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Illustrations: Shira Inbar

The Nobel Prize-Winning, LSD Dropping, Yet Problematic Scientist Who Invented PCR

'The world owes him some gratitude, but he was not pleasant'

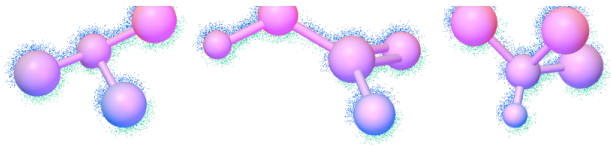
Every day, hundreds of thousands — if not millions — of molecular reactions are happening in laboratories worldwide. Small droplets of liquid that give us a lens into an individual's respiratory pathways are analyzed for whether or not they contain the pathogen of the year: SARS-CoV-2, the virus that causes Covid-19. The technique used for this analysis is called polymerase chain reaction (PCR), and it exploits the ability of genetic material to replicate. Although imperfect, it's been critical in diagnosing the disease by amplifying genes specific to SARS-CoV-2. When it's accurate, PCR helps confirm positive cases, slows the spread of infection, and allows health officials to treat individuals who have Covid-19.

In a sense, Covid-19 has popularized PCR. Over the last nine months, as the virus ballooned, PCR has transformed from a technical term used nearly exclusively by scientists — and one that would be flagged as jargon by many science editors — to one that has become a part of the general vernacular. While PCR is now well-

life by documenting the discovery of DNA in the 1950s, Kary Mullis, PhD, decoded it with PCR. Mullis came up with the idea in 1983, and a decade later, won the Nobel Prize in recognition of his work.

Without PCR, science and the world as we know it — including having a testing method for Covid-19 — wouldn't exist. "PCR is veritably synonymous with biotechnology itself," says Richard Doyle, PhD, a historian of science focusing on information biology at Pennsylvania State University. Without it, projects such as the Human Genome Project, an ambitious endeavor to understand the secrets of our genes, would not even be conceivable.

Mullis passed away last year at 74 in his home in Newport Beach, California, due to complications from pneumonia. He has frequently been described as "eccentric" and "quirky" for his open use of psychedelics, belief in astrology, and an encounter with a glowing raccoon. Some may even argue that Mullis was an unlikely Nobel laureate, a maverick. But those descriptions belie some of Mullis' more problematic aspects: He used his platform as Nobel laureate to flout that HIV causes AIDS and that climate change was real. He had a proclivity for pursuing women in his earlier days and sexually harassed a female journalist who interviewed him. Which makes one wonder: If Kary Mullis contains multitudes — as we all do — how should we remember him?



Kary Mullis was born in 1944, in Lenoir, North Carolina, a town at the foothills of the Blue Ridge Mountains.

His childhood was rife with youthful curiosities. When it was time to pick what he wanted for Christmas, seven-year-old Mullis leafed through catalogs and landed on a Gilbert Chemistry Set. "Something about tubes filled with things with exotic names intrigued me," he wrote in his memoir *Dancing Naked in the Mind Field*. "My objective with that set was to figure out what things I might put together to cause an explosion."

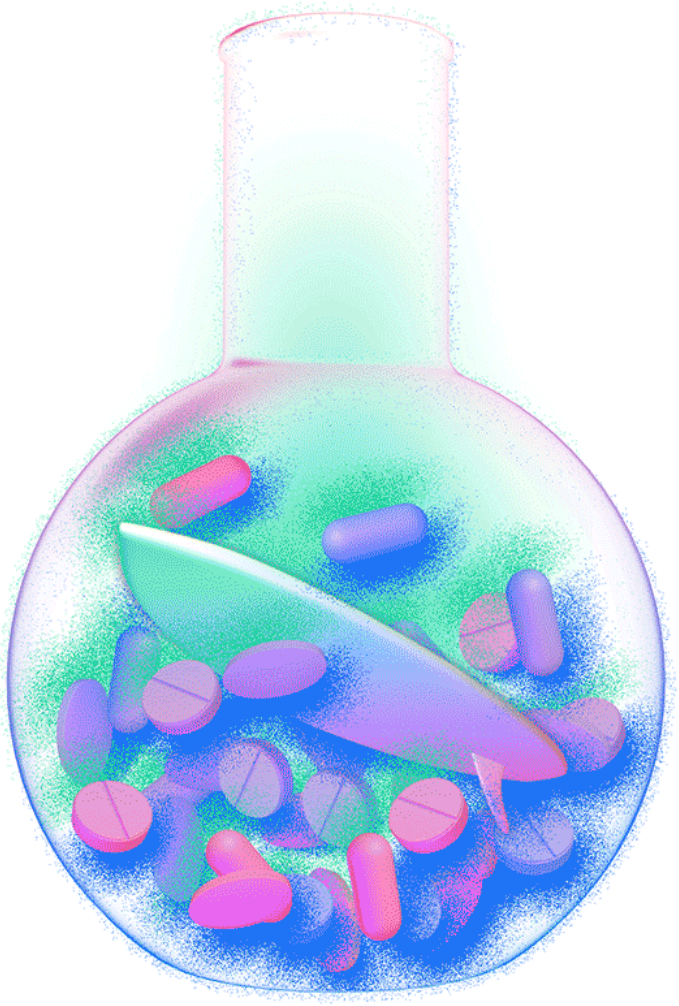
After high school, Mullis started immersing himself in the world of chemistry. His father got him a job at Columbia Organic, a supplier of research chemicals. By the time he made it to the Georgia Institute of Technology in Atlanta for college, he married Richards Haley, with whom he had a daughter. Despite his obligations to his family, Mullis was a good student and got good grades, and graduated with a degree in, fittingly, chemistry.

After college, Mullis was torn between studying biochemistry or astrophysics. He

but try discussing it at a party with a 22-year-old woman who never thought about neutral kaon decay rates," he wrote in his memoir. "Then talk to the same woman about why ethylamino derivatives of safrole like MDA will make you want to take off your clothes and feel warm and cuddly for about eight hours. A strong social impulse will lead you away from astrophysics and towards biochemistry."

Mullis moved his family across the country to Berkeley to pursue his PhD. It was the 1960s and the heyday of the counterculture revolution in the Bay Area. In his first year, Mullis befriended a man named Brad, the only guy in his class with long hair. "I figured he would have LSD," Mullis wrote. His early, mind-altering forays with LSD led him to synthesize other psychedelic chemicals in the lab — some with unexpected, bad consequences.

At Berkeley, after completing his PhD, Mullis bought a cabin in Mendocino County. Throughout the remaining years of his life, Mullis returned frequently to it. It was there that he planted trees, foraged for mushrooms, and even, according to Mullis, encountered an extraterrestrial glowing raccoon while walking outside his cabin.



After his PhD, his second wife went to Kansas for medical school, and Mullis

During his tenure at UCSF, Mullis attended a talk which described efforts to clone the gene for somatostatin, a master controller of hormones, and was inspired to delve in the world of DNA synthesis. He was hired by the now-defunct biotechnology company, Cetus Corporation, in 1979, to synthesize short strands of DNA or RNA called oligonucleotides.

The idea for PCR came to him one evening in 1983, when he and his then-girlfriend, a chemist at Cetus named Jennifer, were driving up to his cabin in Mendocino. Their relationship at that point was rocky, and Jennifer fell asleep to avoid conversation with Mullis.

The moment of discovery, as Mullis described it in his memoir, seemed psychedelic. “Lurid blue and pink images of electric molecules injected themselves somewhere between the mountain road and my eyes,” he wrote. Later on, in a BBC interview, Mullis wondered, if not for LSD, would he have been creative enough to have invented PCR? “I don’t know. I doubt it. I seriously doubt it,” he said.

To come up with the idea behind PCR, Mullis says he tapped into his understanding of computer programming. He reasoned that in order to “find” a particular segment of DNA, he needed to design DNA fragments that bookended specific gene sequences to narrow his search. And because DNA replicates under the right conditions, the isolated segment could “reproduce the hell out of itself” in an iterative fashion.

“Holy shit!” Mullis veered onto the shoulder of the road and jotted down what he just envisioned. At that moment, he knew the possible impact that this idea would have. “Everybody on Earth who cared about DNA would want to use it. It would spread into every biology lab in the world,” he wrote. He went as far as to prophesize, “I would be famous. I would get the Nobel Prize.”

In the lab at Cetus, Mullis tried to make his roadside revelation a reality. But he ran into challenges. Mullis, along with his colleagues Henry Erlich, Randall K. Saiki, Steven Scharf, Norman Arnheim, and Fred Faloona, were trying to develop an assay for diagnosing sickle cell anemia. Whereas Erlich, Saiki, and Arnheim were attempting to use PCR in human cells, Mullis and Faloona opted to try it out first in a simpler system, looking for the sickle cell anemia gene in a circular piece of DNA. When Erlich, Saiki, and Arnheim successfully detected the beta-globin gene on a gel by using a radioactive probe, Mullis struggled to get even a signal: The method he conceptualized seemed to have amplified all DNA segments, not just the very specific fragment that he was searching for.

Erlich, Arnheim, Saiki, and Scharf first figured out how to find the gene using PCR in a much more complex system. When Erlich tried giving Mullis some pointers, Mullis was sometimes unwilling to adopt these ideas. In 1985, the Cetus researchers published the first paper on the use of PCR to diagnose sickle

cell anemia, in the prestigious journal, *Science*. Although they used Mullis’ idea,

Photo: Erik Charlton

Mullis, however, still wanted to publish independently on the technique itself. But both *Nature* and *Science* rejected this manuscript. *Science*, which published the team's original 1985 paper, told Mullis that perhaps his technique paper could be published in a secondary journal. "Fuck them," Mullis thought. (The PCR paper was eventually published two years later, in *Methods of Enzymology*. Later, *Science* called PCR the "invention of the year.")

Mullis' behavior at work didn't win him any favors. He kept beer in the same fridge where he kept radioisotopes. He had conflicts with Cetus' safety officer, who he called the "danger officer." Mullis and Jennifer's volatile relationship extended into the workplace; at one point, he threatened to bring a gun into work because he thought someone was going out with Jennifer.

"He was generally a pretty difficult guy, and didn't play well with others," Erlich told *Elemental*. "But he had a great idea that had enormous consequences once it had been reduced to practice."

In 1986, just as PCR was beginning to be more widely used, Mullis quit his job at

"Hoffmann-La Roche paid Cetus Corporation for the patent rights to my PCR invention without bothering to even send me a card celebrating my 17,520th day [of life]…. Screw Cetus and the Swiss!"

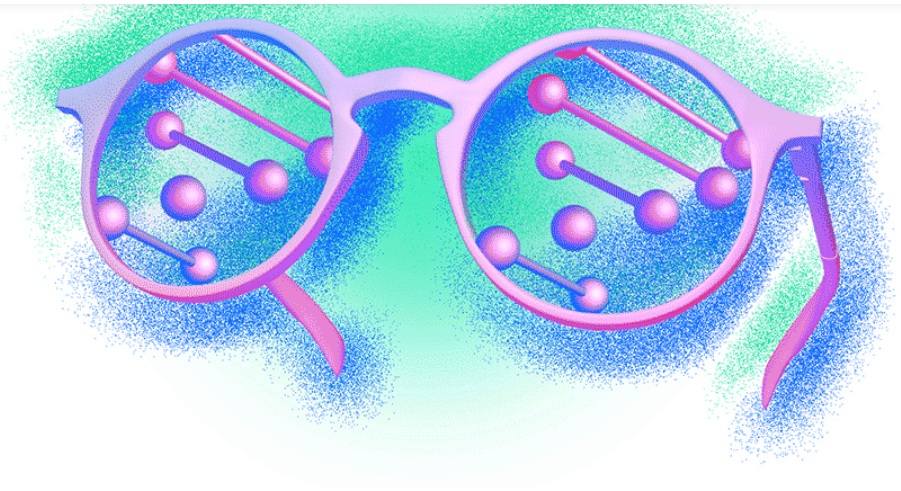
DuPont was another biotechnology company interested in buying the rights to PCR, but lost the sale to Roche. In 1991, they subsequently tried to dispute Mullis' patent for PCR, saying that PCR had already been described in the early 1970s. Despite butting heads at Cetus, Erlich and Mullis' former colleagues came together to support Mullis' case as the sole inventor of PCR.

A year later, in 1992, Mullis started getting the recognition he was seeking for his idea. In December, he arrived home to a letter from the Japanese Ministry of Technology informing him he had been awarded the Japan Prize. He spent the evening contemplating the yen to dollar exchange rate, and if he would end up rich. Then, on October 13, 1993, on his mother's birthday, Mullis received a call at the crack of dawn. When Mullis called back, the speaker on the other end said, "Congratulations, Mr. Mullis. I am pleased to be able to announce that you have been awarded the Nobel Prize."

"I'll take it!" Mullis exclaimed. Ecstatic, he hung up, called his mom, then met up with his friend, Steve Judd, to go for a celebratory surf.

A year later, Emily Yoffe, then a freelance magazine writer living in Los Angeles, heard about "the surfing scientist" winning a Nobel and pitched a profile of Mullis to *Esquire*. The magazine commissioned the piece, and Yoffe drove to La Jolla to meet with Mullis. During the interview, Mullis answered Yoffe's questions between glasses of wine, and at one point forcibly grabbed her by the neck for a kiss. Yoffe narrowly skirted him and chastised him. Mullis said, "You're missing your chance to really know me. How can you say you know me without sleeping with me?"

> The pharmaceutical company GlaxoSmithKline paid him a check of $6,048 to not speak at their annual conference.

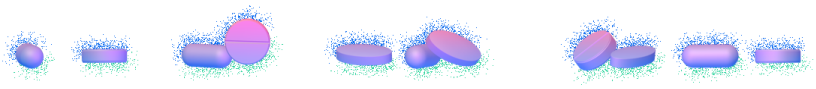


“We’re not sorry he became a scientist,” Yoffe told *Elemental*. “We wouldn’t be able to test for Covid. The world owes him some gratitude, but he was not pleasant, and was an obnoxious and outrageous person.”

After he won the Nobel, Mullis was asked to give talks around the world. But instead of talking about PCR, Mullis opted to talk about AIDS and to dispute the idea that HIV caused AIDS. (At the time, Mullis didn’t find any evidence that infection with the virus would indeed cause disease.)

“He used his clout as a Nobel laureate to promote harmful ideas,” says Angela Rasmussen, a virologist at Georgetown Center for Global Health Science and Security. “ That’s harmful in itself.”

Mullis continued to be invited to lecture after winning the Nobel, but when he made it clear that he wanted to talk about HIV and AIDS, some organizations rescinded their letters of invitation. The pharmaceutical company GlaxoSmithKline paid him a check of $6,048 to *not* speak at their annual conference.



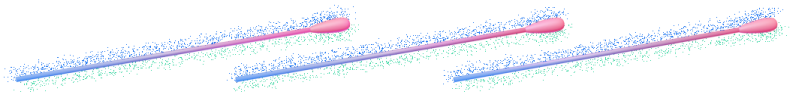
Things took a turn for the better when Mullis when he started dating Nancy Cosgrove in 1997.

The two married shortly after they got together. Nancy, Mullis’ fourth wife, says she was initially uneasy when Mullis brought up stories about his previous relationships. But Nancy says she turned Kary around: The photographs of women he had plastered on his refrigerator were taken down early into their relationship when a friend came to visit and Nancy asked for them to be removed. His surfing days died down when he and Nancy moved from La Jolla

and away from his surfing partners; Mullis didn’t like to surf alone. When they

Nancy became Kary's personal assistant, public relationships manager, travel agent, and book editor. She accompanied him as he traveled worldwide. Mullis stopped speaking about AIDS during his talks because he stopped keeping up with the field, says Nancy. Through the course of their 22-year marriage, Nancy got to revel in his punchy, dry humor, and unadulterated curiosity as he foraged and planted trees around his cabin.

In 1999, the pair moved to Newport Beach when Mullis was hired to work at a biotechnology company in Irvine. When the company collapsed, Mullis decided to revisit an old idea: redirecting immunity. With the emergence of new infectious diseases, Mullis wondered if there would be a way to use the body's existing immune responses to go after new pathogens. "Kary came up with the concept before I met him in 1997," Nancy said. "For some reason, he put it aside but didn't forget about it." This idea became reality in 2003, when Mullis brought Altermune Technologies to life, to investigate new ideas for the immune system. Altermune came up with ways to link existing immune components to molecules that would bind to new pathogens. In 2016, the technology Altermune was developing was acquired by Centauri Therapeutics.

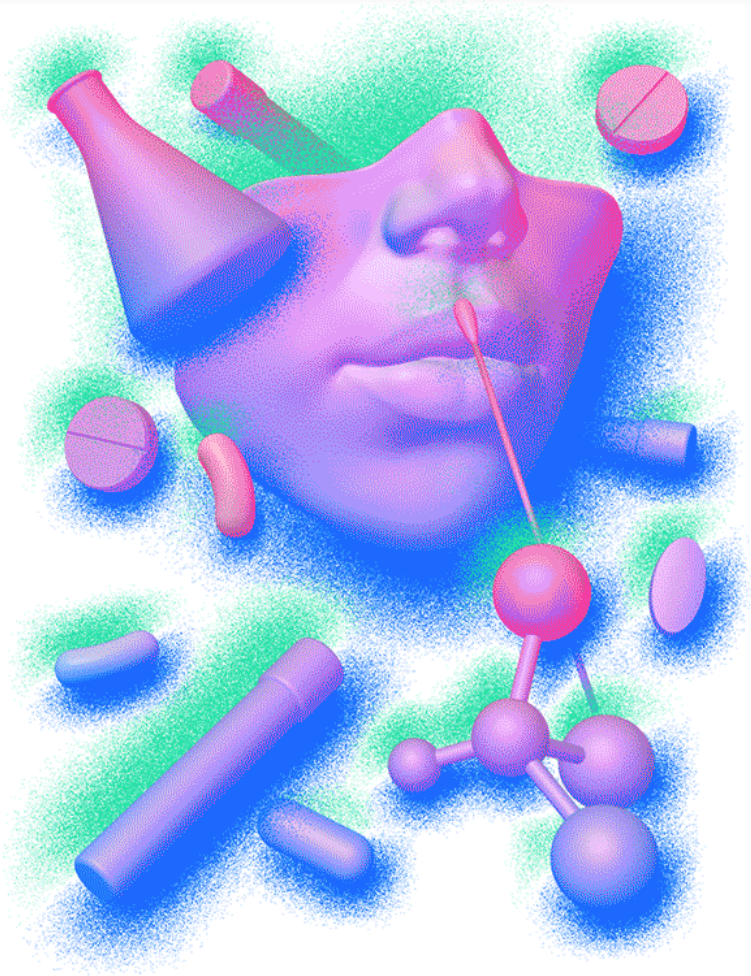


Kary Mullis had a great idea that revolutionized the world in many ways. He was also problematic in many ways. It's a complicated story that seems to repeat itself among men in science: James Watson publicly made sexist and racist comments; the renowned theoretical physicist Richard Feynman — who also won a Nobel — was misogynistic; among other examples.

"We don't get to choose where the good ideas come from," says Doyle, the historian at Pennsylvania State University. But Mullis' story is also one of change. "Just as PCR is a recursive technology, it can affect itself," Doyle says. "That's one of the qualities of consciousness: that we can affect ourselves. There isn't anything written in our genes, really. In that way, we can also affect ourselves." That, in essence, is what happened to Mullis later on in life.

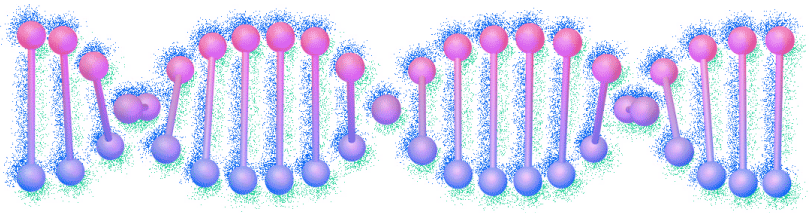
Some argue that Mullis shouldn't get all the credit for PCR. Sure, he had the idea, but he never was able to put it in practice. Other researchers stepped in and came up with key ideas to automate the process. The biggest breakthrough, arguably, came in 1993, when David Gelfand at Cetus published his work on purifying a heat-stable DNA polymerase from bacteria that thrived in the hot springs of Yellowstone National Park. This enzyme, called Taq polymerase, could help amplify DNA in a temperature-dependent way, which helped automate PCR. And around the same time, also at Cetus, it was Russell Higuchi who developed a way to make PCR quantitative, which allowed the method to determine relative

expression levels of genes, and led to tests for viral load, including that for Covid-



In his memoir, Mullis describes how the Nobel opened doors, that “it’s a free pass for the rest of your life.” But should it be? Describing Mullis primarily as quirky and eccentric, Rasmussen argues, diminishes the more problematic parts of him by not explicitly naming them as what they are: He publicly espoused false scientific ideas, and he sexually harassed women.

“When you’re a public figure, you have an obligation to be publicly accountable to redeem yourself,” argues Rasmussen. “His brilliant idea shouldn’t outweigh all the bad things. We need to look at his contributions in the context of what they were.”



This story has been updated with the correct spelling for Henry Erlich.