

yale medicine

From one generation to the next

How ideas, traditions, physical
traits, and even diseases become
the legacies we inherit.





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spring 2015 departments

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Thank you for articles on children and microbes

What a wonderful recent edition of *Yale Medicine* [Spring 2015]! Two articles particularly affected my pediatric mindset and got me thinking (a little harder to do at my age):

“How children rebound from their worst nightmares” and “A bug’s journey.”

I have been concerned about so many children in our prosperous country receiving little “parenting” or supervision. Surrogate “caregivers,” in my mind, just can’t cut it. Without instruction or modeling, a child doesn’t just automatically metamorphose into a good kid that has no need for behavior-modifying drugs. Contrast the prosperous with the opposite—occupants of a Syrian refugee camp.

I witnessed penicillin as both a miraculous germ killer and as the ineffective antibiotic it became for strains of *Staphylococcus aureus*: first as a Navy hospital corpsman treating the “sins” of returning Marines with aqueous penicillin delivered by a syringe with a huge needle on one end; and

later, witnessing the discovery that newborns with Staph pneumonia were dying in spite of penicillin’s being administered. As time progressed, I realized that I needed more knowledge of how our immune systems work and how pathogens could outsmart us. I attended seminars on immunology that, I have to admit, were over my head.

If only I had read this article 40 (maybe 50) years ago. I loved the teaching of the difference between RNA viruses and DNA bacteria in the context of their mutation “mistakes” or other means of change.

A very interesting edition.

Thank you.

*Ralph K. Campbell, M.D. '50
Polson, Montana*

**SECOND OPINION
BY SIDNEY HARRIS**



“So - WHICH GENES HAVE BEEN BOTHERING YOU?”

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Abbreviations used in *Yale Medicine* include HS to denote the final year of residency for house staff, FW for the final year of a fellowship, and YNHH for Yale-New Haven Hospital.

Yale School of Medicine

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“Almost every disease is influenced in some manner by inheritance”

HOW DO OUR INHERITED TRAITS, both genetic and environmental, determine who we are? We asked Yale faculty and students to reflect on this question in many ways for this issue of *Yale Medicine*. Dean Robert J. Alpern, M.D., discussed what he has inherited from those who served as dean before him, and the importance of evolution and heredity to science.

This issue of *Yale Medicine* explores the concept of inheritance from many angles. What makes this subject so rich?

Almost every disease is influenced in some manner by inheritance, including not only genetics and epigenetics, but that which we “inherit” from the environment our parents establish for us. While many diseases involve random environmental factors, our response to those elements is determined by our genetic background.

As a scientist, what interests you most about inheritance?

Evolution has a profound effect on everything we are, including the diseases that affect us and our response to those diseases. When humans were content to live until their children became independent, evolution was our friend. Now we live long past the age required for survival of our species, and we are on our own with no support from evolution.

You are the 16th dean of the School of Medicine. What have you inherited from your predecessors?

I have inherited many great things from previous deans, among them the Yale system of medical education, and a preeminent medical school.

What do you imagine our legacy—that of YSM of the early 21st century—will be?

I hope that our legacy will be that we have advanced excellence in education and research, while introducing a renewed commitment to an outstanding clinical practice.



Alum's appointment as surgeon general a "home run"

IN MARCH 2001, Esther K. Choo, M.D. '01, then a medical student, was bouncing around in a jeep on bumpy desert roads in Gujarat, India, feeling sick from the heat and the antiretroviral medications she was taking. At her side was fellow medical student Vivek H. Murthy, M.D. '03, M.B.A. '03. They were part of a team from Yale that was providing relief after an earthquake. On this mission they also addressed medical needs unrelated to the immediate crisis. While drawing blood samples at a screening for diabetes and cardiac disease, Choo pricked her finger with a used needle. She and Murthy were scouring the countryside for the woman whose blood she had been exposed to, so they could test her for HIV. They found the woman, and she tested negative. "Vivek volunteered to go with me to hold my hand and keep me from freaking out," Choo said. "He is just that kind of person."

While in Gujarat, said Choo, now an emergency physician at Brown University, one of their faculty preceptors told the students that they were all bright but that Murthy would make his mark in a very big way. “None of us took offense, because it was so obvious,” Choo said. “He was the moral center of the group. He was unflappable and calm, no matter what was going on.”

In January the U.S. Senate confirmed Murthy’s appointment as the nation’s 19th surgeon general. His nomination by President Barack Obama had been on hold for more than a year due to opposition from Republicans and the National Rifle Association. His offense? A 2012 tweet on gun violence: “Tired of politicians playing politics w/guns, putting lives at risk b/c they’re scared of NRA. Guns are a health care issue.” He was also criticized for his youth and relative inexperience—he is 38. Yet support came from more than 100 national health organizations, including the American College of Physicians, the American Public Health Association, the American Cancer Society, and the Association of American Medical Colleges, as well as from two former Surgeons General.

Anyone at the med school between the fall of 1998, when Murthy matriculated, and 2003, when he graduated, probably has a story about him. As one student of that time put it, “Everyone knows Vivek.” He arrived at Yale with a record of



accomplishment dating back to his high school days in Florida, when he got his classmates to mentor middle school students. As a Harvard undergrad, he launched a peer education program that trained American college students to teach students in India about HIV/AIDS. He also started a community health partnership in rural India that trained young women to be health educators and basic health care providers. During his first year as a med student, he was profiled in *The Chronicle of Philanthropy* for his efforts.

When he spoke, classmates said, others paid attention. “He would often listen quietly to a discussion of a controversial topic,” former class president Andrew D. Norden, M.D. ’02, M.P.H., now a neurologist in Boston, wrote in an email. “He would wait until the opposing viewpoints were on the table and finally make a critical comment that recognized an understanding of each position, and suggest a thoughtful path to resolution. He frequently got the last word in because once he had spoken, everyone could be seen nodding in agreement.”

Auguste H. Fortin VI, M.D., M.P.H., associate professor of medicine, recalled Murthy returning from a visit to the

Vivek Murthy became the first graduate of the School of Medicine and the first American of Asian descent to be confirmed as the U.S. Surgeon General. Vice President Joe Biden swore him in during a ceremony on April 22.



ONLINE EXCLUSIVES

Watch the first TV interview with the new surgeon general on cbsnews.com. Vivek Murthy is the first Yale alumnus to serve in the post and one of the youngest in recent memory.

And for more on Murthy's swearing-in ceremony, visit yalemedicine.yale.edu/murthy.

University of California, San Francisco (UCSF), where he'd sat in on "The Healer's Art," a class that explores the human dimensions of medicine, taught by Rachel Naomi Remen, M.D.

"He came back very excited and enthusiastic," Fortin said. "He said we have to do this at Yale. He recognized that there was a need for students to talk about meaning in medicine."

Murthy worked with Fortin and Margaret J. Bia, M.D., FW '78, professor of medicine, to establish The Healer's Art, a small-group elective now in its 15th year. Over four weeks, students discuss such topics as what it means to be a healer, what it's like to lose a patient, and how to avoid burnout. Yale was the first medical school after UCSF to offer the course, and now more than 70 medical schools have followed suit. "I think we have Vivek to thank for that," Fortin said.

After graduating from Yale, Murthy founded TrialNetworks, social networking platforms for clinical trials that enhance communication, collaboration, and overall efficiency. During the 2008 presidential campaign Murthy and colleagues founded Doctors for Obama. After the election, the group became Doctors for America, a grass-roots organization of doctors and medical students working to improve access to health care. In 2011, President Obama appointed Murthy to the national Advisory Group on Prevention, Health

Promotion, and Integrative and Public Health. The following year Murthy served as co-chair of the health care advisory committee for Obama's re-election campaign.

During the more than year-long wait for a vote on his nomination, Murthy remained optimistic. And when he returned to Yale as the medical school's Commencement speaker last year, students wore decals on their gowns that read "Yale Stands with Vivek."

"Those of us closest to Vivek during this time maintained our optimism," said one of his mentors, Howard P. Forman, M.D., professor of diagnostic radiology, of economics, of management, and of public health (health policy), and director of the M.D./M.B.A. Program. "We were very certain there was a window of opportunity, and that his many supporters, including those in the White House, would use that to the best advantage. Despite the rhetoric before the confirmation, I think that he is a thoughtful, nonpartisan, very deliberate physician who sees the role of the Surgeon General as an amazing opportunity to be the nation's leading spokesperson on health and public health issues."

"Vivek does everything so selflessly and is one of the brightest, off-the-charts-smartest people that I know," said Choo. "We hit a home run getting Vivek into this role."

—John Curtis



Defending the "good" bacteria

When faced with dangerous bacteria like *Salmonella*, the gut releases inflammatory molecules to destroy the invaders. That immune response is so nonspecific that in theory at least, it should kill indiscriminately. Yet the many healthful and even beneficial bacteria that reside in the gut seem unaffected by the friendly fire. So-called commensal strains persist for years through one inflammatory event after another.

A group of researchers led by Andrew Goodman, Ph.D., assistant professor of microbial pathogenesis and a member of the Microbial Sciences Institute at West Campus, recently figured out why: many of the most prominent and stable commensals wield a protein that fends off the antimicrobial peptides (AMPs) that the host uses to attack the invaders. The team reported in *Science* in January that the protein LpxF serves a little like an umbrella, allowing bacteria to readily shed AMPs at concentrations thousands of times higher than those that kill pathogens.

The discovery, said Goodman, opens the door for researchers to learn "not only how the host tolerates the microbiome—which is well studied—but how the microbiome tolerates the host."

LpxF works by removing a negatively charged phosphate group from the bacterial surface. That keeps the positively



charged AMPs—the gut’s defenders—from binding to bacteria and destroying them.

The LpxF discovery and its satisfying simplicity may mean that the field—which has focused mostly on describing its species diversity—is now poised to move into an exploration of how the ecosystem functions. Understanding that ecosystem is a sine qua non for pursuing potential therapeutic targets.

Goodman, who is trained in both microbial genetics and ecology, had previously assumed that the host-pathogen commensal relationship would be byzantine and difficult to study. Now he is optimistic.

“It’s a glimmer of hope that it’s not going to be so irreducibly complex that we won’t be able to make any headway,” Goodman said, “[and] that

there are dedicated mechanisms that we can identify and potentially target.”

LpxF is likely to be one of many resiliency factors waiting to be discovered in the gut, some of which may point to new drugs. This line of study is especially important because faulty or damaged resiliency systems might explain certain forms of disease. Studies of the gut microbiome have typically focused on the bacterial communities of healthy people. But understanding how these communities behave in sick people is crucially important, too. That’s Goodman’s next goal.

—Jenny Blair



A caring surgeon, struck down in an act of senseless rage

Michael J. Davidson, M.D. ’96, was a heart surgeon, one of a fraternity well-known for its bravado, but family, friends, and colleagues remember him as one of the gentlest souls ever to wield a scalpel.

He practiced in an area of medicine where a clear divide separates cardiac surgeons from cardiologists, but he trained as both. He spent unhurried hours with patients and their families, answering their questions, calming their fears, and earning their gratitude—until, one morning in January, the son of a patient shot Davidson outside an exam room at Brigham and Women’s Hospital (BWH) in Boston. Davidson died hours later, despite the best efforts of his colleagues.

His assailant, a 55-year-old man from the Boston area, was subsequently found dead, apparently from a self-inflicted gunshot wound. Police said the shooter blamed Davidson for his mother’s death in November.

“Surgeons are not known for their bedside manner, but Michael had it in spades,” said Terri Halperin, M.D., Davidson’s wife. “That is why the fact that a patient’s family member would take Michael away from us makes it all the more devastating.”

At his funeral in Wellesley, Mass., Davidson was recalled as a problem solver who could take



ONLINE EXCLUSIVES

How two second-years launched a course in health justice

Yale med students join in national protest

Storytelling at the heart of the medical enterprise

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apart and fix a refrigerator or install a hardwood floor. He did his own electrical work. Before coming to Yale, he earned his bachelor's degree at Princeton, where he was a competitive fencer and president of the soaring club. In college he taught himself to play the guitar and played in a rock band. He decided to run the Boston Marathon on his 40th birthday and finished with a respectable time.

"We would have everything from live lobster races on the floor of our apartment, to the annual tradition of our Passover turkey, to 10-course, free-form Asian explorations with five woks going," recalled Joshua M. Rosenow, M.D. '96, his medical school roommate for three years.

In interviews, others who knew him struggled to understand how Davidson had become the object of rage. "None of it makes sense," said Jamie M. McCabe, M.D. '04, who trained under Davidson at BWH for two years. "He was a calm and thoughtful guy, an extremely hard worker, and very dedicated. He was just a genuinely sweet person." Davidson's thesis advisor, Robert J. Touloukian, M.D., remembers him as "very soft-spoken, intelligent, inquisitive."

"There are people in surgery who are fundamentally aggressive. Mike was fundamentally a very gentle and caring person," said Samantha Hendren, M.D. '96, M.P.H., a colorectal surgeon at the University of Michigan. "That makes it all



Classmates Michael Davidson, right, and Josuha Rosenow, together on Match Day in March 1996. Rosenow recalled the moment upon seeing the photo in February 2015 for the first time: "Michael had just received his match results, and I was holding up one finger because he got his first choice."

the more unjust that his life ended violently."

Davidson was director of endovascular cardiac surgery at BWH and a member of the faculty at Harvard Medical School. During his residency, he moved from Duke to Boston to be with Halperin, and he completed fellowships in endovascular surgery and cardiac catheterization and in cardiac surgery.

Frederick C. Welt, M.D. '92, met Davidson at BWH. With their colleague Andrew C. Eisenhauer, M.D., they led the team that implemented transcatheter valve replacement at BWH. The minimally invasive technique had been pioneered in France in 2002 and, according to Welt, "involved cooperation between surgeons and cardiologists—not always an easy thing to do."

"Mike was incredibly talented. He was already obviously a well-trained surgeon, yet he took a year out of his life to cross-train in the world of interventional cardiology," Welt, now at the University of Utah, wrote in an email. "It was an effort that took time away from the OR, and he paid a financial price for that in terms of the operative time that he gave up. But he was completely committed, and ... he developed into somebody who was really as good with those skills as anyone at the table."

Davidson recognized that the dividing lines between disciplines were "weird and arbitrary," added McCabe, his former trainee, "and that the best way forward was building those really tight bonds between interventional cardiology and cardiothoracic surgery to provide a kind of whole new spectrum of care."

According to Michael J. Zinner, M.D., chair of the Department of Surgery at BWH, Davidson "was one of only two or three cardiac-trained surgeons in the country who were doing this kind of work and would go on ... to make incredible innovations in this area."

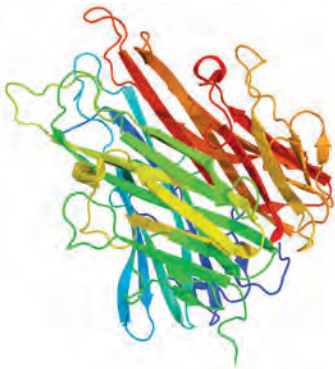
Davidson's former chief, Ralph M. Bolman III, M.D., agreed. "Mike had a vision for a new heart doctor, one who is really going to be, and is, the doctor of the future," Bolman said. "He was one of the very first to act on this vision."

—Michael Fitzsosa

round up

a collection of recent scientific findings

THE “NOISE” IN HUMAN CELLS



A Yale-led team of scientists has developed a method for mapping cellular “noise,” variations in how human cells react to chemical signals. Their findings, published in *Proceedings of the National Academy of Sciences*, could help tailor drug delivery and advance semiconductor chip design. The method, devised by systems biologist and biomedical engineer Andre Levchenko, Eng.Sc.D., is based on each cell’s unique reactions to chemical signals—some cells react strongly, while other cells may not react at all. “Knowing how variable the activity is allows us to better target the spectra of activities in those networks,” said Levchenko, the John C. Malone Professor of Biomedical Engineering and inaugural director of the Systems Biology Institute at West Campus.

PSYCHOLOGIST DECODES “TEARS OF JOY”



Why do people emit a nervous laugh in uncomfortable situations? And why are parents who cry at their child’s graduation also more likely to pinch a cute baby’s cheeks? Yale psychologist Oriana R. Aragón, Ph.D., ’14, now understands why people cry when they are happy. “People may be restoring emotional equilibrium with these expressions,” said Aragón, lead author of work published in *Psychological Science*. “They seem to take place when people are overwhelmed with strong positive emotions, and people who do this seem to recover better from those strong emotions.”

SURGEONS AND ENGINEERS JOIN FORCES ON 3-D ORGANS



Yale surgeons and biomedical engineers are working with a biology company to develop 3-D printed tissues for transplant research. With demand for transplanted organs and tissues increasing and supplies shrinking, 3-D organs would shorten the amount of time patients would have to wait. Since the transplanted cells would come from the patient’s

own body, the technology would eliminate the need for immunosuppressive drugs. “This field may provide a unique and new opportunity where we can print 3-D organs that can supplement or replace the shortage of organs out there worldwide,” said John P. Geibel, D.Sc., M.D., vice chair and director of surgical research and professor of surgery (gastrointestinal)

and of cellular and molecular physiology at the School of Medicine. In the first phase of the collaboration with Organovo Holdings Inc., Yale researchers would develop 3-D arteries and veins that would replace plastic stents as connective tissue in transplants. The second phase of the project would involve printing an entire organ—the small intestine.



THE BIGGER YOUR PARIETAL CORTEX, THE BIGGER THE RISK YOU’LL TAKE

A Yale team led by Ifat Levy, Ph.D., assistant professor in comparative medicine and neurobiology, reported in the *Journal of Neuroscience* in September that people who have larger volume in a particular part of the parietal cortex are willing to take more risks than those with less volume. “Based on our findings, we could, in principle, use millions of existing medical brain scans to assess risk attitudes in populations,” said Levy. “It could also help us explain differences in risk attitudes based in part on structural brain differences.”

From one generation to the next

How ideas, traditions, physical traits, and even disease become the legacies we inherit.

IN THE LATE 1970s, an archaeologist exploring the Colombian Andes for tombs and relics of past civilizations met an elderly farmer who told him of a field where, as a child, he had been forbidden to play. The field was dangerous, his mother told him, because of the two-headed monster that lived there. The archaeologist and his team excavated the site—buried in the field, they found the full-size statue of a man with two heads.

Who made the statue and how it came to be buried there remained mysteries. Yet somehow, as in a game of Telephone, knowledge of the statue had passed down through the generations. With each telling, the story changed. DNA similarly passes from generation to generation, but it doesn't always come out right. Ideas move through time, and they change with the times. We inherit many things from our ancestors, be they blue eyes and brown hair, notions of right and wrong, or just habits and ways of being. In this issue of *Yale Medicine*, we look at the ways in which these inheritances emerge intact—or sometimes not.

This issue's feature articles explore what DNA reveals about human history, how med school traditions endure or fall by the wayside, and how one family copes with an inherited disease.

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Six degrees of Paul Beeson

THE IRON TERNS, as they were known, began their internships in medicine under Paul Beeson, M.D. (fifth from left, front row) in the 1960s. Jack Levin, their chief resident, coined the name at a softball game marking the end of their internship year. The name was an abbreviation of *intern* and their moniker of “iron men” for their stamina on the wards. Of the 14 physicians in this group, nine went on to become full professors; four held endowed chairs; five became department chairs; one became a medical school dean; and two became division chiefs. Collectively, they published more than a thousand articles. The legacy of Paul Beeson, dubbed the “Beeson mystique,” has been handed down through them to later generations of physicians. In June 1965, the Iron Terns posed on the steps of the Sterling Hall of Medicine with Beeson and the assistant residents in internal medicine.

1 Stephen Ross, M.D., HS '69, FW '73, was in private practice in Maine.



3 James J. Fischer, M.D., Ph.D., HS '65, was chair of therapeutic radiology at Yale for 30 years, and played a major role in improving radiation therapy.



5 Michael Viola, M.D., HS '66, delivers health care in the developing world as the chief medical officer of Medicine for Peace, which he and his wife founded along with the MFP Center for Torture Victims in Washington, D.C. In his earlier career he was a professor of medicine at the University of Connecticut and SUNY Stony Brook.



6 Ira Silverstein, M.D., HS '65, was in private practice in psychiatry in New York City and Laguna Beach, Calif. He was also a member of the part-time faculties of the schools of medicine of Columbia University and the University of California, Irvine.



2 Dave Dear, M.D., HS '66, a cardiologist, lowered the mortality rate in heart surgery from 50 percent to 1 percent in just one year in a hospital in Mississippi.



4 Larry Knight, M.D., HS '67, FW '68, was both chief of staff and chair at the Elkhart Clinic in Indiana, an early multi-specialty clinic.



7 Lewis Landsberg, M.D. '64, HS '70, was dean of the medical school at Northwestern University. As a researcher, he made major contributions to the understanding of hypertension and the role of the sympathetic nervous system.



Paul Beeson, M.D., chaired internal medicine from 1952 to 1965 and taught the importance of treating patients as human beings. He mentored scores of young doctors who went on to make their mark in medicine.

8 Richard Lee, M.D., '64, HS '70, FW '71, was a professor of medicine, obstetrics, pediatrics, anthropology, and social and preventive medicine. He wrote 44 essays for the *American Journal of Medicine*; 81 essays and commentaries; and a book on his medical travels.



9 John N. Forrest Jr., M.D., HS '70, FW '71, has directed student research at Yale for 29 years, and has seen more than 2,500 medical students pass through the program.

10 Jack Levin, M.D., '57, HS '65, though not an iron tern, served as their chief resident. He was a professor of medicine at Johns Hopkins and professor of laboratory medicine and medicine at the University of California, San Francisco. At the Marine Biological Laboratory in Woods Hole, Mass., with his colleague Frederik Bang, M.D., he developed the Limulus ameocyte lysate test, which is used to detect bacterial endotoxins in parenteral drugs, intravenous fluids, and medical devices.



11 Hugh Tilson, M.D., Dr.P.H., HS '65, an epidemiologist and outcomes researcher, was director of product surveillance at Burroughs Wellcome, and of epidemiology, surveillance, and policy research at GlaxoWellcome. Most recently, he has served as a county health officer in Bath, Maine, and adjunct professor at the UNC School of Public Health in Chapel Hill.



12 Peter Gross, M.D., HS '66, FW '71, spent much of his career in epidemiological surveillance and quality improvement, and was chair of medicine at Hackensack University Hospital in New Jersey.

13 John Burke, M.D., HS '67, was one of the first to use modern computer technology for surveillance of patients with infectious diseases. He trained 70 fellows in infectious diseases at the University of Utah.



14 Thomas Spackman, M.D., HS '69, moved into the business world after a career at the University of Connecticut. He became the chair, CEO, president, or managing director of companies in medical imaging and medical care.

15 Harold Federman, M.D., HS '65, personally delivered hospice and palliative care to hundreds of patients while establishing a hospice organization in Cooperstown, N.Y.



Written in blood

Ken and Judy Kidd's bank of 2,600 cell lines contains the secrets of our evolution and perhaps our future health—why would they destroy it?

By Kate Wheeling | Robert A. Lisak Photos

In 1959, in a burgeoning riverside market town in what was then the Belgian Congo, a Bantu man fell ill.

An unknown virus was replicating furiously in the white blood cells circulating in his veins. A sample of his blood, taken for a study of the genetic diseases of red blood cells, was frozen and forgotten for nearly three decades. It contained traces of the mysterious virus that would take some 20 million lives worldwide by the year 2000: the human immunodeficiency virus (HIV), a retrovirus that thrives within the very cells meant to fight off invaders.

Blood is an ephemeral substance. Red blood cells, which make up nearly half of the blood's volume, have a life span of just 120 days, give or take a week. Four

months from now, every one of the 25 trillion or so biconcave blood cells sailing through the body's veins and arteries at this moment will have been consumed by macrophages and replaced by brand-new oxygen-toting cells. Outside the body, blood cells break down in 24 hours or less.

Frozen blood, on the other hand, is a liminal substance—neither alive nor dead. The Bantu man's frozen blood became a snapshot of the past, and as medical technology and tests advanced, a resource for the future. Eventually, the Bantu man's blood would help scientists trace the origins of one of humanity's deadliest epidemics.

Not only can frozen blood be used to track the spread and evolution of the diseases that plague humans, but it can also transcend disciplines, providing valuable insights to geneticists, anthropologists, and immunologists alike. Within those blood cells are traces of humanity's evolutionary history.

For more than four decades, blood has been the main focus of the work of Kenneth K. Kidd, Ph.D. A professor of genetics, of ecology and evolutionary biology, and of psychiatry at Yale, Kidd got his start in genetics at the University of Wisconsin, where he studied blood group typing to identify and register purebred cows.

In the 1980s, when population geneticists acquired the tools to look directly at DNA, Kidd and his wife, Judith R. Kidd, Ph.D. '93, switched to human subjects. "We gradually moved more and more into population studies, just because they're fascinating," said Ken. The Kidds became interested in the genetic variations that occur between geographically distinct populations.

"There is just a terrific amount you can learn from the study of human populations," said Judy, a retired research scientist in the Department of Genetics who earned her Ph.D. in anthropology. "When Ken was studying cattle genetics as a graduate student, I thought, 'Oh, that's interesting.' But once he moved to humans, I thought, 'Oh, *that's interesting!*'"

Their work on genetic variation has helped to piece together the human genetic map. The Kidds have scoured the genome for genes involved in complex neuropsychiatric disorders, narrowing down genes that play a role in Tourette syndrome, schizophrenia, and alcoholism. They've also used DNA polymorphisms to trace human origins. Their research has shown that sub-Saharan African populations tend to have more variation in certain genes than other populations throughout the world, which could mean that the genes have had more time to accumulate mutations



Kenneth and Judith Kidd have collected blood samples from around the world. Those samples have yielded clues to the history of humankind.

and diversify in those African groups. This work bolsters the theory that modern humans spilled out of Africa to populate the rest of the world.

The Kidds share all the data on genetic variation they collect in a publicly accessible bioinformatics database that they affectionately call ALFRED, short for the Allele Frequency Database. But the physical cell lines themselves are locked inside steel-colored freezers in their New Haven lab. As the Kidds wind down their careers, what will happen to their collection is an open question.

a “cold chain” to move blood

Cold storage is not new; insulated iceboxes have been around for at least 200 years. Your grandmother probably had a mechanical refrigerator to keep her perishables cool before one was ever used to chill blood.

Joanna Radin //

“Choices made in the past have consequences for the present, and what might have seemed ethical in one place and time will change.”

Mechanical refrigeration replaced consumer iceboxes in the 1930s—before that, commercial refrigerators were as likely to catch fire, explode, or leak toxic gas as they were to keep things cold—but the technology didn’t take off in the scientific world until World War II.

Soldiers scattered across the globe in need of blood transfusions led to the creation of a “cold chain” for blood transportation. This chain moved stateside blood donations to soldiers on the front lines, requiring not just fridges and freezers at collection sites, but also something to keep blood cold in transit: dry ice and liquid nitrogen.

Yale medical historian Joanna Radin, Ph.D., found that by the 1960s, scientists had reversed the flow of these cold channels, using the infrastructure devised during wartime to learn more about human biology. Blood collected from remote populations around the world could be shipped to high-tech laboratories for analysis, said

Radin, an assistant professor in the history of medicine whose work examines the ways in which technologies of cold storage have transformed the practice of biomedicine and public health. This chain was not without kinks. In 1968, a World Health Organization (WHO) report advised researchers to scratch serial numbers directly onto the glass vials after several shipments of specimens were unidentifiable upon arrival at labs—presumably, the labels had washed off in melted ice.

The WHO, famous for its work on infectious diseases, was quick to recognize the potential benefits of cold storage. The agency saw the collection of serum, the liquid component of blood, as a way to expand the study of current diseases in remote parts of the globe and to prepare for the diseases of the future. As new diseases—and tests for their detection—emerged, researchers could thaw frozen serum samples and study them in light of such medical advances.

The agency established four serum banks, repositories of frozen samples, to serve as a biomedical resource. The only one in the Western Hemisphere was

opened at Yale in 1960. The WHO chose John Rodman Paul, M.D., to direct it.

Paul, chair of the Section of Epidemiology and Preventive Medicine at Yale, had used blood samples to study the spread of diseases like polio and was an early proponent of freezing biological specimens. In the 1940s, while investigating antibody patterns in Eskimos in northern Alaska, he froze serum samples so that he could reanalyze each one as tests for newly discovered antigens became available. After more than a decade of studying the same samples, Paul still found the frozen serum to be a fruitful source for epidemiological research. “Indeed,” he wrote in 1961, “the epidemiologic story which this work has gradually been unfolding is not yet finished.”

The reference serum bank at Yale, whose rise was the subject of Radin’s research, quickly became a hub

Cell lines offer a look into the past

for the advancement of epidemiological research. In 1966, Alfred S. Evans, M.D., M.P.H., professor of epidemiology, took over as the second director of the bank. In that year alone, more than 21,000 serum samples were handed out to scientists who wished to study them. Before the decade was out, the Yale collection had grown to over 25,000 individual samples. Yale could no longer house the substantial collection, and the bank moved to a building owned by the New Haven Cold Storage Co. By the 1990s, when the collection moved from Yale to the National Cancer Institute in Bethesda, it contained over 50,000 unique serum samples—and untold insights into the infectious and chronic diseases of the past and present.

A prescient WHO report released in 1959—the same year the Bantu man’s blood was collected and frozen—stated: “If samples of the sera collected in these surveys are stored in such a way as to preserve antibodies, it will be possible to examine them in the future and so to determine the past history of infections as yet unknown and to follow more clearly the changing pattern of communicable disease all over the world.”

Two decades later, HIV emerged as a devastating pathogen. In the early 1980s, young, otherwise healthy people the world over began to waste away, dying of infections that usually felled only the old: tuberculosis, bacterial pneumonia, cryptococcosis, and herpes among them. Eventually, researchers discovered that HIV was at the heart of this immune system failure. Scientists sought the origins of this viral invader, hoping that understanding where the virus came from might provide clues for a cure or, at the very least, a way to contain it. In 1998, researchers from The Rockefeller University tracked it down to a freezer at Emory University in Atlanta. The freezer held more than 1,000 blood samples collected in the Congo in 1959 for a study of an inherited blood disorder common among some Africans. Once HIV was isolated as the cause of AIDS, an Emory scientist told a colleague about those samples. Only one sample, belonging to a Bantu man from a riverside market village, tested positive for HIV antibodies, making it the oldest biological trace of the disease ever documented.

With this and other preserved HIV-positive tissues, researchers used the known mutation rate of the



In the early days of genetics research, it took a lot of DNA to look at one polymorphism, so the Kidds transformed their blood samples from a hodgepodge of cells and proteins into immortal cell lines from which they could extract DNA whenever they ran low. To create cell lines, the pair infect blood cells with Epstein-Barr virus, a common human herpesvirus. Once inside the cell, the viral genome makes its way into the cell’s nucleus and begins creating copies of itself. As the virus replicates, it produces proteins that provoke the human cells to proliferate indefinitely. The Kidds freeze each cell line until they need the genes for research. They use chemicals to break open the cell walls, spilling out the cellular structures and DNA alike, then use a centrifuge to separate the genetic material from the debris. In addition to being a source of DNA, the cells are also potentially useful as living cells for a variety of research questions. To date, the Kidds have collected samples from 55 populations throughout the world and created nearly 2,600 cell lines.

virus to approximate when the epidemic began. By 2008, scientists had estimated that HIV crossed over to humans from chimpanzees somewhere in southeastern Cameroon a century earlier, about 1908. And a greater understanding of both the origin of the virus and its mechanisms of action has contributed significantly to medical advances against the disease.

a question of ownership

The WHO didn’t advocate preserving biological samples just because they might come in handy in the future, Radin has shown; the agency was equally interested in preserving the past. Frozen blood samples could also serve as permanent genetic snapshots of indigenous populations that began disappearing almost as soon as

they were discovered, and help to unravel humanity's evolutionary history.

By the mid-20th century, globalization was heating up. The WHO envisioned a future of both environmental and cultural upheaval, in which lands and peoples would be overwhelmed by the spread of Western influences. According to Radin, the WHO considered so-called "primitive" island populations to be unique laboratories "in which nature had run experiments on humans for thousands of years."

These populations provided unique windows into our evolutionary past, and according to the WHO, they were also vanishing. Scientists scrambled to collect blood samples from remote and endangered peoples to preserve their genetic fingerprints. Yale would become the home of a second massive collection, different from Paul's bank of serum samples because it contained cell lines. Today, one of the largest collections of anthropologically relevant cell lines resides in the Kidds' lab, according to Radin.

"Some of these samples are never going to be collectable again," said Ken Kidd. Their collection contains samples from diverse populations, from the Atayal tribe in Taiwan to the Zaramo people of Tanzania. But these isolated populations are not necessarily dying off, as WHO officials imagined they might, but rather integrating into societies that have grown up around their territories. According to Ken Kidd, whether indigenous groups are dying or assimilating, such change "obliterates a window into the past."

Still, many of the cultures that the WHO expected to disappear are alive and well. "Cold War-era scientists' vision of the future did not include a world in which the barriers to collecting such blood would come from these peoples themselves," wrote Radin.

There are many reasons why a group would object to how their blood samples might be used. The Havasupai, a community that lives deep within carved cliffs of the Grand Canyon, is a prime example. In the 1960s, rates of diabetes among tribe members mysteriously skyrocketed. Thirty years later, a geneticist at Arizona State University in Phoenix parsed the tribe's DNA for the cause. Roughly 100 tribe members volunteered blood samples, but when they later learned that those samples had been used for other studies, including one that proposed a theory of the

tribe's origins that contradicted the group's own creation myth, they balked. After a lengthy legal battle, the university paid reparations and returned the blood samples.

Ten years after their cells had been immortalized in a cell line, another group of Native Americans, whom the Kidds prefer not to name for legal reasons, asked that their cells be returned to them even though they had originally given full informed consent. But because the process of transforming a cell into a cell line involves infecting it with a virus, those cells are designated a biohazard—the Kidds couldn't ship them to anyone without a functioning lab and a qualified technician. The group settled for having the cell lines and DNA destroyed. "The head of the Human Investigation Committee here at Yale watched us thaw out and destroy all the frozen cell lines," said Ken. The DNA that had been isolated from those cells was "cooked" in an autoclave.

"That was painful," Ken said of the ordeal. "Oh, it was heartbreaking," added Judy. Today, the Kidds' entire collection faces an uncertain future.

Judy retired in 2011, and Ken is likely to retire by 2016. It's unclear what will become of the cell lines they've spent their careers studying. "It's a matter of interest and responsibility and money," said Judy. "There are lots of things we could do that wouldn't make me feel as good as keeping those cell lines right here at Yale." Ideally, the collection will remain at Yale, perhaps in the Peabody Museum as a frozen gallery of sorts, where a technician can watch over the cells, monitor liquid nitrogen levels, and send cell lines to qualified researchers. The scientist or organization, at Yale or elsewhere, who takes responsibility for the cells will be responsible for ensuring both the immortality of the cells and the immortality of the promises that were made to donors when they gave their blood to research. If both needs aren't met, all 2,600 lines will have to be destroyed.

If the cells remain in the freezers, they could yield untold knowledge for future generations of researchers. The issue remains, however—the needs of science may conflict with the social and ethical questions raised by the maintenance of cold blood. "They are not always likely to be in alignment," Radin said. "Choices made in the past have consequences for the present, and what might have seemed ethical in one place and time will change." [/yale medicine](#)

Kate Wheeling was Yale Medicine's 2014 writing intern.



Was pharaoh's odd appearance genetic?

AKHENATEN, THE EGYPTIAN RULER who was husband to Nefertiti and father to Tutankhamen, is best known for two things: he was the first historical figure to embrace monotheism, and he was “one funny-looking pharaoh,” according to Irwin M. Braverman, M.D. ’55, HS ’56, a Yale dermatologist with overlapping passions for art and medicine.

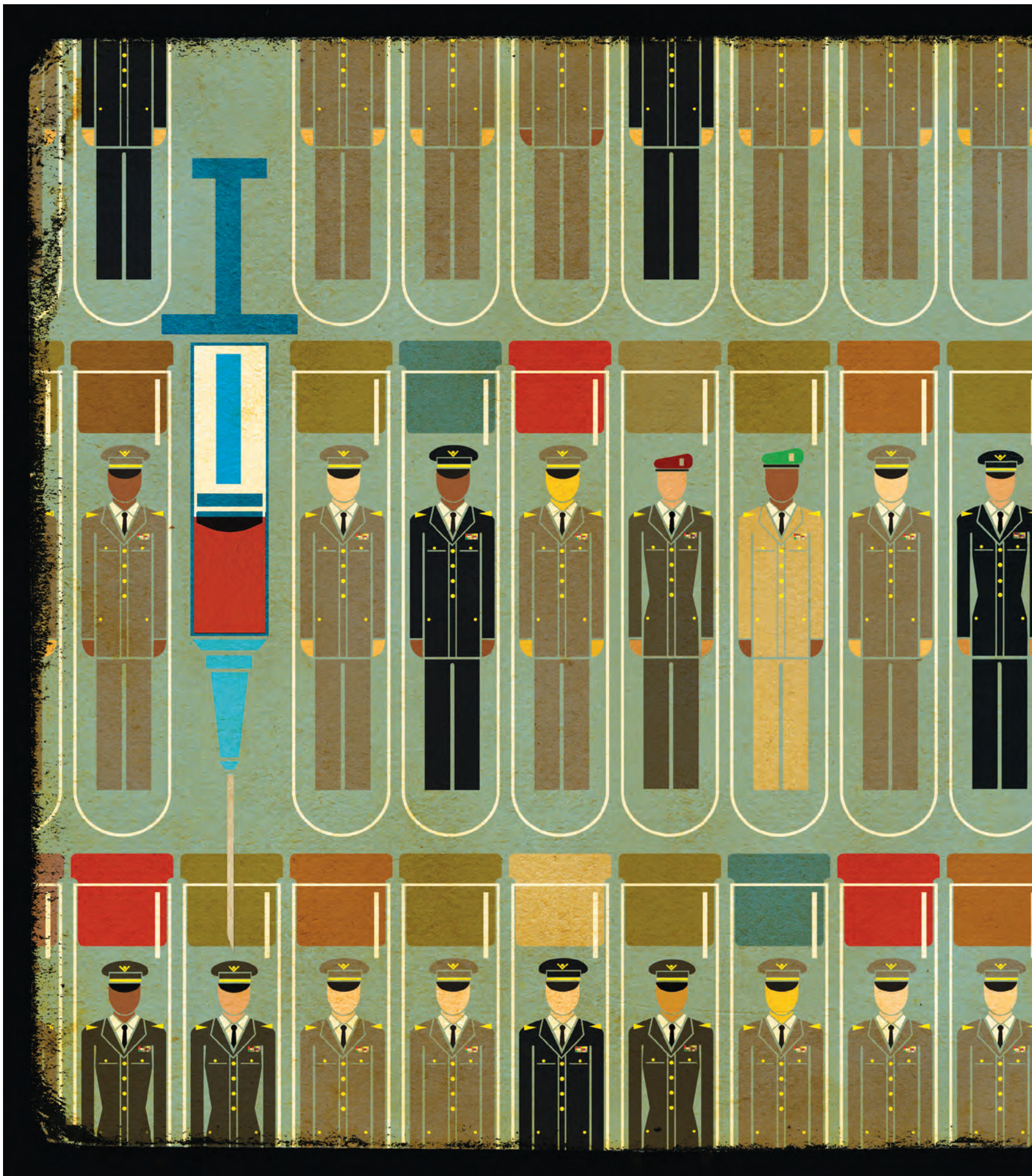
Scholars have attributed this odd appearance—androgynous, with wide hips, an elongated head, almond eyes, square jaw, and womanly breasts—to various causes. Early representations

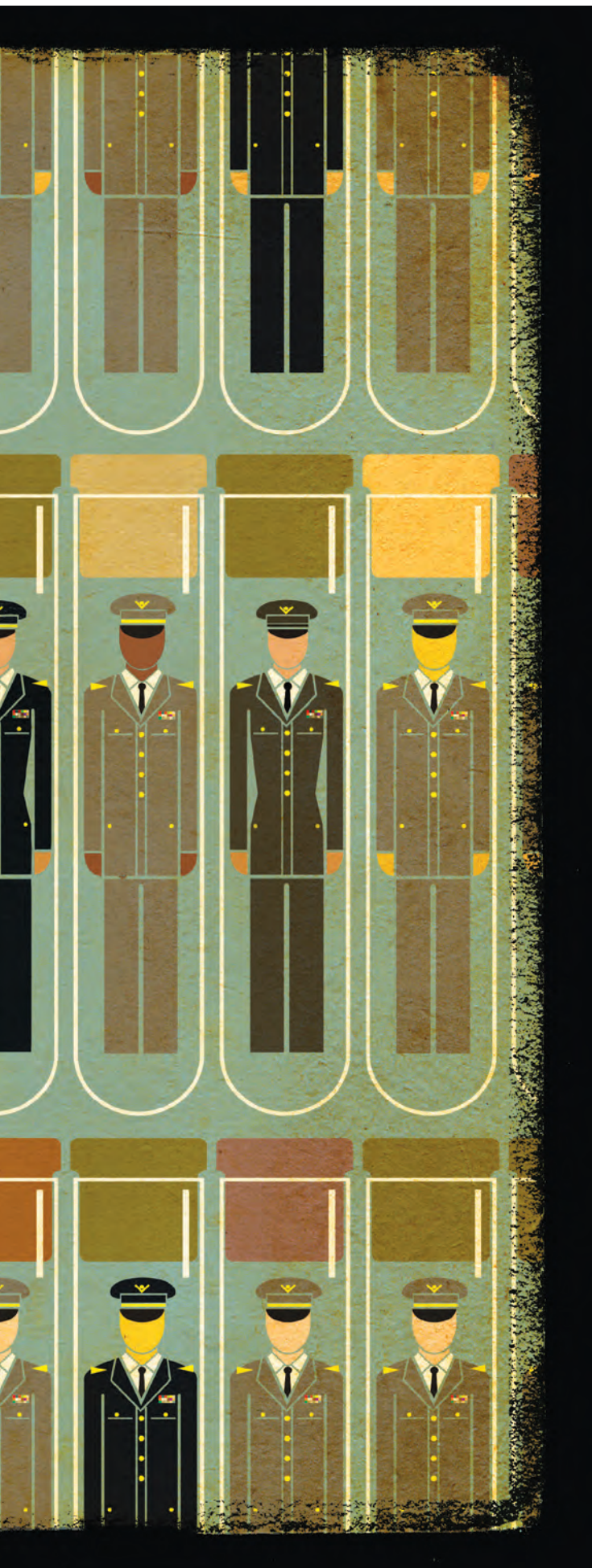
of the pharaoh depict a normal head and body, but after Akhenaten embraced the Sun-disk god, Aten, as the one and only deity, his gender in sculptures and carvings became more ambiguous. His changing appearance has led to speculation that the depictions were metaphorical, meant perhaps to portray Akhenaten as the father and mother of all humankind.

Opposing explanations suggest that the changing images were realistic and reflect a genetic disorder. Braverman is firmly in this second camp. “This is not just artistic license,” says Braverman, professor emeritus of and senior research scientist in dermatology and co-author of a 2009 paper in the *Annals of Internal Medicine* that examined the issue. With colleagues from Maryland and Pennsylvania, he proposed that two familial disorders—aromatase excess syndrome and sagittal craniosynostosis syndrome—were the most likely candidates. A third possibility is a mutation in the gene for a class of enzymes that was responsible for both the cranial and endocrine abnormalities of members of Egypt’s 18th dynasty. Braverman would like to settle the question through DNA analysis of mummified remains, but attempts to obtain samples have been unsuccessful.

If Akhenaten passed down gene mutations that conferred his strange physical characteristics on his progeny, he did not pass on his most notable quality, belief in only one god. Despite the pharaoh’s single-minded concept, the Sun-disk did not endure. After Akhenaten’s death in 1336 BCE, the cult that he had established faded from prominence, and Egypt returned to the worship of the many gods and goddesses that had preceded Akhenaten.

—Michael Fitzsouza





Building a biobank

... a million veterans at a time

By Bruce Fellman | Greg Hall Illustration

The exhortation to “enlist” wasn’t as dramatic as that of the famous “I Want You” poster featuring a red-, white-, and blue-clad Uncle Sam, but William Koob, 71, a seaman’s apprentice in the early 1960s, found the call almost as compelling. Koob, a bank auditor, was semi-retired and working at the VA Connecticut Healthcare System campus in West Haven when he heard about an initiative called the Million Veteran Program (MVP).

Launched by the Department of Veterans Affairs in 2011 and co-directed by a Yale faculty member and a School of Medicine alumnus, the MVP hopes to recruit a million veterans over the next five to seven years. Genetic information and electronic health histories of that “mega-cohort” of vets will reside in an enormous biobank for scientists and clinicians exploring the connections among genes, the environment, military service, and disease.

To date, said John Concato, M.D., M.S., M.P.H. ’91, professor of medicine and one of the project’s two principal investigators, nearly 350,000 veterans have signed up. Koob was one of them.

“All MVP required was giving a blood sample, allowing my VA health record to be accessed, and filling out health questionnaires—and I quickly realized how valuable this information could be,” said Koob. “It was another opportunity to serve, and I was happy to contribute.”

The project, it turns out, is not the only endeavor looking for a million good men and women. As part of his 2016 budget, President Barack Obama announced in January that he wanted to invest \$215 million to create the Precision Medicine Initiative (PMI): a massive biobank—compiled from both emerging and existing databases (possibly including data from the MVP)—of genetic information and electronic medical records of a representative sample of U.S. citizens, a million strong.

Michael Gaziano //

“Just like the Hubble Space Telescope opened up ways of seeing the universe ... we think that MVP will allow us to explore the genomic universe.”

The PMI, said the president, could “lay a foundation for a new era of lifesaving discoveries.” (Richard P. Lifton, M.D., Ph.D., chair and Sterling Professor of Genetics, has been named co-director of the PMI.)

The president’s initiative, if funded, would allow researchers to cull genetic secrets about the origin and development of physical and mental disorders—insights that might lead to more custom-tailored and cost-effective treatments, particularly for cancer. The MVP, while its goals are similar, is targeted toward a more specific population—a group whose “can do” attitude and eagerness to enlist is typical, said Concato, who directs the VA’s Clinical Epidemiology Research Center in West Haven and has conducted extensive research on prostate cancer epidemiology and screening. “When you consider that this project is not going to benefit any of the participants directly,” he said, “their altruism is very impressive.”

None of the information an individual provides, including the fruits of the DNA samples, goes into the veteran’s personal medical record. Instead, this nationwide “big data, big science” effort will allow researchers and clinicians “to better identify those at risk of getting a disease, those who might be prone to do worse with that particular ailment, and what medications might work best as treatment,” said Concato. “This is the promise of personalized medicine, and MVP stands to greatly improve our ability to provide it.”

exploring the genomic universe

It’s too early to know what discoveries might be made, say Concato and the other principal investigator, J. Michael Gaziano, M.D. ’87, M.P.H., a professor of medicine at Harvard. Advances in understanding the interplay of genes and such illnesses as cancer, diabetes, and heart and circulatory problems, and such mental illnesses as service-related post-traumatic stress disorder (PTSD) are possible long-range program benefits.

“Just like the Hubble Space Telescope opened up ways of seeing the universe that Earth-bound telescopes couldn’t provide, we think that MVP will allow us to explore the genomic universe,” said Gaziano, scientific director of the Massachusetts Veterans Epidemiology Research and Information Center, chief of the division of aging at Brigham and Women’s Hospital, and director of the VA Boston Healthcare System’s Geriatric Research and Education Center.

The MVP is one of several similar efforts around the world, among them biobanks in the United Kingdom and China, each of which has about 500,000 participants, and at Vanderbilt University and Kaiser Permanente, which include about 175,000 and 200,000 people, respectively. The MVP, if it meets its target, will be the largest among them.

All these efforts link at least two streams of genetic and medical data; the MVP links three. The first is genomic information gleaned from different DNA sequences: general genotyping; the sequencing of just the coding part, or exome, of the genome; or, in a small number of cases, whole-genome sequencing. The second stream includes health and treatment information from each vet’s electronic medical record. The third part, unique to the MVP, is a health and lifestyle survey that includes questions about military service which will give researchers a better understanding of possible genetic underpinnings of conditions like PTSD that might affect people in the armed forces.

“MVP couldn’t have been built without the existing VA research infrastructure,” said Concato, who, with Gaziano, directs a staff of about 20 in West Haven and Boston, with key support from the Office of Research and Development in Washington, D.C.

One key to the program’s eventual utility is the VA’s reach: data are being collected at about 50 VA health care facilities around the country, each of which has two staff members dedicated to the MVP. Another is the availability of its pioneering electronic medical record, which can look backward and forward in time and follow vets wherever they live. A third aspect is data security—the VA made security the highest priority from the moment it started its EMR implementation. Last, recent developments in information technology, from automated bios-storage data retrieval to computer analytic capabilities, allow researchers to manage massive amounts of data.

“Maybe the biggest enabling technology is having a chip that allows us to do cheap genetic testing,” said Gaziano. “We can now look at the genetic variation in about 750,000 places on a person’s genome for \$75—that’s \$52 for the chip and the rest for processing—and this ability to generate data, coupled with the information we’ll get from hundreds of thousands of vets, will let us start to answer questions we couldn’t have even asked before.”

One area of interest is an aging population. “We hope that MVP will be a pluripotent resource that can be used by researchers and providers to look at how to best deal with that group, from studies of frailty to understanding variations in medication-related enzyme metabolism,” said Gaziano.

at the beginning of a revolution

Like Concato, Gaziano is no stranger to big-data projects. “I’ve been working in the large cohort business since I arrived at Brigham and Women’s in 1988,” he said. He’s had leadership and research roles in the Brigham and Women’s-based Physicians’ Health Study, which has followed a cohort of more than 30,000 doctors in the United States to examine a variety of health questions, as well as the Nurses’ Health Study and the Women’s Health Study, both of which are affiliated with Brigham and Women’s and have enrolled cohorts of more than 100,000.

“While it builds on earlier work,” Gaziano said of the MVP, “it’s really something new.”

Early epidemiological studies were primarily descriptive and involved small numbers of subjects or issues, such as the relationship of smoking to lung cancer. The famous Framingham Heart Study (FHS) in Massachusetts has since 1948 tracked 5,000 adults to ask fundamental questions about the epidemiology of cardiovascular disease. The FHS used multivariate computer modeling to examine the impact of a half-dozen risk factors.

But with 20,000 to 25,000 protein-coding genes in the human genome, a cohort needs hundreds of thousands of people so that scientists can determine “how genes interact with other genes and environmental factors to contribute to health and disease,” said Gaziano. “There are enormous numbers of variables, so we need mega-cohort studies like MVP to solve the signal-to-noise problem that genetics gives us. We’re at the beginning of a very exciting revolution.”

Two “alpha” studies have begun testing the biobank’s ability to deliver useful information. Concato, Gaziano, and their colleagues have mined the database for mentally healthy vets who can serve as a control group for comparison with 9,000 vets with schizophrenia or bipolar disorder. “The pending genomic analyses can advance our understanding of the etiology of, and treatments for, two major psychiatric disorders,” the researchers wrote last year in the *American Journal of Medical Genetics*.

The second alpha test, co-directed by Joel Gelernter, M.D., the Foundations’ Fund Professor of Psychiatry at Yale, is using the biobank to find a cohort of vets with PTSD to compare with an MVP-assembled control group without the disorder. The hope is to identify genes that increase the risk of this often-devastating condition and to develop more effective methods of detecting and treating it.

Last year, MVP leaders issued a nationwide call for proposals, said Concato. About 20 have survived the first review round, and those approved will investigate an array of topics from heart disease and lung cancer to mental health disorders and problems with water metabolism. Funding decisions will be made later this year.

“It’s important to remember that MVP is an infrastructure project,” said Concato. “Our role is to help design the program so that researchers can use the biobank effectively, securely, and ethically, and have the right information available to ask the right questions.” */yale medicine*

Bruce Fellman is a freelance writer in North Stonington, Conn.

Whispers on the medallion, the Society of Wu, and Frisbee on the lawn

WHAT DO YOU HAVE TO DO to get into the School of Medicine? According to Dan Okin, a fourth-year medical student, a superstition handed down by students directs you to the medallion beneath the rotunda in the Cushing/Whitney Medical Library—where you stand and whisper your name and the phrase “Please let me in!” Thanks to architectural magic, they’ll hear you in the admissions office, which once occupied space above the rotunda.

“Our tour guides on interview day have the applicants stop in the center of the rotunda and say a few words to hear the mystical echoes,” said admissions director Richard A. Silverman.

If you ask alumni of the School of Medicine which traditions they remember best, they often mention venerable and well-established ones first—donning a white coat for the

first time; honoring donors who willed their bodies to the anatomy lab; or raising money for the homeless in an annual auction. But quirkier traditions, customs, and habits have appeared through the years at Yale Med, too. Passed down from student to student, these activities continue to evoke fond memories. Some have survived; some haven’t, though we don’t always know why.

For a time, students would sneak into the Brain Room, locked deep within a subbasement of Harkness Hall. A historic collection of brains

preserved by neurosurgery pioneer Harvey W. Cushing, M.D., was moved there in 1979, along with haunting photographs of his patients. The collection was forgotten for decades except by students in the know, who would break the lock or kick in a door panel to get in, then add their names to a graffiti-like sign labeled “Brain Society.” Brain Room expeditions ended after the collection was spruced up and moved in 2010 to the Cushing Center, a dedicated space within the medical library.

Some student customs were very much of their time. In the late 1950s, recalls Malin Dollinger, M.D. ’60, students sought birth-control advice from ob/gyn fellows living in Harkness dormitory. (Condoms were then illegal in Connecticut.) He and his classmates used the dormitory lawn to play with a newly invented toy, the Frisbee. Years later, Jilda N. Vargus-Adams, M.D. ’95, and her class gamboled on a Wham-O Slip ’n Slide there after exams. (A 1993 national recall, with reports of quadriplegia in adults too tall to dive onto the toy, may have dampened enthusiasm for the slide.)

Alcohol has given rise to traditions both raucous and not. In the 1990s, for instance, the Society of Wu (why it was so named has apparently been lost to the ages) held a keg party in the Harkness basement just before exams. “The Yale system would dictate that you not take tests too seriously—surely you could go and partake in the Society of Wu the night before,” Vargus-Adams explained. (The Society seems to have mysteriously disbanded



before this writer matriculated in 2000.) The same philosophy invested Thursday night dances at the Graduate and Professional Students Center at Yale, also known as GPSCY. After late nights at GPSCY, she recalled, whether from fatigue or hangovers, attendance and energy were low at Friday morning anatomy lab.

More prosaically, Dollinger's classmates volunteered for paid studies at the Yale Center of Alcohol Studies on the main campus. They had to phone for rides back to the medical campus when they became too drunk to walk. That tradition presumably ended when the center relocated to Rutgers in 1962.

Harkness wasn't the only locus of party culture. In the early 2000s, the Pink House, an institution of sorts in the East Rock neighborhood that housed a revolving and brotherly clan of medical, law, and physician associate students, hosted monthly rotation-switch parties. Alas, Roberto Lugo, M.D. '04, who lived in that house, noted sadly on a recent reunion visit that it is no longer pink.

Yale Med's longest-standing tradition, of course, is the Second-

Year Show. Begun in 1949, it has burgeoned into a satirical extravaganza; the camaraderie and dedication it inspires make it the cherry on top of the Yale system. What few students these days know, though, is that the show began as a fourth-year activity. (The second-year show arose in the mid-60s; by the end of that decade, the fourth-years ceded the stage.)

The timing of the fourth-year show had its advantages, explained Victor A. Altshul, M.D. '60. "We gave it just before graduating, so that the attendings we were lampooning couldn't retaliate," Altshul recalled. "And boy, did we ever give it to them."

—Jenny Blair, M.D. '04

History of heredity

By John Curtis | Jennifer Stockwell Illustrations | Benjamin Hecht Photos

LONG BEFORE ANYONE DISCOVERED DNA, chromosomes, or genes, humans had figured out something important about the world around us. When we turned from hunting and gathering our food to growing and raising it, we realized that we could breed plants and animals to bring out desirable traits. Wild grasses became wheat under human cultivation; we also domesticated and bred cows, pigs, and sheep to produce food, leather, and wool. And we also noted similarities between parents and offspring without knowing what causes these similarities. The concept of heredity preceded the science of genetics, but it is genetics that explains why all living species carry inherited traits and qualities. This timeline lists some of the key advances in thinking about heredity and genetics.



During the Neolithic era, about 12,000 years ago, as humans move from hunting and gathering to growing their food and raising animals, they learn to breed desirable traits into wild grasses (1) and domestic animals.

In the fifth century B.C., Hippocrates (2) speculates that “seeds” are produced by various body parts and transmitted to offspring at the time of conception.

Theophrastus (3), a Greek scholar of the late third century B.C., who studied under Aristotle and is considered the “father of botany,” proposes that male flowers cause the ripening of female flowers.

Aristotle (4) proposes in the fourth century B.C. that male semen and female menstrual blood mix at conception and that offspring receive traits from both mother and father.

Abu al-Qasim (5), an Arab physician from about A.D. 1000, who is considered the father of modern surgery, describes the hereditary nature of hemophilia.

William Harvey (6), a seventeenth-century London physician, wonders why offspring sometimes resemble the father, sometimes the mother, and sometimes progenitors both maternal and paternal.

During the late seventeenth century, the Dutch lensmaker Antonie van Leeuwenhoek (7) describes “animalcules” in the semen of humans and animals.

Around 1800 the notion of heredity enters debates among physicians, animal breeders (8), and naturalists, and becomes a fundamental concept of biology.

The Austrian monk Gregor Mendel (9) describes patterns of inheritance in peas in the mid-1800s, but his theories are ignored, to be rediscovered only in 1901.

In the mid-nineteenth century, the English naturalist Charles Darwin (10) proposes the theory of evolution, with natural selection and heredity as its mechanisms.

In 1869 a Swiss physician, Friedrich Miescher (11), discovers a microscopic substance in pus obtained from discarded surgical bandages. He isolates DNA from those samples and calls it “nuclein” because it resides in the nuclei of cells.

Hugo de Vries (12), a Dutch botanist and geneticist, postulates in 1889 that “inheritance of specific traits in organisms comes in particles,” and calls the particles “(pan)genes,” a term that would later be shortened to *gene*.





In 1902–03, Walter Sutton (13), an American physician, and Theodor Boveri (14), a German biologist, independently propose the chromosome theory of inheritance: chromosomes, which segregate in a Mendelian fashion, are hereditary units.

William Bateson (15), an English geneticist, coins the term *genetics* in 1905.

In 1931, Barbara McClintock (16), an American pioneer in cytogenetics, provides the first proof that genes are physically positioned on chromosomes.

In 1944, Oswald T. Avery (17), Colin MacLeod (18), and Maclyn McCarty (19) conducted an experiment at the Rockefeller Institute that isolated DNA as the substance that causes genetic transformation.

James Watson (20), Francis Crick (21), Maurice Wilkins (22), and Rosalind Franklin (23) elucidate the structure of DNA at the University of Cambridge in 1953.

2001–2003: The first draft sequences of the human genome are released by the international Human Genome Project and Celera Genomics in February 2001; two years later, the Human Genome Project is considered complete, with 99 percent of the genome sequenced to a 99.99 percent accuracy.

So you've decided to become a doctor

APPENDICITIS LANDED XIANG (AVELINE) LI in the emergency room during her junior year at Bowdoin College, where she was majoring in biochemistry. Her parents, both physicians, were living halfway around the world in China and she was frightened and unsure about what was happening. After the appendectomy, complications required a second surgery and two more weeks in the hospital. During her recovery Li gained firsthand insights into the needs of patients. Prior to her illness, she'd been exploring medicine to see whether she wanted to become a doctor. Becoming a patient helped confirm her decision.

While Li was recovering, Nidharshan Anandasivam, also a college junior, was studying biomedical engineering at MIT and exploring volunteer opportunities to see whether medicine was in his future. Having injured his ankle several times while playing basketball, Anandasivam

wondered whether he would be able to integrate his passions for sports, health, and science into a career. His physician parents had encouraged him to pursue his interests in college and see where they led.

What influences a child of physicians to choose a career in medicine? For Li and Anandasivam, students in the Class of 2018, a future in medicine was not a foregone conclusion even though their parents are physicians.

Fascinated by high school biology and the human body, Li's interest in medicine grew as she sought opportunities to engage patients and observe the physician's role. During high school she volunteered at the Veterans Health Administration and worked with a physician on reducing patient waiting times. "That experience had a big impact," she said. "Seeing how happy patients were to see their doctor and observing the mutual trust involved in the doctor-patient relationship was inspiring." In college, she volunteered at a local hospital and the American Cancer Society. "Each new volunteer experience confirmed that I wanted to become a doctor," Li explained.

Li's maternal grandfather had been a doctor and her maternal grandmother had been a nurse. But her father, a neurologist, and her mother, a pediatrician, had no expectation that Li would go into medicine. In fact, because of the consuming nature of the profession, they initially tried to dissuade her. Li didn't grow up seeing her parents working with patients, because they lived in Canada and the United States, where neither parent was licensed to practice. They instead did genetics research, and when Li started college they returned to China to practice medicine. During visits to China, Li observed the very limited time her parents could spend with their patients. She valued the patient-physician relationship and was determined to practice medicine in a different way. "China's large population means my parents don't have time to do what I'm learning at


Yale—the patient-centered interview,” she explained.

Anandasivam’s family is from Sri Lanka, but he grew up in Rancho Viejo, Texas, where his father is a nephrologist and his mother is an internist. During high school, strong interests in math and physics pointed him toward engineering. But his college classes, research, and volunteer activities increasingly pulled him toward medicine. Anandasivam carefully chose volunteer opportunities that exposed him to different aspects of medicine, including working as an EMT Basic with MIT’s EMS service and participating in the MIT MedLinks program, a dorm-based peer-to-peer health advocacy group. He also worked with LIFT, a community service program, where he enjoyed helping people solve problems and find resources. “My experiences in college serving the community were the driving forces in my choice,” he explained.

Anandasivam said that his parents and especially his grandmothers, who lived with his family and helped raise him and his younger brother, modeled the importance of service. “They were ‘service first’ people and that had a big effect on me,” he said. As he experienced the service side of medicine in concert with the intellectual side, it became clear that medicine was a good fit.

The influences that led Li and Anandasivam to choose medicine were multifaceted. They enjoyed the intellectual challenges of medicine and valued serving others. For Li, meeting outstanding clinicians—including the surgeon who performed her second surgery—also

confirmed her decision. His engaging bedside manner provided a role model for the type of doctor she wants to become. Anandasivam said his parents’ enthusiasm for their profession helped him see



Nidharshan Anandasivam and Xiang Li are both children of doctors. How much did their parents influence their decision to enter medicine?

how rich a life in medicine could be. “I would’ve been less enthusiastic about it if my parents’ work compromised their ability to perform their other important responsibilities,” he added. “But they spent a lot of time with us and showed us that it’s possible to have an engaging career and fulfill your role as a parent and spouse.”

—Katherine L. Kraines





When a gene goes awry

Medical and genetic sleuthing unravel the mystery of an infant's death and a father's fevers

By Jill Max | Harold Shapiro Photos

When Mustafa K. Khokha, M.D., first saw the Drewniak baby in the summer of 2012, he was worried. The baby boy, first treated at Norwalk Hospital, had a high fever and severe diarrhea that was getting worse. Clinicians at Yale–New Haven Hospital's Pediatric Intensive Care Unit were frantically trying to keep up with fluid losses. Infection, the most likely culprit, had been ruled out. Khokha, associate professor of pediatrics (critical care) and of genetics, wondered whether an underlying genetic cause would explain the baby's condition, and called Richard Lifton, M.D., Ph.D., chair and Sterling Professor of Genetics. Genome sequencing, Lifton felt, might yield clues to the infant's ailment. Both Lifton and Khokha thought that the baby might have a new genetic mutation—a *de novo* mutation—since both of his parents were healthy.

They used high-throughput exome sequencing to analyze the 21,000 protein-coding genes in the genomes of the baby and both his parents. Meanwhile, Neil D. Romberg, M.D., assistant professor of pediatrics

Susan Kazmierczak, Neil Romberg, Richard Lifton, and Mustafa Khokha were part of a team of clinicians and scientists who determined that a defective gene was behind a family's health problems.

(immunology), examined the baby for a rash. Romberg recognized it as the first sign of a massive immune response, and lab tests indicated that the baby had widespread inflammation. “Inflammation in the absence of infection is usually a genetic problem,” said Romberg.

The Yale Center for Genome Analysis rushed the sequencing and analysis. Completed in just a few days—a heroic effort—test results arrived the day after the 3-week-old baby died. The analysis found no *de novo* mutations that explained his illness.

A few days after the funeral, Erik Drewniak was still reeling from the loss of his infant son when he came down with a fever. He didn’t think it was anything to worry about. All his life he had had fevers that spiked as high as 106 degrees. But this time the fever persisted and he was having difficulty breathing. Concerned about pneumonia, he went to the emergency room. At Norwalk Hospital, Drewniak’s condition deteriorated. He went into respiratory failure and was put into a medically induced coma so that he could be intubated. Soon afterward, he was in intensive care at Yale-New Haven Hospital where tests showed he was suffering from inflammation and hemorrhaging of the bowels, lungs, and brain. His condition was serious, but he improved and went home nine weeks later.

a clue in a random mutation

With every sequencing of a patient’s genome, new, previously unseen protein-altering variants in genes emerge. These random mutations are due to variation in the human population. When Romberg suggested that the baby might have had an autoinflammatory disease, Lifton invited him to his lab to look at a list of variants. Romberg recognized a mutation in *NLRC4*, a gene involved in the innate immunity pathway—the first line of defense in the body’s response to infection—that could contribute to disease, although it had never been shown to have such an effect. That same day, while gathering information about the baby from Norwalk Hospital, Lifton’s research coordinator learned that Erik Drewniak was hospitalized with a severe illness. For Lifton, that was an “aha” moment.

“We recognized at that point that the variant in *NLRC4*, which was shared between the father and the baby, might link their diseases,” he said. It turned out that Drewniak

and his infant son shared a genetic mutation causing an illness that had never before been described.

Advances in genomic sequencing technology, combined with clinical expertise and biochemical analysis, allowed Yale doctors to identify the mutation, home in on the pathway it affected, and devise a personalized therapeutic strategy that saved Drewniak’s life. Using whole-exome sequencing to diagnose diseases is increasingly proving to be both useful and practical. Five years ago it would have cost about \$10,000 to do the exome sequencing performed on the Drewniak family; today it costs about \$500. Not surprisingly, this service is rapidly expanding. Last year, Yale sequenced about 500 patients; this year about 1,000 will be sequenced. The Drewniaks’ experience is just one example of the ways in which personalized medicine, which is being supported by President Obama’s recently announced Precision Medicine Initiative, is gaining ground.

passing on a gene

To confirm that the Drewniaks’ illnesses were caused by the newly identified mutation, the Yale team sequenced other family members, including Erik’s parents and two children who are half-siblings of his infant son. While his parents and daughter do not have the *NLRC4* mutation, the sequencing showed that his son, now 7, does. Like his brother, he was hospitalized as an infant, although in his case it was due to kidney failure. Like his father—who was also hospitalized as a baby for a fever and severe diarrhea—he suffers from periodic high fevers. The mutation was in fact *de novo*, but it first occurred in Erik Drewniak, who passed it on to two of his children. His young son has a 50/50 chance of passing it on to his offspring.

Once a genetic mutation emerged as the likely cause of disease in three Drewniak family members, the next step was to understand how a single change in this particular protein code could wreak such havoc. “Exome sequencing by itself is not the solution,” said Khokha. “It’s just the first step.” Romberg enlisted Barbara I. Kazmierczak, Ph.D., M.D., associate professor of medicine (infectious diseases) and of microbial pathogenesis, who had been studying *NLRC4* in mice. *NLRC4* belongs to a group of intracellular proteins that react when bacterial toxins breach the cell wall. Kazmierczak and Romberg’s research showed that the mutated *NLRC4* protein activates a powerful inflammatory pathway that sent the Drewniaks’ immune systems into overdrive, even though no bacterial

infection was present. “Their system is always on when it should be off,” said Kazmierczak.

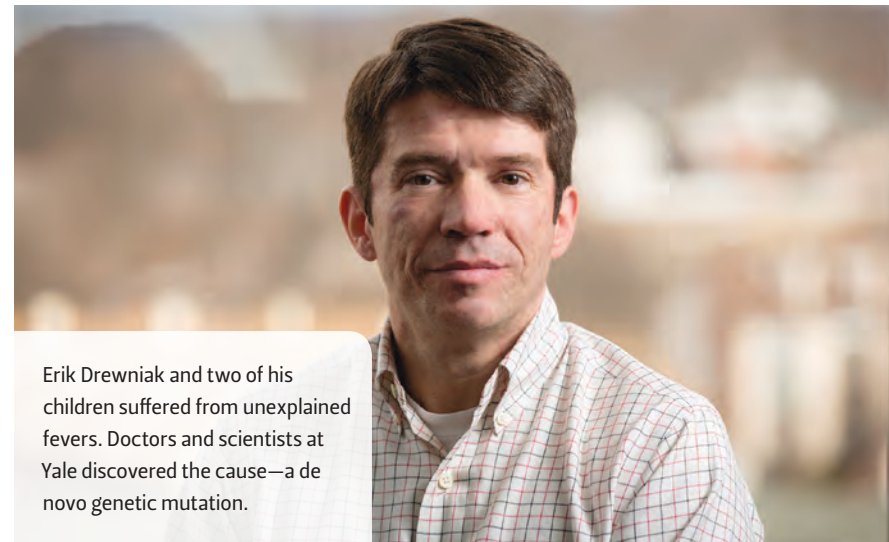
Today, Erik Drewniak is healthy, as he has been for much of his life. “It didn’t affect me when I was growing up,” he says of his illness. He played in bands and was on the tennis team in high school, missing only an occasional event because of a fever. His son is also relatively healthy. “He does kung fu and other typical kid stuff,” said Drewniak. But the mutation they share causes a constant state of inflammation in their bodies that can become dangerous.

When Erik Drewniak was hospitalized in 2012, Nikolai A. Podoltsev, M.D., Ph.D., assistant professor of medicine (hematology), treated him for what appeared to be hemophagocytic lymphohistiocytosis (HLH), another disease in which the immune system becomes overstimulated. Drewniak’s condition, while different, closely resembles HLH and responded to powerful anti-inflammatory medication and immunosuppressants, which are used to treat HLH.

understanding the disease

Now that Podoltsev and Romberg (who treats Drewniak’s son) know the mechanism of this disease, they are better equipped to treat it in the future. “Of course it’s easier to manage him going forward understanding what we’re dealing with,” said Podoltsev. The Drewniaks’ care involves managing the inflammation and monitoring symptoms. The mutation causes production of high amounts of cytokines—in this case interleukin 1 beta—that cue the immune system to start reacting to an infection, so interleukin 1 inhibitors could be useful if either of them experiences a flare-up.

Beyond the therapeutic implications of these discoveries, the ability to pinpoint the cause of mysterious illnesses is invaluable. “When a baby dies of diarrhea, it’s very disturbing because it doesn’t happen in this country,” said Khokha. “It feels like a failure.” Being able to tell his parents why their baby died provided some solace. Fortunately for families like the Drewniaks, diagnosing rare genetic illnesses is becoming more common. “We’ve gotten to the point where genetic sequencing is fast enough and cheap enough and we’ve done enough of it, that this is no longer science fiction,” said Romberg.



Erik Drewniak and two of his children suffered from unexplained fevers. Doctors and scientists at Yale discovered the cause—a de novo genetic mutation.

“It’s clear there will be many more cases like this one,” said Lifton. Of the 21,000 protein-coding genes in the human genome, he said, scientists know what happens when about 3,000 of them are mutated. “When I’m asked what remains to be done, the answer is practically everything.” Researchers are beginning to tackle this undertaking. The Yale Center for Mendelian Genomics is one of three national centers created by the National Institutes of Health to try to understand the genetic causes of diseases like the one in the Drewniak family. The center has identified about 250 new disease genes since it was established in 2012.

Meanwhile, Khokha and his colleagues often see children with birth defects or unexplained illnesses that they are unable to diagnose. A new program, Pediatric MAP, supported by the Yale School of Medicine, the Yale Center for Clinical Investigation, and Yale-New Haven Hospital will allow them to carry out the research that was done for the Drewniaks on a broader scale. The hope is that by formalizing the program, Yale doctors will be able to provide answers for these families by identifying genetic mutations and unraveling their biology with the ultimate goal of developing new therapeutic approaches.

For Drewniak, the knowledge of what caused his infant son’s death is empowering. “Genetics is something you can latch on to as a definite explanation,” said Drewniak. “It’s not the environment, it’s not something you did or didn’t do, it’s genetics. It made me understand not just him, but all three of us. Everything just came together and now it all makes sense.” /yale medicine

Jill Max is a freelance writer in Trumbull, Conn.

The New Haven home of Daniel Colón-Ramos, Ph.D., his wife, Emily Wang, M.D., assistant professor of medicine, and their triplet daughters is a Tower of Babel. The 4-year-olds Alexandra, Beatriz, and Caysani speak Spanish among themselves, with their dad, and with their nanny, and speak Mandarin with their mom. Mom and Dad speak to each other in English, and each speaks a bit of the other's native tongue. Watching how his daughters play and communicate led Colón-Ramos, associate professor of cell biology, to write an article for the TEDBlog in December 2012, when the girls were toddlers. In "On nature versus nurture: A neuroscientist knee-deep in diapers reflects," he described the lessons he's learned from his daughters, how they've changed his brain, and the futility of the debate over nature versus nurture. Since he wrote the article, Colón-Ramos tells us, what he said then remains true today.

Reflections of a neuroscientist

I COULDN'T HAVE DESIGNED A BETTER EXPERIMENT IF I'D TRIED.

I am a neuroscientist and I am the father of 2-year-old triplets—two identical and one fraternal. As a professor at Yale University, I spend most of my time designing experiments, researching or teaching about the brain and the nervous system. The rest of my time I spend surrounded by my three daughters. To understand the dynamics in my household, think terrible-twins, and then cube it.

In the quiet sanctity of my lab, we study how the nervous system forms during development. In all animals, from humans to the tiny worms that we use for our experiments, neurons connect to each other and form circuits that

underlie behaviors. Genes (made of DNA) underpin many aspects of development—from how our brain forms to the color of our eyes.

My identical twin daughters look identical because they share all of their DNA; they are essentially clones of each other. They teethed exactly the same day, and their funky hairstyle is not the result of a visit to a stylist, but of genetics. Their personalities, however, are not

identical. Not even close. The twins' personalities, which share 100 percent of their DNA, are curiously more similar to that of their fraternal sister than to each other.

That certainly came as a surprise to me. After all, argue all you want about nurture, but behaviors do have genetic underpinnings in the animal kingdom. Take reptiles; soon after hatching from its egg, a baby crocodile can hunt dragonflies with the same dexterity that its parents can hunt antelopes. Who taught the baby crocodile to hunt? Genes.

I reflected about this a lot as I held my newborn daughters in the nursery room of the hospital. Human brains at birth do not appear nearly as impressive as a reptilian brain. For crying out loud, the tiny nematodes we use in the lab for our experiments can move around better at birth than a human baby! Newborns appear as blank slates. Are we really a tabula rasa? What are the roles of nature (genes) and nurture (our environment) in the development of our brains, in making us human?

My epiphany came with the first visit to the pediatrician. She closely monitored our daughters as they met, in unison, one developmental milestone after the other. As a neuroscientist, I knew what this timely emergence of complex behaviors meant: it is a hallmark of preprogrammed brains. But our preprogrammed brains are not for hunting dragonflies. The evolutionary pressures that have shaped our brains are different from those that have shaped the brains of swamp-bound reptiles.

We are born into complex societies and quickly have to learn to negotiate our place within them. My three kids, the ones playing with my iPhone, are the same species as my ancestors, who 40,000 years ago were figuring out how to sharpen a rock and fit it into a spear. The *Homo sapiens* brain is wired in a very particular way: to allow us to connect to other human brains.

Our home is testament—a cross between the Tower of Babel and a Univisión soap opera. It is filled with sound, from the tonal Chinese my wife has taught the triplets to the slurred Puerto Rican Spanish they have learned from me. During the past two years I have witnessed how each of my daughters has masterfully decoded the complex rules of language and social interactions in three very different and overlapping cultural contexts, and simultaneously. They confidently navigate between languages in a way that sometimes neither my wife nor I can follow. Chatty conversation and festive giggles are only one disagreement away from despair and temper tantrums over a train set, a Crayola, or a dinosaur shirt. But most meltdowns end with hugs, sometimes all three at the same time, as they can't wait to make up.

My daughters' desire to connect is not just cute, it's a matter of survival. So important is our need to connect to other human brains that extreme cases of child neglect have resulted in developmental problems not unlike those seen for mental retardation. These extreme cases tell us something profound about the brain. It tells us that even in cases



Emily Wang and Daniel Colón-Ramos speak to each other in English. Wang speaks Chinese to their 4-year-old triplets, Alexandra, Beatriz, and Caysani. Colón-Ramos speaks to them in Spanish, which the girls speak among themselves.

in which normal genetics prime the brain to connect to other brains, the absence of human input cripples brain development. Our brains need other brains to develop properly.

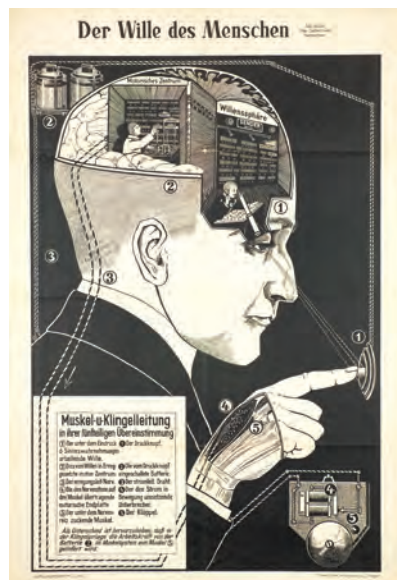
These seemingly delirious thoughts of a sleep-deprived scientist are neither new nor original ideas. Today it is broadly accepted that trying to separate nature from nurture is as asinine as trying to debate whether a cake is made out of milk or flour. But this is important beyond a mere academic debate. In science, extreme cases are used to understand concepts. If no human contact during critical developmental periods can cripple brain development, what are the consequences of reduced stimulation due to a defective and underfunded educational system? The United States

incarcerates more of its youth than any other country in the world—what are the consequences of growing up in a prison? We are social and codependent animals—what are the hidden costs to our society when we ignore the “nurture” part of the human development equation?

The human brain has over 100 billion neurons—there are more neurons in a single human brain than stars in the Milky Way. When a parent stares at the lost, unfocused gaze of a newborn child, they are literally staring at a constellation of possibilities, at a brain primed through evolution to connect to other brains, to devour information, to adapt and to reach its potential. In truth, I'm highly trained, but not that special; we are all born scientists, and our brains are molded by our favorite subjects of study, other humans. And I have the perfect experiment to prove that—my brain, which has been transformed by my daughters.

—Daniel Colón-Ramos

CLOCKWISE FROM TOP: Fritz Kahn, a German gynecologist, conceived of a series of popular books, *The Life of Man*, to make the science of the human body accessible to a broad audience. Kahn, considered a pioneer in infographics, composed the text, and designed or approved ideas for the illustrations. In *The Will of Mankind*, Kahn provided a depiction of the functions of the mind and brain.



An earlier effort at illustrating the workings of the human body comes from a Japanese artist, Utagawa Yoshitsuna, in the mid-19th century. *Model for Men's Dietary Care*, a polychrome woodblock print, shows a subject digesting a meal of fish and sake. As with Kahn's illustrations, it uses the metaphor of workmen performing familiar tasks to demonstrate the actions of the internal organs.

In *Man as an Industrial Palace*, Kahn depicted the human digestive and respiratory systems as a chemical plant.



OPPOSITE PAGE: **TOP** A French advertising poster from the early 20th century borrowed from Kahn's imagery to advertise the beneficial results of a popular laxative. It appeared around the time of Kahn's posters published with *Das Leben des Menschen*.

BOTTOM From *The Life of Man*, a depiction of the human respiratory system also uses the visual analogy of a factory.

Man as industrial palace

A view of the human body in the Industrial Age

By Christopher Hoffman



The nearly life-sized poster titled *Der Mensch als Industriepalast* (*Man as an Industrial Palace*) depicts the human body as a complex machine, a wonder of the industrial age.

Workers stand at power plant-like control panels and operate the body's central nervous and respiratory systems. Oxygen and carbon dioxide travel in automated bucket lines down pipes to and from the lungs. The heart's chambers are a pair of pistons, the stomach a conveyor belt, and the spinal cord a telephone system with switchboard operators directing calls.

The arresting image is the work of Fritz Kahn, M.D., a German gynecologist who in the 1920s wrote a series of popular books titled *Das Leben des Menschen* (*The Life of Man*) that strove to explain science and medicine to a broad audience. The colorful, intricately drawn diagram is one of three—all originally inserts in *The Life of Man*—displayed at the Harvey Cushing/John Hay Whitney Medical Library in January.

Largely forgotten until recently, Kahn's books were famous for their detailed, innovative, and aesthetically pleasing illustrations, said Susan Wheeler, the medical library's curator of prints, drawings, and historical posters. "I think he had an

idea of making ideas handsome and accessible," she said.

Today, Kahn is widely recognized as a pioneer of information graphics, the use of images and visual metaphors to convey information and ideas. He is often mentioned in the same breath as the Austrian Otto Neurath, who at about the same time invented isotype, the communication of data through pictographic charts.

Both men did their most famous work in post-World War I Central Europe, a time and place of social and political upheaval as well as technological and artistic innovation. That ferment sparked "a fireworks display of new aesthetic form," wrote Uta and Thilo von Debschitz in their 2013 book, *Fritz Kahn*. In the introduction to the von Debschitz's book, graphic design historian Steven Heller likens Kahn to astronomer Carl Sagan in his ability to make science accessible to the ordinary person.

"The art of analogy was Kahn's forte," Heller wrote. "Kahn employed whatever visual trick he could cobble together for the end result: popular comprehension."

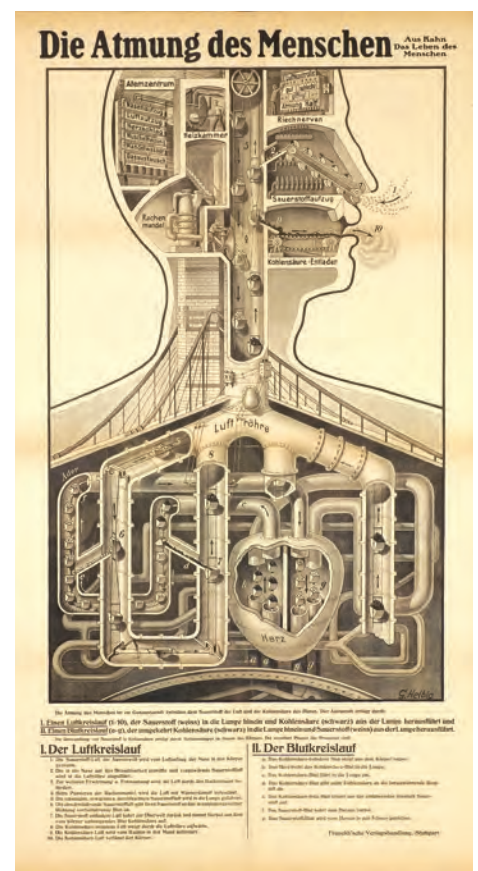
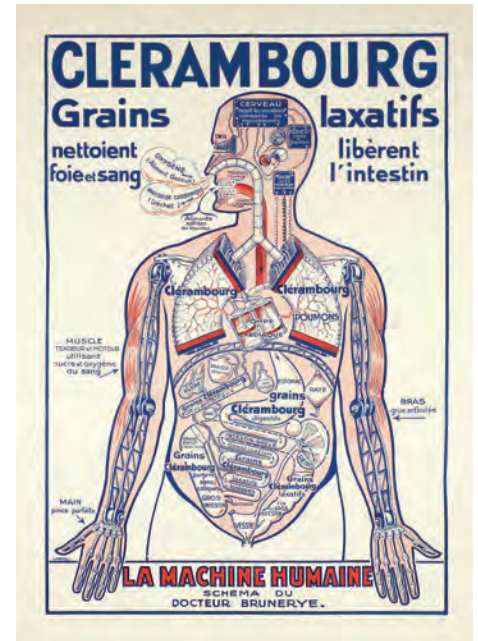
The Life of Man series made Kahn Germany's most famous popular science writer of the 1920s. A terrible artist, he commissioned others to render his ideas into illustrations.

Kahn, who was Jewish, fled Germany when the Nazis seized power. The new regime banned and burned his books. But in an ironic twist, Nazi authors plagiarized his work and illustrations, adding chapters on supposed racial superiority. Kahn later lived in France, the United States—gaining entry with the help of fellow German Jew Albert Einstein—Switzerland, and Denmark. He died in 1968, his work largely forgotten.

The other two Kahn posters displayed at the medical library are as fanciful as *Man as an Industrial Palace*, his most famous image. In one, an operator using a telescope and control panels illustrates how the brain tells the finger to press a doorbell. In the other, a warren of chambers containing conveyor belts, storage tanks, and other industrial devices demonstrates the circulation of blood and air through the body.

Wheeler said that the posters, donated to the medical library in the late 1970s and shown here for only the second time, elicited fascination and delight.

"There's a kind of awed response to [them]," she said. "Visitors ask the same kind of questions, which is who did them and what were they for? But everyone expresses extreme enjoyment of them."





Bringing new cancer treatments to the clinic

IN MANY WAYS, Patricia M. LoRusso, D.O., has realized one of her main missions in life—bringing the latest therapies to people with advanced cancers through clinical trials. For many patients, a few months can make a difference and help them get to the next new treatment.

“We saw so many patients die of melanoma within a couple of months of phenomenal immunotherapies going into clinical investigation,” said LoRusso, who joined Yale Cancer Center in August 2014 as associate director of innovative medicine. “It isn’t over until it’s over, and we often don’t know what the next drug is going to offer.”

Among her accomplishments, LoRusso heads one of the first multi-institutional investigator-initiated personalized medicine clinical trials, in collaboration with national melanoma leaders, as part of her role as co-leader of the Stand Up to Cancer/Melanoma Research

Alliance Melanoma Dream Team. She came to Yale from Wayne State University’s Barbara Ann Karmanos Cancer Institute, where she was director of the Phase I Clinical Trials program and part of the Eisenberg Center for Translational Therapeutics.

At Yale she sees her role as a mix of clinical research and translational medicine, in which she can apply her experience developing novel drug therapies and designing clinical trials.

For LoRusso, bringing novel therapeutics to the clinic is highly personal. She was still in high school when she lost her mother to cancer. A short time later, her father succumbed to lung cancer. Through her grief, LoRusso realized her life’s path—to become a physician and help improve outcomes for people with cancer.

“It became a defining moment in my life,” said LoRusso, who has more than 25 years of expertise in medical oncology, drug development, and early-phase clinical trials. “At the time my parents died, there weren’t good therapies, and I was determined to develop new, better drugs to treat cancer.”

Today, the Detroit native is internationally recognized for bringing promising early-stage anticancer therapeutics to the clinic, among them TDM-1, now known as ado-trastuzumab emtansine, or Kadcyla®. As a clinical investigator assisting Genentech in developing Kadcyla, she studied “such questions as



Patricia LoRusso, Yale Cancer Center's new associate director of innovative medicine, sees her role as a mix of clinical research and translational medicine.



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whether the drug impacts on conduction mechanisms of the heart, how it is dosed in patients with liver dysfunction, how it interacts with other agents in terms of toxicity and potential efficacy.”

Clinical trials, she said, have evolved in such a way that there is less distinction between Phase I and II trials. This means more targeted, tumor-specific therapies are being studied and at earlier stages. LoRusso and other researchers are seeking patients with specific tumor types as they “carry out clinical trials to answer pivotal clinical questions in anticipation of FDA submission and eventual approval of drugs.”

Most of the patients LoRusso and her team care for have recurrent cancers that have defied conventional treatments.

“It’s a huge motivator when you can help [extend the life of] a patient who would otherwise be dying of advanced cancer,” she said. Even more motivating are those occasions when she cannot help them at all. “You realize how much harder you have to work.”

But she sees the future as bright, thanks in large part to a greater understanding of the biology and genomics of the disease. “This is undoubtedly the most exciting time to be developing new cancer drugs, and we are making progress,” said LoRusso. “My mother would have had a much better prognosis and may actually have been cured of her disease had she been diagnosed in 2014 instead of 1970.”

LoRusso, who earned her doctorate in osteopathic medicine at Michigan State University in 1981, lives in Hamden with her husband, Julian. They have three (now adult) adopted children. “They are my best friends, and we have a lot of fun together.”

—Amanda Crowe



How an 18th-century doctor enticed a librarian to study the history of medicine

Melissa J. Grafe, Ph.D., likes to reach back in time to tell the story of John Archer, the first graduate of an American medical school program. Practicing in 18th-century Pennsylvania, and confronted with a child whose symptoms resembled what we now call diphtheria, Archer discovered a treatment using a native American plant. A dose of Seneca snakeroot, a powerful emetic, allowed the suffocating child to breathe again.

Use of the treatment began to spread after Archer told his five physician sons and 35 apprentices about his successful experimentation with Seneca snakeroot.

“I started to delve into the story of this man, and his sons, and his apprentices,” Grafe, the John R. Bumstead Librarian for Medical History, said of the physician who was the subject of her dissertation at Johns Hopkins University. In 1768 Archer became the first graduate of the School of Medicine of

the College of Philadelphia, now the University of Pennsylvania. “His story is why I became interested in medical education and apprenticeship. People learn medicine in so many different ways. How does it play out in a family whose members are all so interested in medicine?”

Her interest in the history of medicine had begun earlier, during her undergraduate days at Ursinus College in her native Pennsylvania, when she read the Pulitzer Prize-winning *A Midwife’s Tale*, by Laurel Thatcher Ulrich.

Now, Grafe pursues her interests in medical education and the history of medicine at work every day. As director of the Medical Historical Library, she helps students and scholars navigate its collections, housed within the Cushing/Whitney Medical Library. She curates exhibits that showcase materials from the library’s more than 140,000 volumes, as well as thousands of manuscripts, drawings, prints, incunabula, and other items spanning every era of medical history. Recent exhibits range from the 16th-century anatomical drawings of Vesalius, some of which incorporate an ingenious lift-the-flap design not unlike what we see in children’s books today, to 1970s-era Technicolor posters highlighting the dangers of excessive drinking.

After college, Grafe worked at historical sites in Pennsylvania and North Dakota, curating exhibits, conducting tours, and

working on community outreach and education. In North Dakota, where the distance to a hospital can be great, she also trained as an EMT. It was then, Grafe said, that “I became interested in how people heal themselves.”

Grafe completed her Ph.D. at Johns Hopkins in 2009 and then did postdoctoral work through the Council on Library and Information Resources. She was a librarian at Lehigh University when the position at the Medical Historical Library became open. She jumped at the opportunity. “This is a once-in-every-20-or-30-year position,” she said. “This is the kind of collection you want to be a part of.” Grafe came to Yale in 2011 and lives in North Guilford with her husband and two young sons.

In addition to overseeing library collections, Grafe works with medical school faculty. “They find great materials in their own departments and want to do something with them, or want to know more about the history of their own fields.” She and the library staff have been working with members of the Department of Surgery, helping them locate materials for an upcoming book and exhibit on the department’s history. “By going back 20, 30, or 40 years, you can get to understand how a field has changed,” Grafe said, “and why it is the way it is now.”

Digitization of the library’s collections is another important piece of Grafe’s work. “Our



goal is to make our collections widely available to everybody. That’s why we digitize; we want the collections to be used.” The library also offers alumni the chance to digitize their own medical school theses and add their own work as Yale students to the online archives.

Though online access is vital, nothing, Grafe noted, can replace seeing the collections in person. “A digital image gives you a snapshot, but if you actually come to see the physical piece, you end up understanding more about it; it generates new questions.” And, she said, there is always the “wow”

factor: the chance to be in the presence of the past’s medical heroes. The library holds pieces from many scientific greats: Newton, Kepler, and Copernicus, to name a few.

“Can you imagine touching a letter written by Charles Darwin in 1859?” Grafe asked. It is this kind of irreplaceable experience a library can provide, one that can inspire a scientist to experiment anew.

—*Jeanna Canapari*

Melissa Grafe’s doctoral dissertation on an 18th-century Pennsylvania doctor sparked her fascination with the history of medical education and apprenticeship.



Nicole McNeer, a recent graduate of the M.D./Ph.D. Program, was included in *Forbes* magazine's 2015 list of 30 under 30 in Science & Healthcare, which recognizes rising stars in the field.

Who is Nicole McNeer and how does she win so many awards?

OVER THE PAST TWO DECADES only a handful of M.D./Ph.D. students have completed the program in six years (the average is seven or eight). Among them is Nicole McNeer, M.D. '14, Ph.D. '14, whose career path straddles pediatrics and biomedical engineering. While she was fast-tracking through the program, she also earned three prestigious awards—for the med school graduate who best exemplifies the qualities of a pediatrician; the most outstanding dissertation by an M.D./Ph.D. student; and exceptional achievement in engineering research.

“As far back as I can remember,” says McNeer, “I thought that research and science were the coolest things in the world.” Her parents, chemists who came from Bangladesh and now work at Kodak and 3M in Minnesota, encouraged her with chemistry and electronics kits.

In January, McNeer garnered yet another honor. *Forbes* magazine included the 27 year old in its 2015 list of 30 under 30 in Science & Healthcare, which recognizes young people with a record of achievement and promise. Soon after, McNeer spoke with *Yale Medicine*.

When did you become interested in biomedical engineering?

I had always been a math and physics nerd. When I was thinking about doing an M.D./Ph.D. program, getting the clinical and research experience, I wanted to try and use my math and physics background. Biomedical engineering seemed like a good fit.

What was the subject of your thesis?

My research is focused on site-specific gene editing. That's like taking a little piece of whiteout to the instruction manual, getting rid of the one- or two-letter typo that you have, and replacing it with the correct letters. There are several ways of doing this. I have been using synthetic small molecules that are similar to DNA. Instead of the regular sugar type of backbone that DNA has, they have a protein type of backbone that binds to the DNA in the cell. It makes it look like there's a lesion in the cell, which the cell wants to fix. The cell brings in its own correction machinery, and if you include a template with the sequence that you want, in some cases you're lucky and the cell uses your sequence

as the correct one. Most of my thesis focused on delivery of these small molecules using nanoparticles. The second part of my thesis was about applying this technology to editing the gene responsible for cystic fibrosis. It's caused by a single gene defect, so it was a very amenable target for this type of technology.

How did you choose pediatrics?

I knew I would do something that had to do with hematology, and I had done some rotations in adult hematology and oncology, which was interesting. I really enjoyed my rotations in pediatric hematology and oncology. I liked working with families and I liked how pediatric oncology is set up from a research standpoint.

You're also known around campus as a member of the Yale Belly Dance Society.

My sister, who went to Harvard with me, convinced me to take an introductory course. I'd never done any other type of dance, but I found the class really fun. When I came to Yale, I tried out for the Yale Belly Dance Society, practiced very hard, and got in. I have taken a break from the group because of the demands of

internship. Dancing, dressing up, and seeing friends have all gone by the wayside.

How are you juggling your internship and research?

For the past few months my research has been mostly writing and paper revisions—stuff I can do wherever I am. I'll have my computer with me, and when I have a moment I'll work on writing, or editing, or data analysis. There are a number of people who are continuing various aspects of the projects I'd been working on. It has been really cool to see the projects branch out in different directions.

How did you meet your husband, James McNeer?

It was my freshman year at Harvard, and he was a sophomore. He was looking on Facebook for a girl who was interested in video games. We played StarCraft against each other; then we started dating. Since college he's been working at a small hedge fund.

We got married five years ago. We had his pastor from Massachusetts and one of my uncles, who was training as an imam, preside over the wedding, with readings from the Koran and the

Bible. I think the audience was confused about when we were married because there were 10 different times when they said "you are married" in multiple languages.

How did you get nominated for 30 under 30?

A friend who was in *Forbes'* 30 under 30 last year nominated me, and *Forbes* asked for information about me, from me and other people. I am not sure who all the other people were. It was a little bit embarrassing. This type of subjective award is about 5 percent what you do and 95 percent luck and who you know and having someone nominate you. Within Yale there are a lot of people who are equally qualified, but it was an honor to be lucky enough to be picked for this prize.

What are your career goals?

My ideal job would be as a pediatric physician/scientist at an academic institution; to have my own lab; and also my own clinical practice, most likely in pediatric hematology and oncology.



watch a short film about
Nicole McNeer at
youtube.com/YaleMedicine

To nominate a subject for Q&A, contact

Yale Medicine, 1 Church Street, Suite 300, New Haven, CT 06510 or email yymm@yale.edu

Lifestyle strategies and alternative medicine

Yale M.D./Ph.D. takes unconventional path to develop a new paradigm of care

By Cathy Shufro

When he returned to his native Colorado 20 years ago to treat people with multiple sclerosis, Allen C. Bowling, M.D. '88, Ph.D. '88, believed he was well prepared. After earning a medical degree and a doctorate in pharmacology at Yale, he completed his neurology residency at the University of California, San

Francisco, and spent three years as a fellow at Harvard.

"I was thinking, 'Wow! I have such a great toolbox for doing clinical practice at a high level.'" Before long, however, Bowling recognized gaps in his knowledge. "There's so much I don't know, so much I didn't get, in more than a decade of training."

This realization grew out of the nature of multiple sclerosis (MS): this disease of the central nervous system is incurable and unpredictable and causes a constellation of symptoms. Although his patients generally took conventional medications for MS, Bowling discovered that most were interested in how such lifestyle issues as diet and exercise affect the disease. More than half pursued strategies not dreamed of in the medical school curriculum: reflexology, removal of dental fillings, marijuana, magnets, pressurized oxygen, and prayer. However, at that time, there were not any reliable sources of MS-specific information in these areas.

"I realized that the quality of MS care could be improved by providing objective information about the safety and efficacy of these lifestyle and unconventional approaches to people with MS and also to health professionals.

"My patients were immersed in these therapies that clearly were important to them—whether there was evidence that they worked or not." Even physicians and scientists who were patients used unconventional therapies and were interested in lifestyle approaches, said Bowling, who runs an MS practice affiliated with the Colorado Neurological Institute and is a clinical professor of neurology at the University of Colorado.

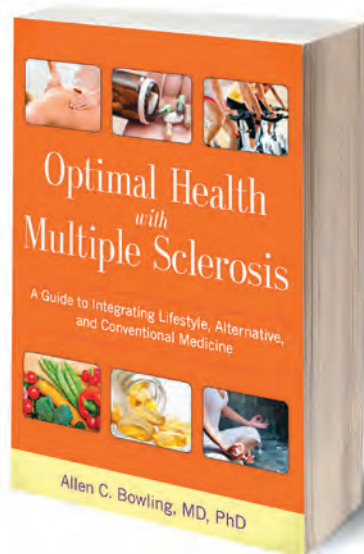
Bowling set out to evaluate these unconventional and lifestyle strategies. His approach is to critically review articles on a topic related to lifestyle or alternative medicine and distill them into a form that's user-friendly for clinicians and people with MS, he said.

The result is *Optimal Health with Multiple Sclerosis: A Guide to Integrating Lifestyle, Alternative, and Conventional Medicine*. For each of the main manifestations of MS, the book briefly describes potential therapies and lifestyle modifications.

Under "walking problems," Bowling mentions the standard medications and then lists 10 other "possibly effective lifestyle and unconventional therapies," including cooling, tai chi, and therapeutic horseback riding. Much of the book is given over to Bowling's elaboration on 49 approaches from acupuncture to yoga. For each, Bowling discusses effectiveness, possible interactions with standard care, hazards, and side effects. He cites studies and recommends further reading. Lifestyle, alternative, and conventional medicine strategies are integrated into a seven-step approach that may be easily followed by patients and professionals.

"I encourage my patients to explore things and extract what's helpful to them," said Bowling. He has tried much of what his patients pursue, both to understand his patients' experiences and for his own well-being. For instance, he now eats a vegetarian diet on weekdays and has worked to understand his psychological makeup, aided by "a few decades of free psychotherapy at home" thanks to his psychologist-wife, Diana S. Bowling, Ph.D.

Bowling provides information about lifestyle and unconventional therapies on his website, neurologycare.net/CAM



{ Send notices of new books to
Yale Medicine, 1 Church Street, Suite 300, New Haven, CT 06510 or email yymm@yale.edu

All welcome Dumbledore!!!

“PROFESSOR DUMBLEDORE” (aka Richard Belitsky, M.D., HS ’82, FW ’83, deputy dean for education) came to the School of Medicine in January to introduce a traveling exhibit created by the National Library of Medicine (NLM). “Harry Potter’s World: Renaissance Science, Magic, and Medicine” uses the seven books about the boy magician as a launching pad for an exploration of science. The magic in the books is based in part, says the NLM, on Renaissance traditions—alchemy, astrology, and natural philosophy—that had a role in developing Western science. Middle and elementary school students enjoyed a scavenger hunt, which had them scouring the library for the initials of someone wearing a wizard’s hat, a paw print from Finn the Therapy Dog, stickers in the library’s brain room, and other items. Jun Wan, a visiting research scientist, donned Harry Potter glasses for a photo with “Professor Dumbledore.”

“If I can conjure up just a little bit of magic and wizardry,” said Belitsky, the Harold W. Jockers Associate Professor of Medical Education, “I’m going to try to make myself disappear and hope that all of you forever forget this moment.”

—John Curtis