the physiology and mechanism of supraventricular tachycardia and ventricular tachycardia and development of successful interventions. Josephson is recognized as an inspirational teacher and mentor who stressed the lifelong need to contribute to advancements in the field of cardiac electrophysiology. He contributed over 400 original scientific manuscripts and 200 book chapters and reviews and is the sole author of the "bible" of electrophysiology, *Clinical Cardiac Electrophysiology: Techniques and Interpretations*; the fifth edition was published in 2015. Josephson took enormous pride in his fellows, with whom he shared his expansive technical knowledge as well as ethical insights in the field of medicine. Over the course of his career at BIDMC and Penn, he trained more than 250 cardiac electrophysiology fellows to become clinical and research leaders in their field.

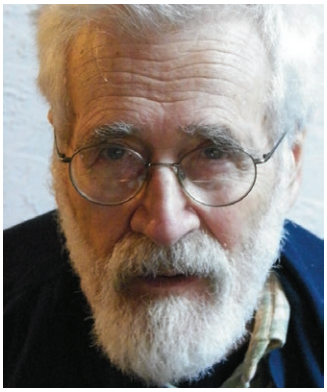
2010s

Ari Frosch, M'19, a second-year student at the Perelman School of Medicine; Sept. 22, 2016. He completed his undergraduate degree at Colorado College in 2012, before completing post-baccalaureate work at Bryn Mawr and working at the National Cancer Institute. He volunteered at Puentes de Salud, a Philadelphia healthcare non-profit. He was the son of James P. Frosch, MD'76 and brother of Zach Frosch, MD'14.

FACULTY

Peter Berman, MD, emeritus professor at the Perelman School of Medicine and senior neurologist at Children's Hospital of Philadelphia; Sept. 1, 2016. Berman was born in Vienna, Austria and fled the Nazi regime to London before emigrating to the Upper West Side of New York City. He earned his medical degree at New York University College of Medicine and completed an internship in pediatrics at Bellevue Hospital, New York City, followed by a residency in pediatrics at the University of Minnesota Hospital, Minneapolis. Berman's work focused on clinical child neurology and pediatric epilepsy. He joined Penn in 1969 as an associate professor of pediatrics and neurology. He then became a professor of pediatrics and neurology in 1979 and held that role until 2011, when he retired and became professor emeritus of neurology. He continued to work at CHOP until his death. Berman served as president of the Child Neurology Society from 1991-1993 and received the society's highest honor, the Hower Award, in 2003.

Constantin "Stan" Cope, MD, emeritus professor, inventor, and a founding father of interventional radiology. Born in Paris to Polish Jewish parents before moving to England, Cope grew up during the London Blitz, then later moved to the U.S. to earn his medical degree from New York Medical College. Upon gaining citizenship, he served in the U.S. Army as a medical officer in the Korean War. While working at Albert Einstein Hospital in Philadelphia, he was the only non-radiologist in the Philadelphia Angio Club, a core group of pioneers of the earliest inter-



ventional procedures in radiology. Catheters and other tools for interventional radiology were not widely available at the time because the field was so new, so the inventive Cope made them using materials he purchased at hardware stores and the Army/Navy supply shop. He joined the Radiology faculty at Penn in 1986. His numerous inventions include the locking Cope loop catheter and thoracic duct embolization, a novel procedure that laid the groundwork for modern lymphatic interventions.

Norig "Skip" Ellison, MD. See Class of 1961.

Charles R. Koch, MD. See Class of 1960.

Mark Josephson, MD. See Class of 1975.

Peter Nowell, MD. See "Remembering Peter Nowell," p.10.

Stanley Spoont, MD. See Class of 1948.

Decades-Long Passion for Penn Medical Students Leads to a Bequest

Lou Kozloff, BA'65, MD'69 and Rene Kozloff, BSN'67.

Lou Kozloff, BA'65, MD'69, may no longer be an eager student athlete, but his days as a Penn swimmer inspired him to establish the Kozloff Family Room, which adjoins his beloved Palestra and the former site of Hutchinson Pool. Similarly, though Kozloff's years as a medical student are far behind him, he has shown his devotion to Penn and Penn Medicine through philanthropy and many years of volunteer involvement. Just two years ago, he helped name one of the classrooms in the new Henry A. Jordan, M'62 Medical Education Center, along with his medical school roommates Ed Anderson, BA'65, MD'69, and Bill Thompson, MD'69. Like so many Penn alumni, Kozloff is deeply committed to several areas within the University—the Red and Blue runs deep.

"My classmate, Ed Anderson, and I are committed to helping students navigate the challenging costs of medical school so that they can reap the same benefits we did by attending what we consider the best medical school in the country," he explained. Kozloff recently signed a gift agreement detailing how a gift from his or his wife Rene's estate would be combined with gifts made by Anderson to endow a medical school scholarship fund for a deserving student. "Our hope is that the **Edward T. Anderson, C'65, M'69—Louis Kozloff, C'65, M'69 Scholarship** recipient may closely remind us of ourselves at that stage in our lives: a graduating Penn student who is going on to the medical school, and hopefully also a student-athlete," he said.

The bequest for Penn Medicine was easy for Kozloff to add to his will because the planned giving team at Penn Medicine helped with the language his attorney needed. Bequest gifts are a popular choice for many donors and are only one of the many great ways to give back.

Kozloff has a longstanding familial connection with Penn, starting with his father, Henry Kozloff, BA'35, MD'40. Since then, 35 Kozloff family members have earned Penn degrees. "I am proud of my association with the University," Kozloff said. "And I am thrilled that, through planned giving, I can do something to help young people along the same path that has proven so rewarding for me and my family."

> 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 the website at: www.plannedgiving.med.upenn.edu.

Looking Back and Forward

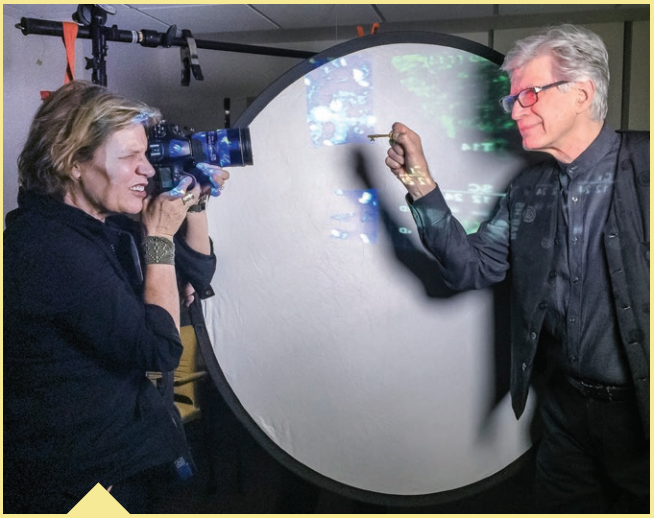
In celebrating the life and legacy of Peter Nowell in this issue of *Penn Medicine*, my first as editor, I have tried to test out a formula that you may see much more in this magazine in the future: taking a subject and looking both back and forward to show a wider view of that piece of the world. Remarkably, the life that Nowell lived, and the scientific advances he both foresaw and personally achieved, laid the groundwork for newer advancements on the horizons of science today.

This is a microcosm of Penn Medicine's larger story. Steeped in a rich history including our nation's first medical school—predating the nation itself—and its first hospital, Penn's medical enterprise continues to foray into firsts that, in my opinion, make this one of the most mind-bendingly amazing places to glimpse the future of new advancements in science. Histories and futures are deeply intertwined.

I take the reins of *Penn Medicine* from an esteemed former colleague, John Shea, who retired in the fall of 2016 after closing the previous issue. John's 18 years as editor saw the magazine and the institution of Penn Medicine through a profound period of transformation. I was lucky enough to be present for a few of those years during my prior tenure working at Penn Medicine. Then, specializing in digital communications, I led the launch of the Penn Medicine News Blog and found inspiration in the pages of this magazine for many of my early posts. I'm grateful to John for making this publication one I'm proud to inherit.

That brief look back ties in nicely to a new look forward: *Penn Medicine* is newly available as a full, hyperlink-enhanced web version at **PennMedicine.org/magazine** as part of the Penn Medicine Communications department's newly redesigned website. You can also subscribe to the email edition at **PennMedicine.org/news/subscribe**. And you'll see more connections between the printed magazine and the web, with online extras that take you behind the headlines. I suggest starting with a visit to the Penn Medicine News Blog for a behind-the-scenes post about reporting from Guam by the author of this issue's South Pacific medical mystery feature.

Behind the Scenes



Photographer Peggy Peterson shoots an Alzheimer's "skeleton key" cover concept with John Trojanowski.

Writer Steve Graff visits Umatac Cemetery in Guam with Lucy Cruz, a local nurse whose mother died of lytico-bodig disease.

To see more behind-the-scenes photos and a behind-the-story blog post from this issue, visit: PennMedicine.org/magazine/winter17ed

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In the Spring Issue: As the millennial generation advances in the biomedical workforce, how are younger doctors and scientists redefining the future of their fields in terms of diversity, innovation, and more?

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Musician, Heal Thyself

By Sally Sapega

While research has long suggested listening to an orchestra's performance of such well-known pieces as Beethoven's 5th Symphony and Mozart's Marriage of Figaro may boost the audience's brain power—a hypothesis aptly named The Mozart Effect—Penn Medicine experts suggest those playing in the orchestra may derive the most benefits of all.

In December 2016, those positive effects hit close to home when the Penn Medicine Symphony Orchestra performed selections from these pieces at the group's debut concert, held at Penn's Irvine Auditorium.

Gina Chang, a second year medical student in the Perelman School of Medicine, started the orchestra last spring with fellow student Dan Zhang. Both had to cut back on their music considerably since starting medical school. "When we discussed the possibility of starting an orchestra, we realized how much we missed playing and [in his case], conducting," she said. And they clearly weren't alone. From across the Perelman School and the Hospital of the University of Pennsylvania, more than 40 Penn doctors, nurses, and grad students answered their call to participate, squeezing out time from their overloaded schedules for something they loved … and missed.

"It allows me to pull out of the sometimes psychologically and physically draining day-to-day caring and witnessing of injured patients, particularly those suffering tragic events such as death by gun violence," said Jose Pascual, MD, PhD, a surgeon in the Trauma Center at Penn Presbyterian Medical Center. Plus, it provides "the opportunity to produce beautiful art with my [14-year-old] son, Mateo," who also plays in the orchestra. His son agreed: "It helps bring us closer."

Playing an instrument may also be one of the best ways to keep the brain healthy. "It engages every major part of the central nervous system," said John Dani, PhD, chair of Neuroscience in the Perelman School of Medicine. For example, playing the violin—which, like many instruments, requires the right hand to do something different than the left—uses the peripheral nervous system, which controls finger movement, as well as gross and fine motor skills. The brain's executive function—which plans and makes decisions—comes into play as a musician plays one part but keeps focus on what's coming next. Couple that with the total sensory input—visual, auditory, and emotional all at the same time—and it becomes a total "workout" for the brain. "Recent studies suggest that music may be a uniquely good form of exercising your brain," he said. "Fun can also be good for you."

"We were amazed by and grateful for the musicians' enthusiasm, engagement, and dedication," Chang said. No matter where their lives and medical careers take them, she said, "the orchestra is proof that music can and should remain a part of us." ▽

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The legacy of visionary scientist, Penn Medicine alumnus, and longtime faculty member Peter C. Nowell, MD (1928-2016) stretches far beyond his famous 1960 discovery of the Philadelphia chromosome. His influence in cultivating the current and future landscape of precision therapies for cancer lives on.

See more on page 10.