DISTILLATIONS

Best of
VOL. 1

STORIES FROM THE SCIENCE HISTORY INSTITUTE'S ONLINE MAGAZINE

Heat Therapy

THE HEALING BURN OF HOT PEPPERS

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SCIENCE HISTORY INSTITUTE'S
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Letter from the Chair

For 37 years the Science History Institute and its earlier incarnations have been sharing knowledge about the history of science and its role in understanding the world. We started with simple printed newsletters, which evolved into a 48-page magazine. *Distillations*, the most recent version of that publication, went digital-only in early 2019. Since then some of our friends and supporters have told us how much they enjoyed the materiality of the print version. We have responded by creating an annual print issue that includes the best of the past year's stories. The magazine now in your hands is the first in this new annual series.

We investigate a variety of stories that range in time and space: an alchemist who in failing to create gold discovered a new element; a Philadelphia chemist who doubled as a Soviet spy; a precious substance given to Marie Curie on her only visit to the United States. We also offer plague, wizards, and hot peppers. And in honor of the International Year of the Periodic Table, we display a table of unusual shape devised by one of the great chemistry educators of our time.

The arrangement of chemical elements in the periodic table continues to fascinate us: Dmitri Mendeleev proposed its present form in 1869 when he listed the 63 then-known elements and left spaces for elements he predicted should exist. Now the number has risen to 118 and includes human-made elements whose half-lives are so short they cannot be found in nature. One group of elements is especially important to our future: the rare earth elements. All have their own specific properties and are much in demand today.

We invite you to visit us online at **sciencehistory.org/distillations** to read our stories, listen to our podcasts, and watch our videos.

RICHARD J. BOLTE JR.
CHAIR, BOARD OF DIRECTORS
SCIENCE HISTORY INSTITUTE

BEST OF

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VOL. 1

Features

Marie Curie, Marie Meloney, and the Significance of a Gram of Radium

In the 1920s a pioneering journalist summoned the might of American women to revive a Nobelist's career.

BY SAM KEAN

Marie Meloney wasn't used to feeling nervous. She'd started reporting for the *Washington Post* at age 17 and was the first woman to win a seat in the U.S. Senate press gallery. By May 1920 she was editing a popular magazine, the *Delineator*, and during a press tour of Europe that year, she had interviewed H. G. Wells, J. M. Barrie, and Bertrand Russell. She was a seasoned reporter and knew her stuff.

Still, Meloney was nervous about her next encounter: Marie Curie. A few years earlier reporters in Paris had exposed the widowed Curie's love affair with the married physicist Paul Langevin and published their private letters. Langevin's wife threatened to kill Curie, and Langevin himself challenged the publisher to a duel. (That was just one of *five* duels the scandal inspired.) All in all it was an exhausting, humiliating ordeal.

Ever since, Curie had loathed the press, and Meloney felt anxious the morning of her interview. So you can imagine Meloney's surprise at what happened next. Before she could ask her first question, Curie flipped the script and started interrogating *her*. What, Curie asked the editor, do you know about radium?

Curie's name had been inextricably linked to radium ever since she and her late husband, Pierre, had discovered it in 1898. They'd toiled for years, refining and processing literal tons of mineral ore, all to extract a single gram of element 88.

That gram won Curie the 1911 Nobel Prize, her second, and as the basis of much of her research, it was the most precious thing in the world to her. When World War I erupted in August 1914, she stayed in Paris to protect the radium despite the threat of the invading German army. Later she personally escorted the gram to Bordeaux in western France for safekeeping.

Curie and Meloney in the United States, ca. May or June 1921.

MUSÉE CURIE (COLL. ACJC)

U.S. NATIONAL LIBRARY OF MEDICINE

But war heroics weren't what interested Curie. She wanted to talk to Meloney about the eye-popping cost of radium—over $100,000 per gram ($1.3 million in today's dollars). Worse, the French government had appropriated Curie's original gram and redirected it to doctors for cancer treatment. Given the cost, Curie couldn't afford to purchase more. The very woman who'd discovered radium had seen her research grind to a halt for lack of it.

After this outpouring the interview proceeded, and Meloney's story appeared in the *Delineator* a few months later. In it she called Marie "the greatest woman in the world," praising her as both a brilliant scientist and a "woman of rare beauty." On returning to New York, though, the editor couldn't stop thinking about Curie's difficulties. The high price of radium had shocked her—as had the dilapidated state of Curie's lab. Compared with the labs of other scientists Meloney had interviewed—Thomas Edison, Alexander Graham Bell—Curie's equipment looked like junkyard scraps. It wasn't right.

So with her typical moxie Meloney decided there was only one thing to do. If France wouldn't support Marie Curie properly, then the United States of America would. Meloney would just have to buy a gram of radium herself.

Meloney had always been politically active: her mother had founded a school for freed slaves, and Meloney had absorbed her mother's activism. She began working her network of contacts. First she asked the wives of 10 wealthy businessmen to donate $10,000 each. All of them turned her down. Undeterred, Meloney made a virtue of necessity and cast her net wider. She would make her fundraising more democratic and appeal directly to the women of the United States.

American women had won the right to vote in 1920 and were feeling empowered. Meloney harnessed this energy by penning a plea in her magazine to support Curie, as a pioneering female scientist. "Life is passing," she warned *Delineator* readers in April 1921, "and the great Curie getting older, and the world is losing, God alone knows, what great secret."

Logistically, Meloney modeled her campaign after fundraising efforts for the Statue of Liberty. (The statue itself was a gift, but the United States had to pay for the pedestal.) Meloney assembled brigades of housewives to knock on doors nationwide, collecting a dollar here, two dollars there. Schoolgirls chipped in, scrounging for dimes and sending those along.

The campaign's success surprised even Meloney. Coins and dollar bills poured in, and when the final pennies were totted up, she had raised $156,413 ($2 million today). Meloney quickly secured a bid for a gram of radium and used the extra cash to set up a trust fund for Marie and her daughters.

Seizième année. — N° 779 — Huit pages : CINQ centimes — Dimanche 10 Janvier 1904.

Le Petit Parisien

SUPPLÉMENT LITTÉRAIRE ILLUSTRÉ

DIRECTION : 18, rue d'Enghien (10e). PARIS

UNE NOUVELLE DÉCOUVERTE. — LE RADIUM

M. ET Mme CURIE DANS LEUR LABORATOIRE

The Curies discover radium in this illustration from French newspaper *Le Petit Parisien*, January 10, 1904.

The radium drive helped announce that American women had become a political and economic force. And in exchange for their help Meloney thought it only fair for Curie to give something back. She invited the scientist to tour the United States and let the women of the country see her.

Curie hesitated. She was a retiring person by nature, and her health was faltering after years of exposure to radioactive elements. But she coveted the radium too much to say no. So in May 1921 she and her daughters—Irène, 23, and Ève, 16—sailed across the Atlantic.

A 1938 Cuban postage stamp commemorating Pierre and Marie Curie's discovery of radium. The stamp was issued to raise funds for the International Union against Cancer.

They docked in New York to find huge crowds awaiting them, including several troops of Girl Scouts. Well-wishers tossed roses. Brass bands played. Curie shook so many hands that day her arm began aching; it would end the seven-week tour in a sling.

For their part Irène and Ève enjoyed America—swimming in Lake Michigan, touring Coney Island. Marie, though, quickly tired of the fanfare and the endless litany of speeches and luncheons. She didn't care about meeting Vanderbilts or Carnegies and began suffering from dizziness and a ringing in her ears. At one point before a train ride in Santa Fe, a chaperone found her with her face buried in her hands, saying she couldn't get on, not with people staring at her like a wild animal.

Observers noticed her plight, too. One reporter described how "her arms hung lifelessly [and] her features were ashen gray. . . . The deep lines on her face . . . showed how seriously the unaccustomed strain of her whirlwind visit to America has affected her." Another worried that Curie's admirers were forcing her "to pay with her own flesh for our gift, the mere satisfaction of our pride."

Still, Curie did enjoy some of her travels. She delighted in Niagara Falls and the Grand Canyon, which she'd always longed to see. And she was captivated with her tour of Standard Chemical Company, near Pittsburgh, which had isolated the radium for her. Scientists there spent six months on the job, using industrial-scale processes to whittle down 500 tons of ore into a gram of silvery grey powder. Their method required 500 tons of acids and other chemicals; 1,000 tons of coal; and 10,000 tons of water—work that Marie and Pierre had done by hand in the 1890s.

Curie also met with President Warren Harding at the White House, where she was presented with a protective case for the radium. The case was lined with lead and weighed 130 pounds; a gold key opened it. The press was led to believe that the radium was inside the case, but for security reasons the gram was locked away at a nearby government lab. Curie played along, and in a short speech she said she'd been honored "as no woman has ever been honored in America before."

Curie arrived back in Paris on July 2. No doubt to her relief there were no crowds waiting for her. She could finally get back to work.

Curie and the scientists at her institute used the radium in several important research projects. Among those scientists were Curie's daughter Irène and Irène's husband and scientific partner, Frédéric Joliot. Amusingly, before Irène and Frédéric married, Marie forced him to sign a prenuptial agreement renouncing all rights to the radium if he and Irène ever divorced. She needn't have worried. Irène and Frédéric had a long, loving marriage and an equally blessed scientific partnership. In 1934 the gram helped them discover that stable atoms could be artificially turned into radioactive atoms, a key step in producing a nuclear chain reaction. This work won them the Nobel Prize in 1935.

> "The radium drive helped announce that American women had become a political and economic force. And in exchange for their help Meloney thought it only fair for Curie to give something back."

Sadly, Marie had passed away by then from complications associated with chronic radiation poisoning. The irony is sobering: she'd endured several exhausting weeks touring the United States simply to get her hands on more of the very substance that would kill her.

As for the gram of radium, it had a lively afterlife. When Nazi troops reached Paris in 1940, Irène and Frédéric packed the radium into its 130-pound lead case and fled west to Bordeaux, just as Curie had done with the original gram at the start of World War I. (Bravely, Irène later smuggled the radium back to Paris under the noses of the Nazis.) And when Irène and her two children escaped from war-torn France to Switzerland in June 1944, they survived by using money from the $56,000 trust fund Marie Meloney had established.

Meloney herself remained a force in American journalism, scoring coveted interviews with Benito Mussolini and Adolf Hitler in the 1930s and rising to the editorship of one of the biggest publications in the United States, the *New York Herald-Tribune*'s magazine. In between work she also continued to champion the Curies. She convinced New York mayor Fiorello La Guardia to name a Bronx street after Curie and became something of a mentor to Curie's daughter Ève, who aspired to write.

Sadly, Meloney died of the flu in 1943, so she never heard how a third generation of Curies benefited from the largesse of American women. But she died knowing her fundraising had reinvigorated research at Curie's institute. And more than that, those close to Curie said despite the stress of the American tour, surviving the media glare gave Curie a new confidence in herself. Though never gregarious, she emerged from the trip more at ease with crowds and more willing to engage with people. She also gained a deeper understanding of what she meant to women around the world. Never mind the cost of the radium: what Marie Curie had given them was priceless. D

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Meloney and the Curies, on their arrival in New York, May 11, 1921.

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Disability and the Myth of the Independent Scientist

Movies and television shows like to portray scientists as lone geniuses. But scientists with disabilities know the reality is much more complex.

BY JESSICA MARTUCCI

In Season 11 of the medical drama *Grey's Anatomy,* the talented but troubled physician Amelia Shepherd performs the impossible when she excises a lethal tumor from a fellow doctor's brain. Saving her colleague establishes Shepherd as a truly gifted surgeon, one who can single-handedly pull her patients back from the brink. From Shepherd's heroics to the solo tinkering of *The Big Bang Theory*'s characters, scientists are repeatedly portrayed in the media as lone geniuses. In these popular depictions they are social outsiders, disconnected from functioning networks of family and community—completely and utterly independent. While this may make for good storytelling, it gives people a false understanding of how science really works. Successful scientific research requires the work and support of friends, family, and fellow professionals, efforts that often go unrecognized and unpaid. The necessity of such support networks is particularly true for scientists with disabilities.

> "The life narratives of scientists with disabilities suggest that spouses are not the only people who provide support. These scientists also rely on parents, siblings, family friends, paid staff, students, and mentors."

Take the life and work of Bradley S. Duerstock, the founder and director of the Duerstock Institute for Accessible Science at Purdue University in Lafayette, Indiana. In 1989, when Duerstock was about to enter West Point Military Academy, a diving accident that led to quadriplegia forced him to reconsider his plans. He went to Purdue, a public university, thanks in part to the passage of the Vocational Rehabilitation Act (1973) and the Americans with Disabilities Act (1990).

Section 504 of the 1973 Rehabilitation Act was the first civil-rights legislation to focus on disability. It required publicly funded institutions to provide reasonable accommodations for students with disabilities, such as wheelchair-accessible dorms and bathrooms. Seventeen years later the ADA regulations expanded to prohibit discrimination in employment, public services, and accommodations on the basis of disability. Even after the passage of the ADA, however, accommodations for college students with disabilities have remained spotty. When Duerstock got to Purdue, he found that curb cuts, the now-ubiquitous ramps built into sidewalk curbs, were still few and far between. Duerstock's older brother lived with him, providing caretaking assistance throughout his undergraduate years. His parents also lived close by, offering frequent help and support. "The family support [is] invaluable . . . doing these little bitty things," he said in an interview with Science History Institute staff in September 2017. "I had a wheelchair-accessible vehicle, but things break down. Getting it fixed involved traveling to Indianapolis, which [is] an hour away."

At graduate school Duerstock learned how to hire and manage his own paid personal-care attendant, though his brother remained nearby. "It was a big deal to get a personal-care attendant. You know, this is a stranger that [you're] asking to do everything from go into the bathroom, to getting dressed, bathing, overnight. You need assistance to turn. This was a big transition. I found an individual, Mark, and he has been with me as an attendant [for] over twenty years." (Duerstock received his PhD in neuroscience from Purdue in 1999.)

PURDUE RESEARCH FOUNDATION

Bradley Duerstock (*right*) and Jeff Ackerman, cofounders of a Prehensile Technologies, an assistive device company.

Like all research scientists, Duerstock requires support to do his work. He relies on a team of postdocs and graduate students who contribute to his overall research agenda and output; they may also help get him a soda from the vending machine. Duerstock credits much of what he has accomplished in his career to his partnership with his wife, Sally Irvin (who sadly passed away in January 2018). "My wife has been invaluable for helping me, putting up my reference lists—some things it just takes me a long time to put together. My bibliography for a paper, she would do. She's a very intelligent woman, and she can help with the family things, so I can focus on [my] career. . . . It'd be very tough for someone in my position to be where I'm at now [without that kind of support]."

The network of people in Duerstock's life have been more important to his success than any fancy gadget or adaptive technology. His family gave him the time and the physical and emotional care required to heal from his injury and to learn how to be successful in his changed body. Purdue University provided an environment in which Duerstock felt comfortable, safe, and generally supported, and gave him the training and economic stability he has needed to thrive. His partnership with his wife enriched his life, while also providing supportive, caring, unremunerated labor that helped him advance his career.

In pointing out these "supports" I do not mean to differentiate Duerstock's scientific success from that of any other research scientist. Duerstock's story helps bring into focus the extent to which *all* scientific work leans heavily on these often invisible networks of support and caregiving. Whether in the lab, in the home, or both, this additional labor is necessary for creating the conditions in which scientific work can flourish. This phenomenon has received more attention in recent years, aided by #ThanksForTyping, which helped call attention to the nearly ubiquitous presence of wives-as-typists in the acknowledgment section of scholarly books. The life narratives of scientists with disabilities suggest that spouses are not the only people who provide support. These scientists also rely on parents, siblings, family friends, paid staff, students, and mentors.

We must do a better job of acknowledging these networks of assistants, students, family members, and other kinds of helpers that all scientists rely on. Understanding that these needs are universal will make science more welcoming to people with disabilities.

And such an acknowledgment encourages us to question the arbitrary boundary between what we see as an "accommodation" for someone with a disability (such as the personal-care attendant who assisted Duerstock in graduate school) and what we see as a "privilege" awarded to academics regardless of physical ability (such as Duerstock's grad students who help him conduct his research). Acknowledging these efforts helps us see that scientific work is made possible by many people who are not scientists in the traditional sense. This diverse and expansive pool of scientific workers—caregiving laborers—has long played a crucial role in the creation of scientific knowledge. D

Jessica Martucci is a research fellow in the Institute's Center for Oral History where she leads the Science and Disability Project.

The Death of Jesse Gelsinger, 20 Years Later

Gene editing promises to revolutionize medicine. But how safe is safe enough for the patients testing these therapies?

BY MEIR RINDE

PHOTO ILLUSTRATION BY CLAY CANSLER; DOUGLAS GRAHAM/SCOTT J. FERRELL/CONGRESSIONAL QUARTERLY/ALAMY STOCK PHOTO

By all accounts Jesse Gelsinger was a sweet, sharp-witted, if not particularly ambitious kid who loved motorcycles and professional wrestling. In 1999 he was living in Tucson, Arizona, with his parents and siblings, attending high school, and working part-time as a supermarket clerk. As he got older, he became more independent and, like many teens, a touch rebellious; in his case that led to life-threatening health problems.

Jesse had a rare metabolic disorder called ornithine transcarbamylase deficiency syndrome, or OTCD, in which ammonia builds up to lethal levels in the blood. Babies born with OTCD usually fall into comas soon after birth and suffer brain damage. Half of them die within a month. Jesse's milder version of the deficiency was diagnosed when he was two years old, and he managed the condition with a low-protein diet and a regimen of nearly 50 pills a day.

Still, he had occasional health crises. When he was 17, he stopped taking the drugs regularly. One day his father came home to find him curled up on the couch, vomiting uncontrollably. He had to be intubated and kept in an induced coma until his ammonia levels were brought under control.

So when a doctor told Jesse that a clinical trial for a potential OTCD treatment was in the works, he was very interested. Researchers at the University of Pennsylvania in Philadelphia were developing a fix for the *OTC* gene, which produces an enzyme that prevents ammonia buildup. Patients would be injected with working copies of the gene that had been attached to an adenovirus, a type of cold virus. The virus, altered to be harmless, would infect the patients' liver cells and integrate the added gene into their chromosomal DNA.

The field of gene therapy had so far helped just a few people with genetic diseases. But the researchers' experimental treatment had lengthened the lives of lab mice bred to be deficient in OTC enzymes, and the scientists were hopeful the gene-repair method they were testing could eventually be used to treat many liver diseases. The trial Jesse would join was a safety study, aimed at moving toward a treatment for babies with OTCD, and was not intended to improve the participants' health. But Jesse was eager to help, and he flew to Philadelphia in September 1999 to take part.

Jesse was the 18th person to receive the modified virus. Previous patients in the trial had experienced flu-like symptoms, but he had a much worse reaction. Within a day he became disoriented and showed signs of jaundice. He had an intense inflammatory response and developed a dangerous blood-clotting disorder, followed by kidney, liver, and lung failure. Four days after receiving the shot Jesse was declared brain dead and taken off life support. The team of doctors and nurses caring for him were stunned by his rapid decline and death.

Jesse Gelsinger's father, Paul, testifies at a Senate subcommittee hearing on gene therapy and patient risk, February 2000.

Albert Maguire examines the eyes of gene-therapy patient Misa Kaabali at the Children's Hospital of Philadelphia, October 2017. Kaabali received Luxturna, which treats a form of hereditary blindness.

AP PHOTO/BILL WEST

The news that an experimental treatment had killed a basically healthy volunteer rocked the field of gene therapy and the broader world of biological research. News coverage portrayed the trial researchers as overeager and undercautious, taking shortcuts and disregarding rules meant to protect the people in their care.

"The death is the latest in a series of setbacks for a promising approach that has so far failed to deliver its first cure and that has been criticized as moving too quickly from the laboratory bench to the bedside," the *Washington Post* reported, in the first of many articles about Jesse's death and the ensuing crisis it set off.

In a flash the field of gene therapy collapsed, taking its grandiose promises of miracle cures along with it.

Biochemist Jennifer Doudna, who later discovered the CRISPR-Cas9 gene-editing mechanism, remembers feeling the shock waves as a young researcher, even though her work had nothing to do with gene therapy or any kind of medical research.

"We were all very much aware of what happened there and what a tragedy that was," she said in a recent interview. "That made the whole field of gene therapy go away, mostly, for at least a decade. Even the term *gene therapy* became kind of a black label. You didn't want that in your grants. You didn't want to say, 'I'm a gene therapist' or 'I'm working on gene therapy.' It sounded terrible."

Of course, the field eventually rebounded. In the 20 years since Jesse's death, private and public ventures have invested billions of dollars in efforts to cure diseases by altering or replacing our faulty genes. To date, these efforts have produced just a few marketable medicines—two therapies for lymphoma, a treatment that reverses a form of inherited blindness, and most recently, a therapy for spinal muscle atrophy. But innovation has accelerated in the past few years thanks to CRISPR, which has enabled highly targeted editing of genes that is vastly cheaper and quicker than earlier methods. Treatments for hemophilia, muscular dystrophy, and other genetic diseases now seem almost within reach.

Scientists say this new generation of gene-therapy research is safer. But how safe is safe enough? How much risk is acceptable, how can researchers assess the risks, and who should bear them?

Investigating the Investigators

In the weeks after Jesse's death James Wilson, the director of the University of Pennsylvania's Institute for Human Gene Therapy, and the other doctors involved in the trial tried to understand what happened. They focused on the possibility that the adenovirus had triggered a fatal immune response for reasons that were not yet clear.

Meanwhile, journalists and federal health officials discovered several troubling lapses in the conduct of the study. For example, the researchers had earlier told the FDA they would tighten up the trial's eligibility criteria, but they never followed through. When two patients suffered serious side effects, the scientists did not immediately inform the agency or put the study on hold as required. It turned out Jesse's pretrial test results showed he had poor liver function, indicating he arguably shouldn't have received the *OTC* gene injection.

But perhaps most damning were failures in the informed-consent process. Researchers hadn't told Jesse about the earlier patients' side effects or about two lab monkeys killed by high doses of adenoviruses. If he had been properly briefed about these previous issues, he might have dropped out of the study and still be alive today. Wilson was also accused of a conflict of interest: he had a stake in the company that owned the gene-transfer technology and stood to benefit if the trial succeeded.

Wilson denied that financial considerations affected the study and said it was impossible to predict that Jesse would suffer such a bad reaction. Nevertheless, the Gelsinger family sued, and the university quickly settled for an undisclosed sum, while declining to take responsibility for Jesse's death. In January 2000 the FDA suspended human research at Penn's Institute for Human Gene Therapy, and the university eventually shut the program down.

The FDA charged Wilson with several violations, and in 2005 he agreed to restrictions on his human research for five years. The university also paid the federal government a $514,000 settlement.

The investigations drew attention to wider problems in oversight of gene-therapy experiments and human research generally. For example, the FDA and NIH revealed that 691 volunteers in gene-therapy experiments had either died or fallen ill in the seven years before Jesse's death; only 39 of these incidents had been reported promptly as required. The agencies tightened monitoring of trials, increased inspections, and created a new system for reporting serious side effects, among other steps. Penn responded to the crisis by strengthening the institutional review boards that oversee its trials, putting in new protections for patients, and prohibiting researchers from having financial stakes in their trials.

Yet as the pharmaceutical industry continued growing and its profits soared, demand for test subjects increased, and more research was undertaken by private companies rather than academic or government institutions. That raised new fears that patient safety could be compromised in the rush to get products to market.

"Contrary to hopes of human research reform spurred by Jesse Gelsinger's death, oversight has flattened, profit motives have become more entrenched in medical research, and the pool of potential human subjects has come to focus on the vulnerable, both at home and abroad," wrote Osagie Obasogie, a professor of bioethics at the University of California, Berkeley, in 2009. "And the confidence behind recent attempts at gene therapy often exceeds the evidence for its safety and efficacy in humans."

Ashanthi DeSilva, age 6, March 1993. On September 14, 1990, at the age of 4, DeSilva became the first gene-therapy patient when she was treated for a form of severe combined immunodeficiency, often called bubble boy disease.

TED THAI/THE LIFE PICTURE COLLECTION/GETTY IMAGES

Putting Safety First

After the government's investigation, Wilson remained at Penn but fell into a kind of professional disgrace, his career as a leading researcher in tatters. It was a striking reversal for a renowned scientific pioneer. In 1992, in one of gene therapy's first triumphs, he had successfully treated a woman for extremely high cholesterol, demonstrating that the field could actually improve patients' lives. Yet a few years later he found himself branded as careless and even dangerous to the people he was trying to save. Wilson briefly considered leaving science entirely. Instead, he turned his focus to understanding why Jesse's immune system had gone haywire and how to avoid such outcomes in the future.

He and his team concluded that the teenager had probably experienced a rare phenomenon called antibody-dependent enhancement. Jesse had been previously exposed to the adenovirus that was used in the trial, they surmised, which created antibodies that supercharged the subsequent reinfection rather than fighting it. It seemed that altering adenoviruses would perhaps never make them safe enough to put into people.

> Even the term *gene therapy* became kind of a black label. You didn't want that in your grants. You didn't want to say, "I'm a gene therapist" or "I'm working on gene therapy." It sounded terrible.

Wilson turned instead to the study of another class of gene-delivery vehicles called adeno-associated viruses, or AAVs, which were known to provoke little or no immune response.

"I really thought a lot about, should we try to make the more efficient vectors safer, or should we make the safer vectors more efficient?" he said in a phone interview. "We decided to go with the latter—really start from a platform of safety and just incrementally try to make them better. We've made a lot of advances in making them better. What you don't see are all the failed experiments. There are some circumstances where in our attempt to make them more efficient, their safety profile was compromised. So we don't even bring those forward."

His research group tested hundreds of AAVs, finding that some penetrate cardiac tissue most efficiently, while others work best for the liver or brain. Those discoveries have been crucial to the production of a new generation of medicines. For example, Editas Medicine, a gene-therapy company based in Cambridge, Massachusetts, uses one of Wilson's vectors to deliver its treatment for Leber's congenital amaurosis type 10, an inherited blindness condition. Using that particular virus helps ensure the therapy only penetrates (is trophic for) the vision cells that need to be altered and doesn't end up causing effects elsewhere.

"We cannot say there's zero exposure to the rest of the body," Editas CEO Katrine Bosley said during a talk at the Science History Institute last fall. However, "the virus that we're using, AAV5, is particularly trophic for photoreceptors."

AAVs have been used safely in many studies, and last month the FDA approved an AAV-based gene therapy for a lethal disorder for the first time. The drug, Zolgensma, treats spinal muscular atrophy, an inherited disease that destroys nerve cells and is the most common genetic cause of death of infants. In a press release announcing the FDA approval, Wilson said, "This approval is a huge milestone for the rare disease community because the approach can be leveraged across many different diseases."

But he now balances such celebration with hard-earned prudence. In 2018 Wilson published a paper warning that animals receiving high doses of AAVs in tests of a therapy for spinal muscular atrophy sustained nerve and liver damage, raising questions about the volume of viruses humans can safely handle. Researchers from his lab also reported that AAVs may unexpectedly mutate during the virus-manufacturing process, causing changes in the way they function. The report described a way to stabilize the viruses' structure.

He has also warned of the pressures that can lead to dangerous errors and oversights. In 2009 he published a cautionary article in response to the first clinical trial that used embryonic stem cells, a technology that, like CRISPR, stoked massive hype over its promise as well as fears of unethical genetic tinkering.

In the essay Wilson urged scientists not to reenact gene therapy's "hyperaccelerated transition to the clinic" of the 1990s. That ill-fated rush to experiment on human subjects was driven by simplistic modeling suggesting the approach "ought to" work, as well as the "fervent hopes" of charitable foundations seeking cures for lethal diseases, he wrote. He also blamed overenthusiastic scientists, uncritical media coverage, and investors who eagerly funded therapies that weren't backed by actual results.

"Some would call it kind of irrational exuberance," he said in his interview with *Distillations*. "The hope exceeds the science, and expectations are not met."

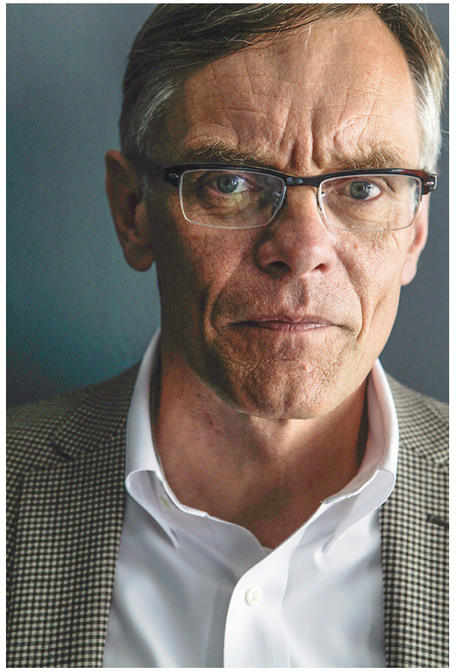
Doudna expressed similar concerns about CRISPR.

"I hope that we don't get ahead of ourselves with this technology. As exciting as it is, I really would like to see . . . people take a very measured and responsible path forward, where there's careful vetting along the way," she said. "Of course, the challenge is that patients are waiting, so you don't want to delay unduly. But you also want to be safe."

Facing Unknown Risks

Gene therapy had its first success early on, nearly a decade before the OTCD trial. In 1990 doctors partially reversed a case of severe combined immune deficiency, or SCID, also known as "bubble boy syndrome," in a young American girl, Ashanthi DeSilva. They drew her white blood cells, used a retrovirus to insert a working gene into the cells, then injected them back into her body, which helped give her a functioning immune system.

French researchers conducted a similar trial with 10 children in 2002, using stem cells taken from the patients' bone marrow. The treatments worked, but within a few years four of the children developed leukemia and one of them died. The retroviral vectors had been integrated near oncogenes, which can cause cancer, apparently triggering the leukemia.



CHRIS GOODNEY/BLOOMBERG VIA GETTY IMAGES

James Wilson, June 2015.

Reducing the risks of cancer and other harmful effects is a central task of gene-therapy research, but much work remains. Even CRISPR, celebrated for enabling highly specific, targeted genetic edits, still has the potential to go awry.

CRISPR is a fundamentally new way to change genes. The basic technology consists of an enzyme that cuts DNA and a segment of guide RNA that tells the enzyme where to snip. The package may include other components, such as a new piece of DNA code to plug into the edited area. The cell's natural repair mechanism completes the edit. Scientists can deliver CRISPR using AAVs, as Editas is doing, but that's not the only option; CRISPR can be encapsulated in bubbles of fat, injected directly into cells, or sent through a hole created by an electric current, among other techniques. Editing is meant to occur when the enzyme comes in contact with the target DNA, and only then.

"The hope that we have now for CRISPR technology is that it literally is a way to program enzymes to go to exactly the place in the DNA where a change is desired, and nowhere else, and make a precise alteration," Doudna said. "It's a very different way of altering genomes that is controllable. The potential is clearly very, very exciting."

But cell biology is complex, and learning how to avoid unintended consequences remains a work in progress. Last year, for example, two groups of researchers said they found a possible problem when they tested CRISPR on retinal cells and stem cells. The intended edits often didn't work because they triggered a cell's p53 gene, which responds to DNA damage by telling a cell to self-destruct. The gene plays an important role in keeping mutations from becoming cancerous, yet CRISPR worked better in cells with a dysfunctional p53 gene. In other words, CRISPR apparently subverted one of the body's disease-fighting mechanisms, making healthy cells die and allowing potentially cancerous ones to remain.

No one has seen lab mice get cancer after CRISPR treatment, but it's unclear if they have been observed long enough to allow tumors to develop. In the French SCID study, the children were diagnosed with leukemia years after their treatment. Potential long-term side effects are a concern with gene therapies because the treatments are basically permanent; they can't be washed out of the body the way a conventional drug often can. The discovery of the p53 issue and the uncertainty about its importance are reminders that scientists simply don't know everything that could happen when CRISPR is put into a human body.

Wilson said the question of whether a gene edit could inadvertently cause mutations elsewhere in the chromosome and cause cancer in a patient, much as SCID gene therapy caused leukemia, will not be resolved soon. "It's definitely a theoretical concern, and it's going to be a challenge to quantify what the risk is. That's going to be a huge challenge," he said.

That doesn't mean clinical trials of CRISPR-based therapies shouldn't happen, but it does affect the risk-benefit calculation, he said. Many patients with devastating diseases, such as muscular dystrophy, cystic fibrosis, and Huntington's disease, as well as certain cancers and rare diseases for which few treatments are available, will accept the unknown chance they'll experience some harm from an experimental therapy if it also might lessen their symptoms or extend their lives.

Trials that include such patients are ethically acceptable, whereas the possibility of serious side effects may make trials of less urgent therapies unacceptable. A clinical trial of a CRISPR-based treatment for color blindness, for example, might not be worth the risk.

"For [gene] editing you're going to be focused for a while on diseases in which there is significant unmet need, not a lot of alternatives, and where the risk tolerance would be higher," Wilson said.

"It's going to be a long road before we get to the point where editing would be deemed safe enough for diseases other than those that have really significant morbidity and mortality," he added.

Biotech firms go to great lengths and spend hundreds of millions of dollars trying to make sure their products are effective and safe, but preclinical testing in animals and cell cultures goes only so far. Bosley said during her talk at the Science History Institute that the only way to see if a treatment really works is to put it into a person.

"The genetic context of a mouse or a rat has nothing to do with human genetic context. You just can't know. You are taking a greater leap into the unknown with these kinds of experimental medicines," she said.

"The FDA has learned lessons, the industry has learned lessons, and I think we are all seeking to be very careful in how we advance," she said. Yet "the risk never goes away. That's what it takes to make new medicines." D

Meir Rinde is a freelance writer based in Philadelphia.

INTERVIEW

Sangeeta Bhatia

Distillations talks to the 2019 Othmer Gold Medal winner about her work using nanotechnology to detect and treat disease.

Sangeeta Bhatia works at the intersection of medicine and engineering, using nanotechnology—the "tiny technologies"—to develop tools that can diagnose cancer, liver diseases, and other conditions without biopsies or other invasive procedures. As a graduate student Bhatia pioneered a method of growing mini-livers that are used by pharmaceutical companies to test medicines. At the MIT lab she now heads, they are investigating how to grow liver tissue to help people with hemophilia and other diseases.

Distillations writer Meir Rinde sat down with Bhatia in May 2019 when she visited the Science History Institute to accept the Othmer Gold Medal. What follows are excerpts from their discussion, condensed and edited for clarity.

On her long-standing interest in the liver

I like to say that I fell in love with the liver the first day of graduate school, and it's been a lifelong journey. I just was never done with it. It's vital for life, it has 500 functions, it can regenerate without a stem cell. As an innovator, what's drawn me to it and kept me with it is that it's a field of medicine where we have shockingly little to offer. That's in comparison, let's say, to cardiology, where we have bypass, we have stents, we have medicines, we have a whole host of interventions. In the liver really all we have is transplant, beginning and end of story. That makes it feel like anything you do would be potentially impactful.

It's been an area that has long been under-studied because it's hard [to research], and it's deep in the body, but also for all kinds of social reasons here in the West. [Liver ailments were] seen for a long time as a class of diseases that were self-inflicted. So [there's] alcohol, and then there's hepatitis, which is blood-borne. For the first time the liver's really having its heyday. Gene therapy—CRISPR, genome editing, RNA interference—can very readily be delivered to the liver. Now everyone's really interested in liver disease. I've been working in this field for 20 years and nobody cared. All of a sudden everybody's at my party, which is great.

I have two daughters, and my oldest daughter is taking biology. She's in her sophomore year in high school. I was looking at her book to see what does it say about the liver, which is the first thing I always ask. And it's like one paragraph on one page, and it says vague things like "metabolism." Even the way we teach it is so uninteresting. I can see why it hasn't drawn attention over the years.

Growing liver tissue and its clinical potentials

What we've been really interested in is [whether we can] position liver cells using some 3-D printing techniques so that if you implant them, they would recruit blood vessels and they would grow. The reason we knew they should be able to grow is because the liver can regenerate, unlike other tissues. Those are the experiments we've been doing, and it's working. In mice we can get them to spontaneously vascularize. We put [the liver cells] in just the right arrangement and they grow about 50 times in the setting of a liver injury. We are just now starting to think about [taking] this to patients to do a start-up.

There's a class of liver diseases where you don't need a whole transplant to fix them. Most of them are metabolic liver diseases. Those are diseases that you could fix with 1% to 2% of the liver mass. Hemophilia is an example. You get to therapeutic levels of some of the clotting proteins without needing a whole new liver. For some of these applications our idea's not to replace the liver but to make a little satellite liver. So that's what we would start with.

Using nanoparticles to screen for disease

These teeny, tiny particles [about a thousand times narrower than a human hair] can be injected in the bloodstream and circulate in your body looking for disease. We make them responsive to certain enzymes that are disease associated. When the particle finds the enzyme that it's been designed for, there's a chemical reaction and they emit a little reporter, a little synthetic signal, which is a chemical molecule that's not found in your body. That molecule finds its way into the urine after about an hour. The patient gets a shot, the molecules roam and look for disease, and then an hour later you do a urine test. If you find these signals in the urine, then you could diagnose this disease.

There are about 550 enzymes in the family [of enzymes] that we're measuring. They are connected to almost every kind of disease: cancer, infection, inflammation, blood clotting.

CONRAD ERB

Sangeeta Bhatia speaks at the 2019 Othmer Gold Medal presentation.

In the lab we realized we could make panels [that test for 10 to 20 conditions at once]. So far we've done about a dozen diseases, and it seems to work pretty well. About three years ago we realized that we should take this to patients. We did that by starting a company called Glympse. They are going to start clinical trials [in the third quarter of 2019]. We're really excited to see how this plays out in the marketplace.

We actually invented [nanosensors] by accident. We weren't trying to invent sensors that would come out in the urine. We were trying to make nanoparticles that would be smart contrast agents: when you go to get an MRI scan, it would give you some functional information. It so happened when we were doing the experiments with mice that had tumors, the urine was lighting up. We had this "aha" moment, like, "Oh, we don't need an imager at all. We can do a noninvasive test."

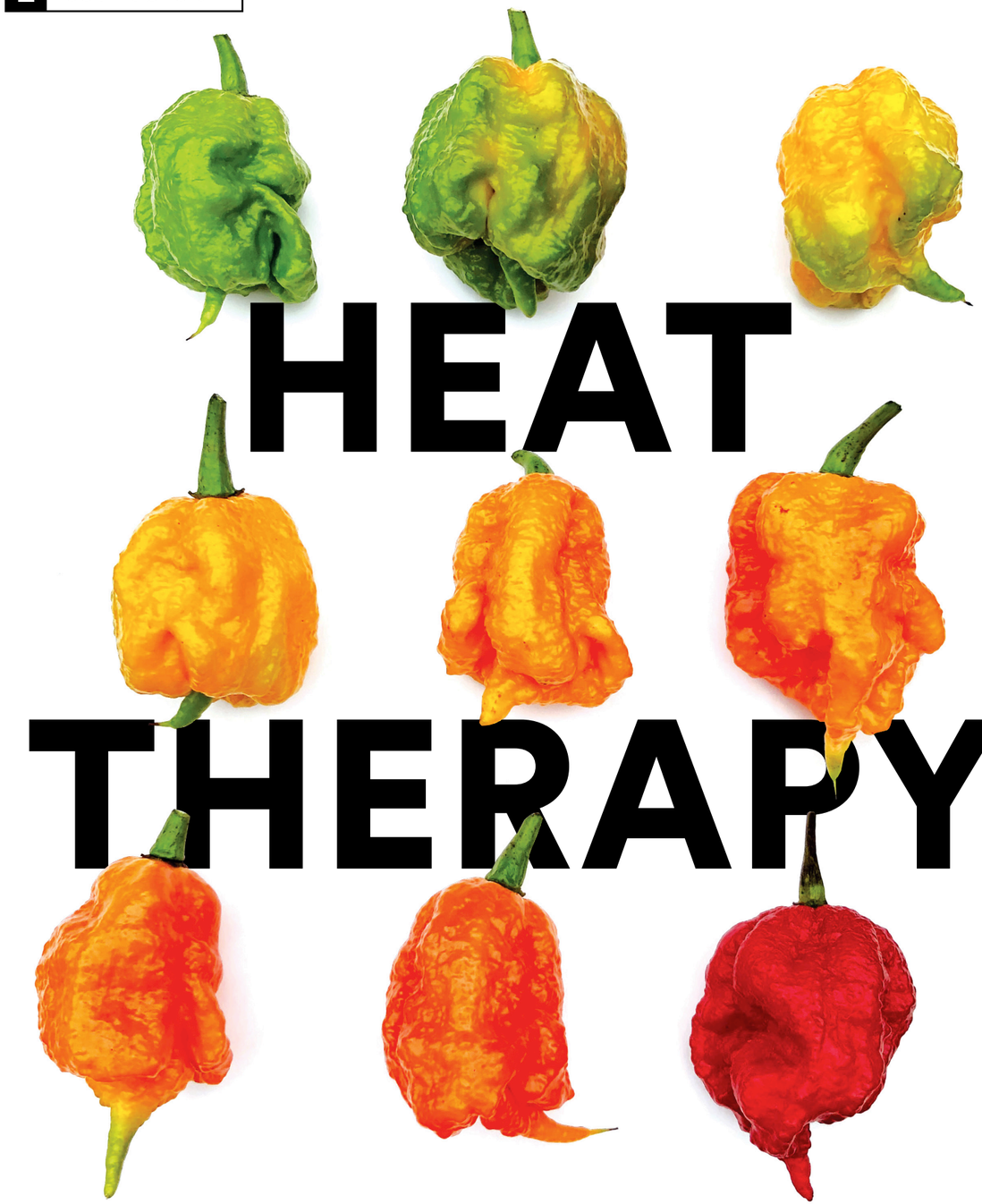
The role nanoparticle screening could play in patient care around the world

One of the diseases that we're really interested in is NASH, nonalcoholic steatohepatitis. There's fat accumulation in the liver, the liver gets damaged, and eventually it scars. Right now the only way to test for that is to do a biopsy. That's a full-day procedure that's got some finite complication rate, and it turns out that all of these enzymes that we're capable of measuring are involved with that disease.

We also have a test for blood clotting. We have a test that we're developing for pneumonia to see if you have bacterial or viral pneumonia. We have a test to see if in the setting of prostate cancer, is it aggressive prostate cancer or slow-growing prostate cancer?

One of the most appealing use cases that we've imagined is that you could have an oral formulation, a pill—which we don't have yet, but we're working on—and then a urine test that would have a paper-strip readout. At the point of care and in the absence of clinical infrastructure, you could do really high-end molecular diagnostics. That starts to get you into thinking about how transformative diagnostics could be around the world, where we don't have the infrastructure that we have here. Cancer screening is an example. If there is no colonoscopy, no mammogram, and no Pap smear available, can you imagine doing a urine test on a paper strip and taking a picture with a smartphone and sending it to another provider? For us it's been really exciting to think about how to point this to the biggest unmet medical needs.

I'm of Indian origin. When I was growing up, we used to spend summers in India. An aunt [who] was a physician would take me to the clinic, and I would see what medical care is like in a low-resource setting. That stuck with me in the back of my head. I've always wanted to get back to inventions that could make an impact. D



HEAT THERAPY

Humans have a masochistic love of capsaicin, a molecule responsible for the burn in hot peppers. That connection could be a key to pain relief.

BY LEAH SHAFFER

PUBLISHED JUNE 18, 2019

At first glance the room looks like something out of an old-time apothecary shop, with rows of colorful, tiny bottles lining the shelves. But on closer inspection the scorpions, skulls, and hazmat signs decorating the bottles come into focus. These little vessels hold hot sauce, some of the hottest in the world, and all the warning signs serve as a welcome mat.

The ability to love something innately negative is a general feature of being human, says Paul Rozin, a University of Pennsylvania psychologist who has spent his career studying what he calls "benign masochism." Hot peppers offer one of the best examples of this paradoxical attraction. After all, they are pain and pleasure all wrapped up in one colorful package. Chemists and other researchers have also explored this duality, studying the molecular mechanisms that produce the heat, and have found that the compounds responsible may unlock a way to blunt pain.

Capsaicin, the most common source of the burn in a hot pepper, is the basis for several painkillers. The benefits of the compound will come as no surprise to pepper enthusiasts.

"There's a group of people who actually catch a buzz from eating a super-hot food," says Ed Currie, who breeds the hottest pepper in the world, the Carolina reaper. Currie's reaper sauce sits on the top shelf of the hot-sauce shop I frequent, out of reach of any "chili head" amateur.

You can see videos of Currie, always sporting a beige cap with the logo for his Puckerbutt Pepper Company, trying sauces and pepper oils on his YouTube page. In one clip Currie calmly steers a van full of friends down a highway while downing concentrated pepper oil, a concoction four to five times hotter than the hottest pepper in the world.

"We're idiots," he says, laughing when I ask him about the videos.

This is what capsaicin does: it makes otherwise mellow, middle-aged men giggle like teenagers. It burns and comforts; it can bring relief to arthritic knees, itchy skin, aching sinuses. It shapes entire cuisines. Here's how.

We get to enjoy the fact that our body is telling us something should be rejected or avoided, but we know that we're really safe. We're smarter than our body, and that gives us a certain pleasure.

Naturalist Maria Sibylla Merian's illustration of the stages of development of red peppers and Sphingidae, a family of moths, from *Metamorphosis insectorum surinamensium* (1705).

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There are two main reasons plants may have evolved the chemical ability to produce capsaicinoids, a group of compounds that includes capsaicin and a few others that cause heat in hot peppers. The capsaicinoids kill some plant pathogens and also discourage certain animals, such as rodents, from chewing the plant's seeds. Birds, which lack the ability to detect capsaicin, are the plants' preferred target since they will swallow the seeds whole and disperse them in their droppings. By producing capsaicin, plants are creating fruit that "burns" mammals but not birds. We humans never got the memo. It's still up for debate as to why people started eating peppers in the first place. One reason may have to do with capsaicinoids' ability to protect plants from pathogens. Researchers have linked higher levels of capsaicinoids in wild peppers in South America to lower levels of a fungal pathogen. Capsaicin's antimicrobial effects seem to protect these plants from the fungus, and by doing so the compound may have made such fruit more appealing to humans. Plus, adding hot peppers to a meal could mask the taste of rancid meat.

Others suggest that humans started eating hot peppers for many reasons, including what chili heads describe as the high they get from the rush of heat and the counterintuitive cooling effect hot pepper–induced sweating can cause. It could be humans started eating hot peppers just because they were there and kept eating them because of the cultural practices that sprang up as people embraced benign masochism.

"We get to enjoy the fact that our body is telling us something should be rejected or avoided, but we know that we're really safe," says Rozin. "We're smarter than our body, and that gives us a certain pleasure."

While it's hard to tease out what led people to stick with the pepper long enough to build cultures around it, anthropologists and scientists have some ideas. Scientists have found evidence of wild pepper harvesting in Mexico 8,000 years ago and cultivation of the pepper in the Americas at least 6,000 years ago. The pepper made its way to Europe after the Spanish conquest of South America in the 1500s and spread to the rest of the world by 1540.

Different cultures may in part define their identities based on how they use the hot pepper. In a 2009 essay Esther Katz, an anthropologist at France's Institute of Research and Development, argues that in Europe and Mexico the pepper serves as a regional identity marker. Mexican food culture is associated with the dried hot chili pepper, while Hungarian culinary identity is synonymous with dried, powdered bell pepper in the form of paprika. Meanwhile, mild bell peppers are tied to the cuisines of southern Italy and Spain. In *Peppers: Botany, Production and Uses* archaeobotanist Linda Perry writes that people in both China and India insist the pepper's origin lies in their continent. "Clearly, chilies are of such cultural significance," Perry writes, "that they were not only quickly adopted into different cuisines, they were also rapidly incorporated into local histories."

Ed Currie is part of the ever-evolving culture surrounding hot peppers. For him hot peppers offer something unusual—a safe vice. Currie quit drugs and alcohol in 1999. These days he gets a rush from spicy foods.

"I've been in recovery for 20 years, so it's the closest thing to getting high that I can do without having any bad reaction," he says.

Currie eats peppers "every day, all day long." On the day of our interview he says he'd taken capsaicin drops four different times, tested a sauce, probably consumed 8 to 10 peppers' worth of material, "and the day is young." Currie is a self-taught gardening guru—learning on the fly and from his mother, who was a master gardener. He started growing peppers in 1981 while living in Michigan, dropping into and out of college. He wanted to tap the peppers' health benefits to counter his wild lifestyle. "I was looking for a way to keep on partying," he says.

Peppers ended up changing his life in more profound ways, especially after he quit drugs and alcohol.

"I met a young lady who wouldn't give me the time of day, and I heard her say she liked salsa," says Currie. So he whipped up some salsa for her, which got her attention. One thing led to another, and nine months later the two were married. It wasn't long before Currie had turned his new wife's yard into a "pepper field."

He managed to turn this obsession into his livelihood. Soon after getting married, in 2001, Currie began breeding peppers for heat. The hot pepper he created came from crossing about 10 varieties of pepper. Within a couple of years he had produced the pepper eventually dubbed the Carolina reaper, named after his adopted home, South Carolina. In 2013 Guinness certified it as the "hottest pepper in the world." (The specifics of Currie's breeding program are a trade secret: fending off title contenders is an ongoing challenge.)

The Carolina reaper is far beyond what most people even get close to tasting. On the Scoville scale—a metric that rates a pepper's heat based on its concentration of capsaicinoids—the reaper clocks in at an average 1.614 million Scoville heat units. Contrast that with the more commonly consumed jalapeño, which measures from 3,500 to 8,000 units, and you get the idea. Or maybe you don't. It's hard to describe the experience of eating an incredibly hot pepper. The one time I bit directly into a fresh habanero (100,000 to 350,000 on the Scoville scale), I started drooling uncontrollably. But later I felt elated. It's a fond memory: I don't remember the pain, just the pleasure, stupidity, and audacity.

Somewhere in that mix lies a medicine. Currie believes in the potential for hot peppers to help with many ills, from opioid addiction to obesity. Of course the delivery method is the problem because, he says, not a lot of people "will just eat hot stuff." He jokes, but he's not far off base: unlocking the health benefits of capsaicin without the burn remains a challenge for drug developers. And though we've been consuming hot peppers for thousands of years, only in the past 20 years have we begun to understand the mystery of how our sensory nervous system responds to these chemicals.

Much of the work happened in a place not known for fiery cuisine: Hungary.

Ed Currie, 2011.

AP PHOTO/THE HERALD, MELISSA CHERRY

Dried guajillo peppers for sale in a market in Oaxaca, Mexico. Despite claims from pepper-loving cultures around the world, hot peppers originated in Mexico.

Though we've been consuming hot peppers for thousands of years, only in the past 20 years have we begun to understand the mystery of how our sensory nervous system responds to these chemicals.

Chemist Gábor Jancsó literally grew up with capsaicin research. Until he was eight years old his family lived in one of the research departments at the University of Szeged in Hungary. Jancsó and his sister played soccer in the hallways of the university. He remembers the lab animals, including a guinea pig named William, the way most people remember childhood pets, only his pets were regularly dosed with capsaicin. His father, Nicholas (known as Miklós), and mother, Aurelia Jancsó-Gábor, researched capsaicin's effect on pain sensation.

It was Miklós who discovered the phenomenon of capsaicin desensitization. On repeated exposure to the skin, nerve endings stop responding to capsaicin and other irritants, such as mustard oil. This phenomenon is how people build tolerance to hot food. (Miklós wrote up this discovery for a conference in 1949, but much of his other research was not published until after his death in 1967.)

In other experiments Miklós found that capsaicin could increase body heat. He painted one side of his face with capsaicin, used the other side as the control, and found that the capsaicin side was hotter, had greater blood flow, and was burningly painful. "I remember that experiment," says Jancsó. "I caught my father red-faced." Over a period of days and repeated exposures, the skin temperature returned to normal as he became less sensitive to the capsaicin.

Miklós's research provided the first hint that capsaicin could affect how we feel pain, and it revealed a gateway to understanding our peripheral nervous system, the nerve fibers that send signals to the brain.

Jancsó also became a prominent researcher at the same institute, but father and son never had the chance to work together: Miklós died at age 63, just as Jancsó was entering adulthood. But the younger Jancsó followed in his father's footsteps. In 1977 he coauthored a paper with his mother, published in *Nature*, showing that exposing infant rats to capsaicin blunted their ability to feel pain from the compound and other irritant chemicals for the rest of their lives.

Jancsó has written a history of his family's capsaicin research. In it he recounts the harsh rejection he received from a prominent journal in 1987 after suggesting capsaicin be used as a painkiller. (His father had also faced skeptical audiences in his early capsaicin research.) It turns out each was a little ahead of his time.

GÁBOR JANCSÓ VIA RESEARCHGATE

Aurelia Jancsó-Gábor and Nicholas Jancsó at the University of Szeged, late 1950s.

RICHARD ELLIS/ALAMY STOCK PHOTO

Think of your nervous system as a series of channels, with certain compounds as the keys to opening those channels. Thanks primarily to the work of the Jancsó family and Hungarian colleagues, such as János Szolcsányi, researchers knew repeated use of capsaicin had the almost counterintuitive effect of blunting pain, closing channels that send pain signals to the brain. But exactly how that worked remained unknown until 1997.

During the 1990s, research into the molecular mechanisms behind pain took off, and the rest of the world began to take note of the earlier Hungarian research. Capsaicin had such a marked effect on nerves it was thought there existed a capsaicin receptor, a special channel on nerve cell membranes that opened for the compound.

"Everybody sort of knew that identifying this receptor, if it did exist, could be what people would refer to as the holy grail of pain research," says David Julius, chair of the Department of Physiology at the University of California, San Francisco. Such a receptor would provide one of the first molecular insights into how sensory nerve cells worked.

But capsaicin research required a major time commitment, with no guarantee that a single gene encoded for a capsaicin receptor, or channel. If there were multiple genes involved, it would make the search much more difficult. In the mid-1990s, Julius and his postdoctoral fellow at the time, Michael Caterina, began investigating whatever scraps of previous data they could find, including work done by Gábor Jancsó, Szolcsányi, and scientists at University College London.

What they found suggested capsaicin acts on a nerve cell's membrane, maybe via ion channels. These channels, proteins that shape themselves to form a passage through the cell's membrane, open to let ions flow in or out, and in doing so they cause a nerve cell to fire, sending a signal to the brain. In the case of capsaicin, as Julius and Caterina later learned, the molecule binds to its receptor and triggers an influx of positively charged calcium ions that then set up the cell to fire a message to the brain, telling it something is hot. As more and more of these ions flood in because of continued exposure to capsaicin, a feedback mechanism blocks the channel from bringing toxic amounts of calcium into the cell. This is thought to be one way capsaicin can break the function of the very channel it targets. And this is why people build up tolerance to spicy foods.

Julius and his colleagues eventually found a gene that encoded for the mystery channel, which was named transient receptor potential vanilloid subfamily member 1, or TRPV1. It turned out to be the first of many temperature-sensitive ion channels, or TRPs. Julius's lab and others went on to discover at least eight more TRP channels that respond to heat and cold. Tantalizingly, they offer the potential to block not just pain from hot-pepper heat but many types of chronic pain as well.

Hungarian researchers weren't the first to figure out chili peppers could blunt pain. As the pepper made its way around the world, it left a mark not only in cuisine but also in traditional medicine. In India the chili pepper was used to a treat a variety of maladies, including arthritis and toothaches. Among native communities in Nagaland, a state in northeastern India, chili plants were crushed up and rubbed on the skin to counter itching. One of the first formulations of topical capsaicin available to modern consumers came in the late 1980s with a low-dose capsaicin cream originally marketed to treat pain from shingles. But its effects were weak, and researchers concluded it was not much more effective than placebo cream. In 2009 pain researchers developed a patch for patients with chronic neuropathic pain that delivered a higher concentration of capsaicin (8%), more than 100 times the dose of the original creams, which does seem to provide more effective pain relief compared with lower-dose creams.

Companies have tried to create a painkiller, particularly in pill form, that would mimic and enhance capsaicin's effect on the TRPV1 channel, jamming the pain pipeline to the brain. But drug development stalled after trials showed the drugs induce fever and people taking TRPV1 blockers lose their ability to detect heat of any kind. Such side effects make drug company executives nervous.

"They kind of put the kibosh on all this," says Julius. "They get skittish about stuff."

But the search continues. There are approximately a dozen compounds in various phases of research at different drug companies. For instance, Centrexion Therapeutics has finished two clinical trials for its injectable pain medication, which uses a synthetic form of capsaicin to relieve knee pain in those suffering from osteoarthritis.

Other firms seem to have solved the problem of keeping body temperature normal for subjects taking these drugs. NeoMed Institute in Montreal has developed a pill that blocks the TRPV1 receptor without increasing body temperature or affecting the skin's ability to detect hot surfaces, according to its chief medical officer Dan Chiche. But NeoMed takes drug development only to phase-2 trials; they need funding from a larger company to take the next step.

Janssen Pharmaceuticals has finished its phase-1 trials of a pill, a TRPV1 blocker that also treats knee osteoarthritis. But what happens next is uncertain.

"My hope is that drug companies will circle back to these and other targets, especially now that there's much more awareness of problems with opiates and overuse," says Julius.

Drying chili peppers in Isleta, New Mexico, 1940.

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B.ZHOU/SHUTTERSTOCK.COM

A chef stirs a huge hot pot in downtown Chengdu, Sichuan, China, February 2019.

Turning capsaicin into medicine may be a funny notion: in the drug business nothing moves quickly, but the hot-pepper business thrives on impulse. Watch people eat a hot pepper, and you can see the side effects immediately: faces turn red, people sweat, and they yowl and whoop in pain. And yet, as painkillers go, these are pretty mild side effects compared with the pain of opioid addiction or the liver and cardiovascular damage that can occur with some anti-inflammatory pain relievers. At worst it seems a drug that trips up TRPV1 makes your body warm and somehow numbs your ability to feel heat.

Peppers can do more than blunt pain: they play a role in all sorts of physiological phenomena. They may even fight cancer. That's why Currie started crossbreeding for hotter peppers in the first place back in 2001. He hoped the potent capsaicin would help his mother after she was diagnosed with an aggressive form of lung cancer. Studies have shown capsaicin suppresses tumor growth, but research has not progressed much beyond the lab.

That lack of real-world evidence didn't stop his mother from eating as many peppers as she could until the last year of her life, Currie says. She believed it helped her live longer, five years past her diagnosis. "Not a lot of people last that long with lung cancer," he notes.

And the benefits don't come from capsaicin alone: according to Currie all the components of the peppers working together bring health gains. He counts the feeling of joy as one of those benefits.

Scientists have teased out the chemistry of capsaicin in exquisite detail, yet the reason for the appeal of hot peppers remains a mystery. They seem to make people happy, but does benign masochism alone account for that joy? According to psychologist Paul Rozin, the culture that emerges around its eating is what perpetuates the pepper.

In other words, eating hot things is probably more fun because you associate the experience with laughing friends, family, and tasty food.

Currie sees this every day in his store: tame consumers converted to chili heads.

"The proof is in the pudding," says Currie. "People come into our store and they say, 'Oh, I only like the mild stuff,' and within a year they're eating the hottest stuff in there." D

Leah Shaffer is a science writer based in St. Louis.

Hennig Brandt and the Discovery of Phosphorus

An engraving in the Science History Institute's collections hints at the ways art and science were intertwined in the Age of Enlightenment.

BY BERT HANSEN

One night in 1669 German physician Hennig Brandt attempted to create the philosophers' stone. This elusive goal had been pursued by alchemists for centuries for good reason: it could transform base metals into gold.

Brandt had spent most of that day in his laboratory, heating a mixture of sand and charcoal with a tar-like substance produced by boiling down about 1,200 gallons of urine over two weeks. He then maintained the mixture at the highest temperature his furnace could reach. After many hours a white vapor formed and condensed into thick drops that gleamed brightly for hours. The glowing, waxy substance had never been seen before. Brandt called it *phosphorus*, a Latin term for things that give off light.

Brandt's was an era that still saw a world made up of four elements: fire, air, water, and earth. And like the fascinated colleagues to whom he showed his new compound, Brandt assumed it was composed of these elements. (A little more than a hundred years later Antoine Lavoisier replaced this worldview with another, of elements as simple substances that could not be further decomposed.) Whatever his categories, Brandt's phosphorus was a spectacular sight. Artist Joseph Wright of Derby immortalized this moment a century later in his painting *The Alchymist*.

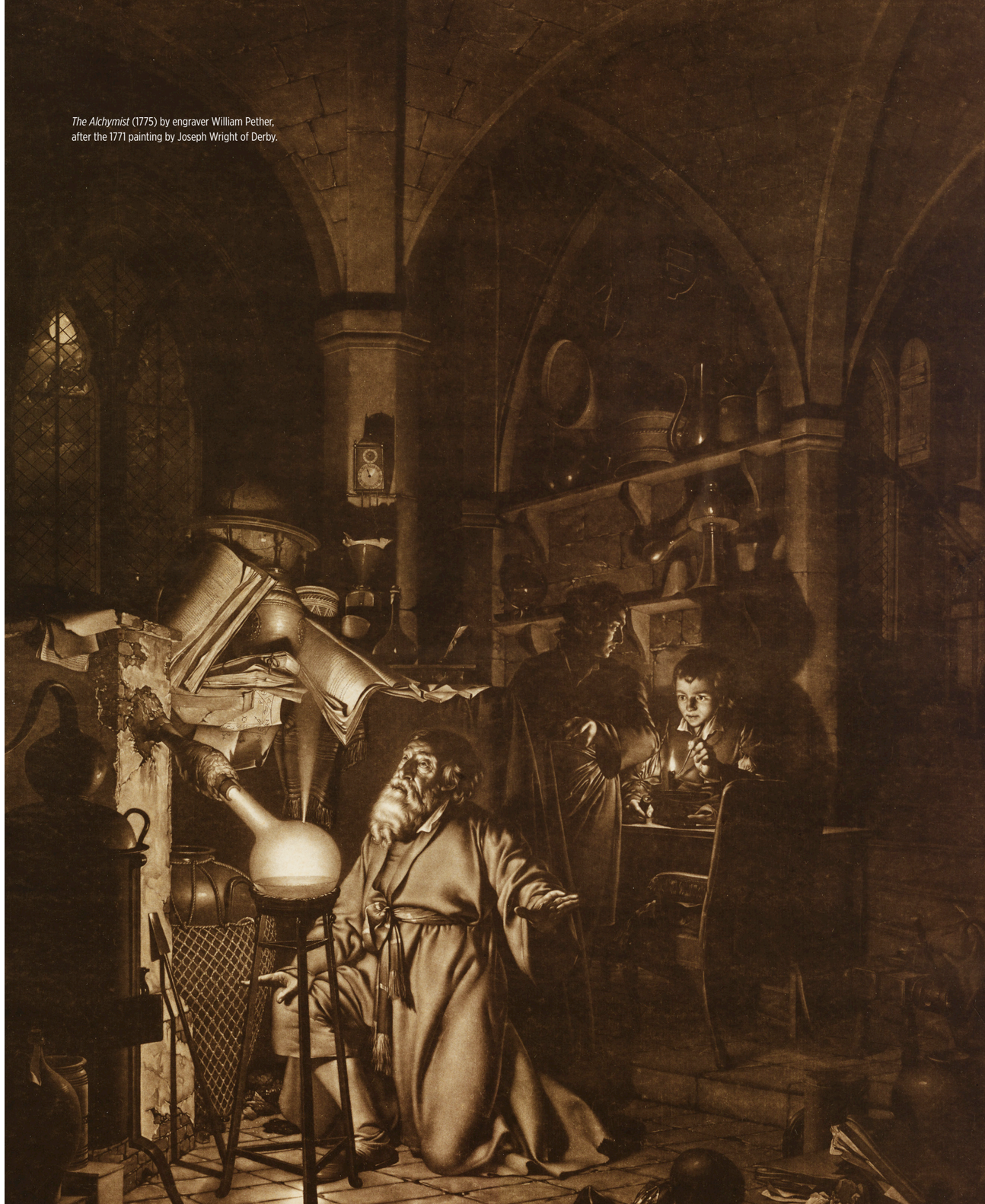
Within 50 years of its discovery phosphorus was being produced and sold to apothecaries, natural philosophers, and showmen, who made the element the centerpiece of demonstrations at princely courts and scientific societies. Within 100 years phosphorus was appearing in chemistry textbooks, such as P. J. Macquer's popular *Elements of Theoretical and Practical Chemistry*. Within another 50 years the element was making its way into matches, fertilizer, and bombs, once mineral phosphates had replaced urine as the best source material.

Brandt's name wasn't prominent in the earliest accounts of the discovery, but Macquer gave him formal credit in his textbook, writing that "the phosphorus here described was first discovered by a citizen of Hamburgh named Brandt, who worked upon urine in search of the Philosopher's stone." Macquer understood such transformations to be impossible, but in his unusually sympathetic interpretation he noted that such chemical manipulations "proved the occasion of several curious discoveries." Wright, who knew Macquer's book, was inspired by the latter's understanding that misguided experiments could lead to real discoveries.

At about this time Wright was part of an intellectually engaged circle of physicians, scientists, and industrialists in the English Midlands. Their conversations and chemical experiments prompted Wright to re-create Brandt's historic moment of scientific discovery. Wright's decision to paint an action portrait of a pioneering chemist was unprecedented. For centuries the genre of history painting had featured saints, military leaders, and royalty; never had such artwork featured a specific physician, alchemist, or philosopher at work.

The 1660s had been a lucky time for Brandt; the 1760s were fortunate for Wright. In his era an artist's renown depended on high-quality engravings of his paintings. Prints were most people's only access to art, and printmakers had just recently perfected an entirely new engraving technique called mezzotint. This innovation made it possible for printers to reproduce painterly contrasts from bright whites to rich velvety blacks. William Pether, a leading English engraver, produced spectacularly subtle and nuanced renderings of *The Alchymist* (painted by Wright in 1771), as well as a dazzling mezzotint of Wright's *Orrery* (1766), also in the Science History Institute collection. These engravings are among the very finest of the 18th century. D

Bert Hansen is the author of Picturing Medical Progress from Pasteur to Polio.



The Alchymist (1775) by engraver William Pether, after the 1771 painting by Joseph Wright of Derby.

SCIENCE HISTORY INSTITUTE

HARRY GOLD

SPY IN THE LAB

BY SAM KEAN

PUBLISHED APRIL 25, 2019

Chemist, spy, idealist, traitor, convict, humanitarian? Who was Harry Gold?

PHOTO ILLUSTRATION BY CLAY CANSLER

As the battered, blue Buick pulled up to the church in Santa Fe, a short, tubby man stepped out to meet it. He climbed into the passenger seat and the car took off, winding its way to the edge of town, then up into the mountains.

It was a warm September night in 1945. The two men sat inside the car and talked like old friends, watching the lights of the city below. After a while, as the desert cooled, they headed back to Santa Fe. Just before parting, the thin, bespectacled driver handed his passenger a package. They shook hands warmly and, despite promises to visit, knew they'd probably never see each other again.

After the car rattled off, the tubby man schlepped to the bus station. Maintaining his grip on the packet, he sat on a bench and tried reading a book, *Great Expectations*. But he couldn't concentrate. He kept popping up and scanning the crowd, worried he was being followed. He looked jumpy, even paranoid, and with good reason: he was a Soviet spy, and the packet in his hands contained the blueprints for an atomic bomb.

After a bus ride to Albuquerque he caught a plane to Kansas City and a train to Chicago. The train was so crowded he had to sit on his suitcase, but he clutched the papers tight and didn't complain. After several delays he eventually reached New York—but too late to meet his Soviet contact. The backup meeting wasn't for two weeks, which meant two more weeks of carrying the packet around, two more weeks of paranoia. For 14 days he never let the package out of his sight, even taking it grocery shopping. Indeed, there was only one place he felt safe during that fortnight—his chemistry lab.

As soon as he got his experiments running, the stress of atomic espionage lifted a little. He could lose himself among the crucibles and test tubes and let his guard down. And when he finally handed off the blueprints, he once again buried himself in lab work to push the matter out of his mind. Some people drink to forget troubles; Harry Gold did chemistry.

Today Gold is best known as a spy and a snitch. He accepted top-secret documents from Manhattan Project physicist Klaus Fuchs and delivered them to Soviet agents. And when the FBI finally caught Gold, his testimony helped land Julius and Ethel Rosenberg in the electric chair. But if anyone had asked Gold what he would call himself, his answer would have been simple. He was a chemist.

★

A combination of anti-Semitism and economic hardship first pushed Gold into espionage. He grew up in a rough neighborhood in South Philadelphia, where his family suffered discrimination as Jews and immigrants. Gangs threw bricks through people's windows and beat up the short, slight, bookish boy on the way home from the library.

Gold's father, Samson, a carpenter at a phonograph factory, had it even worse. His boss hated Jews and once snarled at him, "You son of a bitch, I'm going to make you quit." He then removed everyone but Samson from the assembly line and forced him to sand down all the wooden cabinets by himself. He had to work at a frantic pace, and Gold remembered him coming home with bleeding fingertips night after night. But the young Gold admired how his old man never complained and never quit.

Samson was laid off, however, in 1931, which put Gold in a tough position. He'd worked during his teenage years at the local Penn Sugar plant, starting off washing spittoons and glassware before working his way up to lab assistant. He liked the work enough to start taking classes toward a chemistry degree. But when his father lost his job, Gold had to quit school and become the family's breadwinner. Unfortunately, the Great Depression just kept getting worse, and when Penn Sugar cut Gold loose in December 1932, the family faced the real possibility of losing their home.

After several desperate months Gold's friend Tom Black found him work at a soap factory in New Jersey for $30 a week, a good wage for the time. Gold was deliriously grateful. But there was a catch. Black was an ardent Communist, and he insisted Gold accompany him to meetings.

SOME PEOPLE DRINK TO FORGET TROUBLES; HARRY GOLD DID CHEMISTRY.

Although Gold leaned left politically, the Communists he met disgusted him. He dismissed them as "despicable bohemians who prattled of free love . . . lazy bums who would never work under any economic system . . . polysyllabic windbags." A few months later, when Penn Sugar rehired Gold, he left Jersey behind and refused to attend any more meetings.

But Black kept hounding Gold, badgering him to join the Communist Party. The Soviet Union, Black explained, needed to build up its industrial base and improve people's standard of living. But American firms were stingy about licensing technology. Could Gold swipe some trade secrets?

Gold hesitated. Penn Sugar had been good to him—not many firms would have let a spittoon-washer become an assistant chemist—and the company had subsidiaries in several different industries, meaning he could work in almost any field he fancied. But Black's plea for help moved him. Gold liked the idea of saving the huddled, starving Soviet masses—people like his own family. Soviet agents often appealed to the scientific idealism of people like Gold as well. By liberating trade secrets, they would simply be pooling information, which is crucial to scientific progress.

Communist demonstration in Philadelphia, May Day, 1935.

SUEDDEUTSCHE ZEITUNG PHOTO/ALAMY STOCK PHOTO

But what really moved Gold was the fight against anti-Semitism. The Soviet Union, Gold concluded, had outlawed discrimination against Jews; it was the one nation on Earth where Jewish people were truly equal. In reality of course this wasn't true: the U.S.S.R. was as prone to anti-Semitism as anywhere. But Gold believed otherwise. He could still remember his father's bleeding fingertips and the gangs smashing windows in South Philly, and he burned to do something "on a much wider and effective scale than . . . smashing an individual anti-Semite in the face." Supporting the great Soviet experiment was his chance to fight back. As he later grumbled, the Communists "played me very shrewdly."

So Gold started spying. He'd riffle through file cabinets at work and sneak documents out—occasionally at first but with increasing frequency as the months passed. He'd then spend hours after work, sometimes full nights, copying them line by line. From various subsidiaries, he took papers on lacquers and varnishes, on solvents and detergents and alcohol. He never meant to take so much, but he was always thorough about his work, illicit or not. And every time Black asked for another report, he'd think of the poor Soviet people—people who loved science and hated anti-Semitism—and steel himself to take more. Overall, he remembered, he "looted them pretty completely."

At first Gold just handed the copies to Black. Eventually, he started running them up to New York himself, a task that seemed thrilling at first but that he grew to loathe. The rendezvous often meant an overnight train ride and hours of wandering around the city to lose potential tails. (He might sit through half a movie, for instance, before ducking out a side exit.) He then might have to wait for Soviet agents in snow or rain. Overall, "it was a dreary, monotonous drudgery," he recalled, and the need to deceive his family troubled him: "Every time I went on a mission . . . I must have lied to at least five or six people." But Gold was submissive by nature and made trip after trip.

Each year got a little more hectic, and Gold was soon near collapse, often working 18- to 20-hour days. In addition to working full time he was taking evening classes at Drexel University, still trying to get that chemistry degree. Some weeks he barely slept, and his weight had ballooned to 185 pounds.

But no matter how ragged he felt, Gold always found time for lab work. One favorite research project involved thermal diffusion, a way of imposing a temperature gradient to separate a mixture; in particular, he wanted to isolate carbon dioxide from waste exhaust to make dry ice. He described himself as a methodical chemist, a plodder rather than a "one-shot genius": he made "every possible error in the book until, by the tedious process of elimination, only the correct answer remained." One afternoon he dropped a rack with 22 crucibles and watched a full week's worth of labor spill onto the floor. "I did not sit down and cry; nor did I

While Gold claimed to be disgusted by the Communists he encountered, he was seduced by their antifascist stance, by false assertions of ethnic equality in the Soviet Union, and by the idea of improving the lives of everyday Russians with the technological know-how he was pilfering. **OPPOSITE PAGE** Jewish hatmakers in the Soviet Union, ca. 1920s. **LEFT** The October 1932 cover of *Der Hammer*, a Yiddish-language Communist magazine published in New York, illustration by William Gropper. **RIGHT** Poster advertising a fundraising lottery for the Society for Settling Toiling Jews on the Land, better known by its Russian acronym, OZET, 1930.

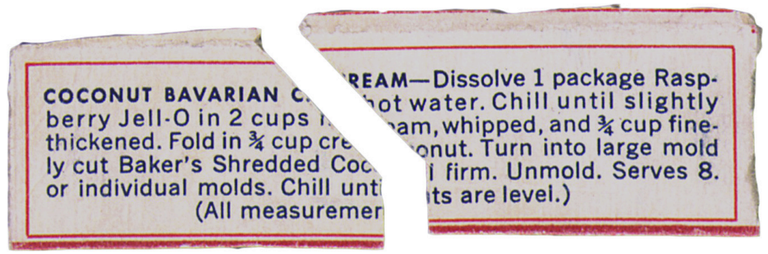
HERITAGE IMAGE PARTNERSHIP LTD/ALAMY STOCK PHOTO; ERIC CHAIM KLINE BOOKSELLER; WILLIAM GROPPER COLLECTION; THE WOLFSONIAN, FLORIDA INTERNATIONAL UNIVERSITY

go out and get drunk, as much as I wanted to," he recalled. He simply worked for two days and two nights straight to redo everything.

Gold was on the verge of quitting espionage when, in 1938, the Soviets surprised him. He'd always longed to finish his degree, and his handler suddenly offered to pay for his tuition at Xavier University in Cincinnati. This wasn't a selfless gesture: the Soviets were developing a spy at an aeronautical installation near Cincinnati, and Gold would be around to courier documents. But he didn't care: he loved every second of collegiate life, putting in long hours at the lab and cheering rabidly for the Musketeers basketball and football teams. He stayed at Xavier until 1940 and later called his time there some of the happiest years of his life.

The idyll ended on his return to Philadelphia, where Gold—despite his hopes to extricate himself from the Soviets—resumed spying on a regular basis. It's not clear why he did so. Always a lonely guy, he perhaps enjoyed the companionship and sense of purpose. Or maybe he felt indebted to the Soviets for paying for part of his education. Moreover, world events soon compelled him to keep snooping. After Nazi Germany invaded the U.S.S.R. in 1941, the Soviets were desperate for defense help, including technical expertise. Gold hated the murderous Third Reich and resigned himself to more espionage to help the Soviet Union survive.

But the tedium and guilty feelings were as bad as ever, and when Gold found himself waiting for yet another late-night train in New York in the fall of 1942, he finally resolved to cut ties. And he might have—if a drunk at the station hadn't started harassing him. Gold was 31 years old then, of draft age, but the army had rejected him for having high blood pressure (the navy would soon do the same). So when the souse called him a "yellow draft dodger" and a "kike bastard," Gold was incensed.



The Jell-O box top used by Gold and David Greenglass.

As Gold later said, "I would have smashed him—hard—but I withheld because I could not afford to be involved in a scrape in New York, where I had absolutely no business to be. So I just walked away. But as I did, so went my resolution to quit espionage work. It seemed all the more necessary to . . . work with the most increased vigor possible to strengthen the Soviet Union, for there such incidents could not occur. To fight anti-Semitism here [in the United States] seemed so hopeless."

Thus resolved, Gold continued spying, albeit with some changes. He shifted away from industrial espionage to more military work. He also took on new roles; he accepted documents and even a sample of explosives from scientists in defense labs and interviewed these contacts for reports. Handling sources was delicate work, requiring both technical know-how and psychological savvy. But Gold excelled: he was what the Soviets might call a "disciplined athlete"—a cool, reliable spy. So when the top scientist in the Soviet spy ranks got transferred from England to New York in late 1943, Gold was the obvious choice to handle him.

★

On February 5, 1944, just before 4:00 p.m., two men began converging on a vacant lot near a playground on Manhattan's East Side. One was thin and prim, wearing tweeds and glasses. He was carrying a green book and, despite the winter chill, a tennis ball.

Seeing the ball and book, a short, jowly man—wearing one pair of suede gloves and clutching another—sidled up and asked for directions to Chinatown.

"Chinatown closes at 5 o'clock," the thin man answered, completing the recognition signal. And with that, Klaus Fuchs and Harry Gold began walking.

Gold introduced himself as "Raymond" and after a short walk hailed a cab. But before long Gold stopped the car and hustled Fuchs into the subway to lose any tails. (There Gold might also have shown Fuchs one of his favorite evasive maneuvers—darting out of the train car just before the doors closed.) The circuitous route eventually landed the duo at a steak house on 3rd Avenue. Gold was proud of his tactics, but Fuchs dismissed them as juvenile. He also scolded Gold for his habit of constantly swiveling his head as they walked, looking for tails. That only attracts attention, he said.

Having laid down the law, Fuchs started talking business. Although German born, he'd been run out of Nazi Germany for Communist activities and had moved to England to work in nuclear physics. He'd recently transferred to New York to work on the Manhattan Project, which he explained to Gold was inching toward a bomb of unprecedented power.

After this first meeting several more followed over the next few months—in Brooklyn, the Bronx, Queens, at movie theaters, bars, museums. Every so often Fuchs handed Gold a thick envelope; inside were pages filled with diagrams and mathematical derivations in a tiny, neat script—all top-secret bomb work.

Sometimes the scientists chatted, although each man remembered their conversations differently. Fuchs recalled professionalism—terse exchanges and strict discipline. Gold recalled a budding friendship. In between spy talk they discussed chess and classical music, and Fuchs opened up about his family, including a sister in Massachusetts. Gold in turn told Fuchs about his twin children and his wife, a redhead who had modeled for a department store. This was a complete fabrication—the fantasy of a lonely man.

Gold also tried impressing Fuchs with his scientific knowledge. It didn't go well. During one meeting Fuchs admitted that his team was having trouble separating uranium isotopes, the first step in building a bomb core. Gold jumped in and suggested they try thermal diffusion, the process he'd been tinkering with at work. Fuchs dismissed the idea as amateurish, which stung Gold. (Unbeknownst to Fuchs the Manhattan Project had in fact just opened a thermal diffusion plant; without it there would have been no uranium bomb in 1945.)

In July 1944 the pair had their eighth meeting scheduled, near the Brooklyn Museum. Fuchs didn't show. This worried Gold, given how precise Fuchs always was, but they had a backup meeting scheduled a few days later near Central Park. So Gold took off.

NATIONAL ARCHIVES AND RECORDS ADMINISTRATION/WIKIMEDIA COMMONS

NATIONAL ARCHIVES AND RECORDS ADMINISTRATION/WIKIMEDIA COMMONS

Fuchs missed the next meeting, too. Thoughts of muggers flashed through Gold's head, and he returned to Philadelphia distraught. An invaluable spy—and a man he considered his good friend—had suddenly gone AWOL.

He needn't have worried. Fuchs was fine—better than fine. Through a combination of luck and lax security, this top Soviet spy had just wrangled an invitation to the inner sanctum of the Manhattan Project—the weapons lab at Los Alamos.

★

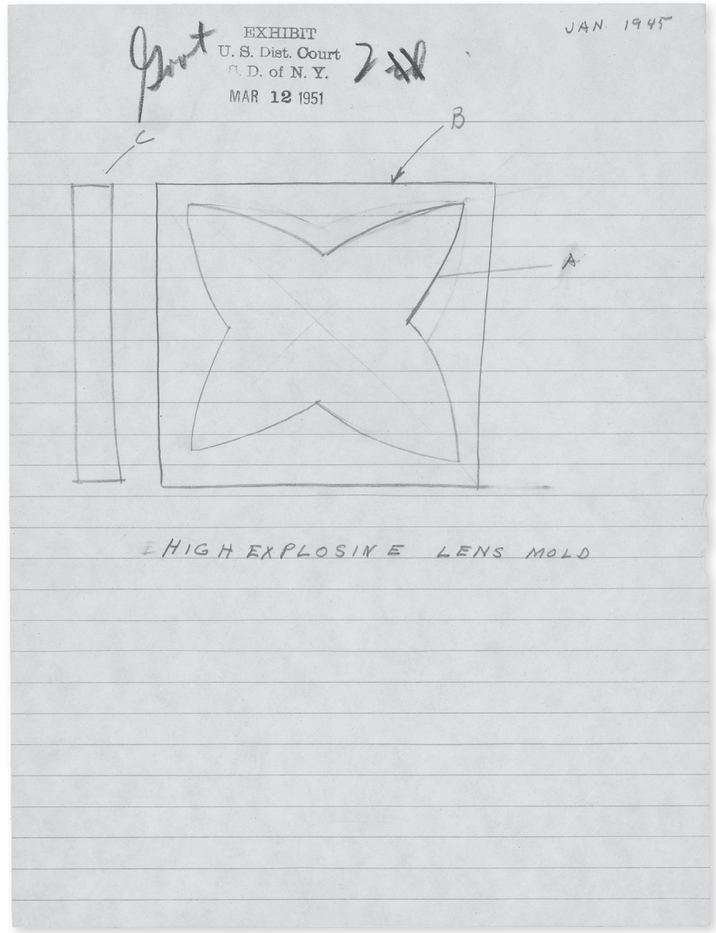
Neither Gold nor the Soviets knew where Fuchs was, but after months of searching Gold finally tracked down his friend through Fuchs's sister in Massachusetts. The two spies agreed to meet in Santa Fe on Saturday, June 2, 1945.

Just before the trip Gold met his Soviet handler at a bar to iron out the details. The handler ordered Gold to take a roundabout journey by train and bus, with stops in California, Colorado, and Texas, to avoid possible surveillance. But for once Gold stood up for himself. He had already borrowed $500 from Penn Sugar to finance the New Mexico trip and couldn't afford to take more time off. He insisted on traveling there directly.

But if Gold won that argument, he would lose a second, more important one that day. After wrapping up the details of the Fuchs meeting, the handler told Gold something surprising: the Soviets had a second mole inside Los Alamos. This mole would be in Albuquerque, not far from Santa Fe, while Gold was visiting, so Gold needed to make a side trip there to pick up additional papers.

In any normal business this request would be reasonable. In espionage it was anathema, a huge security risk for everyone involved. So Gold, feeling his oats, stood up for himself again: "I . . . got up on my hind legs and almost flatly refused," he later remembered.

This time his handler slapped him down. "I have been guiding you idiots through every step!" he snarled. "You don't realize how important this mission to Albuquerque is."



David Greenglass's drawing of a mold used to make the explosive lens of an atomic bomb. It was presented at the espionage trial of Julius and Ethel Rosenberg in 1951.

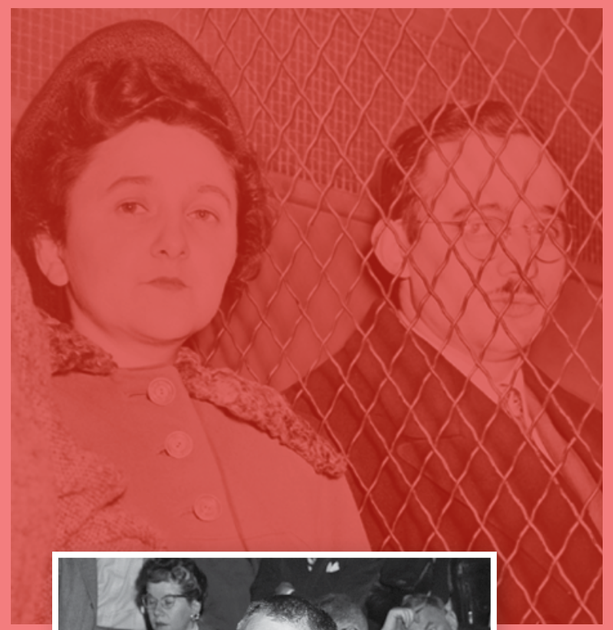
As the tirade continued, Gold backed down and submitted as usual. His handler finally gave him an address in Albuquerque and a last name, Greenglass. The handler then gave Gold half a Jell-O box top, which had been cut into a jigsaw shape. He passed the puzzle piece over to Gold. You'll know it's Greenglass, he said, because he'll have the other half.

★

Gold's bus pulled into Santa Fe on Saturday, June 2, at 2:30 p.m. With 90 minutes to kill he grabbed a map from a local museum and wandered along the nearby river. It looked pitiful, he thought, smaller than most creeks back home.

Fuchs arrived late in his sputtering Buick. They drove to a deserted road and took a short walk together. Fuchs discussed his work on the new plutonium bomb but assured Gold, wrongly, that the war would be over before it was ready for use against the Japanese. He then handed Gold a packet, and they parted. All in all a good meeting.

The second meeting proved different. Gold took a bus to Albuquerque, arriving around 8:00 p.m., and went straight to the address on the onionskin paper, 209 High Street. He felt nervous holding documents from Fuchs and wanted to skip town soon. But David Greenglass wasn't home.



CLOCKWISE FROM THE TOP LEFT Julius and Ethel Rosenberg leaving court after being convicted of espionage, March 29, 1951; David Greenglass's mug shot, undated; Klaus Fuchs after his release from an English prison, June 6, 1959, after which he immediately defected to East Germany; Harry Gold at a Senate hearing on Americans spying for the Soviet Union, April 26, 1956.

LIBRARY OF CONGRESS; NATIONAL ARCHIVES AND RECORDS ADMINISTRATION/WIKIMEDIA COMMONS; KEYSTONE PRESS/ALAMY STOCK PHOTO; AP PHOTO/HENRY GRIFFIN

HE WAS WHAT THE SOVIETS MIGHT CALL A "DISCIPLINED ATHLETE"—A COOL, RELIABLE SPY.

Gold struggled to find lodging in a town packed during the weekend with servicemen and workers from the nearby military installations. (Ironically enough, it was a policeman who directed the atomic spy to a private boardinghouse.) After a wretched night on a cot in a hallway there, Gold returned to Greenglass's home the next morning and trudged up the narrow staircase. He knocked on the door at the top, and when it opened, he almost fell right back down in shock. The man who answered was wearing army trousers. Gold had no idea that members of the U.S. military had been dragged into this.

Composing himself, Gold asked if he was Greenglass. Greenglass said yes. "I come from Julius," Gold responded.

"Oh," Greenglass said and turned to retrieve a Jell-O box top from his wife's purse. Gold held out his half, and the pieces matched. Gold then asked if Greenglass had any materials ready. Greenglass said no, that he hadn't gotten around to it and Gold should come back that afternoon.

Grumbling, Gold found some breakfast and waited. When he returned, he and Greenglass took a walk in the summer sun and made the handoff. The packet included diagrams of high-explosive lenses, one of the most crucial aspects of the plutonium bomb.

Gold caught a train that evening and spent the next two days rattling east, glad to have escaped. But his side trip to Albuquerque would prove costly. It just so happened that David Greenglass had a sister in New York named Ethel, who was married to a man named Julius Rosenberg.

★

Gold visited Santa Fe again in September. World War II was over, but the Soviets were ramping up for the Cold War. Fuchs delivered one last packet to Gold before returning to England; it contained data on the Hiroshima and Nagasaki bombs, as well as technical details about making bombs. This was the trip where Gold missed his contact in New York, forcing him to spend two weeks carrying the papers around. The fortnight exhausted him, and given the expense and added stress of trips to New Mexico, he decided yet again he was done with espionage.

Espionage, however, wasn't done with him. In 1946 Penn Sugar laid Gold off again. He applied to the KGB for funds to open a thermal diffusion lab, and when they turned him down, Gold went to work for a fellow chemist—and fellow Communist spy—in New York named Abe Brothman. It was a huge mistake. Gold's handlers had warned him the FBI had its eye on Brothman, but Gold either forgot this fact or ignored it. Sure enough, Brothman soon ran afoul of the FBI and implicated Gold in espionage. The two were summoned to testify before a grand jury in July 1947.

A weary Brothman had been threatening in private to confess his role in the Soviet spy machine, but he pulled himself together on the stand and denied everything. Nine days later came Gold's turn to testify. The night before, Gold swung by Brothman's apartment, and they went for a drive. Gold wanted to discuss his testimony, but every time he brought the topic up Brothman started ranting about the impending death of capitalism. Appalled, Gold stopped to eat some watermelon with Brothman and finally gave up at 4:00 a.m.

He needn't have worried: Gold proved every bit as deft at lying under oath as Brothman had, making himself look like a bumbling, absent-minded chemist. And while the FBI didn't believe either man, it couldn't poke any holes in their stories, and both of them walked.

Still, thanks to Brothman, the FBI now had a file on Gold. And agents in England were about to reel in a spy who had much more incriminating material on him—none other than Klaus Fuchs.

★

Brothman paid Gold erratically if at all. ("When there was no money, I was a partner," Gold said of his time there. "When there was money, I became an employee.") So in mid-1948 Gold quit and took a job in the Heart Station at Philadelphia's General Hospital. Not only was he doing good, solid chemistry—he studied electrolyte levels in the blood and how potassium affected muscle function—he was saving people's lives and would go on to earn a promotion to chief research chemist. He even met the love of his life there, biochemist Mary Lanning. "I had never been happier . . . in my life," he later said.

Over the next year or so Gold proposed to Lanning twice. She always said no—but not because she didn't love him. Rather, she sensed a "lack of ardor" on his part—which stemmed from Gold's fear of exposure as a spy. But he simply couldn't bring himself to tell her the truth. When he accidentally mentioned Santa Fe once, he then had to cover his tracks by saying Penn Sugar had sent him down to check out a Coca-Cola plant nearby—obvious baloney. They finally broke things off, Gold fearing that if they married and he got exposed, it would ruin her life.

He was right to worry. In September 1949, four years after his last meeting with Fuchs, Gold answered the door at the house he shared with his father and brother and found a Soviet agent there. He tried to slam the door, but the agent quickly said the code words, so Gold let him in. Desperate to be rid of the man—Gold's family still had no idea he was a spy—he agreed to visit New York two weeks later. They rendezvoused during a downpour, and the agent, to Gold's horror, urged Gold to defect to Eastern Europe. He refused to explain why.

Everything became clear a few months later. On February 2, 1950, Klaus Fuchs was arrested in England. The United States was still reeling from the news that the Soviet Union had detonated a nuclear bomb the previous August, and the capture of an atomic spy made headlines worldwide. Fuchs confessed he had an American contact named "Raymond."

Reading this, Gold panicked and decided that, if caught, he would kill himself with sleeping pills. But his old friend Tom Black, who'd first pushed him into espionage, talked him out of it.

Meanwhile, the FBI began what one agent called a "raging monster of a quest" to find Raymond. The bureau investigated 1,500 suspects, with 12 agents working full time and 60 more working part time. Because they knew Raymond had a background in chemistry, they requested information on 75,000 combustible material permits issued in New York City in 1945. They even sent agents to bus stations across New Mexico to ask employees if they remembered a husky white fellow back in 1945 holding an envelope.

The FBI finally caught a break when agents (illegally) broke into Abe Brothman's lab in New York and found several papers Gold had written on thermal diffusion. This discovery excited them because Fuchs had worked in *gaseous* diffusion for the Manhattan Project. In truth the two processes have nothing in common, but apparently the FBI didn't quite grasp that. (Sometimes it's better to be lucky than smart.) They cracked open Gold's old case file and, using this and other clues, linked him to Raymond.

On May 15 two agents in Philadelphia paid a visit to Gold at his lab. He agreed to accompany them downtown to answer questions. He never cracked but was so rattled by the visit he had to put in several hours in the lab to calm himself.

Feeling he had no choice, Gold submitted to more hours of interrogation that weekend. When they asked him if he'd visited New Mexico during the war, he denied ever being west of the Mississippi. When they put a picture of Fuchs before him, he admitted recognizing the spy—but only from magazines. Rashly, he also agreed to "settle the matter" by letting the FBI search his home—but only on Monday, when his brother and father were absent. The agents couldn't have been happy with this arrangement; it would give Gold the chance to purge anything incriminating. But lacking a warrant they agreed to the delay.

Incredibly, though, Gold didn't purge a thing. He headed to the lab instead. He had a few experiments running, on ways to detect potassium, and couldn't bear to leave them unfinished. He then had one last evening with his brother and father on Sunday—"to salvage a few more precious hours" of normalcy, as he put it.

Only at 5:00 a.m. on Monday did he begin the purge. Digging through his room, Gold found a letter from a Soviet agent, a plane ticket stub, and a draft report. He scrambled to flush some items down the toilet and buried others in the rubbish bin in the cellar.

He'd just finished when two FBI agents knocked around 8:45 a.m. Wearing pajamas, Gold led them up to his room, which they began to ransack, pawing through drawers and pulling books off shelves. Still a "disciplined athlete," Gold watched them and chatted.

A little after 10:00 a.m. one agent pulled down a favorite book of Gold's—a well-thumbed copy of *Principles of Chemical Engineering*. But of all the books he owned, this one would betray him. As the agent opened it, a tan street map slipped out titled "New Mexico, Land of Enchantment." Gold had grabbed it at the museum before his meeting with Fuchs.

The agent picked up the map. "So you were never west of the Mississippi."

Gold all but collapsed into a chair. He asked for a minute to think, then bummed a cigarette, which he normally hated. Even at this point Gold probably could have walked. The FBI had no hard evidence, and it seemed unlikely that Fuchs would turn stool pigeon. But after a decade and a half of espionage, he was simply too tired—tired of lying, tired of running, tired of the burden. All he could think about was how to break the news to his brother and father.

He finally turned to the agents. "I am the man to whom Klaus Fuchs gave the information."

On his arrest Gold vowed he'd never rat out anyone else. *I'll accept my punishment*, he thought, *and stay quiet*. Then his brother visited him. "How could you have been such a jerk?" he asked. At that moment, Gold remembered, "a good half of that mountainous mental barrier that I had erected against squealing went crashing down."

Even more wrenching, Gold's father came to visit later. His old man had always been so proud of Harry—his smart son, the chemist, the one who'd gotten them through the Depression. Now he was weeping, looking frail and bewildered. "This won't affect your job at the Heart Station, will it?" he asked.

The question broke Gold's heart. "Down went another section of the mountain."

★

Gold pled guilty and spilled everything he knew without even asking for a plea deal. He wrote up a 123-page document detailing his spy work and submitted to endless hours of questions. One agent compared interviewing Gold to "squeezing a lemon—there was always a drop or two left." And having finally unburdened himself, his health bounced back and his blood pressure dropped and he quickly lost dozens of pounds.

The FBI opened 49 separate espionage cases based on Gold's testimony. But history remembers one of them above all—the Rosenberg case. Gold couldn't recall the name of David Greenglass, Ethel Rosenberg's brother, but he did remember Greenglass's wife's name might have been Ruth and a description of their street in Albuquerque. Greenglass's furlough also coincided with the time frame Gold provided for their rendezvous. When caught, Greenglass confessed everything and claimed he'd been pushed into espionage by Ethel and her husband, Julius.

Greenglass ultimately doomed the Rosenbergs to the electric chair, and he was savaged for turning against his own sister. But Gold's reputation took a beating, too, from all sides of the political spectrum. Communists smeared him as a "pathological liar" and lonely "weakling" who made himself seem more important by inventing fabulous tales. Anti-Communists, meanwhile, condemned him as a stooge who'd betrayed his country. With no plea deal in place the prosecutors at Gold's trial demanded he serve 25 years in jail. The judge gave him 30. When Gold arrived at Lewisburg Penitentiary in central Pennsylvania, his fellow inmates made their scorn obvious as well. Thieves, rapists, hitmen—they enjoyed respect at Lewisburg. But when Gold the stool pigeon strolled over to play some pick-up basketball one day, every last player walked off the court.

Once again chemistry proved Gold's refuge. Lewisburg had an unusual prisoner health program that combined medical care for inmates with biomedical research. Gold jumped at the chance to return to the lab and even took shifts in the nearby sick ward to nurse fellow inmates back to health, which went a long way toward rehabilitating him in their eyes. He also spearheaded new research. He studied diabetes and thyroid disease at Lewisburg and even volunteered to be injected with hepatitis-laced blood to help investigate a vaccine. As his crowning achievement, in 1960 he earned a U.S. patent, from prison, on a speedy blood-sugar test using indigo disulfonate.

This lab work established Gold as a model inmate, and in April 1966, after serving 16 years, he earned parole. On the day of his release his lawyer came to pick him up and was terrified to hear an uproar inside. It sounded like a riot. But it was just Gold's fellow prisoners, cheering. After his years of selfless dedication they were giving him a roaring sendoff.

On his release Gold settled into a quiet life doing hematology and microbiology in another Philadelphia hospital. (He'd spent the last several months of his sentence studying lab textbooks in his cell at night to catch up on new techniques since his arrest.) He also began mentoring young scientists there, a kindly uncle figure. The only time the façade cracked was when someone mentioned the Rosenberg case. Once, during a news broadcast, a picture of David Greenglass flashed onto the screen. To his coworkers' shock Gold erupted and screamed at them to turn it off.

Eventually Gold's heart grew weak, a congenital effect possibly exacerbated by the hepatitis from the tainted blood he'd received in prison. In August 1972 he underwent a risky valve-replacement surgery and died on the operating table at age 61. People in his lab cried when they heard the news.

Gold had once hoped to make a name for himself after prison as a scientist: "Sometime in the future I shall be able to make far greater amends than I have done to date. And this restitution shall not consist in informing and giving evidence to the FBI . . . [but] in the field of medical research."

It was another fantasy. Gold is still vastly better known for espionage than chemistry: he simply betrayed too many secrets and too many people. But unlike most Communist spies Gold had higher ideals than politics. Deep down he was a chemist first and last—a man who preferred finishing experiments to saving his own neck, even with the FBI hot on his trail. History will probably never rehabilitate his reputation, but other scientists can at least nod along at Gold's story—his passion for lab work, his meticulousness, the sheer delight he took in chemistry—and say, truly, he was one of us. It was all Harry Gold ever wanted. D

Sam Kean is a best-selling science author. His latest book is The Bastard Brigade: The True Story of the Plot to Stop the Nazi Atomic Bomb.

Gold leaving federal prison after being paroled, May 18, 1966.

AP PHOTO

San Francisco's Plague Years

As officials spread disinformation, a deadly epidemic edged its way into the United States

BY REBECCA REGO BARRY

DAVID K. RANDALL. *Black Death at the Golden Gate: The Race to Save America from the Bubonic Plague.* W. W. Norton, 2019. 373 pp. $27.

For many people the words *black death* or *bubonic plague* evoke the medieval world, specifically the 14th-century pandemic that killed millions throughout Asia, Africa, and Europe. Or perhaps it calls to mind 17th-century London, where an infamous outbreak felled 20% of the population between 1665 and 1666, prompting diarist Samuel Pepys to write about bodies piling up in the streets and the endless tolling of funeral bells. But those were just two of many plague epidemics during the past 1,500 years. In the 19th century, China, Hong Kong, and India endured devastating bouts as the disease circumnavigated the globe, moving from port to port. Then, at the turn of the 20th century the dreaded plague found its way to the United States, where obstinate politicians and power brokers, concerned more about commerce than public health, tried to pass off evidence of the plague as "fake news."

In this way David K. Randall's riveting history of this unfamiliar outbreak, *Black Death at the Golden Gate: The Race to Save America from the Bubonic Plague*, takes us into familiar terrain: arguments over media influence, government-supplied information, and the legitimacy of scientific research, particularly as it applies to medicine and the current vaccination debate. The author, a reporter at Reuters, scoured old newspapers and scholarly books and journals, parlaying that research into a straightforward narrative for nonspecialized readers. The result is edifying without being overbearing—a palatable book about plague. Many readers will find it a surprising—and hair-raising—chapter in American history, one that contains lessons of the "doomed to repeat it" variety.

◆

In December 1899 the plague made landfall in a Hawaii still 60 years from statehood. After several deaths among Chinese immigrants the local board of health quarantined Honolulu's Chinatown, trapping 10,000 residents within an eight-block space patrolled by armed guards. Many people, including some doctors, believed Asians were carriers of this strain of plague, writes Randall, a reminder of the extreme anti-Chinese sentiment of the time.

When the disease spread beyond the barrier to a white teenager who subsequently died, the panicked board turned to a more drastic solution—purification by fire—and burned down an apartment complex that had housed 85 Chinese, Japanese, and Hawaiian residents. The officials were attempting to re-create London's Great Fire of 1666 but on a smaller scale. That fire was widely believed to have hastened the plague's end while reducing most of London to ash. In Honolulu burning down a couple of buildings thought to harbor germs didn't have the same effect. Though doctors had recently identified the rod-shaped bacterium *Yersinia pestis* as the source of plague, there was no consensus on how the disease spread. Nevertheless, Hawaii's health officials remained undeterred. So as the plague claimed more victims, the officials responded by setting fire to more structures. In January a wayward ember sparked a chaotic, 18-day blaze, which finally stemmed the epidemic.

At least one American doctor was paying close attention to Hawaii's plight. Joseph Kinyoun had been reassigned to San Francisco's Marine Hospital Service only six months earlier. His boss, Surgeon General Walter Wyman, jealous of Kinyoun's rising star in public service, had him shipped cross-country to run the nation's largest quarantine station, which sounds impressive but wasn't. Angel Island, in San Francisco Bay, was short of potable water, littered with garbage, and ill-equipped for medical research—a humiliating setting for a man who was the very definition of a lab rat. Kinyoun was a pioneer in the field of bacteriology at a time when many doctors had little faith that lab research could ever help patients. He knew that *Y. pestis* would somehow hop from Honolulu to San Francisco—what mattered was whether they had the resources to stop it in time, which he doubted.

Kinyoun was a prickly man, and he had already bristled when San Francisco's board of health and its coroner had disagreed with him over the cause of death of two sailors. So when a Chinese immigrant named Wong Chut King died in March 1900 after showing signs of bubonic plague—specifically painful, swollen lymph nodes called buboes that appear in the groin or on the neck—Kinyoun and the board of health were again set for confrontation. City officials refused to wait on Kinyoun's painstaking identification of the bacterium and quarantined 20,000 residents of Chinatown. One newspaper, calling the disease "largely racial," informed its white readers that there was no cause for concern, adding that "the most dangerous plague which threatens San Francisco is not of the bubonic type" but instead "a plague of politics." The *San Francisco Chronicle* likewise viewed the quarantine as a scheme by officials at the board of health to boost their budget appropriation. That corruption was rampant from the mayor on down was true, Randall writes, but it was also true that Wong had died from plague; Kinyoun's lab results—and dead lab animals—didn't lie.

As local officials played down the threat of plague to protect interstate trade and travel, city physicians also rebuffed Kinyoun's professional opinions, reporters mocked him, and even Wyman, his lily-livered boss, caved to political pressure and withheld his support. But then more bodies began turning up, abandoned in alleyways and boardinghouses. The city responded with inspections in Chinatown that were at best demeaning and at worst violent. When these same officials came around with an experimental vaccine made with plague cells sourced from cadavers, many Chinese residents believed it to be an attempt to poison them, a fear that continues to underpin antivaccination movements, most recently in the United States (measles) and in Africa (Ebola).

WELLCOME COLLECTION

A plague-infested rat descends a ship's mooring rope in this illustration by Albert Tarter, ca. 1940s, from an unfinished educational film about bubonic plague.

Marine Hospital Service workers clean up a cluttered San Francisco backyard, ca. 1907–1908.

Kinyoun continued to push for vaccination as well as health screenings for those leaving California by sea and rail. The Chamber of Commerce tried to dissuade Kinyoun through bribes and coercion, but he dug in his heels and as a result made lots of enemies. The press began referring to him as "Suspicious Kinyoun." He even caught flak from the president of the United States, William McKinley, a man easily swayed by both congressional delegates and the owner of the *San Francisco Call*, a wealthy Republican influencer who wanted Kinyoun to stand down.

As the naysayers tried to control the narrative, the plague worsened, and a commission of local doctors verified Kinyoun's findings. Meanwhile, California's governor, along with steamship and railway executives, persuaded a group of newspaper editors to maintain a complete news blackout on the commission's report while the city and state quietly agreed to fund a "full sanitation campaign in Chinatown." Wyman, in cahoots with the crooked governor, had Kinyoun transferred out of the city.

But news of the plague had begun to leak, first in a medical journal, then in the *Sacramento Bee*, and finally in national newspapers. San Francisco's papers remained silent, except for bashing bacteriology or insulting Kinyoun's successor, Rupert Blue. The *San Francisco Chronicle* went as far as congratulating the city on refusing "the baseless allegations of the men who attempt to make the world believe that it is necessary to use microscopes to discover an epidemic."

Blue was facing an uphill battle, but he approached the problem differently: instead of insulating himself he set up a lab in Chinatown. He talked to its residents and walked its streets, finding piles of rotting meat, sewage, and dead and dying rats. When a second white victim surfaced, Blue contemplated those rats. As Randall observes, "The link between a widespread die-off of rats and the arrival of plague has been obvious since antiquity," but evidence for transmission by infected fleas jumping from dead rats to living humans was less than certain. At the time many physicians, including Surgeon General Wyman, didn't accept the theory, believing instead that filth—urine and feces—was the primary vector of the disease.

Given such assumptions and a new mayor who vociferously denounced the board of health and any reports of plague, Blue did what little he could. He managed a citywide cleanup in 1903 that included soaking Chinatown's cellars with carbolic acid, laying asphalt sidewalks, tearing down shacks and lean-tos, and trapping rats. Randall believes it unlikely that Blue knew about the work of Paul-Louis Simond, the French physician who had linked rat fleas to plague transmission in the 1890s; instead Blue concentrated his efforts on catching, killing, and dissecting rodents. This was, writes Randall, "the first time in American history that a federal health officer had focused on killing rats as a way to combat a crisis."

The plague wore on slowly but steadily, with more than 100 deaths by early 1905, but then it seemed to disappear. Even the 1906 earthquake that leveled much of San Francisco and forced its citizens into unsanitary refugee camps failed to summon the dreaded disease. But in May 1907 the plague returned and claimed several white victims. Blue ramped up rat exterminations, dispatching as many as 13,000 in a week. He found that 1.5% of them were infected (2% was considered the tipping point for setting off a pandemic). A desperate Blue met with the owner of the city's largest paper, the *San Francisco Chronicle*, and begged him to inform his readers about the plague and the role of rats. The publisher remained unmoved.

The apathy didn't end there. The California State Medical Society decided it should, quite belatedly, organize a summit to discuss the threat of plague. Only 10% of its members showed up, and those who did merely passed a resolution calling on the mayor to back rat eradication. Only the threat of losing a visit from the Great White Fleet, a display of U.S. Navy battleships that would bring both tourism dollars and prestige to the city, finally got most of San Francisco's bigwigs on board with funding Blue's cleanup efforts.

The death toll for San Francisco's second wave of plague reached 65, and yet when compared with the mass deaths in India or Hong Kong, the city had been fortunate. But why? The most common flea in the city was a Northern European species, *Ceratophyllus fasciatus*, which, when it bites, injects less bacteria from its gut into its host than does its Asiatic cousin, *Pulex cheposis*. "The slow spread of the disease—a phenomenon that led the city to doubt Kinyoun's warnings and call the epidemic a fake ploy by corrupt health officials—had hinged on the stomach of a flea, a lucky quirk that spared an untold number of lives," Randall writes.

Bubonic plague has never been fully stamped out in the United States. Infected rats and squirrels made their way out of San Francisco into greater California and beyond. When the plague turned up in a poor section of Los Angeles in 1924, the police quarantined 2,500 Mexican Americans, and, as in San Francisco, the press held off on confirming the facts. Latinos were fired from their jobs, their neighborhoods were cordoned off, and their homes were burned down. If any lessons about medical misinformation had been learned in San Francisco, Los Angeles seemed oblivious to them. The outbreak, which killed 40 people, was ultimately traced to one dead rat.

The rash of plague deaths in Los Angeles 95 years ago was the last of its kind on American soil, and while it's true that each year about seven people in the United States still contract this medieval-sounding disease, modern medicine in the form of antibiotics and factual public health information can save us. If we let it. Recent history shows that when it comes to public health, disinformation continues to sway people, from the AIDS epidemic of the late 20th century to the anti-vaccination movement of the early 21st. Moreover, as in San Francisco during its plague years, reporting of contagious diseases can be lax when tourism dollars are at stake. Cuba's Zika virus outbreak in 2017 may be a case in point.

Rebecca Rego Barry writes about history, literature, and culture and is the author of Rare Books Uncovered: True Stories of Fantastic Finds in Unlikely Places.

A fire set by public health officials burns through Honolulu's Chinatown, ca. January 1900.

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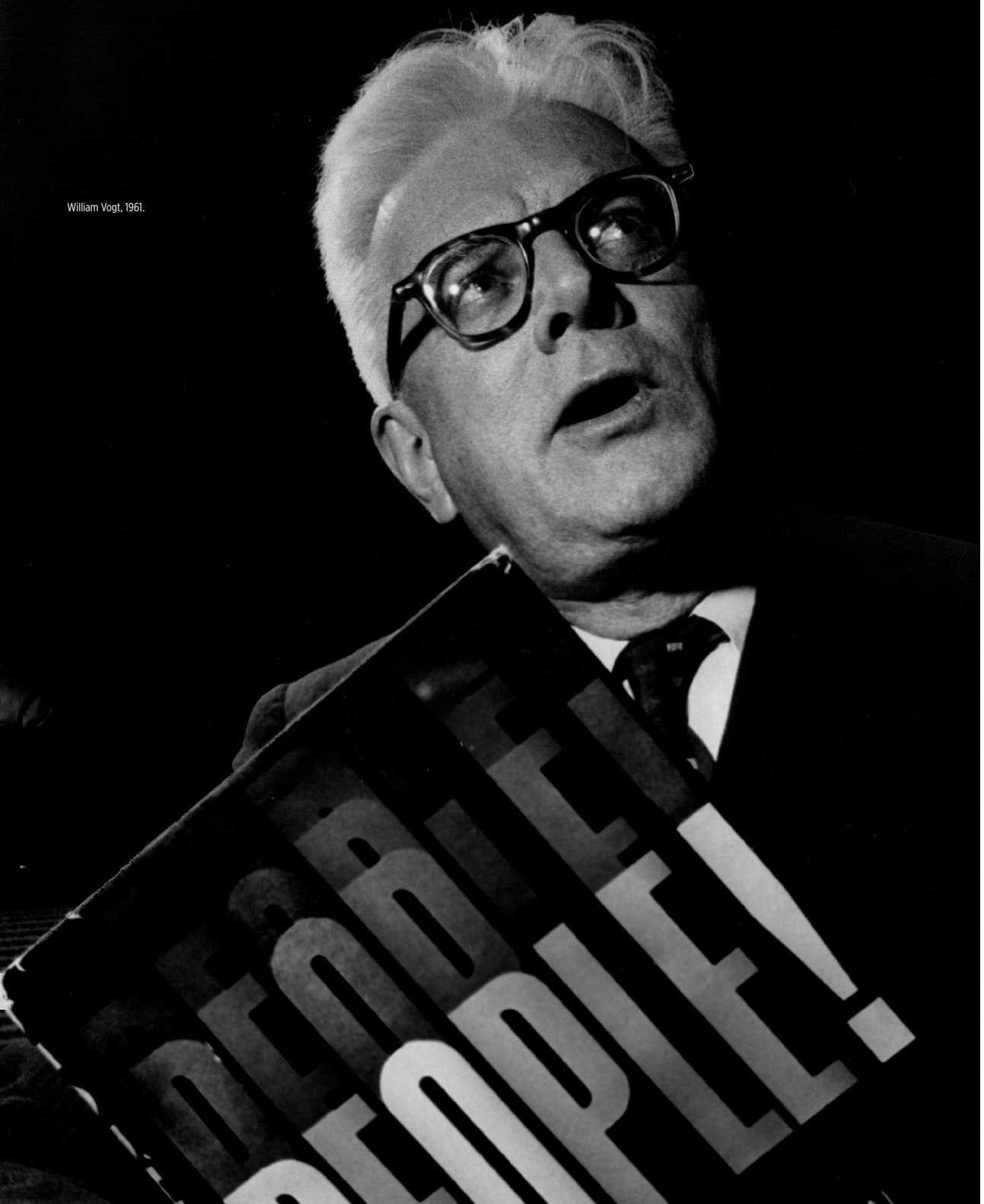


William Vogt, 1961.

DENVER POST VIA GETTY IMAGES

Where Lies Humanity's Salvation—Conservation or Innovation?

Charles Mann's latest book traces how scientists William Vogt and Norman Borlaug took very different approaches to feeding the world and how their feuding ideas anticipated today's environmental debates.

BY SARAH REISERT

Not long ago my running buddy and I were walking to the start line of the Long Island Half Marathon when we passed a fenced-in grassy area. I assumed it was just a retention pond, but when I rounded the corner, a sign rose above the chain-link fencing. The Hempstead Plains, it read.

The Hempstead Plains? The Hempstead *Plains*? I grew up on Long Island and had never heard of us having any plains. I stood among the runners on the eight-lane road that curved around the Nassau Coliseum, an Ayers Rock rising above a stretch of parking lots, and racked my brain. What could this area have looked like before Long Island's suburban sprawl swallowed it with an asphalt sea?

While today only a few acres remain, the Hempstead Plains once stretched for 60,000 acres clear across Nassau County and into neighboring Queens and Suffolk Counties. One of the few natural prairies east of the Allegheny Mountains, it was covered in native grasses and filled with birds. The prairie, originally surrounded by oak forests, had civilization pressing on its borders by the early 20th century. In 1902, in one of the towns flanking the plains, William Vogt entered this world.

A shy and solitary child, Vogt spent many of his early years exploring the mostly untouched Hempstead Plains. "I learned the pleasures of solitude," he said, "the unbroken freedom to see, smell, and listen. These hours alone, though never many at a time, nonetheless sensitized me to the open countryside and prepared me for the enjoyment of winds and skies, plains, mountains, forests and the sea, for the rest of my life." Memories of this time sustained Vogt when his family moved to the congestion and concrete of Brooklyn. When he contracted polio at Boy Scout camp at age 14, long walks became impossible, and he switched to birdwatching.

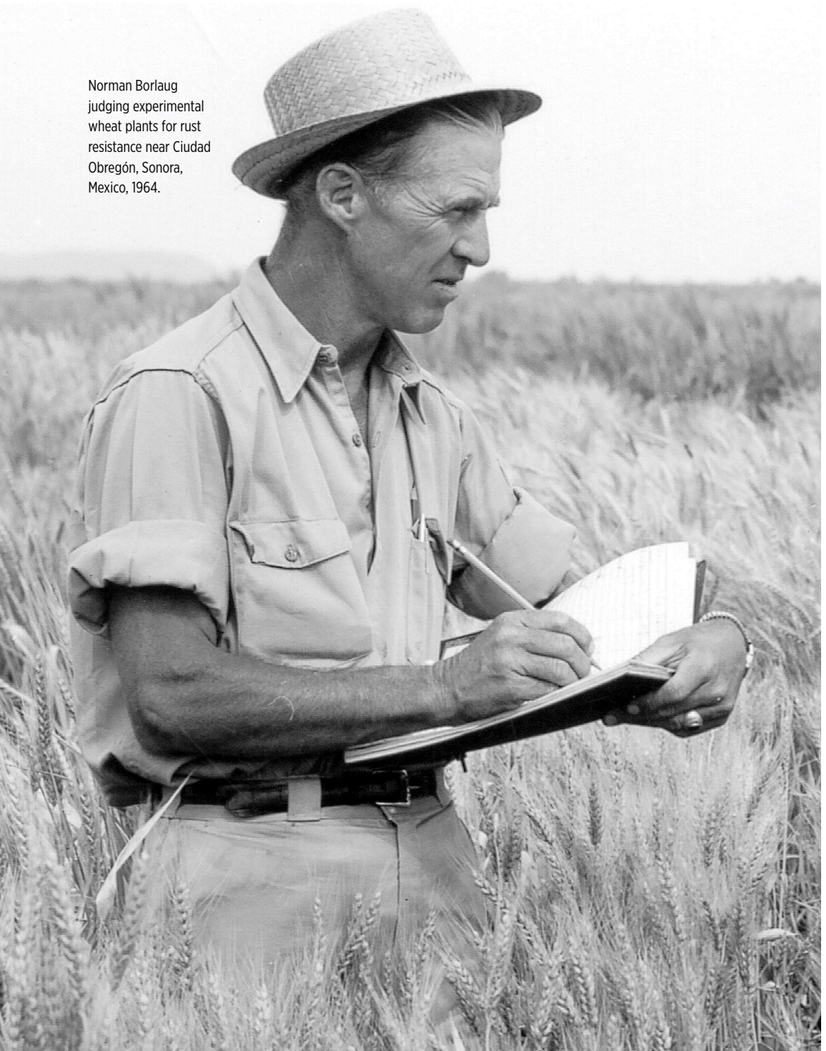
Vogt's love of birding led him to jobs at bird sanctuaries and in the ornithology department of the American Museum of Natural History. Around this time he began to notice the damage modern civilization was wreaking on his beloved wild spaces. In the 1930s drainage ditches were slashed into the marshes and wetlands across Long Island and elsewhere to help control mosquitoes and malaria; Vogt watched in dismay as the birds fled. He used his soapbox as editor of the Audubon Society's journal to rail against these destructive practices and to rally his fellow birdwatchers to fight the good fight and become stewards of the environments in which their favorite creatures lived. Vogt's rants annoyed people who thought they had signed up for a newsletter about birdwatching, and the society soon showed Vogt the door. But he had found his calling: protecting the delicate balance that supports life on Earth.

CHARLES C. MANN. *The Wizard and the Prophet: Two Remarkable Scientists and Their Dueling Visions to Shape Tomorrow's World.* Knopf, 2018. 640 pp. $29.

William Vogt is one of two scientists Charles C. Mann profiles in *The Wizard and the Prophet: Two Remarkable Scientists and Their Dueling Visions to Shape Tomorrow's World*, a book whose origin dates to the birth of Mann's daughter and his worries about her future on an increasingly crowded planet. "Is the world big enough, rich enough for all these people to flourish?" the author asks. "Or have I brought my children into a time of general collapse?" In search of an answer Mann uses the contrasts between his two scientists to illustrate two very different approaches to looming ecological crises.

Vogt is the book's titular prophet, warning the sinful to change their destructive ways before it's too late. "In particular," writes Mann, "[Vogt] founded . . . 'apocalyptic environmentalism'—the belief that unless humankind drastically reduces consumption and limits population, it will ravage global ecosystems. In best-selling books and powerful speeches, Vogt argued that affluence is not our greatest achievement but our biggest problem. If we continue taking more than the Earth can give, he said, the unavoidable result will be devastation on a global scale. *Cut back! Cut back!* was his mantra."

The wizard in Mann's tale—and the counter to Vogt—is agricultural scientist Norman Borlaug, whose early life shaped his worldview as much as the Hempstead Plains shaped Vogt's. Borlaug, who was born in 1914, grew up on an impoverished farm in Saude, Iowa. His family had picked the town for its close-knit Norwegian community rather than the quality of the soil, which was shallow and badly drained. Mann paints a bleak picture: "The wet conditions fostered crop diseases; stem rust attacked wheat so often that most local farmers, the Borlaugs among them, gave up planting it. Poor soil translated into poverty for all and early death for many." Yet farming remained the residents' way of life, and Borlaug spent much of his childhood struggling along with his family, harvesting corn by hand, the sharp leaves slicing through his clothes and leaving him bleeding.



Norman Borlaug judging experimental wheat plants for rust resistance near Ciudad Obregón, Sonora, Mexico, 1964.

CIMMYT

Life changed dramatically when his family scratched together enough to buy a tractor. The Borlaugs no longer needed draft animals to pull plows, so the land devoted to growing feed (half the farm!) could now be planted with crops. "The extra production meant extra money," writes Mann, "which allowed [Borlaug's father, Henry] to buy more fertilizer and better seed, further increasing production. Ultimately, Henry's harvest quadrupled—on the same land." This impressed on young Norm the near-miraculous capabilities of technology to improve people's lives, and he devoted his career to making sure farmers could always grow enough food. It's estimated his work on disease-resistant crops prevented a billion deaths, and it won him the 1970 Nobel Peace Prize. If Vogt's mantra was "Cut back or everyone will lose!" Borlaug's rallying cry was "Innovate so everyone can win!"

Many scientists today could well be classified as wizards or prophets by their response to humanity's impact on the world. While each camp has its own set of noble goals, Mann shows how these goals operate at cross-purposes. Why would we cut back if we can always engineer ourselves out of our problems? But what if the solutions end up causing more problems than they solve? "Wizards view the Prophets' emphasis on cutting back as intellectually dishonest, indifferent to the poor, even racist (because much of the world's hungry are non-Caucasian). Following Vogt, they say, is a path toward regression, narrowness, and global poverty," writes Mann. In return, "Prophets sneer that the Wizards' faith in human resourcefulness is unthinking, scientifically ignorant, even driven by greed (because remaining within ecological limits will cut into corporate profits). Following Borlaug, they say, at best postpones an inevitable day of reckoning."

Which camp is right? Mann ponders the answer by taking four big problems facing humanity—food shortages, dwindling freshwater supplies, surging energy consumption, and climate change—and examines them through the eyes of wizards and prophets. These are difficult challenges being tackled by passionate people who don't always agree on the best way to fix a given situation.

Take, for example, nitrogen fertilizer. The Haber-Bosch process takes nitrogen out of the air and turns it into ammonia for fertilizer, a feat that makes it perhaps the most important industrial process of the 20th century. Its success has quadrupled the productivity of agricultural land, a definite win for the wizards! "Think of the deaths from hunger that have been averted," writes Mann, "the opportunities granted to people who would not otherwise have had a chance to thrive, the great works of art and science created by those who would have had to devote their lives to wringing sustenance from the earth. Particle accelerators in Japan, Switzerland, and Illinois; *One Hundred Years of Solitude* and *Things Fall Apart*; vaccines, computers, and antibiotics; the Sydney Opera House and Stephen Holl's Chapel of St. Ignatius . . . How many would exist if this Wizardly triumph had not produced the nitrogen that filled their creators' childhood plates?"

But the sudden abundance of food enabled a worldwide population explosion (arguably problem number 1) and dumped tons of nitrogen into Earth's waterways as farm runoff, encouraging the growth of algal blooms that deplete oxygen and leave vast dead zones in their wake (problem number 2). Sure, nitrogen fertilizer allowed many people to live who might not have otherwise, but aren't we just hastening the day of our own annihilation by wizardly side effects? Heed our warnings, cry the prophets! Destroy the land and you destroy yourselves! Organic farming is the way to go! Will it produce as much food as scientifically enhanced farming? To prophets that's not the point: "To their minds," writes Mann, "evaluating farming systems wholly in terms of calories produced . . . is a perfect example of the flaws of reductive thinking. It does not include the costs of overfertilization, habitat loss, watershed degradation, soil erosion and compaction, and pesticide and antibiotic overuse; it doesn't account for the destruction of rural communities; it doesn't consider whether the food is tasty and nutritious."

Just as contentious as food supply is freshwater supply. Only 2.5% of Earth's water is fresh water, and of that more than two-thirds is locked up in ice caps and glaciers. Most of what's left is groundwater, which is largely unusable or inaccessible. Despite these limitations the fresh water still available to us is more than we need, but it's not evenly distributed around the globe. "Brazil, which has one-sixth as many people as India, has more than four times as much water," writes Mann. "The total supply is enough for both nations, but there is no way to distribute it from one to the other."

Wizards and prophets disagree on how to deal with this problem. Wizards see opportunity. Desalination plants! Water pipelines! Expanded dams! Prophets, naturally, have other thoughts. Desalination plants, for instance, are energy hogs that pollute the sea and kill marine life with the salt they discharge. Prophets, writes Mann, will point to "an array of small-scale changes that mostly involve nudging people and businesses to change their habits and become more efficient." That's all well and good, say the wizards, but explain how those ideas will work in a region already short of water?

It's unlikely either side will convert the other. And for his part Mann refrains from passing judgment on which approach offers the best way forward. By his own admission he waffles between the two ideologies. Likely some combination of prophecy and wizardry will be the key to making Earth a welcoming home for however many humans come to inhabit it.

Mann closes his book by describing the later, disquieted lives of the original prophet and wizard.

Vogt wore out his welcome almost everywhere he landed. A fund-raising job at the International Union for the Protection of Nature lasted only a year because he had annoyed the U.S. State Department, one of the organization's major funders. The Conservation Foundation, which he helped found, ejected him from their advisory board. Planned Parenthood, where he served as national director, fired him. His attacks on capitalism made him a pariah in a time when communism seemed like a real threat. Vogt ultimately killed himself in 1968.

Borlaug became a target of scorn for the unintended consequences of the Green Revolution. Critics booed him at conferences for the agricultural ecosystems and drinking water spoiled by pesticides, the farmland wrecked by overirrigation and residual salts, and the high energy costs—mainly from fertilizer production—of this new way of farming. Mann presents the indictment bluntly: "Industrial-style Borlaugian agriculture is a significant contributor to air pollution and climate change."

Between 1970 and 1989, 80% of the academic studies on the Green Revolution painted the movement in a negative light, and the antipathy persisted. In 2007 political journalist Alexander Cockburn accused Borlaug of mass murder, claiming Borlaug's " 'green revolution' wheat strains led to the death of peasants by the millions." The attacks stung Borlaug, who maintained that problems were due to bad policy and administration rather than the technologies themselves. In other words, the wealthy often monopolized the benefits of the Green Revolution, while the poor suffered from its side effects.

Both Vogt and Borlaug, who died in 2009, felt that despite having given everything—their knowledge, their hard work, their entire lives—the world was ungrateful. But we'll need both of their approaches if we want the best chance at facing what's ahead. Estimates show Earth's population will reach 10 billion by the year 2050. A sizable percentage will be middle class, with the consumption level to match that status. Harvests will have to increase 50% or more in order to feed everyone. More than 4 billion people could face water shortages as early as 2025. At what point will Earth have nothing left to give despite our efforts? D

Sarah Reisert is the Science History Institute's manager of donor relations, events, and awards.

Ronald Fisher, a Bad Cup of Tea, and the Birth of Modern Statistics

A lesson in humility begets a scientific revolution.

BY SAM KEAN

In offering his colleague a cup of tea, Ronald Fisher was just being polite. He had no intention of kicking up a dispute—much less remaking modern science.

At the time, the early 1920s, Fisher worked at an agricultural research station north of London. A short, slight mathematician with rounded spectacles, he'd been hired to help scientists there design better experiments, but he wasn't making much headway. The station's four o'clock tea breaks were a nice distraction.

One afternoon Fisher fixed a cup for an algae biologist named Muriel Bristol. He knew she took milk with tea, so he poured some milk into a cup and added the tea to it.

That's when the trouble started. Bristol refused the cup. "I won't drink that," she declared.

Fisher was taken aback. "Why?"

"Because you poured the milk into the cup first," she said. She explained that she never drank tea unless the milk went in second.

The milk-first/tea-first debate has been a bone of contention in England ever since tea arrived there in the mid-1600s. It might sound like the ultimate petty butter battle, but each side has its partisans, who get boiling mad if someone makes a cup the "wrong" way. One newspaper in London declared not long ago, "If anything is going to kick off another civil war in the U.K., it is probably going to be this."

As a man of science Fisher thought the debate was nonsense. Thermodynamically, mixing A with B was the same as mixing B with A, since the final temperature and relative proportions would be identical. "Surely," Fisher reasoned with Bristol, "the order doesn't matter."

"It does," she insisted. She even claimed she could taste the difference between tea brewed each way.

Fisher scoffed. "That's impossible."

This might have gone on for some time if a third person, chemist William Roach, hadn't piped up. Roach was actually in love with Bristol (he eventually married her) and no doubt wanted to defend her from Fisher. But as a scientist himself, Roach couldn't just declare she was right. He'd need evidence. So he came up with a plan.

"Let's run a test," he said. "We'll make some tea each way and see if she can taste which cup is which."

Bristol declared she was game. Fisher was also enthusiastic. But given his background designing experiments he wanted the test to be precise. He proposed making eight cups of tea, four milk-first and four tea-first. They'd present them to Bristol in random order and let her guess.

Bristol agreed to this, so Roach and Fisher disappeared to make the tea. A few minutes later they returned, by which point a small audience had gathered to watch.

The order in which the cups were presented is lost to history. But no one would ever forget the outcome of the experiment. Bristol sipped the first cup and smacked her lips. Then she made her judgment. Perhaps she said, "Tea first."

They handed her a second cup. She sipped again. "Milk first."

This happened six more times. Tea first, milk first, milk first again. By the eighth cup Fisher was goggle-eyed behind his spectacles. Bristol had gotten every single one correct.

It turns out adding tea to milk is not the same as adding milk to tea, for chemical reasons. No one knew it at the time, but the fats and proteins in milk—which are hydrophobic, or water hating—can curl up and form little globules when milk mixes with water. In particular, when you pour milk into boiling hot tea, the first drops of milk that splash down get divided and isolated.

Surrounded by hot liquid, these isolated globules get scalded, and the whey proteins inside them—which unravel at around 160°F—change shape and acquire a burnt-caramel flavor. (Ultra-high-temperature pasteurized milk, which is common in Europe, tastes funny to many Americans for a similar reason.) In contrast, pouring tea into milk prevents the isolation of globules, which minimizes scalding and the production of off-flavors.

As for whether milk-first or tea-first tastes better, that depends on your palate. But Bristol's perception was correct. The chemistry of whey dictates that each one tastes distinct.

Bristol's triumph was a bit humiliating for Fisher—who had been proven wrong in the most public way possible. But the important part of the experiment is what happened next. Perhaps a little petulant, Fisher wondered whether Bristol had simply gotten lucky and guessed correctly all eight times. He worked out the math for this possibility and realized the odds were 1 in 70. So she probably could taste the difference.

But even then, he couldn't stop thinking about the experiment. What if she'd made a mistake at some point? What if she'd switched two cups around, incorrectly identifying a tea-first cup as a milk-first cup and vice versa? He reran the numbers and found the odds of her guessing correctly in that case dropped from 1 in 70 to around 1 in 4. In other words, accurately identifying six of eight cups meant she could probably taste the difference, but he'd be much less confident in her ability—and he could quantify exactly how much less confident.

Furthermore, that lack of confidence told Fisher something: the sample size was too small. So he began running more numbers and found that 12 cups of tea, with 6 poured each way, would have been a better trial. An individual cup would carry less weight, so one data point wouldn't skew things so much. Other variations of the experiment occurred to him as well (for example, using random numbers of tea-first and milk-first cups), and he explored these possibilities over the next few months.

Now this might all sound like a waste of time. After all, Fisher's boss wasn't paying him to dink around in the tearoom. But the more Fisher thought about it, the more the tea test seemed pertinent. In the early 1920s there was no standard way to conduct scientific experiments: controls were rare, and most scientists analyzed data crudely. Fisher had been hired to design better experiments, and he realized the tea test pointed the way. However frivolous it seemed, its simplicity clarified his thinking and allowed him to isolate the key points of good experimental design and good statistical analysis. He could then apply what he'd learned in this simple case to messy real-world examples—say, isolating the effects of fertilizer on crop production.

Fisher published the fruit of his research in two seminal books, *Statistical Methods for Research Workers* and *The Design of Experiments*. The latter introduced several fundamental ideas, including the null hypothesis and statistical significance, that scientists worldwide still use today. And the first example Fisher used in his book—to set the tone for everything that followed—was Muriel Bristol's tea test.

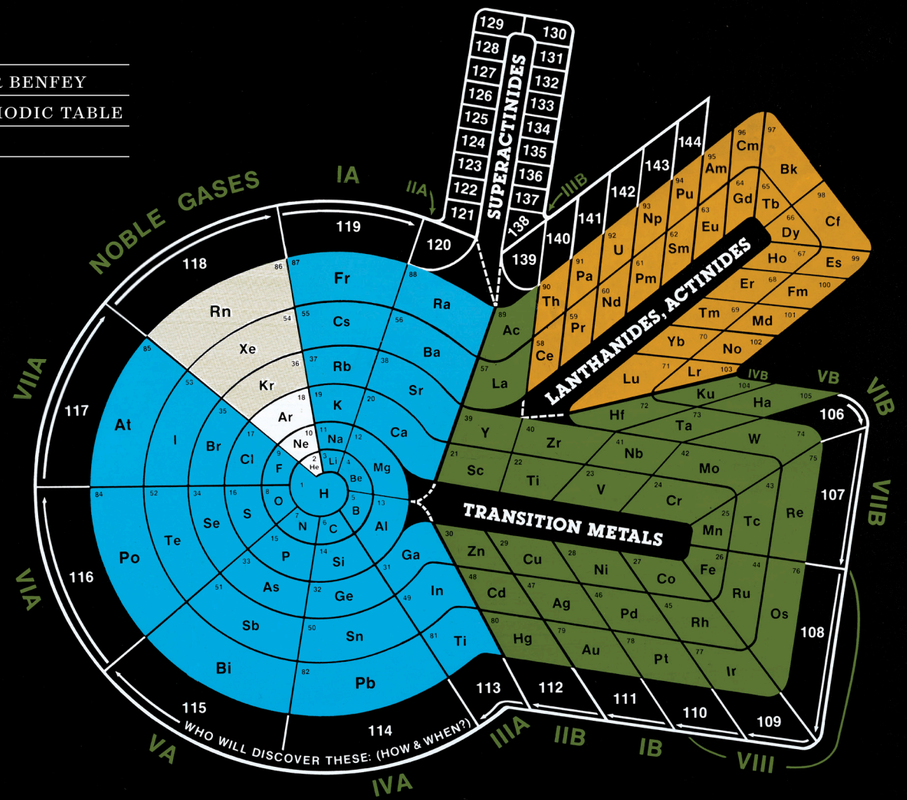
His intellectual acumen, however, did not insulate Fisher from the prejudices of his time when it came to class, race, and colonialism. Fisher was a well-known eugenicist and was steadfast in those beliefs throughout his life. When, in the aftermath of World War II, UNESCO formed a coalition of scientists to wrestle with Nazi science and provide the scientific backbone for the universal condemnation of racism, Fisher was among those who officially objected to what he saw as the project's "well-intentioned" but misguided mission, affirming his belief that groups differed "in their innate capacity for intellectual and emotional development."

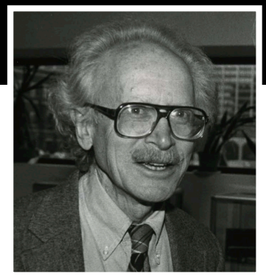
But such convictions have done little to tarnish Fisher's legacy. He became a legend in biology for helping to unite the gene theory of Gregor Mendel with the evolutionary theory of Charles Darwin. But his biggest contribution to science remains his work on experimental design. The reforms he introduced are so ubiquitous that they're all but invisible nowadays—the sign of a true revolution. D

Advertisement for Dutch tea company Van Nelle, ca. 1929.

MEMORY OF THE NETHERLANDS/RECLAMEARSENAAL

WHO: O. THEODOR BENFEY
WHAT: SPIRAL PERIODIC TABLE
WHEN: 1970





Ted Benfey in 1993.

The periodic table, which arrived 150 years ago, was a landmark achievement and the primary reason we still know the name of the man credited for its invention, Dmitri Mendeleev. The table gave a sense of order and predictability to the universe's building blocks and evolved into a clever tool. The properties and potential reactions of an element can be intuited simply by noting its location on the table. It's been amended, augmented, and expanded, and the table's prominence in the chemical practice has endured.

But Mendeleev's creation is not the only way to organize the elements, and in the intervening century and a half many have sought better visual interpretations: spiraling, lopsided helices; bulbous racetracks; teetering, zigzagging girders. One such alternative, the "periodic snail" shown here, was devised by chemistry professor and historian of science O. Theodor Benfey.

Benfey, who as a child escaped Nazi Germany, spent much of his career teaching chemistry at Quaker colleges in the United States. (Later in life Benfey would also edit an early incarnation of the magazine now in your hands.) In the mid-1950s he and colleagues at Earlham College, a small school in rural Indiana, developed novel ways of teaching chemistry, part of a larger overhaul of American scientific education that followed the Soviet launch of *Sputnik 1*. Benfey's curriculum never really caught on in the United States, but he spent the decades that followed promoting the program in Brazil, Ireland, Japan, and elsewhere around the world.

Like its ancestors, Benfey's snail table invites its audience to predict what elements will be discovered next. Published in 1970, it also, quite accidentally, speaks to the scientific gripes and rivalries of the time. The sharp-eyed observer will note that elements 104 and 105 carry symbols different from those found in today's table. The discovery and subsequent naming of these elements and others composed a minor front of the Cold War. Benfey has marked the two as kurchatovium (the Russian choice for 104, after Soviet physicist Igor Kurchatov) and hahnium (the American choice for 105, after German chemist Otto Hahn). The naming disputes wouldn't be resolved until well after the fall of the Soviet Union. D

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