SCIENTIFIC AMERICAN

The Science of Empathy

A Chickadee Mystery

Hope for Sickle Cell Disease

How to Go Back to the Moon

Inside NASA's ambitious, controversial Artemis mission

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CONTENTS
OCTOBER 2024
VOLUME 331, NUMBER 3

SCIENTIFIC AMERICAN

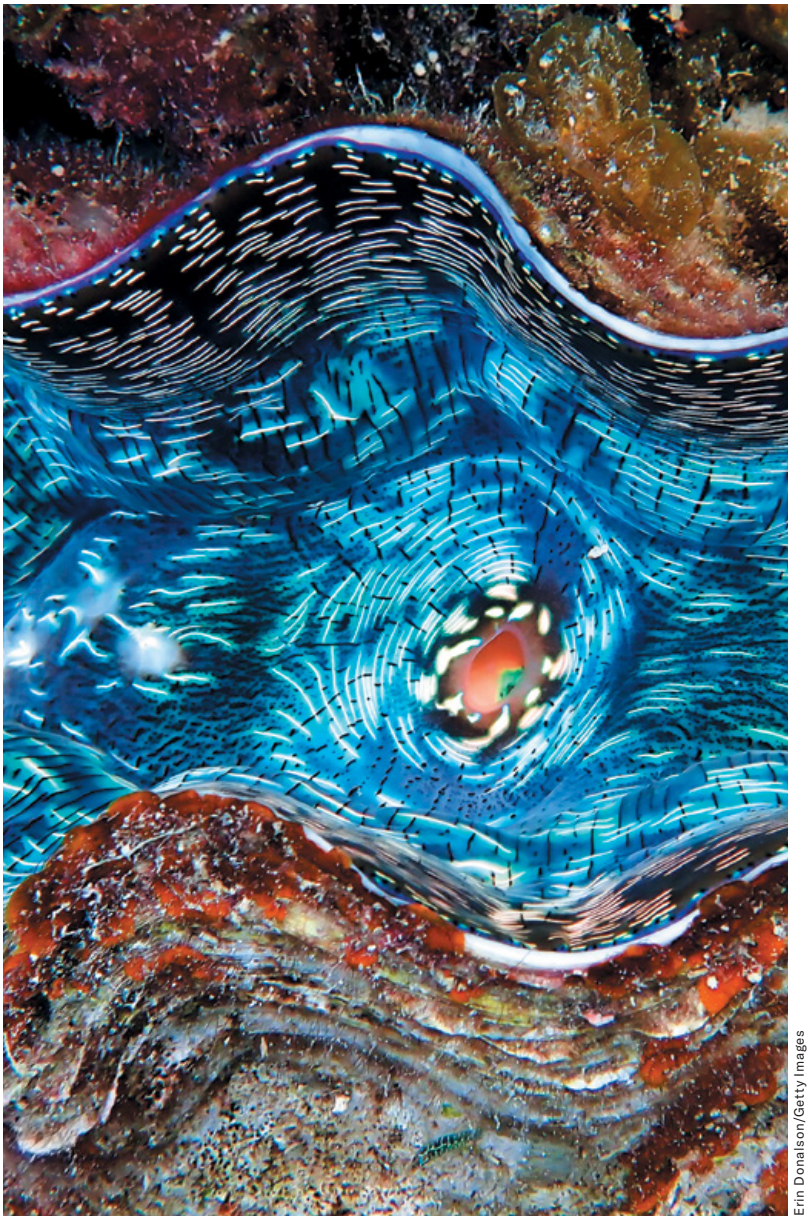
FEATURES

SPECIAL REPORT

ON THE COVER
NASA will send astronauts back to the moon for the first time in more than 50 years under its Artemis program. After delays and budget overruns, the first crewed mission is due to launch in the fall of 2025. But why has it been so difficult and taken so long to repeat the feats accomplished during the Apollo mission in the 1960s?

Illustration by Mondolithic Studios | Chris Wren and Kenn Brown

Glenn Benson/NASA



Erin Donalson/Getty Images

8

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Blurred Boundaries

THERE'S SOMETHING SPECIAL ABOUT CHICKADEES. They're curious (they'll come investigate if you make a pish-pish-pish sound), they're smart (they stash seeds to eat over the winter), and they're so stinking cute. I appreciate a bird that tells you what it is: Whip-poor-will! Bob-white! Chick-a-dee-dee-dee! And there's a lot of hidden drama in chickadees' world, as author Rebecca Heisman relates on page 36.

Multiple species of chickadees live in North America, and it can be tough to tell them apart. To complicate matters, they don't always make much of a distinction: Carolina Chickadees and Black-capped Chickadees regularly mate in the East, as do Black-caps and Mountain Chickadees in the West. (I hope this is some comfort to anybody who has struggled to identify a chickadee's species using a field guide.) Research on hybrid chickadees is revealing how species maintain their boundaries, how birds are specialized for their habitats, and how reckless pairings can occur when a new species moves into another's territory.

Our cover story this month started with what seemed like a simple question: Why is it so hard to get back to the moon? I mean, obviously rocket science is rocket science—complex, dangerous, pitiless. But we figured it out more than 50 years ago, which is eons ago in computer years. *Scientific American* contributing editor Sarah Scoles on page 20 explores the surprising technological and social reasons that the Artemis II flight, scheduled to lift off next year (but don't mark your calendar), seems so much more challenging than the Apollo missions.

Empathy is a complex skill that can improve with training—and researchers have experimented with many different types of training. Regardless of the age of participants or the different backgrounds and experiences that separate them, some patterns come through: listening and being listened to improve empathy, as do perspective taking and practice. But what really matters is motivation because empathy can be cognitively and emotionally exhausting. Supporting empathy as a social norm can make it easier and more rewarding to understand other people. Science writer Elizabeth Svoboda covers the latest science on empathy on page 30.

The opioid overdose epidemic has been one of the most horrific and deadly disasters of the century. The death rate seems to be coming down after what we hope was the peak, during the COVID pandemic. We desperately need better and more treatments for people with addiction, and author Maia Szalavitz on page 44 describes the evidence supporting a new approach. People who have experienced childhood trauma are at greater risk of addiction, and treating the trauma can be the most robust way to prevent or manage addiction.

Learning about sickle cell disease is a great way to understand the history of modern medicine, with all its triumphs and failures. It was the first disease to be understood at the molecular and genetic levels. It shaped our understanding of how evolution can influence disease. And it starkly shows how systemic bias and exclusion can impair research and health care and harm people. Finally, new treatments can now cure sickle cell disease.

Our Innovations In special report on sickle cell disease, starting on page S1, shares perspectives from patients, advocates, clinicians and scientists. It describes the newly available therapies and others in development, featuring a great series of graphics that show ingenious techniques for restoring healthy blood cells. Research on sickle cell is generating valuable insights on chronic and acute pain. And the package demonstrates that making science more inclusive and just can lead to better lives for all. ●

Laura Helmuth
is editor in chief
of *Scientific American.*

KENN BROWN AND CHRIS WREN BACK TO THE MOON, *PAGE 20*

In the 1990s Kenn Brown and Chris Wren met while working at an animation studio in Vancouver. They were both in the background department, Brown using computers and Wren using brushes and pencils. Their skills have always complemented one another, and today they are partners in business and in life, splitting their time between Canada and Nayarit, Mexico. Since 2001 their editorial illustrations—including dozens of covers—have brought a futuristic flair to *Scientific American.* Creating art at the "cutting edge" of science and technology "has actually been a great way to keep educating myself constantly," Wren says. "You must stay on your toes," Brown adds.

This month's cover story by magazine contributor Sarah Scoles on the Artemis II mission to the moon brought them back to a long-standing, shared passion for space exploration. They grew up on the technological optimism of the space race and the cultural optimism of *Star Trek: The Next Generation.* In their art, they enjoy exploring how humanity will change space—and how being in space will change humanity. "We're kind of blessed that our hobby is our living," Wren says. "A lot of the assignments that we've gotten over the past 23 years are things that we would have done anyway."

ELIZABETH SVOBODA
THE EMPATHY INCENTIVE, *PAGE 30*

Over the course of her career as a science journalist, Elizabeth Svoboda has grappled with a big question: "Why," she says, "do we follow our best instincts in some situations and follow our worst instincts in others?" Svoboda explored this question in 2013 in her first book, *What Makes a Hero?,* which is about why some people readily make sacrifices for others. And for her feature story in this month's issue, she dug into the science of empathy. As an idea, empathy "sounds great," she says, but it can be difficult to put into practice, especially when engaging with people who disagree with you in fundamental ways. "My instinct is just to get defensive and anchored in my view—just defending it at all costs," Svoboda says. She wanted to know: "Are there ways to not just teach empathy but motivate it?"

In reporting the story, she found her answer: people are inclined toward empathy when they're surrounded by an empathetic community. She traveled from her home in the California Bay Area to an elementary school in Los Angeles where parents and teachers are participating in a program to intentionally foster empathy. "It's a living experiment," she says—one that felt very different from her more *Lord of the Flies*–style experience of elementary school decades ago. "The environment is changing, and that really gives me a lot of hope."

ROXANNE SCOTT
LIVING WITH SICKLE CELL DISEASE, *PAGE S16*

Roxanne Scott was a social worker in her first career and a teacher in her second. She taught in Costa Rica, Mexico and China. Inspired by the African diaspora that she encountered in each country, she started a travel blog about the global Black experience, which inspired her third and current career as a journalist.

Scott lived in Ghana for a year during her transition to journalism, and because of frequent power blackouts, she consumed news mostly by radio. That's how she became a radio reporter focused on how climate change impacts immigrant communities. In 2021 Scott moved to Queens, N.Y., right before Hurricane Ida caused deadly flooding in New York City that especially affected marginalized groups. She has since immersed herself in reporting on ongoing flooding in these neighborhoods.

For this special report, Scott asked people whose lives have been upended by sickle cell disease to tell their stories in their own words. Gathering first-person perspectives "was right up my alley as a radio reporter," she says, and is especially important for understanding what it is like to live with the condition, which causes excruciating pain that is often overlooked because of systemic racism. Those who shared their stories "were open books," Scott says. "I think they really wanted their voices heard."

JER THORP
FATE OF THE HYBRID CHICKADEES, *PAGE 36*

During the first web boom, Jer Thorp got a job writing code—something he didn't really know how to do. He practiced by making art with software programs and in the process developed a passion for turning numbers into engaging visualizations. As a data artist, Thorp enjoys bringing information off the page or screen and into people's lives by creating physical sculptures and installations, ones that capture immigration statistics or melting glaciers.

Recently, though, Thorp's art has been all about birds. Like many people, he became an avid birder during the COVID lockdown. Even living in Brooklyn, N.Y., "there's not really a moment where you cannot find a bird," he says. For this issue's feature story about hybrid chickadees by writer Rebecca Heisman, Thorp mapped the hybrids' shifting range. He sees these two loves—of birding and of data—as fundamentally linked; he now teaches a course on them and is writing a book called *We Were Out Counting Birds.* "Birders are fundamentally data collectors," he says. Even those who don't add their observations to community science repositories are still keen observers of behavioral data. Birding, he says, "helps you learn how to notice" the natural world.

John Thorp

May 2024

FORCES THAT FASCINATE

"Nature's Strongest Force," by Stanley J. Brodsky, Alexandre Deur and Craig D. Roberts, discusses new discoveries about the strong force, the most potent of the four basic forces of nature. The article describes the strong force as constant beyond a certain distance. Presumably it eventually declines in strength. Otherwise, wouldn't it pull all matter in the universe into a really big black hole?

MIKEL D. PETTY
INFORMATION TECHNOLOGY AND SYSTEMS CENTER, UNIVERSITY OF ALABAMA IN HUNTSVILLE

The article indicates that the strong force reaches a maximum value. Can this predict the largest possible atomic nucleus? Currently up to 118 protons can be packed into an atomic nucleus, and the highest number of neutrons is much greater.

VERNON NEMITZ *VIA E-MAIL*

As a young electrical engineer in the 1970s, I was fascinated to read in *Scientific American* about the emergence of quantum chromodynamics (QCD) theory, which describes how the strong force works. The apparent nature of the strong force just seemed unreasonable; totally different from anything in electromagnetism. So I was surprised when I saw two illustrations in the article with a curve representing data relating to the strong force from the Thomas Jefferson National Accelerator Facility. The shape bears a striking resemblance to the B-H curve describing magnetization of ferromagnetic materials. Is this similarity purely coincidental, or is there some underlying principle?

MAURI LAMPI *MELBOURNE, AUSTRALIA*

THE AUTHORS REPLY: *Regarding Petty's question: A phenomenon called confinement is the solution to this conundrum. As we noted in our article, quarks have a property called color, the strong force's version of charge, and gluons have it as well. Only systems in which all colors cancel out one another can be observed in nature. Both the colored gluons and quarks are imprisoned within hadrons. Because gluons are the carriers of the strong force, their effects are active only within length scales that are bounded by a typical hadron size, which is roughly the proton radius (that is, less than one femtometer). Any leakage is carried by the color-neutral pion and kindred mesons.*

The residual strong force that these mesons mediate is also hugely important. It is largely responsible for the binding of neutrons and protons into atomic nuclei. This residual intranuclear binding force is much weaker than the strong force inside the nucleon. And although the residual strong force's reach is greater, it remains quite limited, being strongly damped at lengths greater than two femtometers.

To answer Nemitz: This is the "dream" of strong force practitioners. Today, however, it lies far beyond the bounds of computational possibility. The total number of neutrons and protons (nucleons) in a nucleus is represented by A*. Calculations with a direct connection to QCD are currently being employed in the first studies of so-called light nuclei (for example, deuteron, for which* $A = 2$*, and triton and helium 3, for which* $A = 3$*). Beyond that, effective quantum equations, built with elementary degrees of freedom among nucleons and QCD-consistent potentials, are used to explain and explore the properties of light nuclei up to* $A = 14$*. Studies that desire to reach* $A > 14$ *involve additional phenomenology and insightful theoretical approximations. Therefore, while theory may be used to describe large-*A *nuclei, it is currently unable to predict the boundaries of nuclear stability.*

In response to Lampi: The similarity between our images showing the strong force's coupling constant (α_s) *at short distances and a B-H curve (the hysteresis curve in magnetism) is that they both reflect a saturation phenomenon. The saturation occurs because the original cause of the growth comes to be suppressed. For B-H curves, saturation results when all magnetic domains become aligned with the external field.*

Regarding α_s*, it represents quantum loops involving massless gluon fields that initially cause the rise with decreasing momentum (increasing separation). Deeply locked within the physics of gluon self-interactions, however, is a mechanism that makes gluons behave as heavy particles at low momentum. Because, quite generally, it is much harder for heavy particles to make loops, the heavy gluon cannot contribute to quantum activity at momenta below the associated gluon mass scale. With nothing left to make the coupling "run," it stops running. This is the saturation seen in our article's figures.*

EXCLUSION AMONG CHILDREN

"The Inclusive Classroom," by Melanie Killen, concerns prejudice among young children and a strategy for combating it in schools. These kinds of interventions are important, but they also need to be more intersectional to address sexual orientation and disability status.

I am an 86-year-old gay, dyslexic man who was deathly afraid of being bullied

"It's critically important that kids who are rejected by their families at least feel included among their classmates."

—PETER MILLS *CLERMONT, FLA.*

and excluded for being different as a child. I was in the closet even to myself until I was 30 years old. That and dyslexia have framed my entire life from a very early age. I did everything in my power to fit in and not let people know I was different. I managed to hide who I was until I was 50 and finally had to come all the way out and separate from a lovely marriage. All this time I was scared that somebody would find out and that people would not accept me.

These two axes of identity, sexual orientation and disability status, are different from race and class in that children and their parents almost always share the same race and class. Queer children and disabled children, however, often have parents who are not queer or disabled. It's critically important for these children to feel included among their peers because they might not find that kind of inclusion and support at home. In many cases that I am familiar with, friends of mine were kicked out of supposedly upstanding and religious households when they were no more than early teenagers. Many were sent to conversion therapy, which does not appear to work and traumatizes the youngsters going through it further. For many queer kids, just mentioning their sexuality at home can be dangerous.

It's critically important that kids who are rejected by their families at least feel included among their classmates. Group exclusion doesn't happen only among one's peers; it appears in some homes and pervades our political and religious systems. It appears that many schools are not prepared to help classes be more inclusive of LGBTQ students and disabled students. I hope that these kinds of initiatives can be embraced and can help young students learn to be more inclusive of broad, intersectional identities.

PETER MILLS *CLERMONT, FLA.*

ERRATUM

"Superheavies," by Stephanie Pappas [June], should have said that Einstein's special theory of relativity suggests that objects moving at nearly the speed of light gain mass and get weird, not that his general theory of relativity does so.

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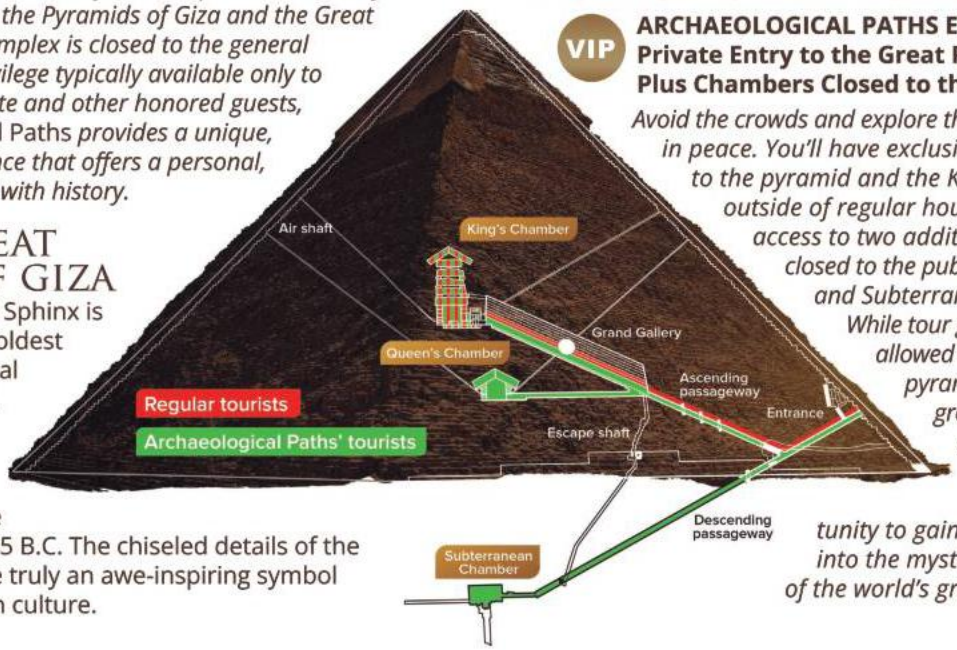
Constructed around 2500 B.C., the Great Pyramid is the last surviving member of the Seven Wonders of the Ancient World. This monumental feat of engineering took several decades to build and was the tallest human-made structure in the world for 3,800 years. The interior contains a maze of passageways and chambers just begging to be explored, yet only few have the privilege to do so.



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VIP VISITS TO UNCOVER THE SECRETS OF THE PHARAOHS

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Situated on the west bank of the Nile near modern-day Luxor, the Valley of the Kings is known to contain 65 tombs built for pharaohs and nobles. Considered the most famous collection of elaborate royal tombs, the complex includes the magnificent tomb of Tutankhamun, discovered in 1922. In 1979, the Valley of the Kings was named a UNESCO World Heritage site, and excavations are ongoing. Currently, only a few out of the 65 tombs are open to the public, but *Archaeological Paths* guests enjoy exclusive access to many more!

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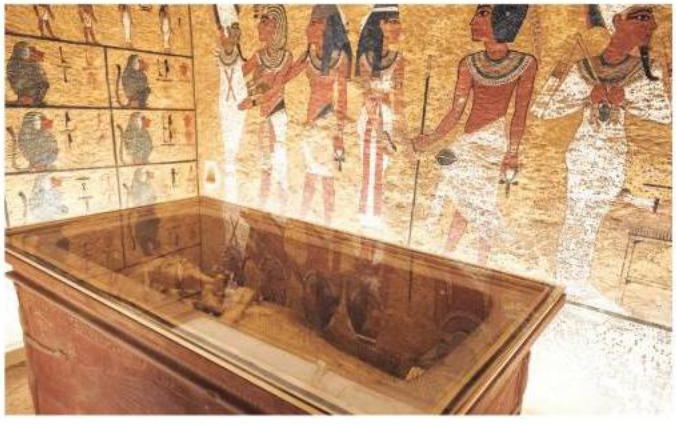

5. GRAND EGYPTIAN MUSEUM

Just north of the Pyramids of Giza lies the long-anticipated Grand Egyptian Museum, opening in late 2024. Bigger than the Louvre, it will be the world's largest archaeological museum and home to the greatest collection of ancient Egyptian artifacts, preserving 7,000 years of Egyptian history through over 50,000 pieces, about 30,000 of which have never been on display. This includes the complete collection of Pharaoh Tutankhamun's treasures—in its entirety for the first time ever.

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Explore this unprecedented assemblage of Egyptian antiquities through an exclusive VIP tour. You'll be accompanied by Dr. Tarek Tawfik, one of the Directors of the Grand Egyptian Museum Project, who will share stories about the collection and secrets that are known to few.

Archaeological Paths *guests will enjoy a private after-hours visit to Luxor Temple.*

EXCLUSIVE ENTRY TO THE ANCIENT TEMPLES

6. LUXOR TEMPLE

The majestic Luxor Temple, a UNESCO World Heritage site, is one of the greatest reflections of the pharaohs' power, and was home to the Opet Festival, the most significant religious celebration in ancient Egypt. Located on the east bank of the Nile in present-day Luxor, the temple's construction began in the 15th century B.C. and continued for several hundred years with additions by Amenhotep III, Tutankhamun and other pharaohs. From the moment you're greeted by the two colossal, seated statues of Ramses II, it's a sight to behold.

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7. KHONSU TEMPLE AT KARNAK

Not far from Luxor Temple, connected by the Avenue of the Sphinxes, lies the massive Karnak Temple Complex. The 4,000-year-old site was built over many centuries by dozens of pharaohs, and contains sanctuaries, kiosks, obelisks and other structures—including the Khonsu Temple that was built by Ramses III as a place of worship to honor the god Khonsu. It is one of the best preserved and most complete of the New Kingdom temples and remains off-limits to all but *Archaeological Paths* guests.

VIP ARCHAEOLOGICAL PATHS EXCLUSIVE: Special Access to Khonsu Temple

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— *Strive for Perfection*, Rolls-Royce Owners Club Publication

ARCHAEOLOGICAL PATHS

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WORLD'S MOST FAMOUS ARCHAEOLOGIST

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Dr. Salima Ikram
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Dr. Ashraf Mohie El-Din
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Dr. Tarek Tawfik
ONE OF THE DIRECTORS OF THE GRAND EGYPTIAN MUSEUM PROJECT

Dr. Mostafa el Feki
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Dr. Tarek el-Awady
DIRECTOR OF EXCAVATIONS AT THE "LOST GOLDEN CITY"

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Dr. Mostafa Waziri unveiling a new discovery at Karnak Temple to Archaeological Paths' guests.

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In 2021, when Dr. Zahi Hawass found the **Lost Golden City**, guests were able to visit the site before the discovery was even announced to the public! As the largest ancient city to be discovered, the "Lost Golden City" is regarded as the second most important archaeological find in Egypt, after Tutankhamun's tomb.

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— Gregory Poplawski, CEO of *Archaeological Paths*.

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It's estimated that only 35 to 40 percent of ancient Egyptian relics have been discovered, so there is much work to be done. To assist in finding and safeguarding these historical treasures, *Archaeological Paths* also sponsors research, excavations, and restoration efforts across Egypt.

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ADVANCES

ENERGY

Solar Seas

Giant, iridescent clams hide hyperefficient solar panels

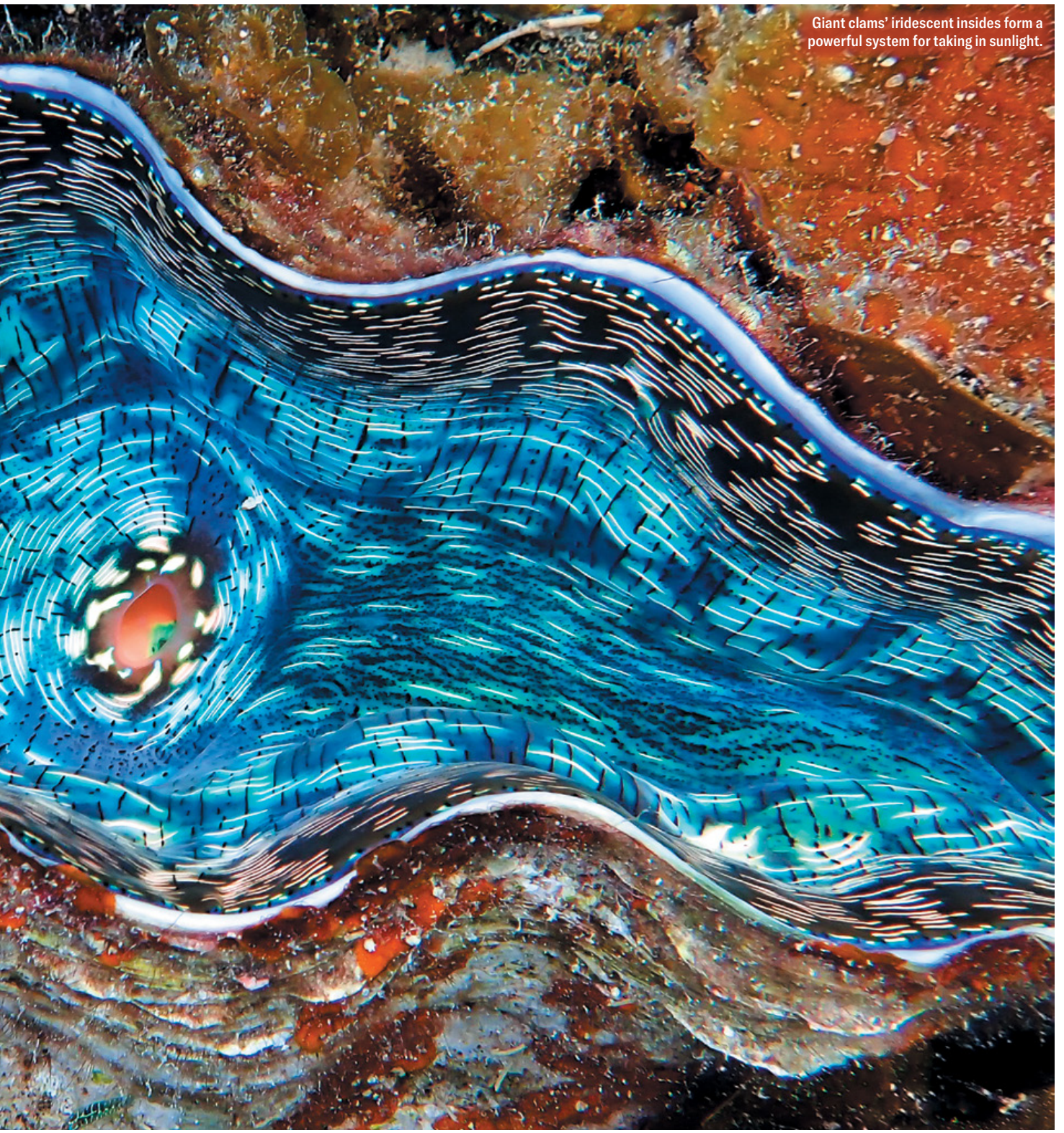
IN THE TROPICAL REEFS off Palau, an island chain east of the Philippines, lie what at first glimpse look like unremarkable (albeit huge) shallow-water clams in the genus *Tridacna*. But a peek at the undulous innards tucked between their four-foot-long shells reveals sparkly blue flesh—hosting what new research shows to be the most efficient solar panels scientists have ever found.

"The fact that nobody could explain why a clam was iridescent really just stuck with me," says Alison Sweeney, a Yale University biophysicist and co-author of the new research. In previous investigations of the distinctive sparkle, Sweeney and her colleagues determined that despite impressive iridescence, these animals' fleshy mantles reflect as little as about 5 percent of the bright sunlight hitting them.

The rest of the incoming light is absorbed, and much of it is channeled to photosynthetic algae the clams cultivate within their bodies as a food source. Absorbing around 95 percent of incoming light is a remarkably strong basis for photosynthesis; terrestrial forests such as the Amazon, for instance, absorb less light, reducing their photosynthetic efficiency from the outset. Sweeney and her colleagues also determined that specialized cells called iridocytes, which line the mantle's surface, contain neatly aligned stacks of transparent, protein-rich platelets that diffuse light while pushing it deeper inside the clam.

In research published in *PRX Energy*, Sweeney and her team studied the arrangement of the clams' symbiotic algae, which settle in tiny modified tubes extending up from the digestive system. The clam's algae form a distinctive orderly pat-

Erin Donalson/Getty Images



Giant clams' iridescent insides form a powerful system for taking in sunlight.

tern, arranged in thin columns that stretch from each iridocyte down into the flesh. "The clam basically plants them as if it were an agricultural field," Sweeney says. (The algae also travel between clams in pellets of poop.)

Sweeney's team modeled this system and calculated that its theoretical efficiency at the first step of photosynthesis, during which chlorophyll absorbs a single photon, is 43 percent—more than twice the efficiency of most current solar panels and three times that of a tropical leaf. Yet previous measurements of these clams in the wild put their comparable efficiency even higher, at more than 60 percent. In the new study, the researchers resolved this discrepancy by factoring in a quirk of clam behavior: there is evidence that clams might inflate and deflate their mantle throughout the day. This could let the clams further optimize their sunlight exposure, the scientists determined—allowing them to clock in at a modeled 67 percent efficiency.

Curious, the researchers then looked for examples of other photosynthetic systems that reflect little light and found themselves studying satellite photographs of old spruce forests. Sweeney says these images reminded her strongly of microscopic views of clam tissue. "There's an immediate, visceral, striking resemblance if you don't know the scale of the image you're looking at," she says. Like the clams' iridocytes, which scatter light inward toward algae, these forests' clouds and fog scatter

Dark Oxygen
Mysterious minerals release oxygen in the depths

OCEANS The dark seabed of the Pacific Ocean's Clarion-Clipperton Zone (CCZ) is littered with what look like hunks of charcoal. These unassuming metal deposits, called polymetallic nodules, contain metals such as manganese and cobalt used to produce batteries, marking them as targets for deep-sea mining companies.

Now researchers have discovered that the valuable nodules do something remarkable: they produce oxygen and do so without sunlight. "This is a totally new and unexpected finding," says Lisa Levin, an emeritus professor of biological oceanography at the Scripps Institution of Oceanography, who was not involved in the current research.

According to Boston University microbiologist Jeffrey Marlow, the idea that some of Earth's oxygen gas may come not from photosynthesizing organisms but from inanimate minerals in total darkness "really strongly goes against what we traditionally think of as where oxygen is made and how it's made." Marlow is a co-author of the new study, which was published in *Nature Geoscience*.

The story of discovery goes back to 2013, when deep-sea ecologist Andrew Sweetman was facing a frustrating problem. His team had been trying to measure how much oxygen organisms on the CCZ seafloor consumed. The researchers sent landers down more than 13,000 feet and created enclosed chambers on the seabed to track how oxygen levels in the water fell over time.

But oxygen levels did not fall. Instead they rose significantly. Thinking the sensors were broken, Sweetman sent the instruments back to the manufacturer. "This happened four or five times" over the course of five years, says Sweetman, who studies seafloor ecology and biogeochemistry at the Scottish Association for Marine Science. "I literally told my students, 'Throw the sensors in the bin. They just do not work.'"

Then, in 2021, he returned to the CCZ on a survey expedition sponsored by the Metals Company, a deep-sea mining firm. Again, his team used landers to make enclosed chambers on the seafloor and monitor oxygen levels. They used a different technique to measure oxygen this time but observed the same strange results: oxygen levels increased dramatically. "Suddenly, I realized that I'd been ignoring this hugely significant process, and I just kicked myself," Sweetman says.

The researchers initially thought deep-sea microbes were producing the oxygen. That idea once might have seemed far-fetched, but scientists had recently discovered that some microbes can generate "dark oxygen" in the absence of sunlight. In laboratory tests that reproduced conditions on the seafloor, Sweetman and his col-

Metal deposited over millions of years forms these nodules, which can somehow generate oxygen.

Carolyn Cole/Los Angeles Times via Getty Images

light down to individual trees, each of which acts like a stack of algae.

Sweeney hopes this work can inform the design of algae-stocked bioreactors, in just one example of how evolution's creative approaches to a single problem can offer inspiration for tackling technological challenges.

"Fundamental studies of biological systems give us new ideas and new strategies that can be applicable in unexpected spaces," says Gabriela Schlau-Cohen, a physical chemist at the Massachusetts Institute of Technology, who was not involved in the new research. "Given the scale of the energy crisis, we need all the strategies we can get."

And that means exploring the natural world far from home, says Sweeney, who grew up in the U.S. Midwest. "My sense of what photosynthesis is comes from deciduous forests and cornfields—and it turns out they're really bad at it," she says. "This lowly bivalve was really the right place to look for smart solutions."

—Meghan Bartels

leagues poisoned seawater with mercury chloride to kill off the microbes. Yet oxygen levels still increased.

If this dark oxygen didn't come from a biological process, then it must have come from a geological one, the scientists reasoned. They tested a few possible hypotheses—such as that radioactivity in the nodules was decomposing seawater molecules to make oxygen or that something was pulling oxygen from the nodules' manganese oxide—but ultimately ruled them out. Then, one day in 2022, Sweetman was watching a video about deep-sea mining when he heard the nodules referred to as "a battery in a rock." That bit of marketing was only a metaphor, but it led him to wonder whether the nodules could somehow be acting as natural geobatteries. If they were electrically charged, they could potentially split seawater into hydrogen and oxygen through a process called seawater electrolysis. (A battery dropped in salt water produces a similar effect.)

"Amazingly, there was almost a volt [of electric charge] on the surface of these nodules," Sweetman says; for comparison, an AA battery carries about 1.5 volts. The nodules may become charged as they grow, as different metals are deposited irregularly over the course of millions of years and a gradient of charge develops between each layer. Seawater electrolysis is currently the researchers' leading theory for dark oxygen production, and they plan to test it further.

It isn't clear, however, whether (or to what extent) these nodules create oxygen naturally on the seabed. In most experiments, oxygen production ceased after two days, which may indicate that the lander caused it by disrupting something about the environment. But it's also possible that the reaction eventually stopped because of a "bottle effect" within the enclosed chamber, Marlow says. "The products build up, the reactants go away, and then the reaction sort of stops. But in an open system … it could be a more consistent process," he explains.

Bo Barker Jørgensen, a marine biogeochemist at the Max Planck Institute for Marine Microbiology in Bremen, Germany, is skeptical that these nodules produce oxygen when they are left undisturbed on the seabed. (Jørgensen was not involved in the research but was one of the paper's peer reviewers for *Nature Geoscience*.) Still, it does seem that the nodules are producing oxygen through electrolysis, he adds, "and that in itself is a very interesting observation that has not been observed before, to my knowledge."

The researchers don't yet know whether this oxygen would be important to life on the CCZ seabed. The nodules and surrounding sediment are a habitat for deep-sea life, from tiny microbes to larger "megafauna," such as fish and sea stars. Half of the ecosystem's megafauna is found only on the nodules. This is a "poorly understood ecosystem," Levin says. "We haven't even discovered most of the species in the deep sea, let alone studied them."

Proposed deep-sea mining projects would extract nodules from swaths of the CCZ seafloor. The International Seabed Authority (ISA) is still drafting rules and regulations for mining the nodules and other deep-sea targets. At least 32 member states of the ISA have called for a moratorium, precautionary pause or ban on deep-sea mining.

These findings are "another thing that we now need to take into account when it comes to deciding, 'Do we go and mine the deep ocean, or don't we?'" Sweetman says. "To me, that decision needs to be based on sound scientific advice and input." *—Allison Parshall*

janiecbros/Getty Images

NEUROSCIENCE

Ultrasound Meditation

Brain stimulation can lead to a mindful state

EVEN WHEN YOU AREN'T DOING anything, your brain is relentlessly active—daydreaming, ruminating, contemplating the past or future. How this mind wandering functions can significantly shape a person's internal conscious experience.

In a recent study of 30 participants, researchers applied low-intensity ultrasound waves to a brain region associated with introspection and off-task mind wandering. Participants who underwent five minutes of ultrasound stimulation reported significantly heightened mindfulness—the ability to be fully present in the moment, without judgment toward others or the self. The results were published in *Frontiers in Human Neuroscience*.

"I haven't seen ultrasound technology used in this way, but this type of neuromodulation has significant potential to change how we think about and enhance mindfulness," says University of Wisconsin–Madison social psychologist Hadley Rahrig, who also studies that state of mind.

The researchers targeted the brain's default mode network (DMN), a constellation of interconnected areas that become particularly active when the mind disengages with the outside world and drifts into activities such as reminiscing or envisioning the future. Abnormal DMN activity and

ECOLOGY

Frog Saunas

Heated enclosures thwart a deadly frog fungus

FROGS AND OTHER AMPHIBIANS the world over are dying in droves from a nasty fungal infection that penetrates their skin and stops their heart. Scientists now have evidence that offering frogs their own little "sauna" in the winter might help them fend off the disease.

The illness, called chytridiomycosis or chytrid disease, was first identified a few decades ago. Since then, it has killed off at least 90 amphibian species worldwide and severely affected hundreds of others. Scientists have noticed that the infection, caused primarily by the fungus *Batrachochytrium dendrobatidis,* seems more deadly in cold, wet climates than in warm, dry ones.

Researchers studying chytrid have previously focused on observing the infection and its effects in the wild. For a new study in *Nature,* scientists took things a bit further: they provided infected frogs with artificial heat-trapping structures akin to saunas.

"It's an idea that's been around for a really long time, that if you can create scenarios where there's warm habitat for frogs, you can protect them from chytrid," says study co-author Anthony Waddle, a conservation biologist at Macquarie University in Australia.

The team focused on an Australian species called the green and golden bell frog (*Litoria aurea*), which has been hit by population declines and territory shrinkages since chytrid arrived. These frogs' green and gold patterning may seem dressy, but they aren't snobs—they are happy to live in disturbed areas and alongside humans, making the animals an attractive species to study. "They're really like the pigeons of frogs," Waddle explains.

Waddle and his colleagues found through experiments that when the frogs could pick their own temperature-controlled environment, they preferred things around 84 degrees Fahrenheit (29 degrees Celsius)—toastier than the temperature range in which chytrid kills most efficiently. Exposing infected frogs to 90-degree-F (32-degree-C) heat helped them clear the infection and gave them resistance against future exposure, although the researchers aren't yet sure precisely why.

The scientists then provided little enclosures that included black-brick structures designed to absorb heat. Half of the enclosures had shades that reduced this heating, and half were left uncovered to let the structures act as saunas. Here, too, frogs offered hotspots were better able to fight off chytrid and gain immunity.

Just because the setup worked with this particular species, of course, doesn't mean it would work for all frogs currently threatened by chytrid. For example, alpine frogs used to cold temperatures would struggle to survive in a sauna, Waddle says. But he adds that the study's findings represent an important change of tone for a field that has recently been dominated by despair.

Ana Longo, a disease ecologist and evolutionary biologist at the University of

connectivity have been linked to anxious rumination and depressive symptoms. "You get stuck, where your mind just keeps going and you can't stop it. We hypothesized that we could use ultrasound stimulation to remove some stickiness and let the network cool off," says the new study's lead author, Brian Lord, a cognitive neuroscientist at the University of Arizona.

Since the DMN was described in 2001, scientists have sought to manipulate it through broad-brush methods such as meditation and psychedelic drug therapy. But it remained difficult to precisely adjust DMN function because of its deep-brain location.

To overcome this challenge, Lord and his team used transcranial-focused ultrasound, a technique that converts electric current into concentrated and localized acoustic waves. (Half the participants received sham ultrasound as a control.) These waves can penetrate brain regions with millimeter-level precision and with greater depth than other noninvasive stimulation methods, which typically use magnetic fields or scalp-attached electrodes to induce electric currents spread over several centimeters.

Functional MRI scans showed that the researchers successfully inhibited activity in the posterior cingulate cortex, a key area in the DMN linked to emotional regulation and concentration during meditation. Through questionnaires and an interview, participants in the treatment group reported at least 30 minutes of subjective effects akin to entering a deep meditative state: a distorted sense of time, fewer negative thoughts and an improved ability to detach from their feelings. Other scientists at the University of Arizona are testing this technique to treat mood disorders such as depression.

"One of the greatest barriers to meditation and mindfulness is the steep learning curve. Brain stimulation can act like training wheels for the mind, helping people achieve that deep state of consciousness," Lord says. "That's our larger goal." —*Lucy Tu*

Frogs fight fungus in cozy saunalike niches.

Anthony Waddle/Macquarie University

Florida, who was not involved in the study, says she would like to see "this very simple but very elegant experiment" tested first in frog species with strong populations and then attempted with animals struggling more in the face of chytrid.

"This gives a precedent that we can try some very bold ideas if we want to do something against this fungus," Longo says. "It's changing the narrative that we can't do something against the spread of this pathogen." —*Meghan Bartels*

SPACE EXPLORATION

Space Rocks

Astronauts may have the guts for Mars travel—but not the kidneys

IN SEARCHING FOR POTENTIAL dangers humans would face on a long Mars mission, scientists are leaving no stone unturned—including the ones that show up at weirdly high rates in astronauts' kidneys.

Healthy kidneys filter blood to balance the body's water, salts and minerals, expelling waste as urine. When this process goes awry, painful kidney stones—hard accumulations of salts and materials such as calcium—can form in this essential organ. Researchers have theorized that astronauts are prone to kidney stones because bones degrade faster in microgravity, increasing calcium levels in the blood. But these stones' surprising frequency among space travelers even years after they return to Earth suggests other factors are involved.

To investigate, the authors of a recent study in *Nature Communications* explored how microgravity and galactic cosmic radiation affect kidney function—particularly parts of the kidney called tubules, which help to maintain healthy salt and mineral levels. The team analyzed data from astronauts in space and from rodents both in space and on the ground: those in space experience the combined impact of microgravity and radiation forces, and ground-based experiments let the scientists isolate the effects of each.

Kidneys are exceptionally responsive and adaptable—but these traits can work against them. When microgravity shifts the body's distribution of internal fluids, kidney tubules tend to shrink; this action hinders the organ's ability to properly filter calcium and salts, increasing the risk of kidney stones and other health issues. And diminished tubules are more vulnerable to high-energy cosmic rays. "There's an unholy alliance between microgravity and galactic radiation," says study lead author Keith Siew, a kidney physiologist at University College London.

Microgravity's effects may be reversible back on Earth. But radiation is "like a bowling ball where you grab it and throw it" at the body's cells, says Evagelia Laiakis, a radiotherapy researcher at Georgetown University. "You're going to damage DNA, proteins and organelles," possibly causing permanent injury. Outside Earth's protective atmosphere, a high-energy particle stream bombards and decommissions power-generating mitochondria while disrupting key protein-production processes. And tubular remodeling caused by microgravity may stiffen vital blood vessels, increasing their susceptibility to radiation-induced inflammation and tissue damage.

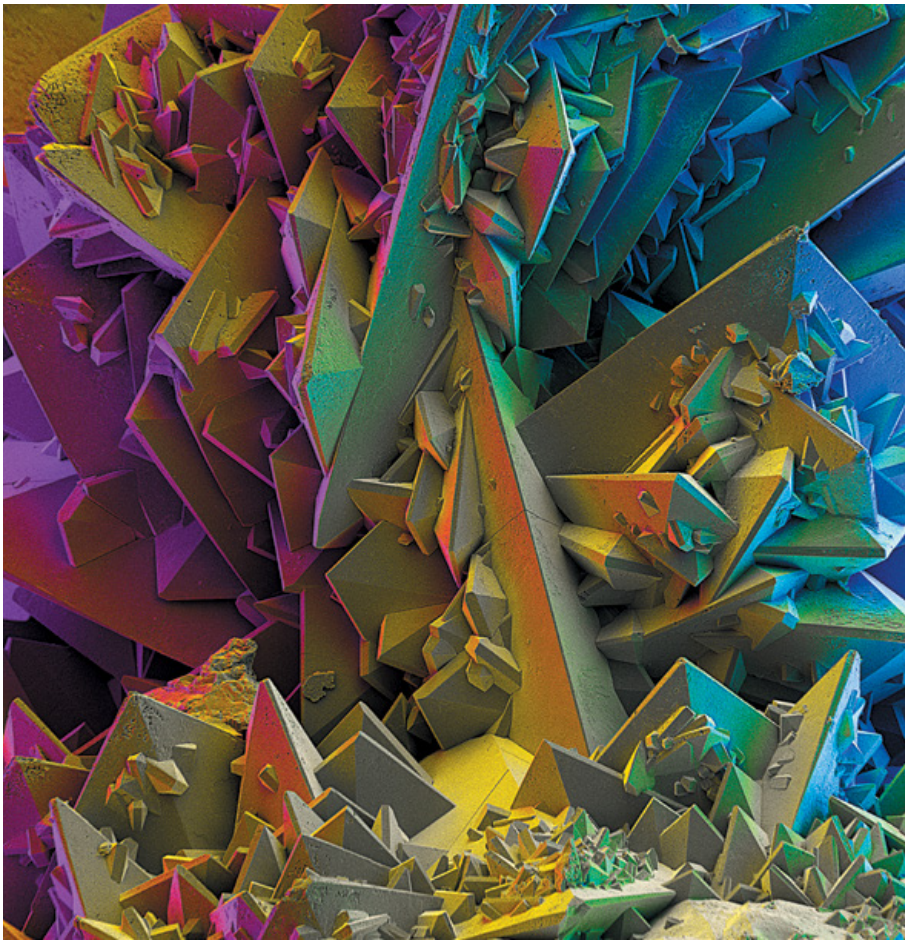
Siew says these daunting results may even underestimate the risks of damage to astronauts' kidneys. More research is urgently needed into how to strengthen spacecraft shields meant to scatter incoming radiation, he adds.

"This is a gateway study," says Matthew Bailey, a kidney physiologist at the University of Edinburgh. The results could help illuminate kidney disease mechanisms on Earth, and they could suggest more effective ways to protect organs from radiation—allowing for expanded radiotherapy against cancer.

"We are restless explorers; there's no question we're going [to Mars]," Bailey adds. "But most people don't think of the needed health research to make it possible."

—Max Springer

Microscopic calcium oxalate crystals on a kidney stone



David Scharf/Science Source

"There's an unholy alliance between microgravity and galactic radiation."

—Keith Siew
University College London

Christoph Hetzmannseder/Getty Images

MATHEMATICS

Tiling Chaos

In high-dimensional space, orderly tiles descend into nonrepeating mayhem

TILING A TWO-DIMENSIONAL bathroom floor is a straightforward home renovation, but researchers have found that in higher dimensions it could blossom into a baffling mess of nonrepeating chaos. New results overturn a long-standing tiling conjecture, showing another way disorder must emerge from the structured realm of mathematics.

Generally speaking, a tiling is a way to cover some space with lots of little pieces (tiles) that fit together without gaps or overlaps. A never-ending bathroom floor or infinitely large car trunk being loaded for a road trip are natural examples in two or three dimensions. A tiling is "periodic" if copies of a single shape fit together in a pattern that repeats itself in every direction to fill the space—akin to the herculean task of loading an endless car trunk with identically sized luggage arranged in a pattern. The periodic tiling conjecture this study took on says every shape that can tile a space without rotating or flipping must be able to do so in a repeating, regular way.

The study authors, publishing in the *Annals of Mathematics,* disproved this conjecture by constructing a strictly aperiodic tile—one that fully covers a space without any regular pattern. To do so, they translated the *geometric* tiling problem into an *algebraic* one defined by a system of equations. Each equation captures constraints to which a tiling must adhere—such as no rotations and no gaps between the tiles—forming a kind of "tiling language," says study co-author Rachel Greenfeld, a mathematician at Northwestern University.

With the addition of more constraints in this language, the potential number of solutions shrinks in the same way that there are fewer possible numbers you can put into a Sudoku square as more of the puzzle is filled in. The ultimate solution, a nonrepeating sequence of numbers, can then be translated back into a strictly aperiodic tile, disproving the conjecture. "Tiling is just not simple enough to be well behaved forever, but it's [also] not complex enough to be crazy forever," Greenfeld says.

In disproving the result, the researchers "almost find a way to turn the shape of a tile into a programming language," says University of Waterloo computer scientist Craig Kaplan. Because the result came from adding more and more constraints, which translate to extra dimensions, the counterexample turned out to operate in an extremely high-dimensional space—something like $10^{100,000}$ dimensions (that's a number with 100,000 *digits*).

"High-dimensional tilings are enormously complex," says study co-author Terence Tao, a Fields Medal–winning mathematician at the University of California, Los Angeles. "The situation seems much better behaved in low-dimensional [space], with three dimensions being the current frontier of research." Comparing this intuitive space with the high-dimensional result, he says, we are "at the boundary between order and complete chaos."

—Max Springer

GLOBAL WAKE-UP CALL HELPS BRING NARCOLEPSY TO LIGHT

People with this difficult-to-detect sleep disorder can go undiagnosed for years and suffer from stigma. WORLD NARCOLEPSY DAY celebrates efforts to raise awareness

▲ Julie Flygare was mystified by her narcolepsy symptoms at first, until she was finally diagnosed in a sleep lab.

Matthew Spaulding

Julie Flygare was 21 when the symptoms started. First her knees would buckle briefly, but only when she laughed. She awoke one night to the sight of a burglar attacking her, while she lay paralyzed and terrified—then realized later there was no burglar and no attack. As a law student the next year, she would read her textbooks diligently for hours, then couldn't recall what she had read. She got so tired on a 15-minute drive to law school one morning that she couldn't remember arriving.

Her bizarre symptoms mystified her, and multiple doctors were also perplexed. Finally, a sleep specialist sent her for a sleep study. She was diagnosed with narcolepsy, a rare neurological disorder that causes excessive daytime sleepiness, brief episodes of muscle weakness, and dream-like experiences.

The diagnosis helped, but she still had to deal with its fallout.

"I would say to people, 'Oh, I have narcolepsy,'" Flygare says. "They'd be like, 'Oh, you're gonna fall asleep right now?' They just tried to make a joke right away."

RECOGNIZING SYMPTOMS IS WHAT'S MOST IMPORTANT FOR DIAGNOSIS. MANY PATIENTS MISINTERPRET THEM FOR YEARS.

Flygare stopped telling people because she didn't like their reactions. "And then I felt just so alone. That was really rock bottom for me," she says.

The experience prompted Flygare to write a memoir: *Wide Awake and Dreaming: A Memoir of Narcolepsy*. She went on to found a sleep advocacy group called Project Sleep, which is devoted to raising awareness about sleep health, sleep equity and sleep disorders. To further raise awareness and reduce stigma, in 2019 she worked with narcolepsy advocacy organizations around the world to help establish September 22 as World Narcolepsy Day.

IN THE SLEEP LAB

Narcolepsy, which affects an estimated four million people worldwide, affects the brain's ability to regulate the sleep-wake cycle. This causes episodes of excessive daytime sleepiness, which can occur at any time and significantly impact daily life.

Diagnosing narcolepsy remains something of an art and can take up to a decade or more, says Andrew Spector, a neurologist and sleep medicine specialist at Duke University. The symptoms are nonspecific and can be mistaken for other conditions such as depression, epilepsy or other sleep disorders, and current clinical tests "are limited at confirming narcolepsy," Spector says. "So even patients who don't test positive for narcolepsy may still have it."

Narcolepsy is usually diagnosed in a sleep lab. "We start with an overnight sleep study, mainly to ensure there aren't any other sleep disorders like sleep apnea that are leading a patient to be really sleepy during the day," Spector says. Then comes the daytime nap test. People with narcolepsy fall asleep in under eight minutes, on average, across five naps, while those without it fall asleep in anywhere from 10 to 20 minutes.

Clinicians also measure whether the person enters rapid eye movement (REM) sleep. "People without narcolepsy tend not to go into REM sleep within 15 minutes," Spector explains. "But a hallmark of narcolepsy is that when you fall asleep, you go right into REM sleep." Individuals who go into REM sleep during two or more of five naps—in addition to having met the criterion of falling asleep in under eight minutes across the naps—get a narcolepsy diagnosis.

Doctors can also confirm the diagnosis by testing spinal fluid for orexin (also known as hypocretin), a neurotransmitter in the brain that regulates wakefulness and sleep. "If you have low levels of orexin in your spinal fluid, the odds of narcolepsy are very high," but normal levels don't rule it out, Spector says.

As a result, he says, recognizing symptoms is what's most important for diagnosis. Nevertheless, many patients misinterpret them for years.

DIAGNOSIS DELAYS

Professional football player Josh Andrews was just 12 when he noticed he had an unusual trait—a tendency to fall asleep anywhere and everywhere. He'd fall asleep while playing video games and in the car while riding with other members of his school's basketball team from tournament to tournament. He would "be passed out in the car," even if he'd "woken up from a good night's sleep," he recalls.

Image courtesy of Project Sleep

▲ **Josh Andrews used to fall asleep anywhere and everywhere, but after treatment for narcolepsy, he played in the NFL.**

Later, he noticed he would start to doze off while speaking, slurring his words mid-conversation. And when he was 18, Andrews rammed his car into the back of another vehicle after falling asleep at the wheel.

Finally, years later, after getting into another car accident, Andrews decided to seek help. "I realized I was endangering other people at that point," Andrews says. "It pushed me to find a diagnosis for what was going on."

Doctors diagnosed him with narcolepsy, his life improved after receiving treatment, and he ultimately made it to the NFL, playing offensive line for the Philadelphia Eagles, Indianapolis Colts and New York Jets. But he wishes he had sought a diagnosis years earlier. Now he's raising awareness about narcolepsy as a spokesperson for Flygare's advocacy group, Project Sleep, and a program called Progress at the Heart run by the pharmaceutical company Harmony Biosciences that addresses disparities and inequities in rare neurological diseases.

BUILDING EQUITY, BUILDING AWARENESS

While narcolepsy remains underdiagnosed for everyone, it may go undetected more often in minority populations, including African Americans, who often receive suboptimal care and are less likely to have adequate access to health care at all, Spector says. To promote equitable care, Spector and his team developed the "Racial Disparities in Neurology Scorecard," with funding from Progress at the Heart. The scorecard tracks clinical decision-making to help ensure all patients are offered the best available treatments for their conditions.

As diagnosis improves, efforts to draw attention to narcolepsy are also having an impact, Flygare says. "What gets me so much is when someone posts on social media saying, 'I wouldn't have shared this, but because it's World Narcolepsy Day, I'm going to share that I'm a person living with this condition." Increasing awareness about the disorder, she hopes, will encourage more people with narcolepsy to speak out and seek the care they need. ■

Learn more about narcolepsy at project-sleep.org. Explore more about Harmony Biosciences at harmonybiosciences.com.

HARMONY BIOSCIENCES

SCIENCE IN IMAGES

Warning Charge

Caterpillars sense their predators' electricity

SOME ANIMALS HAVE EVOLVED an ability to detect the invisible electrical fields that fill the world around us. This seemingly alien power is well known in aquatic animals as electroreception, but it is far less frequently observed terrestrially. Now researchers have shown that caterpillars can sense the electrostatic fields of approaching wasps—the first such predator-prey interaction recorded on land.

The scientists uncovered this phenomenon by first measuring the electrostatic charges of the caterpillars and of their frequent predator, the common wasp. For a study in the *Proceedings of the National Academy of Sciences USA*, they used electrodes to replicate the electrical field produced by a wasp approaching a caterpillar. They then exposed three different caterpillar species to this "fake wasp." (One, *Tyria jacobaeae,* is pictured here.)

All responded with defensive behavior. Two species remained protectively coiled for longer periods; the third bravely fought back by trying to bite the electrodes. The caterpillars reacted more strongly when the field oscillated at a wasp's wingbeat frequency. The researchers determined the caterpillars detect these fields with bristly fibers covering their bodies, which vibrated from the electrical stimulus.

For terrestrial animals that share such a sense, "it's going to be used in combination with other senses like hearing, like vision, basically to just provide an even more reliable sensory picture of whether a predator is there and where it is," says study co-author Sam J. England, a sensory ecologist at the Natural History Museum, Berlin.

University of Bonn neuroethologist Gerhard von der Emde says the study

Nigel Cattlin/Alamy Stock Photo

"shows, very convincingly, a behavior response to electroreception in an arthropod." Acknowledging that it would be difficult, he says he would like to see this behavior studied in nature without synthetic electrical fields.

Pauline N. Fleischmann, a neuroethologist at Carl von Ossietzky University of Oldenberg in Germany, says this study is a great example of "the impressive variety of cues that animals—in contrast to humans—can detect and actually use in their everyday tasks." She adds that "the most fascinating follow-up question is how wasps might try to mask their charge and how the evolutionary arms race between prey and predators continues." —*Gennaro Tomma*

Cyborg Worms Artificial intelligence and a tiny brain team up

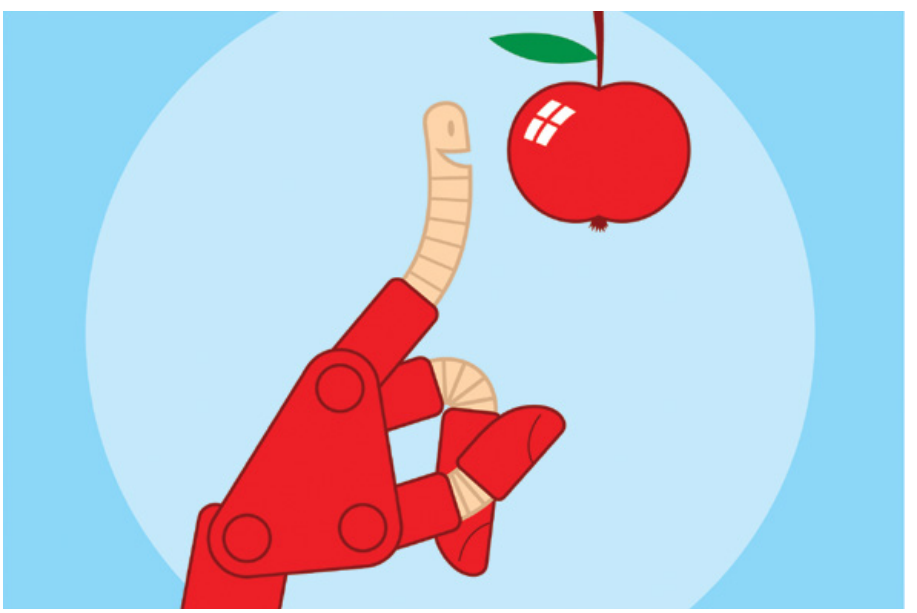
TECH Scientists have given artificial intelligence a direct line into the nervous systems of millimeter-long worms, letting it guide the creatures to a tasty target—and demonstrating intriguing brain-AI collaboration. They trained the AI with a methodology called deep-reinforcement learning; the same is used to help AI players learn to master games such as Go. An artificial neural network, software roughly modeled on biological brains, analyzes strings of actions and outcomes, extracting strategies for an AI "agent" to interact with its environment and achieve a goal.

In the study, published in *Nature Machine Intelligence*, researchers trained an AI agent to direct one-millimeter-long *Caenorhabditis elegans* worms toward tasty patches of *Escherichia coli* in a four-centimeter dish. A nearby camera recorded the location and orientation of every worm's head and body; three times per second the agent received this information for the previous 15 frames, giving it a sense of the past and present at each moment. The agent could also turn on or off a light aimed at the dish. The worms were optogenetically engineered so certain neurons would become active or inactive in response to the light, sometimes prompting movement.

The research team tested six genetic lines in which the number of light-sensitive neurons ranged from one to all 302 the worms possessed. Stimulation had a different effect in each line, making the worm turn, for instance, or preventing it from turning. The scientists first collected training data by flashing lights randomly at the worms for five hours, then fed the data to the AI agent to find patterns before setting the agent loose.

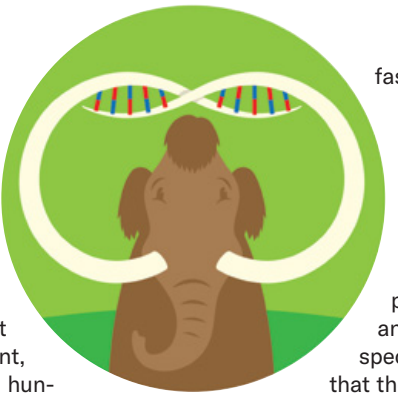
With five of the six lines, including the line where all neurons responded to light, the agent learned to direct the worm to the target faster than if the worm had been left alone or the light had flashed randomly. What's more, the agent and the worm cooperated: if the agent steered the worm straight toward a target but there were small obstacles in the path, the worm would crawl around them.

T. Thang Vo-Doan, an engineer at the University of Queensland in Australia, who has independently worked on cyborg insects, praised the work for its simple setup—reinforcement learning is flexible, and AI based on it can figure out how to perform complex tasks. According to Harvard University biophysicist Chenguang Li, the paper's lead author, "one can easily see how it might be extended to harder problems." Her team is now exploring whether their method can improve electrical deep-brain stimulation to treat Parkinson's disease in humans by adjusting the voltage used and its timing. One day reinforcement learning plus implants might even give us new skills, Li says—artificial and real neural nets united. —*Matthew Hutson*



Illustrations by Thomas Fuchs

Mammoth Assembly Fossilized chromosomes recovered from a “freeze-dried” mammoth



GENETICS In a first, scientists have mapped the three-dimensional structure of DNA belonging to an ancient animal: a 52,000-year-old mammoth found sporting a mulletlike hairdo. This advance, published in *Cell,* let researchers piece together the creature’s genome with unprecedented accuracy and detect traces of past gene activity in its cells.

Ancient DNA usually appears in short, scattered snippets. Where previous efforts recovered shuffled pages from the book of life, the current one captures an ordered stack with dog-eared corners. “This new work opens up major new possibilities of exploring the biology of extinct species,” says Adrian Lister, a paleontologist at the Natural History Museum in London. “This is an astonishing study.”

Geneticists have long doubted these types of structures could last in fossils. In living creatures, DNA molecules twist and coil as proteins turn various genes on or off. After organisms die, however, these molecules begin to shatter, generating fragments that get jumbled up. The mammoth sample’s DNA ran into a rare molecular traffic jam that kept tiny chromosome structures intact.

The team says the sample probably held up so well because it underwent spontaneous freeze-drying. Soon after the mammoth died, permafrost blanketed its body. The low temperature of the tundra slowed the motion of its molecules, and dehydration caused by the dry atmosphere meant there was no water available for the DNA fragments to move through, leaving the leathery sample more shelf-stable than the average supermarket snack.

To recover the mammoth chromosomes’ precise features, the researchers modified a genomic-analysis procedure known as Hi-C to map sections of DNA that were in contact with one another. The mammoth’s genetic material clustered into 28 pairs of chromosomes, which is the same number found in its living descendants, Asian and African elephants—a positive sign that the method produced trustworthy results.

The team then zoomed in further, assembling the DNA sequence for the full genome and assessing more subtle variations in the chromosomes’ shapes. By comparing the woolly mammoth’s chromosomal compartments with those in its nearest relative, the Asian elephant, the researchers identified hundreds of genes that functioned differently in the two species’ skins; they even pinpointed a cluster that was partially responsible for the mammoth’s iconic hairiness and ability to brave the cold. (Over time woolly mammoth fossils tend to lose their hair; the specimen under study, however, flaunted a mullet, earning it the nickname “Chris Waddle,” after a well-known former British soccer star with a similar hairstyle.)

The researchers aren’t sure how likely it is that other fossils would remain as pristine as this specimen, but they suspect that a range of circumstances could produce the necessary molecular conditions, including the hot air-drying involved in mummification. By experimenting on various types of beef, the scientists found that fresh meat would begin to lose its chromosomal structure after three days at room temperature. Beef that was dehydrated, however, by either heat or freeze-drying, retained this structure for more than a year. And these old, dried samples were so hardy that they survived being run over by a car, hit by a fastball and dipped in acid.

Study co-author Juan Rodríguez, a geneticist at the University of Copenhagen, imagines that wider use of the modified Hi-C protocol could generate more precise ancient genomes and allow analysis of new species. The team calculates that the technique could theoretically work on specimens up to two million years old, the current threshold at which the letters in the genome “text” become unreadable. When examining DNA snippets from an ancient specimen, scientists typically guess at the order of the fragments based on the genome of the extinct creature’s closest living relative, but this approach glosses over distinctions between ancient and modern species, and it breaks down in scenarios where the modern species has diverged significantly from the ancient one or where the ancient species lacks a modern descendant. The new 3D structural analysis could help bypass these obstacles.

“We probably can’t even foresee everything [the paper might lead to],” says study co-author and Baylor College computational biologist Olga Dudchenko. After all, she notes, since its advent in the 1980s, the field of paleogenomics has expanded in ways scientists couldn’t have imagined then. The researchers hope their peers who work on other creatures might find their own Chris Waddles. —*Saima S. Iqbal*

MATH PUZZLE

Number Imposter

By Hans-Karl Eder

Among the natural numbers below 100, there are 30 with a special property. Jovan has listed them in the table here.

But Jovan made a mistake, and one of these numbers must be replaced. Which number must be inserted in place of the incorrect number?

6	10	14	15	21
22	26	33	34	35
38	39	46	51	55
57	58	62	65	69
75	77	82	85	86
87	91	93	94	95

For the solution, visit www.ScientificAmerican.com/games/math-puzzles

SPACE EXPLORATION

BACK TO THE

Why is it so hard to repeat the feats of Apollo? BY SARAH SCOLES

ILLUSTRATION BY MONDOLITHIC STUDIOS | CHRIS WREN AND KENN BROWN

MOON

NASA and its partners plan to send astronauts back to the moon on the Artemis II mission scheduled for 2025.

WHEN THE APOLLO 17 ASTRONAUTS RETURNED from the moon in 1972, they couldn't have known that they would be the last humans to travel deep into outer space for more than 50 years. But no astronauts have ventured beyond Earth orbit since, even as Presidents George W. Bush, Barack Obama, Donald Trump and Joe Biden have all planned lunar missions. Finally, NASA is preparing to send people back to the moon on the Artemis II flight, scheduled to lift off in the fall of 2025. Why has it been so difficult?

This new mission is similar to the Apollo 8 flight of 1968, when three people circled the moon without landing and then traveled back to Earth. Artemis II will send four astronauts on a 10-day trip around the moon on the first crewed test of NASA's new Space Launch System (SLS) rocket and Orion space capsule. Although the U.S. has had decades to get better at such journeys, the upcoming trip resembles its mid-century cousin in that it will be far from easy.

Choosing to do things "not because they are easy but because they are hard" is part of the rationale President John F. Kennedy gave in a famous 1962 speech trying to galvanize support for the Apollo program. And what was true then remains so today—in fact, reaching the moon may be even more difficult than it was decades ago.

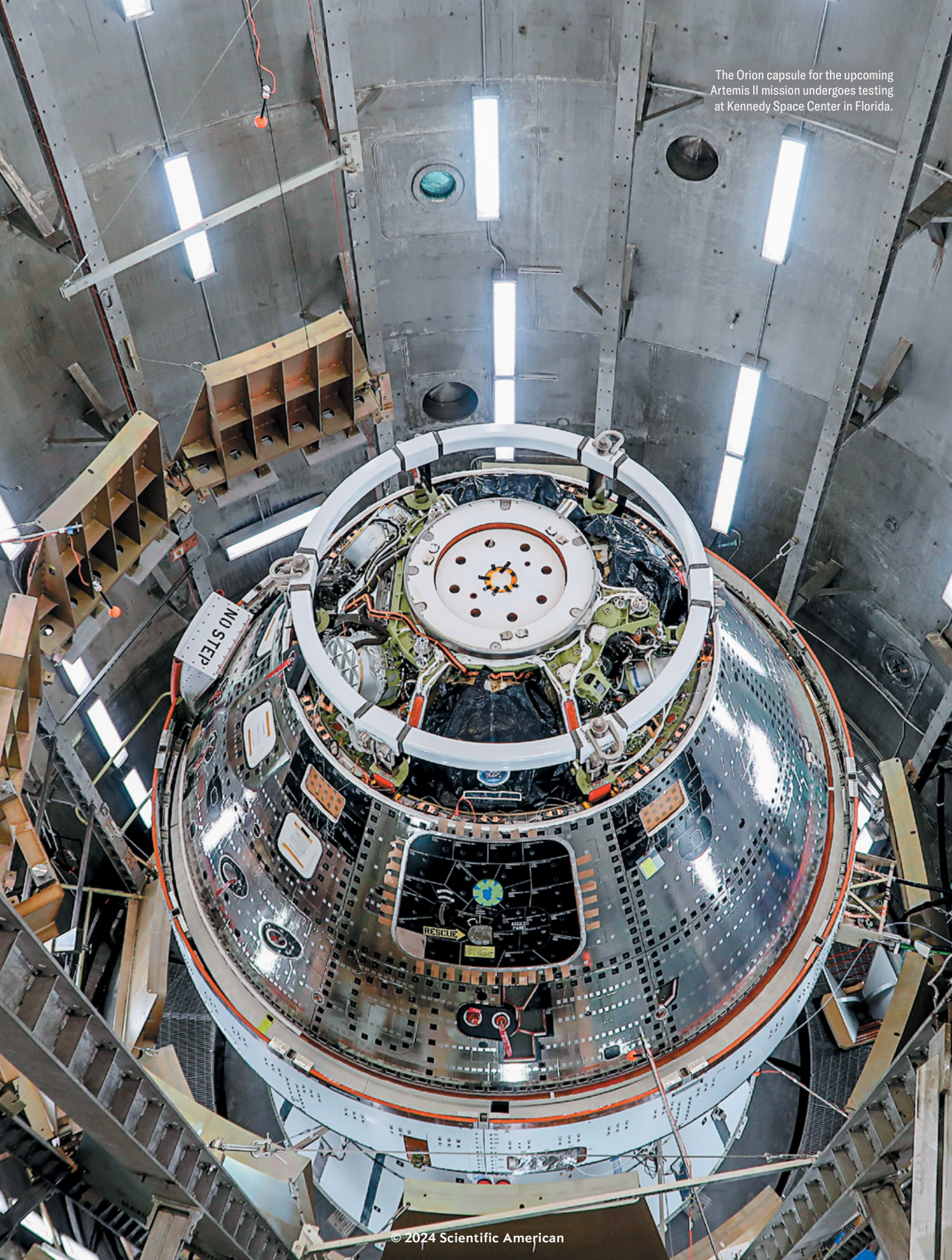
NASA's Artemis program has been plagued by long delays, cost overruns and surprise problems. It has those in common with many terrestrial programs, such as subway upgrades and highway construction, which also seem to take much longer, and often cost much more, than they did in the (dubiously) good old days. Is it really harder to build great things now? And when it comes to the moon, why should replicating a feat the U.S. accomplished more than half a century ago take so long?

ARTEMIS'S NEXT STEP is essentially an Apollo 8 redo, but the program has grand ambitions that reach beyond the moon. "In the end, our stated goal is Mars," says Matthew Ramsey, Artemis II's mission manager. "That's very difficult—getting to Mars and living on Mars—and so we take it in bite-sized chunks."

The program's first mission, Artemis I, sent an uncrewed spacecraft around the moon and back in 2022. After Artemis II, the third through sixth installments

Sarah Scoles is a Colorado-based science journalist, a contributing editor at *Scientific American* and a senior contributor at Undark. Her newest book is *Countdown: The Blinding Future of Nuclear Weapons* (Bold Type Books, 2024).

David Wellendorf/NASA



The Orion capsule for the upcoming Artemis II mission undergoes testing at Kennedy Space Center in Florida.

will put people on our natural satellite and then set up pieces of the Lunar Gateway, a space station orbiting the moon. Later missions will also focus on setting up habitable camps on the lunar surface.

The Artemis program, barely off the ground, has already seen long delays, and the program faces significant problems, laid out in a recent audit from NASA's office of the inspector general. First, it will have devoured $93 billion by 2025, billions more than anticipated. Second, the Artemis I adventure revealed "critical issues that need to be addressed before placing crew on the Artemis II mission," according to the audit. The Orion capsule's heat shield, for instance, broke down differently than engineers had predicted, for reasons they don't yet understand. Bolts on the spacecraft faced "unexpected melting and erosion." And the power system experienced anomalies that could leave the future crew without adequate energy and redundancies and maybe without propulsion or pressurization.

These "anomalies"—the term space types use for big problems—"pose significant risks to the safety of the crew," according to the report. And they came on top of other hardware, data and communications challenges. Furthermore, the inspector general found that the initial launch caused unforeseen damage to the system, resulting in repairs to the tune of more than $26 million, a much heftier bill than the team had budgeted for. That's a lot of hitches and a lot of money—especially for a mission that won't accomplish many firsts we didn't achieve back in the 1960s.

IT MAY SEEM STRANGE that today's lunar missions are so challenging given that we've done this before. But the circumstances aren't the same, says Scott Pace, director of the Space Policy Institute at George Washington University. "The world environment is very different," he says. The U.S. is no longer in a space race—an existential battle to stay ahead of the communists and be the first to do things beyond Earth. Back then, cold war dynamics were at play, and newly independent countries were deciding which governing system to follow—a decision that might (theoretically) be influenced by a democratic nation's ability to explore space. Such "soft power," the thinking went, could show that the American way was the best way while using the country's missilelike rockets to imply hard military dominance. Given those stakes, the U.S. government was willing to throw huge amounts of money at the Apollo program in a short time.

Artemis is expensive, but Apollo was exorbitant: the program cost around $290 billion in today's dollars, according to the Planetary Society, compared with Artemis's $93 billion. In those years NASA was often blessed with 4 percent of the nation's budget. Today it's lucky to get around 1 percent, with the additional burden of many other spacecraft, telescopes and research projects beyond human spaceflight to fund.

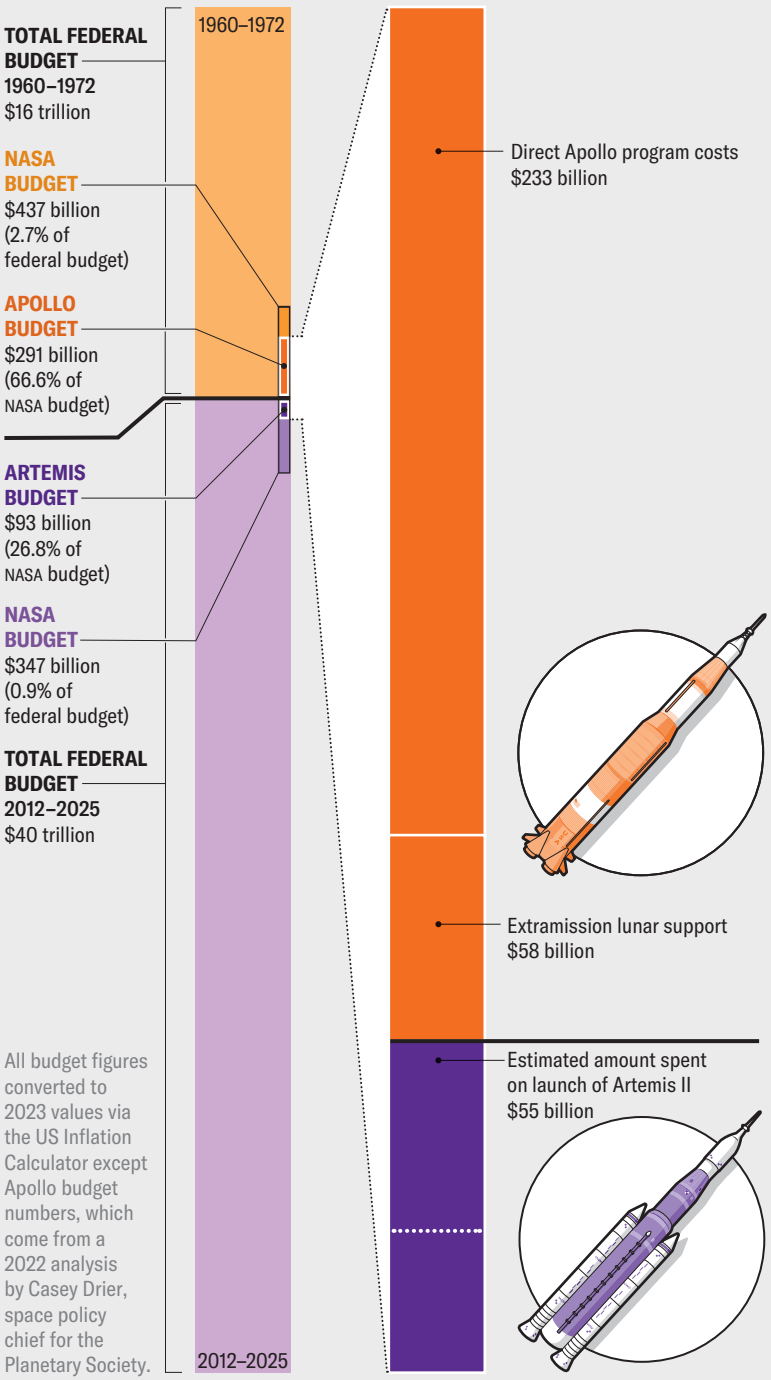
That budgetary decrease makes sense, according

Apollo vs. Artemis

NASA is getting ready to send astronauts on the first lunar journey in more than 50 years. The Artemis II mission, slated to launch in 2025, will send a crew around the moon, and its sequel, Artemis III, will land on our satellite. At first glance these missions look like repeats of some of the feats of Apollo, but they are planning to break new ground—for instance, the Artemis III astronauts will be the first humans to explore the moon's south pole, which might contain useful resources such as water ice. The Artemis program is also happening in a very different, non–cold war context, under altered budget constraints.

BUDGETS THEN AND NOW

Today's total federal budget (*purple*) is more than twice what it was during Apollo (*orange*), but NASA receives a much smaller share of it now compared to then. All figures here are represented in 2023 dollars.

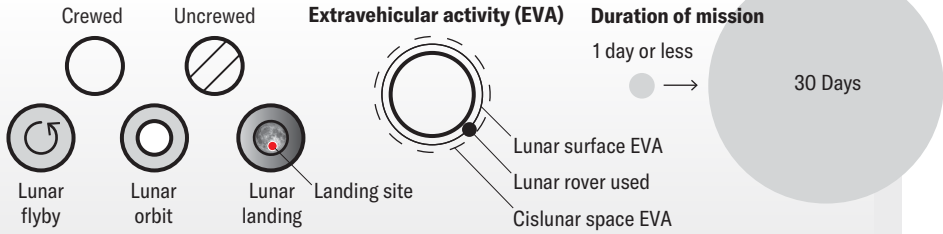


All budget figures converted to 2023 values via the US Inflation Calculator except Apollo budget numbers, which come from a 2022 analysis by Casey Drier, space policy chief for the Planetary Society.

Graphic by Zane Wolf, Spacecraft illustrations by Brown Bird Design

MISSIONS THEN AND NOW

The Apollo program (*orange*) included more than a dozen separate missions, but Artemis (*purple*) has condensed its initial stage into four main flights: an uncrewed test flight of the rocket, followed by a planned human trip around the moon and then two crewed landings. The second will begin to assemble a "Lunar Gateway" moon space station to be used by future missions.



APOLLO

Apollo 1 fire caused the death of the crew and the cancellation of Apollo missions 2 and 3.

Apollo 1

Apollo 5

Apollo 4

Apollo 6

First crewed flight of the Apollo program and first live TV broadcast from an American spacecraft.

Apollo 7

First humans to orbit the moon.

Apollo 8

First separation of lunar and command modules and independent flight of both.

Apollo 9

First flyby of landing site and first color TV broadcast from space.

Apollo 10

First men to set foot on lunar surface, first moon walk.

Apollo 11

First precision landing.

Apollo 12

Technical issues resulted in the mission executing a flyby rather than a landing.

Apollo 13

Longest distanced walked on moon, over 9,000 feet (2.743 kilometers).

Apollo 14

First use of a lunar rover, first test of Galileo's theory of gravity in space.

Apollo 15

Apollo 16

First mission to stay more than 3 days on lunar surface.

Apollo 17

July 1960
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May 1961
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July 1973

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Dec 2017

Eisenhower and Trump administrations launch lunar program policies.

First public announcement of the lunar programs.

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May 2019
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2030
Dec 2030

I
II
III
IV
V

ARTEMIS

Artemis I

Longest mission without docking to a space station, new record for most distance traveled by spacecraft designed for human occupation.

Artemis II

Farthest humans will have traveled from Earth, tentatively reaching 280,000 miles (450,000 km).

Artemis III

Multiple EVAs are planned but not finalized; the blur indicates uncertainty.

Scheduled first U.S. lunar landing since 1972, first exploration of lunar south pole, and first woman and first person of color to land on the moon.

Artemis IV

First humans to inhabit planned lunar space station, Gateway, using it as a base for lunar surface mission.

Artemis V is scheduled for March 2030.

> “Artemis has scientific purposes. But it also is a way of shaping the international environment for space.”
>
> —SCOTT PACE *GEORGE WASHINGTON UNIVERSITY*

to John Logsdon, professor emeritus at George Washington University and founder of the Space Policy Institute. “There’s no reason to spend money like it was a war,” he says. “There’s really no national interest or political interest that provides the foundation for that kind of mobilization at this point.”

Those looser dynamics shrink the wad of cash available and set the planning of space missions on a more meandering path. In the 1960s Kennedy declared the country would go to the moon in that decade, and it did. In modern times spaceflight plans established by one president are often canceled by another, only to be resurrected later in a different form. As a result, the trajectory toward the moon (and beyond) zigs and zags.

The world order has also changed, and space missions tend to be global cooperations now, Pace notes. The Artemis program is a collaboration involving Japan, Canada, the United Arab Emirates and the European Space Agency. That international participation is in fact a big part of the program’s point. “Artemis has scientific purposes—going back to the moon and all that,” Pace says. “But it also is a way of shaping the international environment for space.” That molding is much more important than it was in the 1960s, when humans relied less on above-Earth infrastructure. Today orbiting spacecraft enable everything from GPS capabilities to missile warning to banking. Convincing other countries to see and treat space as a valuable resource, by working with them and establishing behavioral norms, helps us keep space safe and the players up there responsible. “Rules are made by people who show up,” Pace says.

That’s a more nebulous goal than winning a race. “If there were nice, sharply defined motivations, things would be a lot simpler,” Logsdon says. But working with other countries, several of whom are building hardware for Artemis, takes longer than going it alone—just as doing a group project can grate more than simply pulling a solo all-nighter. According to the NASA inspector general, the global nature of the program is also increasing the costs, and NASA doesn’t have an overarching strategy for dealing with all the partners it’s brought onboard.

In Pace’s view, however, none of those factors is the main stumbling block on the lunar trajectory. The biggest challenge, even though the U.S. has already been to the moon, is that we haven’t been to the moon *recently*. “We stopped, and then we forgot,” he says. Just because you ran the Olympic marathon 50 years ago, he continues, doesn’t mean you could do it again tomorrow.

IN THE CASE OF ARTEMIS, the marathon also involves new, more complicated technology. The basics of the rocket side of the equation haven’t changed that much: big rockets are essentially bombs that boost things to space. And many of the players are the same. Boeing worked on the Saturn V rocket that sent Apollo missions upward. For Artemis, the company designed and built the SLS core stage, a massive piece of machinery that stands 212 feet tall and is nearly 28 feet across. This component provides fuel to the engines that heave SLS from the ground and sends it flying the right way—courtesy of the Boeing-created avionics system that’s also onboard. The company, currently beset by controversy over quality-control issues in its planes as well as a malfunctioning spacecraft that stranded two astronauts on the International Space Station, is also responsible for rocket stages for later Artemis missions.

There are some big differences between Boeing’s antique work on Saturn V and its modern cousin. This time they built the rocket stages using computer-controlled machining, as well as a friction-based welding technique that doesn’t melt and warp metal. The company also uses computers to analyze the rocket stages’ states of being and monitor how they’re behaving in real time—a perspective Apollo lacked.

Northrop Grumman, meanwhile, handles the rocket boosters, which are strapped onto the sides of the core stage. These give SLS more than 75 percent of its oomph at launch. Much of the boosters’ engineering hails from the space shuttle program, and in some cases parts of their hardware actually flew on shuttle missions. These boosters, like missiles, use solid rocket fuel rather than liquid. “You want to get away from Earth’s gravity well and out of the thick part of the atmosphere where drag is high as fast as you can,” says Mark Tobias, SLS booster deputy engineer. “And that’s what solid propulsion really does. It’s raw horsepower.”

But the plan to use hardware from previous space programs is a bit cobbled together. The Space Launch System, for instance, was originally designed for the Constellation program, a strategy set up under the George W. Bush administration to finish building the International Space Station and to reestablish a human presence on the moon. Congress mandated that the rocket reuse technology from the then defunct space shuttle program. But Obama canceled Constellation in 2010, and in 2017 Trump anointed the Artemis program, with the goal of finally sending people back to the moon and paving the way for exploring Mars. Again, the new plan required that NASA use some of the technology that had been developed for Constellation, which in turn entailed repurposing old space shuttle technology. These mandates were pushed by congresspeople representing regions that housed manufacturing centers for shuttle parts. But the car-

Engineers connect two parts of the Orion spacecraft, the crew and service modules, at Kennedy Space Center.

Amanda Stevenson/NASA

ryover and conversion of those technologies have proved difficult. According to a report from the NASA inspector general, bringing the rocket parts into the modern era—for instance, replacing asbestos parts—and retrofitting them for a new rocket system has cost much more than anticipated.

Aerospace company Aerojet Rocketdyne builds the engines, and as with the rocket boosters, making old shuttle engines work for Artemis has been hard and expensive. SLS is a much taller rocket than the space shuttle. The stretched dimensions required changing the engines to deal with oxygen flowing in at higher pressures. The engines are also closer to the boosters than they were on the shuttle. "It's an extreme heating environment," says Mike Lauer, director of the engine program, so it requires extreme insulation.

The Artemis engines will also experience a more irradiated environment going to the moon (and later to Mars) than they did in orbit on the shuttle. Dealing with that change involved tinkering with the computer that lives on each engine, which Lauer calls its "brain." Those brains also needed a modernization, as computers are much different than in the 1990s (you might have noticed). The new and improved brains can monitor the engines—including during an impending disaster. "Things can be done to correct or save the mission and, in a worst-case scenario, shut an engine down before it blows up," Lauer says. During Apollo, engineers couldn't have known about problems fast enough to solve them. Today, he says, even though astronauts are basically riding a bomb, "that bomb is being watched very closely."

The retrofit was challenging, though, and required finding new suppliers because many who had worked on the space shuttle didn't make the relevant parts anymore. Ultimately the point is this: sometimes it's easier to design and build the house you want than to renovate a fixer-upper with a bathroom next to the kitchen and cupboards at awkward heights.

SPEAKING OF RIDING BOMBS, NASA treats humans with a softer touch than it did in the 1960s, when it was swooping up fighter pilots and shooting them into space. That's apparent in the design of Orion, built by Lockheed Martin.

Blaine Brown, director of Orion's mechanical systems, and his team ran calculations about what kinds of rigors those systems would hold up against and designed them to withstand multiples of what anyone expects them to experience, whether high temperatures or intense acceleration forces. As they refine the spacecraft, engineers continue to run detailed simulations on Orion's materials and the stresses the capsule will be under, getting down into the details of potential

The core stage of the Space Launch System rocket traveled from NASA's New Orleans assembly facility to Kennedy Space Center in July 2024. It will be readied there for the Artemis II mission.

weaknesses in a grainy way that the slide rules of the 1960s couldn't handle. They also do x-ray inspections of the welds and the blocks that form the heat shield, which keeps the capsule from burning up as it streaks back through the atmosphere. The team will get more data than in the past on how the space vehicle does in flight—just as the rocket contractors do—as well as a better ability to communicate.

"We understand way more" than engineers during Apollo did, Brown says. Still, the unexpected pops up, as with Orion's degraded heat shield, which, despite all the fancy computer simulations, was missing chunks after its first reentry. Even with today's computational power, there's no guarantee of perfect results. Apollo obviously worked without that analysis. But once such predictive capabilities are available, engineers are almost under an ethical obligation to use them to understand precisely what they'll be subjecting the astronauts to.

Society's attitude toward risk has changed since the space race, says bioethicist Jeffrey Kahn of Johns Hopkins University. He's sat on panels tasked with independently analyzing the ethics of astronaut life for the National Academy of Sciences—including which dangers are worth the trip at all. That cost-benefit equation churned out different calculations in the 1960s. The potential big reward of winning the space race against the communists was generally held to be worth more danger. Today the motivations for the mission are murkier, the stakes are lower, and the consequent rewards don't justify as much risk.

Back then, the powers that be were also ignorant of some of the risks we now know exist, space being a new frontier at the time. Astronauts hailed from that "right stuff" mold of old. "Astronauts rode motorcycles and drove fast cars," Kahn says, in addition to being test pilots. Today a wider variety of people go into space for a larger number of reasons. "Astronauts are not some separate species," Pace says. Perhaps, then, we value their lives more like we value our own.

If something did go wrong, the reaction to that hypothetical accident would probably be more vehement than it was when, for example, three astronauts died in the 1967 Apollo I fire. After that tragedy there was minimal call for cancellation or even significant delay. Now, Logsdon says, the Artemis program might not have enough political support to survive a fatality. So Artemis II and the missions to follow all have to be as safe as they can be to continue to be at all.

GETTING BACK TO THE MOON isn't the only modern challenge beset by delays and budget blowups. Many large-scale endeavors have grown harder and costlier over time. The New York City subway system, for instance, was initially built in just over four years and had 28 stops; a new subway line in the city with just three stops, finished in 2017, took 17 years. Scientists developed nuclear weapons from scratch in three years in the 1940s at a cost of about $35 billion in today's money; the current nuclear weapons modernization program will take at least 30 years and cost more than $1.5 trillion. At the end of World War II the U.S. was whipping up an aircraft carrier a month; the most recent one took more than a decade.

Highway delays and big spending are the specialty of Leah Brooks, a professor at George Washington University's Trachtenberg School of Public Policy and Public Administration. Her research has found that asking citizens for input on projects—a requirement of many large governmental enterprises these days—is one significant cause of road woes. This input is often part of an environmental review that is required before a project begins. Taking into consideration the "citizen voice," as Brooks calls it, can result in more expensive routes that have fewer negative environmental impacts or are less disruptive to citizens' lives but also might require additional mitigating infrastructure, such as sound barriers. In the past, authorities didn't have to ask for everyone's opinion (or care much about the environment). Take the Tennessee Valley Authority, Brooks says, an entity established in the 1930s to construct dams to reduce flooding and generate electricity. "They don't consult anybody," she says. "They just build it." Kennedy didn't choose to go to the moon because he had asked what everybody thought, either.

Brooks's findings may apply to any endeavor that involves an environmental impact statement—a document that lays out the consequences for the natural environment and requires an open period of public comment. One such document exists for the previous Constellation program; it was re-upped for NASA's "post-shuttle human spaceflight program."

In Brooks's view, though, the biggest difference between past and present may be that we build things better now, which is expensive and takes longer. That may not be true of, say, home appliances, but it is true of those highway sound barriers and, perhaps, of spaceships. For Artemis, having a more robust rocket system, asking people what they think, keeping people safer and working with global partners are probably better for this world—even if they don't result in expedience off-world. That lack of expedience may even be a good thing. Today, Logsdon says, you don't hear many people arguing against the Artemis program. In contrast, Apollo wasn't actually popular with the public. In 1961 more people opposed government-funded human trips to the moon than were in favor. In 1965 a majority opposed such trips, and in 1967 the gap between "in favor" and "opposed" had grown to nearly 20 percentage points, according to research from space historian Roger Launius.

The new way of going deep into space ultimately results in a safer, better-understood system that might meet with more public approval—at home and abroad. And besides, it's always been true that we choose to do it because it's hard—so what if it's harder? And what's the rush? It's not a race. ●

Ben Smegelsky/NASA

FROM OUR ARCHIVES
Birth of a Rocket. David H. Freedman; June 2015. Scientific American.com/archive

The Empathy Incentive

Taking someone else's vantage point can be mentally taxing. Upholding empathy as a social norm motivates people to make the effort

BY ELIZABETH SVOBODA

ILLUSTRATION BY FRANCESCO CICCOLELLA

AS A GRID OF VIDEO FEEDS blinks into view, attendees across the country prepare for an ideological collision. All have signed up for a virtual forum billed as an "empathy cafe," held to spark dialogue between police and community members. Among the participants are officers as well as people who've been burned in encounters with law enforcement.

The setup seems like a guaranteed powder keg. But as moderator Lou Zweier explains, this forum has some strict rules of engagement. "We're going to do four-minute speaking turns," he explains to the group, which will be separated into smaller breakout rooms. After one person in each breakout room gets a chance to speak about what's on their mind, someone else in the room—a person chosen as the "reflector"—will sum up the speaker's opinions and concerns as best they can, whether or not they agree. The reflector then becomes the next speaker and chooses a new reflector, and the process continues. "The listening and reflecting go around the circle," Zweier says. "Everyone gets a chance to speak and be heard."

This event, led by empathy educator Edwin Rutsch, offers a chance for minds to meet across the kind of yawning divide that's grown commonplace in the U.S. Such forums have popped up in part because trying to understand someone else's perspective doesn't always seem like a social bet that pays off.

Empathy is often defined as the capacity to understand what someone else is thinking and feeling. It is distinct from sympathy, which may imply pity (you might feel sympathy for someone in pain without grasping what they're going through), and from compassion, which involves a desire to ease someone's plight.

Because empathy can allow people to connect across political, racial and economic divides, it lays a foundation for acts of cooperation and caring that allow diverse societies to flourish. Higher levels of empathy are tied to both individual well-being and broader social cohesion.

When psychologist Sara Konrath set out to investigate empathy in the U.S., she found that it had been in decline for decades. She tracked Americans' self-reported empathy levels between 1979 and 2009 and found that people were increasingly less likely to agree with statements such as, "I sometimes try to understand my friends better by imagining how things look from their perspective."

Konrath's follow-up analysis, which tracked empathy levels between 1979 and 2018, did show rebounds in young people's willingness to take others' viewpoints and understand their feelings. But research highlights social and biological factors that continue to make empathy daunting. Polarization has been increasing, meaning that people see the world in fundamentally different ways and trust one another less. What's more, recent studies show that people shrink back from the mental effort it takes to understand what someone else is thinking and feeling. Meanwhile rates of loneliness, resentment and depression in the U.S. are high.

To promote empathy as a collective good, researchers have rolled out a smorgasbord of education programs. There are classroom programs for elementary schoolers, training seminars for employees and

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even immersive empathy retreats. New research shows that empathy instruction can boost people's ability to engage reflectively across political divides. Yet fully grasping someone else's experience is a heavy cognitive lift.

Increasing empathy, says Stanford University social psychologist Jamil Zaki, will take more than teaching skills such as listening actively to others. Empathy is a socially motivated process, Zaki and other researchers say, meaning that people won't necessarily empathize just because they know how. Instead—much as kids with athletic peers often want to excel at sports—people want to understand others when they enter into communities where empathy is the established norm.

NEUROSCIENTISTS ARE beginning to piece together a clearer picture of empathy's neural origins. When researchers elicit empathy by, say, showing people a film clip about what someone else is going through, a series of interconnected brain regions activate on functional MRI scans. Among these regions are the dorsomedial prefrontal cortex, which helps to gauge other people's emotional states, and the anterior insula, which is involved in processing pain. Similarly, researchers have identified single neurons in the dorsomedial prefrontal cortex that encode information about others' thoughts.

Our ability to perceive other people's inner states most likely evolved because it helps to forge the kinds of strong social ties that promote survival. In human ancestral environments, nomadic groups understood one another's emotions and state of mind; the bonds among them deepened, helping the group to function as a resilient unit.

Whereas empathy has long been an adaptive way of ensuring social cohesion, it also exacts a steep cognitive price. Taking someone else's perspective is a complex, challenging operation for the brain, in part because it requires a sophisticated assessment of what the other person may be thinking and feeling. In one 2020 study at the University of Liverpool in England, researchers found that empathy for others' pain requires a host of different brain networks to interact, including some responsible for inferring others' mental state. (When people perceive their own pain, on the other hand, their brain activity related to understanding others diminishes.)

A series of experiments led by Pennsylvania State University psychologist C. Daryl Cameron found that most individuals prefer to opt out of the cognitive effort empathy requires, especially if they don't know the other person well. In multiple rounds of game play, Cameron offered participants in a study two card games to choose from: an "objective deck" game, which asked them to describe the appearance of people on the cards, or an "empathy deck" game, which asked them to describe the people's possible experiences and feelings based on their expressions. Most people stated that they preferred the objective deck.

Empathy has long been an adaptive way of ensuring social cohesion. It also exacts a steep cognitive price.

In part, that's because it's harder to empathize with someone who feels distant or unknown than with a close loved one. "The more shared experiences you have with someone, the more of a rich, nuanced representation you can draw on," Cameron says. But empathy for someone whose experience feels alien—the person who disagrees with you online, the man in a tent outside the subway or even a cousin who spouts extremist views—is a different matter. A host of disquieting unknowns arises: Is identifying with this person going to put you in danger? Will it compel you to sacrifice something important, such as time, money, tranquility?

When such anticipated costs overwhelm people, they're more prone to withdraw altogether rather than trying to understand where the other person is coming from. "We are quite adept at learning how to manage our emotional environments to cultivate what we want to feel," Cameron says. "Empathizing with a stranger, taking on their experiences—either negative or positive experiences—people find it difficult, they find it costly. And the more they feel that way, the less they opt in." In a 2020 study at the University of Lübeck in Germany, fMRI scans of people who'd just heard stories about mass tragedies showed less activation in their brains' core empathy networks compared with those who had not heard the disturbing stories.

But larger structural forces are likely at play, too. Wealth inequality in the U.S. has steadily risen since the 1980s, and people in rarefied income brackets often have little motivation to understand the struggles of those at the poverty line. "We're much more segregated economically nowadays," Konrath says. "That can impair our ability to see and to care and to have those people be our neighbors and friends that we naturally want to help."

The impulse to sidestep empathy's complications also leads people into polarized online echo chambers—many of which also persist in the physical world—where we're less and less likely to maintain friendships with those whose views differ from our own. It's easier than ever to be a water strider, gliding away from others with frictionless ease.

That suspicion and detachment are what Rutsch, a former computer systems administrator turned empathy educator, aims to dissolve through empathy cafes and other similar events. He founded the Center for Building a Culture of Empathy in 2010, with an aim to create a headquarters for the global empathy movement. Rutsch based his approach on that of humanistic psychologist Carl Rogers, who used reflective listening techniques to build trust and rapport with clients.

Rutsch has traveled around the country with pop-up "empathy tents," which he pitches near demonstrations and protests. Once he pitched a tent just beyond a 1,000-person rally in Los Angeles for former president Donald Trump, which was also attended by large numbers of counterprotesters. Rutsch invited in six people from each side. Then he mediated six pairs in listening carefully to one another, then stating their own understanding of the other person's thinking. "Of those six pairs, five of them ended up giving each other hugs afterward," Rutsch says. "On the other side of the street, they were screaming and yelling at each other, and the police were having to keep them apart."

Rutsch attributes such outcomes to the intentional structure of these chats. Even if the other person says a false or off-the-wall statement—for example, that the 2020 election was stolen—"you reflect back your understanding of what they have said," he says. "When it is your turn to speak, you can challenge what they have said. They have to take it into their consciousness to be able to reflect it. That means they have to listen to you. They cannot live just in their own worldview."

In these dialogues, listening and being

carefully listened to in return often begins to soften conspiracists' armor. "Knowing that you were willing to listen to them, they often drop their judgments after a while and get more real," Rutsch says. "You get to a deeper understanding of each other and see each other's humanity. You may get to a deeper fear, perhaps, that is the reason for the lie."

MANY RESEARCHERS HAVE devised programs that similarly help participants hone specific empathy skills. Some, for adults, focus on how to empathize in work interactions; others, for elementary-aged students, teach the nuts and bolts of how to take another person's perspective.

In *Roots of Empathy,* now offered in hundreds of schools across the U.S. and around the world, a local family brings their young baby into the classroom once a month, and trained instructors guide students to practice "perspective taking" by identifying what the baby might be thinking and feeling at different times. In studies, elementary schoolers enrolled in Roots of Empathy were better than control students at understanding others' emotions. They also proved more likely to help others in the classroom by the end of the school year, based on reports from their peers.

Yet established empathy programs such as these often rest on the assumption that once people have empathetic skills in their arsenal, they'll be more apt to put them to use. That's not always the case, says Harvard social psychologist Erika Weisz. Studies show that even when people know how to empathize intellectually, they may not exercise that ability unless they truly feel the desire to do so. If they expect empathy to be costly or unpleasant, for instance, some people will refrain from it no matter their training or skill level.

Like Zaki and Cameron, Weisz frames empathy as a socially motivated process—one that's dependent not just on what someone knows about empathy but on how compelled they feel to show it. She's found that another way to nudge people toward empathy—and keep them there—is to embed them in communities where empathy is a baseline expectation. "People want to increase their empathy if you tell them, essentially, it will help them socially," Weisz says. "That is a perfectly reasonable leverage." Unlike empathy skills training, which teaches specific methods of relating to others, Weisz's approach involves building communities that value and reward empathetic behavior. It draws on a kind of constructive peer pressure.

In a pilot program at four California middle schools, Weisz tracked the effects of establishing empathy as a social norm among students. She held three virtual workshops where seventh graders completed activities such as reading stories their classmates wrote about why empathy was important to them. Several weeks after the workshops, students in the program's social-norm group proved more motivated to show empathy toward others.

Weisz attributes these results to the relative ease and simplicity of following a social norm—as opposed to, say, practicing a just-learned empathy skill every day. "My enthusiasm about motivated empathy interventions comes from the fact that they complement people's existing daily lives," Weisz says. "You don't need to completely add a new variable. It's just like riding a wave that's already cresting."

This approach informs the empathy program at Third Street Elementary School in Los Angeles, which I visited last spring. Drawing on a curriculum from Harvard's Caring Schools Network (CSN), Third Street teaches students empathetic skills—and crucially, the students learn to exercise those skills within a community that models empathy at every level. "Character education programs are in a sense about literacy, that kids know right from wrong," says CSN psychologist Rick Weissbourd. "We're more focused on identity or moral motivation: What makes someone want to be a good person in the world, or what motivates someone to care for other people?"

During a perspective-taking exercise, Laura, a parent volunteer in one of Third Street's fourth-grade classrooms, asked students: "What would you do if you saw a student tease another student because of what they're eating?" The kids then sorted themselves into groups around the room based on how they'd answer: ask an adult for help, ignore the situation, tell the unkind kid to stop, or check in with the person who was teased.

"The person who teases the other person might keep doing it," said one boy, arguing for telling the offender to stop.

Not everyone agreed. "It really honestly depends on who it is," one girl says. "If it was my friend, I would probably go over there." If it's not her friend, she added, she would just get out of the way.

"You don't want to make it a bigger problem than it already is," another girl adds.

As each student chimed in, the rest listened attentively, taking in the conflicting opinions. Through this kind of habitual, focused listening, Weissbourd explains, students learn to better appreciate where others are coming from. And it's not just adults leading this dynamic. If a student is having a beef with someone else, they can approach any kid on campus wearing an orange hat. These peer counselors will listen carefully to their concerns and help them solve the problem.

In surveys at U.S. schools, students who participate in CSN curricula report being more helpful than control-group students, and their listening and perspective-taking skills improve. Third Street is a cocoon of sorts, a chance for kids to marinate in empathetic community. That could help prepare them for more challenging encounters later on, to cultivate empathy for those with whom they disagree profoundly.

"The kind of empathy we see in everyday life, a lot of it is you embedding empathy within valuable social relationships," Cameron says. "One approach might be to think about using that relational value as a starting point and then going to the harder places—extending that out to someone you don't know or even someone who's an enemy."

Socially modeling empathy affects not just how community members behave but the way their brains work, says neuroscientist Grit Hein of Germany's University Hospital Würzburg. In a 2024 study, Hein's adult subjects watched videos of people getting hit with an intense burst of air and reacting in pain. People who watched a person respond empathically to the blast videos were likely to follow suit, whereas those who watched another person shrug off the videos acted equally blasé.

Hein found that people who witnessed an empathetic reaction were more likely to rate the recipient's pain as high, whereas those who saw the low-empathy video rated the pain as low. Those who saw the social example of concern also had more activity in their brain's anterior insula, which governs empathy processing, than people who saw the indifferent example.

"If you're surrounded by empathic individuals, it really has an influence. It increases how your brain responds to the pain of another person," Hein says. "The bad news is, it also works the other way around." In other words, if you're surrounded by people who are indifferent or hostile, you're apt to mirror their social

example as well. One 2023 study shows that people who identify as politically liberal have stronger empathetic brain activation than conservatives, raising questions about whether social norms within each political group might drive empathy differences between them.

COMPARED WITH THIRD STREET students, attendees at Rutsch's online cafe are scattered across the country and navigating political divides. The forum's clear rules of engagement, however, create their own kind of fast-forwarded cultural norm. Only one person speaks at a time; the "reflector" must refrain from passing judgment; each person gets to choose their own fresh topic to discuss.

At first, the tension within the group is palpable. A community member named Sushila says she wants to know why police always dress like they're going into battle. "If I were to see them in riot gear or carrying batons, that would make me very uncomfortable," she says.

After Sushila speaks, Roger, now a lead official at Oakland's Community Police Review Agency, tries to "reflect" what she's saying. "You recognize that how you see them, specifically what you see them wearing, can potentially change that relationship," he says. "You see the militarization as calling for a conversation, for the police to engage the community and explain why they see the equipment that they have as being necessary."

What's interesting about the discussions isn't so much the reflectors' input, which mostly mirrors what the speakers say. It's how, over time, being intensively listened to—and intensively listening in return—seems to influence which new topics each speaker elects to bring up.

As the conversation continues, the participants' stances shift toward curiosity—and even optimism. Sushila talks about planning events to help cops and community members establish a better relationship. She then recalls a time when a sheriff in her city encouraged this kind of rapport by acting in *The Vagina Monologues*. Sushila explains what that meant to her: "The fact that a police authority could show vulnerability and be so real … I think she's doing a great public service."

For the remainder of the chat, people's contributions center on how to forge relationships that benefit both police and community members—and how to keep confrontations between them from spiraling. "We need to get more law-enforcement officers to these events," a security officer named John says toward the end, stressing that further similar exchanges could be valuable in bringing people together.

When people feel heard, they tend to feel safer, allowing them to better process what others are saying.

This dynamic parallels what political scientists Joshua Kalla of Yale University and David Broockman of the University of California, Berkeley, found in studies of more than 6,000 U.S. voters who chatted with canvassers about politicized topics, such as immigration and transgender rights. When canvassers engaged voters in typical back-and-forth arguments, few voters who had prejudicial opinions changed them. But when canvassers showed interest in understanding voters and asked them to share their perspectives, voters' prejudiced views diminished for at least four months following the conversation. Likewise, Stanford psychologist Luiza A. Santos and her colleagues found that when people saw empathy as an asset in communicating with political opponents, they used more conciliatory language, and opponents were more likely to see their messages as persuasive.

The norms of polarized times, though, discourage such nuanced exchanges. Takedowns of opposing views get praised in activist circles and upvoted on social media, and civilly engaging with the other side can feel perilously close to endorsing harmful beliefs. But Kalla and Broockman's research, as well as Rutsch's forums, makes a surprising case for more empathetic, reflective social engagement: it's being thoroughly heard, not condemned, that entices people to reject bigotry.

This style of listening, Rutsch emphasizes, does not mean absorbing others' stances as your own. This kind of spongelike empathy is what Yale psychologist Paul Bloom rejects in his 2016 book *Against Empathy*.

When you take on someone else's feelings, Bloom argues, those feelings rub off on you in ways that can interfere with logical decision-making—and even with helping. He also notes that too much empathy can be exhausting, draining people's emotional resources in ways that put them off engaging with others. (Frontline health-care workers and others who witness trauma at close range may be especially vulnerable to this kind of fatigue.)

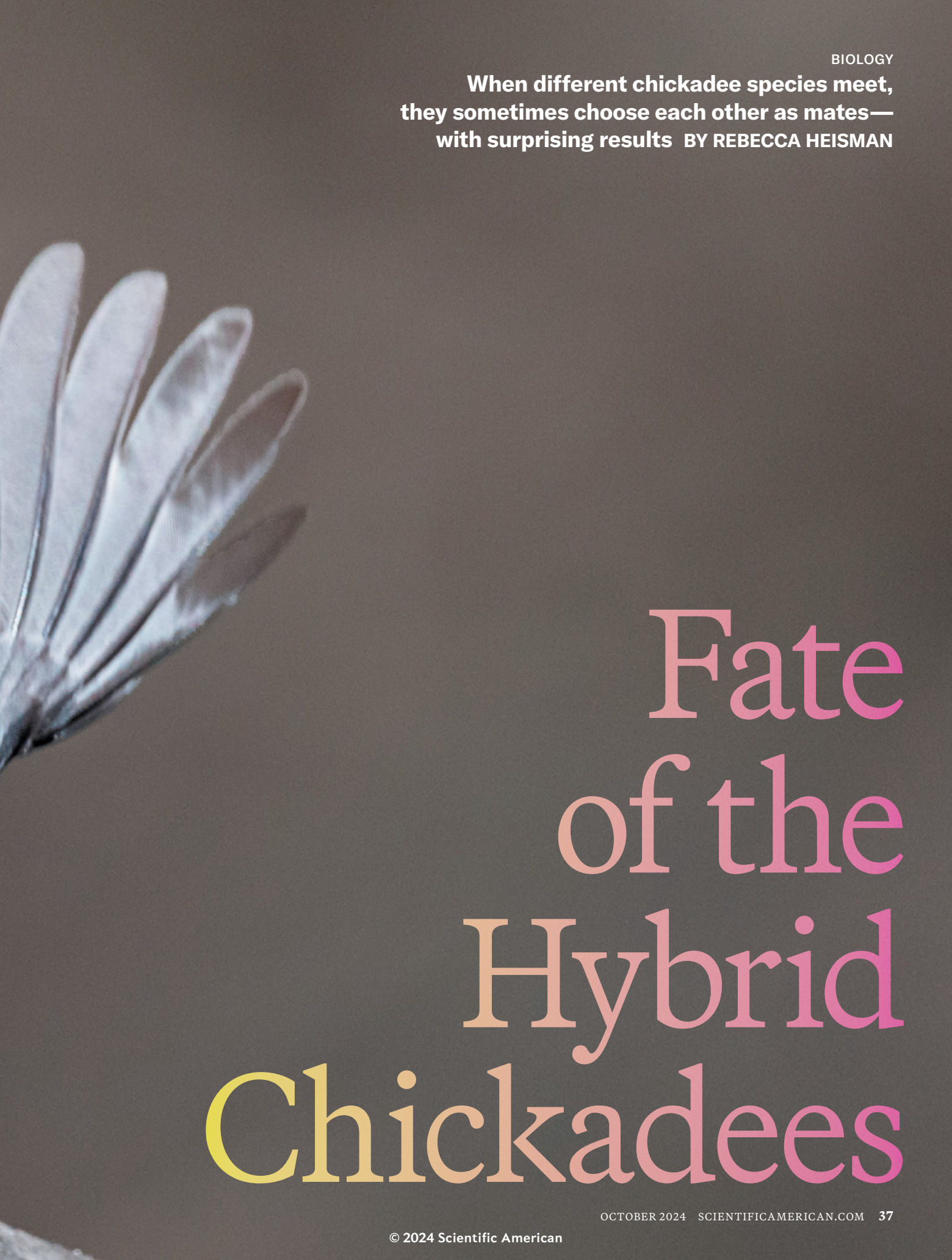
Bloom's critics say empathy can coexist with this kind of deliberative reasoning—and doesn't (or shouldn't) involve identification with others to the point of exhaustion. Empathizing constructively means "sensing into the felt experience of someone else," Rutsch says, "but it's not like you're taking it on to the point where you stop being present with them. It's just about showing that you hear and understand the other person." That understanding, in turn, can actually motivate the informed helping behavior Bloom calls for.

Cognitive science research helps to explain how such virtuous empathetic cycles can pick up speed. When people feel heard and understood, they tend to feel safer, and nervous system fight-or-flight responses recede, allowing them to better process what others are saying. A sense of safety may also help relieve the feeling of being overwhelmed and social angst that fuel the antiempathy bias Cameron describes.

Over time, reflective one-on-one dynamics feed into a broader environment where empathy starts to feel like its own reward. People grow compelled to understand one another in communities that model the practice—whether they're groups of three or four, as in Rutsch's online sessions, or entire workplaces and schools. Weisz hopes researchers can secure funding for future studies of how well social norm tweaks motivate empathy in settings like schools and workplaces.

After the empathy cafe breakout groups merge back into one, some attendees reflect on how to ease people into a practice that can feel, at first, like leaping into the abyss. "I think it'd be really valuable to do this as the first step in a longer process," says a community member named Daniel. "Once you get used to hearing other people and knowing what different opinions are, knowing what different approaches are, then you can get to work on other things." ●

FROM OUR ARCHIVES
The Good and Bad of Empathy. Lydia Denworth; December 2017. Scientific American.com/archive



BIOLOGY

When different chickadee species meet, they sometimes choose each other as mates—with surprising results BY REBECCA HEISMAN

Fate of the Hybrid Chickadees

CHICKADEES, those adorable bandit-masked visitors to bird feeders, are among the most familiar and beloved backyard birds in North America. They're so good at spotting and scolding predators that other birds keep an ear out for their alarm calls, and they're so fearless that they can be coaxed to snatch seeds from people's hands.

Some of the same characteristics that make chickadees appealing to backyard birders—their ubiquity, their boldness, the ease with which their behavior can be observed—also make them ideal study subjects for ornithologists. And where the ranges of two of North America's best-known chickadee species meet, they've created a surprising natural experiment in how the boundary lines between species can shift and even blur.

In the past several decades a small group of scientists have devoted their careers to studying this zone of overlap between Black-capped Chickadees and Carolina Chickadees. Their research has highlighted how human activities are muddling the relationships between species as climate change and habitat alteration change how and where organisms interact. It's also revealed why the hybrids that result—with genes separated by perhaps millions of years of natural selection now suddenly recombined in unexpected ways—sometimes fail to thrive.

It's not all downside, however. Hybridization can also sometimes be a way for a species to adapt more quickly than natural selection would typically allow, letting populations borrow ready-made genetic variations from neighbors adapted for different conditions. The humble chickadee is helping scientists understand how the offspring of novel mixed-species pairings may fare—for better or worse—in our changing world.

EVEN FOR SERIOUS BIRD-WATCHERS, Black-capped Chickadees and Carolina Chickadees are tough to tell apart. Both are members of the genus *Poecile,* with the same black cap and chin, white cheeks, and gray-buff bodies, along with the same love of seed-filled bird feeders and similar cheeky "chick-a-dee-dee!" calls.

It is possible for an experienced observer to tell a Black-cap from a Carolina most of the time, though. For one thing, they typically sing different songs, with Black-caps whistling a two- or three-note tune and Carolinas favoring one with four syllables. But usually the easiest way to tell which of these two chickadees you're looking at is to consult a map. Carolina Chickadees live in the eastern and southeastern U.S., whereas Black-capped Chickadees inhabit most of the rest of North America, replacing Carolinas in the U.S. Northeast, parts of the West, and Canada.

Yet along the extensive, meandering line where the two species overlap, cutting through the Midwest and into Ohio, Pennsylvania and New Jersey, things can get fuzzy. Going back to at least the 1940s, ornithologists working in areas where both species lived occasionally observed Carolina and Black-capped Chickadees that appeared to have paired off to nest and raise young together. Eventually it became clear that the two chickadees don't just cross paths. They share a "hybrid zone" where they regularly interbreed and produce young

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Teresa Kopec/Getty Images *(preceding pages)*

in which their genomes are combined.

Many of us learned in a high school or college biology class that a species is a group of organisms that can reproduce together and produce fertile offspring. This is the biological concept of "species," one of multiple definitions in use today. Although biologists still struggle to agree on what a species is, typically they think of species as being reproductively isolated from one another. Something keeps them from interbreeding—a difference in behavior, for instance, or a geographical barrier.

Still, hybrids between species are surprisingly common. Some hybrids, such as mules—crosses between horses and donkeys—are unable to have offspring of their own. These sterile hybrids are essentially evolutionary dead ends. Other species pairs, however, can interbreed and produce fertile young, blurring the lines between species as they pass on their jumbled genomes. One unique population of brown bears in a remote part of Alaska, for example, appears to be made up of the descendants of a mix of brown bear and polar bear ancestors.

Hybridization is especially common in birds. About 16 percent of all birds have been documented to hybridize with another species at least occasionally in the wild; ducks are particularly profligate hybridizers, with the familiar Mallard Duck on record as having interbred with more than 40 other duck species. Often the placement of the boundary lines between species is little more than a judgment call. Some closely related bird groups have been repeatedly split, lumped and split again over the past century, with the ultimate decisions made by a committee of ornithologists voting on proposals from their peers.

Hybridization often occurs between species that share a common ancestor and are each other's closest relatives. This is not the case with Carolina and Black-capped Chickadees. Genetic research has determined that the true "sister" species of the Black-capped Chickadee is actually western North America's Mountain Chickadee. But after evolving separately for what was probably millions of years, the Black-caps and Carolinas came back into contact with each other as the glaciers receded after the last ice age, and they have been intermingling ever since in the hybrid zone.

In the 1990s, based on repeated surveys carried out by bird-watchers, ornithologists began to realize something particularly odd was happening with these chickadees. Sites that had once been home only to Black-caps now hosted Carolinas as well. The hybrid zone was moving.

Sites that had once been home only to Black-caps now hosted Carolinas as well. The hybrid zone was moving.

IT WAS AROUND THIS TIME that Robert Curry, an ornithologist and behavioral ecologist at Villanova University, embarked on a study of hybrid chickadees that would come to define his career. Curry established three field sites at private nature preserves and state parks along a north-to-south gradient in eastern Pennsylvania: a southern site with Carolina Chickadees, a middle site full of hybrid birds and a northern site that was mostly Black-caps. Across the sites, Curry and his students erected around 500 "nest tubes," cylindrical birdhouses that can be placed in a wider variety of spots than traditional nest boxes. Over the years their work fell into a predictable annual rhythm: they cleaned out the nest tubes in February to prepare for breeding season, then spent April through June tracking nest building and egg laying and eventually captured the adults at each nest to band them and collect blood samples.

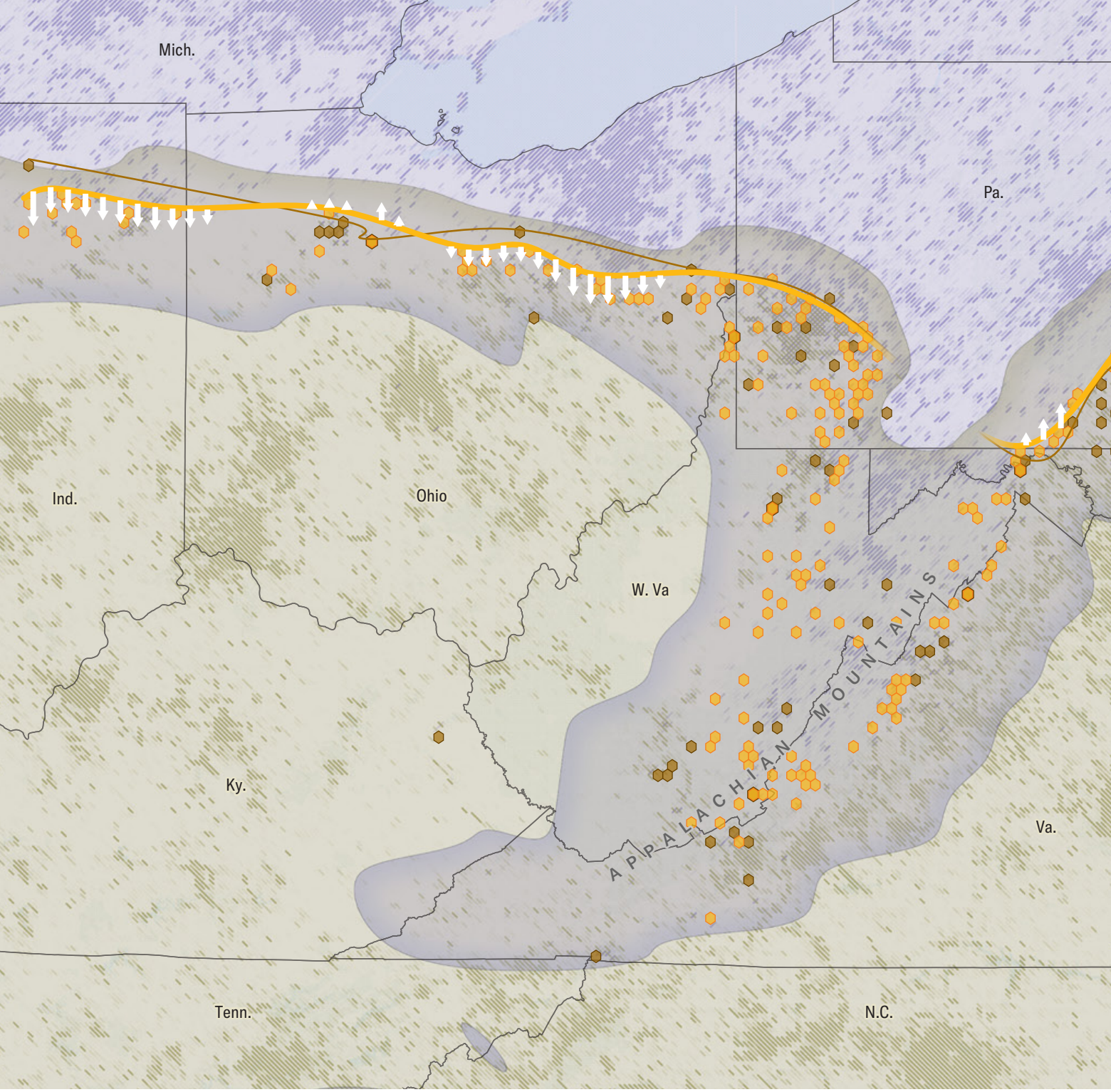
In 2007 Curry and Matthew Reudink, then a student at Villanova, published a paper showing that the hybrid zone had been creeping northward over more than a decade. By that time Curry had amassed years' worth of chickadee blood samples from his field sites, and he had access to tissue samples collected previously by other researchers as well. He, Reudink and their collaborators used genetic analysis to verify the composition of the chickadee population (Carolina, Black-cap or hybrid) at each site and looked at how that composition had shifted over time. (Eventually, as the proportion of hybrids at the northern site increased, Curry added a fourth site still farther north.) The researchers' findings provided confirmation of what bird-watchers had already observed: in a decade and a half the northern edge of the hybrid zone had moved about 20 kilometers north. But why?

In the years following that publication, people asked Curry whether the movement he and his colleagues reported was connected to climate change. "My answer was always, yes, probably, but I don't know how to study that," Curry says. The solution came through a collaboration with researchers at Cornell University. Scott Taylor, then a postdoctoral researcher at Cornell, led an analysis using data from eBird, an online platform where bird-watchers upload their observations. The study showed that the northern limit of Carolina Chickadees' range is roughly the point on the map where the average minimum winter temperature hits minus seven degrees Celsius—and that the rate of their northward expansion in Pennsylvania has been consistent with warming winters. The hybrid zone does indeed appear to be moving because of climate change.

CLIMATE CHANGE is really only half of the story behind the movement of the hybrid zone. It explains why Carolina Chickadees have been able to gradually move north, but it doesn't explain why, when Carolinas expand into a new area, female Black-capped Chickadees sometimes choose to mate with Carolina males instead of males of their own species.

It's not a case of mistaken identity. Although humans may struggle to tell the two species apart, the birds probably know who's who. Fascinatingly, in laboratory experiments, Black-capped and Carolina Chickadees can distinguish between the smell of a member of their own species and that of a member of the other species. But whereas female Carolina Chickadees have a strong preference for the scent of males of their own species, female Black-caps are less particular.

It's impossible to know what's going on inside the mind of a female Black-capped Chickadee when she selects a Carolina as her mate. Curry suspects it has something to do with social dominance. Female Black-caps may be attracted to male Carolinas because they're sometimes higher in the flock's dominance hierarchy, but this idea is hard to test. What scientists *can* study is what happens next. When the genes of two species separated by up to millions of years of independent evolution



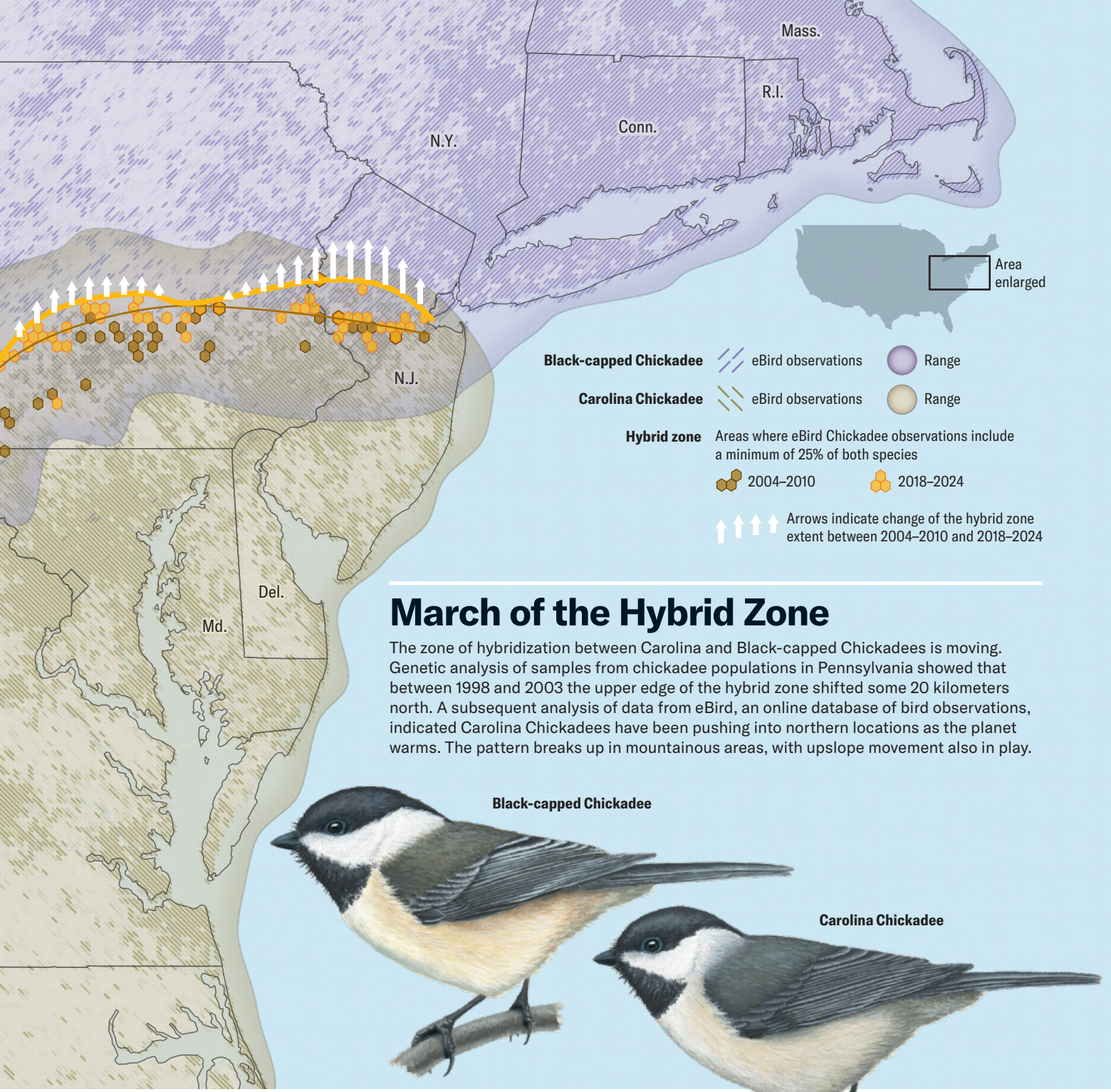
intermingle in a clutch of eggs, what will the hybrid hatchlings be like?

For one thing, not every hybrid egg will hatch. Reproductive isolation between species—the force keeping two species separate—can operate at multiple levels. Animals from two species may choose not to mate with each other in the first place; that's premating isolation, which doesn't seem to always be in play between Black-capped and Carolina Chickadees. But if individuals from different species do pair up, reproductive isolation is still happening if their offspring aren't likely to survive, thrive and produce offspring of their own.

Almost as soon as Curry began collecting chickadee data, he noticed something amiss at the field site with the most interspecies pairs. "We had some nests that just had terrible hatching success," he says. Sometimes only one egg out of a nest of eight hatched.

Working with a Villanova student, Curry set about documenting hatching success rates across the hybrid zone. The results, published in 2022, showed that as the zone moved north, a trough in hatching success swept across the landscape with it. When Carolina Chickadees moved into an area inhabited by Black-caps, the percentage of eggs laid in local nests that hatched successfully would fall; in a different area, as Carolinas became dominant and the proportion of mixed pairs fell, the hatching rate increased.

For those hybrid birds that do hatch, their mixed-up genomes lead to problems.



March of the Hybrid Zone

The zone of hybridization between Carolina and Black-capped Chickadees is moving. Genetic analysis of samples from chickadee populations in Pennsylvania showed that between 1998 and 2003 the upper edge of the hybrid zone shifted some 20 kilometers north. A subsequent analysis of data from eBird, an online database of bird observations, indicated Carolina Chickadees have been pushing into northern locations as the planet warms. The pattern breaks up in mountainous areas, with upslope movement also in play.

A study from another area of Black-cap-Carolina overlap, in Ohio, found that hybrids had higher basal metabolic rates than either parent species—even when sitting still, they need to expend more energy just to keep their bodies functioning.

Hybrids are also, to put it bluntly, a bit dim-witted. Chickadees as a group are famously clever. In preparation for the harsh winter, chickadees hide tens of thousands of seeds to retrieve and eat later. They need to be able to remember where to find them. To accomplish this recall, chickadees grow new neurons in their hippocampus, one brain region that is responsible for spatial memory. Some studies have suggested the hippocampus swells in size every autumn to store the information necessary for winter survival.

Research on Black-capped Chickadee cognition has shown that their spatial-cognition abilities are correlated with their environment. Chickadees living in places with the coldest winters have the best memories. Based on this finding, Amber Rice of Lehigh University hypothesized that Black-capped Chickadees would perform the best at tests of learning and memory, Carolina Chickadees (which live, on average, in milder climates) would do the worst, and hybrids would be somewhere in between.

Rice and her collaborators tested captive

Map by Jer Thorp, Illustrations by Rebecca Gelernter/Near Bird Studios

Carolinas, Black-caps and hybrids on tasks that assessed how well they could remember the location of a hidden treat or solve a simple puzzle. To her surprise, hybrids performed worse than their parents on both tasks. "We looked at our results, and we were like, huh," she says. The findings led Rice's team to start thinking about genetic incompatibilities. All these problems—poor hatching success, inefficient metabolism, inferior cognitive abilities—probably come down to the fact that some sections of Carolina and Black-capped Chickadees' genomes simply don't combine well.

Perhaps no one has spent more time thinking about the intermingling of genes between chickadee species than Scott Taylor, the then postdoc who led the study linking the movement of the hybrid zone to climate change and now a faculty member at the University of Colorado Boulder. Taylor has been interested in hybrids since he was a kid. He recalls really liking Pegasus and unicorns and the idea that they could hybridize to make a "pegacorn."

Taylor has studied genetic patterns in the chickadee hybrid zone across both time and space. "We're particularly interested in regions of the genome that don't move between species when they interbreed," he says, "because they could be particularly important for reproductive isolation."

This movement of chunks of genes across the hybrid zone is called introgression, and when it *doesn't* happen at a certain spot in the genome, that may indicate a specific set of genes does not mix well between species. More recently, preliminary work by Taylor's team has helped reveal the genetics underlying some of the deficits other scientists have observed in hybrids: genes related to metabolism and cognition show especially low rates of introgression.

"I think the chickadee work has clarified one of the most important mysteries of avian hybrid-zone research: What is the actual source of selection against hybrids?" says David Toews of Pennsylvania State University, an expert in hybridization in wild birds. "In many other hybrid zones, we have some inkling about what makes hybrids 'crappy,' but this large body of work studying Carolinas and Black-caps actually tests these ideas."

Hybrid chickadees can be fertile. Unlike famously sterile hybrids such as the aforementioned mules, they can breed with birds of either parent species. But the problems created by their mixed-up genomes mean they presumably leave fewer descendants, on average, than nonhybrid chickadees. This ongoing natural selection against hybrid individuals is what ultimately prevents two species from collapsing into one through interbreeding.

BLACK-CAPS AND CAROLINAS are just two of North America's seven chickadee species—and they aren't the only pair that hybridizes. Where the Black-capped Chickadee overlaps with its closest genetic relative, the Mountain Chickadee, in the West, these two species can also interbreed. Taylor has begun a study of these hybrids. There's no clear hybrid zone cutting across the landscape, however; instead hybrid birds pop up sporadically throughout a wide area.

Working with then graduate student Kathryn Grabenstein, Taylor mapped locations where hybrids had been reported on eBird. (Mountain Chickadees have a distinctive white eyebrow that both Black-capped and Carolina Chickadees lack, and hybrids are relatively easy to identify by sight.) The birds' distribution was oddly patchy with a few clear clusters. They wondered what was driving this peculiar pattern.

FROM OUR ARCHIVES
Human Hybrids.
Michael F. Hammer; May 2013. Scientific American.com/archive

Eventually Taylor and Grabenstein uncovered a strong correlation between the presence of hybrids and the degree to which habitat in an area had been altered by humans. "I think what we've done in these disturbed areas is we've planted trees that favor Black-capped Chickadees," Taylor says, "[which has] increased their populations and then increased the frequency of hybridization between the two species in an artificial way." To study this link further, he has put up more than 400 chickadee nest boxes, from the city of Boulder to the tree line in the mountains above.

Climate change in the East, habitat disturbance in the West: in both cases, human activities are redrawing the boundaries between species. This kind of disruption is most likely only going to increase in the future. So what will happen to these species as their genomes continue to mix? "I often get asked, Is hybridization good or bad? And the answer is, it's neither of those things," Taylor says. "The outcomes are always context-dependent."

THE ADVENT OF GENOMICS revealed that hybridization is everywhere—even in our own evolutionary history. Neandertals may be long extinct, but some of their genes live on in today's humans thanks to long-ago hybridization with *Homo sapiens*. Scientists have linked genetic variants from Neandertals to fertility, diabetes risk and even our susceptibility to COVID. Neandertals themselves might not have died out so much as simply been absorbed into *H. sapiens* populations in a process known as genetic swamping, through which a common species can hybridize a rare one out of existence.

Genetic swamping is just one of many possible outcomes of hybridization. "You can have situations where hybrids have low fitness, [which] can actually make the boundaries between species clearer," Rice explains, or "you can have this merging so that you lose that species boundaries, or you can even have cases where the hybrids form their own species." Hybrid speciation, in which a new species originates from a cross-species pairing, has been documented in butterflies, fish, toads and dolphins.

Hybridization can also help a species flourish, Rice adds, by acting as "a bridge for new genes to enter another species [and] provide fitness benefits in certain environments." As Earth's climate continues to warm and change, the ranges of more species will shift, potentially bringing them into contact with evolutionary cousins from whom they'd previously been isolated. Inevitably, there will be winners and losers. But in some cases, a new set of genes borrowed from a relative could be the difference between extinction and adaptation.

Black-capped Chickadees, Carolina Chickadees and Mountain Chickadees are all considered "least concern" species by the International Union for Conservation of Nature, meaning they're currently plentiful and not in need of focused conservation efforts. But Carolina and Mountain Chickadee numbers appear to be decreasing overall, and Black-caps are declining in the western parts of their range. Some Mountain Chickadee biologists are worried about how these birds will cope with the extreme weather patterns that are forming in their high-elevation homes as the planet heats up. Could a hybrid bird introduce new genes into a population that, someday, could help that group adapt?

"What will happen? We don't know yet," Rice says. "But it will be interesting to see." ●

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MENTAL HEALTH

The Traumatic Roots of Addiction

A new generation of treatments addresses the trauma that often underlies addiction

BY MAIA SZALAVITZ

ILLUSTRATION BY CHLOE NICLAS

WHEN I ENTERED REHAB AT 23, I learned that trauma was a thread woven into most addiction stories. Many people in my program described horrific neglect or maltreatment, including sexual abuse, they had experienced as children. Still, few seemed to realize how traumatizing those things had been. The traces of trauma in my own life were not then obvious to me, either, perhaps because my parents had suffered so much worse. Now, however, I can see that some of my extreme sensitivities, such as my fear of crowds and enclosures, eerily reflect my father's story.

When my father was a kindergartner in Hungary, he and his mother were crushed among thousands of starving concentration-camp victims on a train bound for Auschwitz. It was abandoned by the Nazis as the Allies took control in 1944. My father didn't speak for a year afterward and struggled with depression for most of his life. My mother's trauma was more ordinary: she lost her mother to cancer in early adolescence. They were loving parents, but I grew up feeling unworthy because nothing I did seemed good enough. Easily overwhelmed by sensory and social encounters, I cried often, which led to my being bullied in school.

As a teen, I found that drugs—first marijuana, then psychedelics and, it being the 1980s, cocaine—made it easier for me to connect socially. But heroin, which made me feel calm and satisfied and safe, was my favorite. By 1986 I was injecting daily and had to leave Columbia University. Two years later, when I weighed 80 pounds and had already made many failed attempts to quit on my own, I finally recognized that shooting coke and heroin up to 40 times a day definitely meant I was addicted and needed help.

Like most rehabs even now, the one I attended was based on the 12-step program of Alcoholics Anonymous (AA). The organization was founded in 1935 by a stockbroker and a doctor who believed their own addiction to alcohol had derived from "defects of character," such as being selfish and avoiding responsibility. The main active ingredient of 12-step programs, which now exist for practically every type of addiction—from cocaine to overeating to gambling—seems to be the social support of group meetings. These have helped millions of people, including me. But some of the program's aspects have harmed people who were told that strict adherence to the rules was the only way to recover. One particularly problematic teaching is that recovery requires addicted people to see their misbehavior as the cause of their problems—rather than encouraging them to understand why they might have been especially prone to seeking solace in substances.

Maia Szalavitz is author of, most recently, *Undoing Drugs: How Harm Reduction Is Changing the Future of Drugs and Addiction* (Hachette Books, 2021). She is a contributing opinion writer for the *New York Times* and author or co-author of seven other books.

In recent decades a body of research has established that adverse childhood experiences are critical in the development of substance addictions. A 2021 review found that more than 40 percent of people with opioid addiction reported some type of childhood abuse or neglect, and 41 percent of women had been subjected to childhood sexual abuse, much higher than the rate for the general population. A different study showed that among those with any type of addiction, at least 85 percent have had at least one adverse childhood experience, with each additional experience raising the risk. The link is most pronounced among those diagnosed with post-traumatic stress disorder (PTSD), characterized by flashbacks and other psychological disturbances that can develop in response to a shocking or terrifying event. Among people treated for any substance addiction, one third have active PTSD—and among those with PTSD, 58 percent have had problems with substance use.

This awareness of how addiction and trauma are intimately intertwined has birthed a new generation of treatment strategies that simultaneously address both issues. So far they have been tested mostly for people with both PTSD and addiction—and they reinforce the idea that the trauma drives the substance use. "What we see is remarkable," says Teresa Lopez-Castro, an associate professor of psychology at the City College of New York. "When the PTSD symptoms go down, the substance-use-disorder problems will go down, but the opposite doesn't happen that frequently." My own examination of addiction over the past four decades has convinced me that trauma-informed care is superior to the traditional methods, which often seek to erase a patient's autonomy and thereby risk compounding existing wounds or inflicting fresh trauma.

THE SUFFERING THAT PREDISPOSES someone to addiction doesn't have to be overt. As in my case, it can be as seemingly mundane as being raised by depressed parents or being bullied in school. Other circumstances that increase vulnerability include having addicted or mentally ill parents; witnessing violence; losing a parent; or experiencing a life-threatening illness, accident, conflict or disaster. A study of the entire Swedish population found that undergoing just one of these potentially traumatizing experiences may double the risk for substance use disorders.

Brain imaging and other techniques have teased out the neurological pathways entwining trauma with addiction. Both experiences change the brain's reward systems, which motivate people to seek evolutionary essentials such as food, water, sex—and, crucially, safety. Brain signals are complicated, however, and many seemingly separate "systems" share the same circuitry. Systems that predict reward or punishment are deeply intertwined with the modulation of stress: many of the same neurotransmitters and brain regions involved in motivating us to seek pleasure and satiety also help to keep us safe.

Growing awareness of how addiction and trauma are intertwined has birthed a new generation of treatment strategies.

Dopamine, for example, drives us to seek sources of pleasure linked to survival and reproduction and also to avoid threats. The neurotransmitter acts on the striatum and the prefrontal cortex, both of which are in the forebrain, and helps us predict whether an experience will be rewarding or upsetting. It does so by creating a feeling of "wanting"—either to get more pleasure or to escape from pain. And during scary or stressful experiences, endogenous, or self-generated, opioids known as endorphins and enkephalins are released in the brain. These are guided by hormones from the adrenal and pituitary glands as part of the classic stress-response system, to ease pain and facilitate escape. These opioids also make food, sex and socializing feel good, causing a feeling of "liking" something or someone and of satiety and comfort.

Growing up in a threatening and stressful environment can undermine this circuitry. Studies in both humans and animals show that adversity in childhood alters the regulation of stress hormones such as cortisol. These hormones, released during prolonged or acute stress, change brain regions such as the amygdala, which is activated by strong emotions, especially fear and distress. Stress in early life also alters the nucleus accumbens, a part of the striatum that is key to addiction: it makes us want more of what feels good. Memory areas such as the hippocampus are also profoundly affected, making some memories too strong and others too weak. "Our reward system and our stress system become attuned to trying to meet the needs of reducing threat," Lopez-Castro says.

Research shows that people who have experienced childhood trauma are more aware of and sensitive to signs of a potential threat. Someone whose father was always raging, for example, may interpret even neutral facial expressions as angry. Moreover, rapid responses are often necessary when someone is under threat. But repeating them strengthens emotional brain regions and reduces the influence of the prefrontal cortex, which puts the brakes on impulsive actions. Living with fear and anxiety can therefore impair impulse control—leaving some children more likely to both see threat where it isn't and react to it rapidly, with little consideration of consequences. Such responsiveness can be lifesaving in threatening environments. But it also can be detrimental when impulsive reactions interfere with the child's ability to learn that a situation is in fact safe and thereby lead to behaviors that others perceive as aggressive.

Even after the trauma has ended, these brain changes remain. "Our ability to sort of shift to think-

ing, 'Oh, everything's safe now' is very much compromised," Lopez-Castro says. This impairment can lead to a person prioritizing immediate relief—by, for example, taking drugs—over planning a future that seems either uncertain or unlikely to be better than the present.

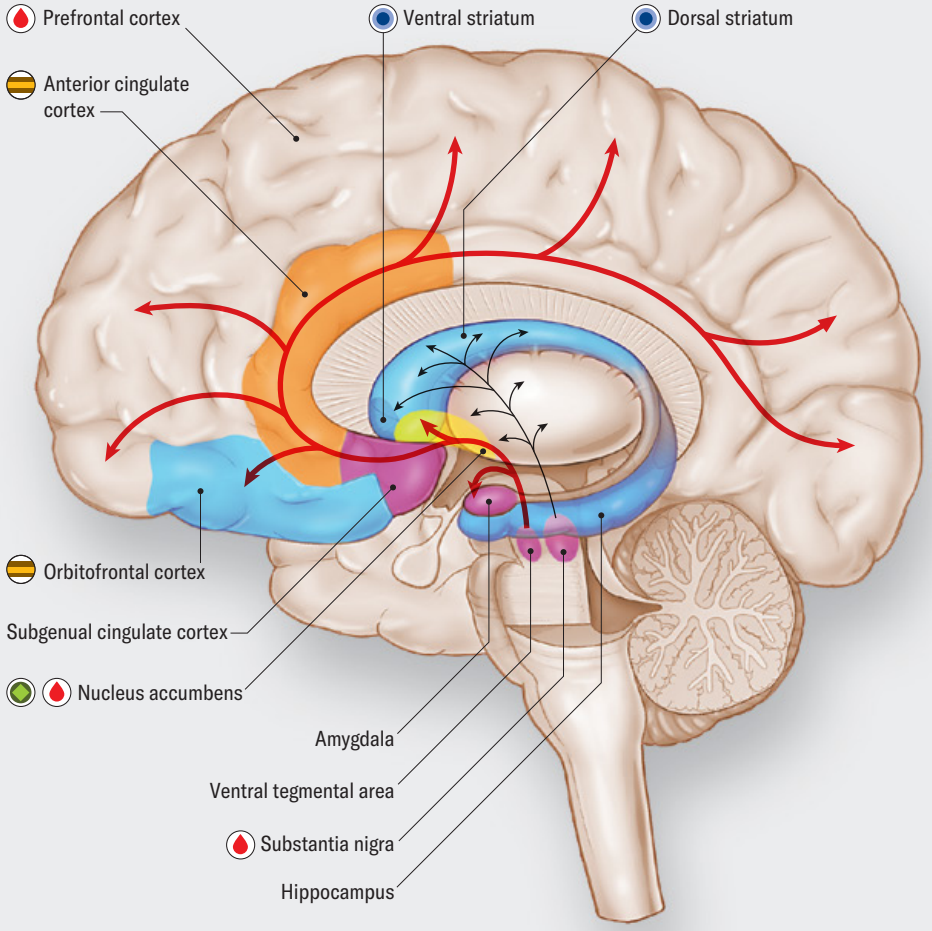
Another possible consequence of early-life adversity is anhedonia, an inability to experience pleasure, which in turn can suppress motivation. My own experience of it was a sense of dread and dullness of mood that I couldn't verbalize but that made me constantly uncomfortable in my own skin. This symptom is a common characteristic of depression and, unsurprisingly, makes people vulnerable to misusing substances that promise relief.

"When trauma happens early in life, it really kind of destabilizes us—but we adapt," Lopez-Castro explains. The relevant adaptations in the reward and stress systems can help people survive, but they also can take a toll on emotion regulation. Overall, severe early stress can create a general sense of dread and pleasurelessness—so if traumatized kids are exposed to drugs that amplify dopamine or activate the brain's own opioid systems, they are highly susceptible to becoming addicted because the drugs offer the excitement and comfort they otherwise lack.

At the same time, genetics affects addiction risk by setting defaults. Some infants are more easily distressed, for example, whereas others have calm temperaments. These variations reflect the responsiveness and resilience of the stress and reward systems. Roughly half the risk for substance use disorders is genetically determined, but the way this predisposition plays out is extremely varied. Some genes put people at risk via personality traits such as being prone to thrill-seeking or having difficulties with impulse control; others work by causing difficulty focusing, low moods or anxiety. Yet others, such as the genes related to the metabolism of alcohol, alter the risks associated with particular substances.

Childhood Adversity and Addiction

Addiction arises from changes in the brain's reward circuits, which are inextricably entwined with stress circuits. That's because flexibly responding to circumstances requires weighing potential rewards such as socializing, food and sex against the stress of risks such as rejection or worse. Childhood adversity can reduce impulse control and the pleasure of natural rewards while tightening the grip of negative emotions such as sadness. These alterations make calming and pleasurable drugs more addictive.



THE BRAIN'S REWARD SYSTEM

Dopamine, which leads to "wanting," and natural opioids, which make for "liking," are both key to addiction. This diagram shows two pathways of the dopamine reward system, the mesocorticolimbic and the nigrostriatal, along with some of the brain regions they involve or impact.

Mesocorticolimbic pathway

Nigrostriatal pathway

HOW TRAUMA ALTERS THE REWARD SYSTEM

Childhood trauma is linked with unusual activity in regions overlapping with the brain's reward system. A 2016 review paper describes changes in areas connected by the dopamine pathways in particular. Several of these regions are involved in addiction.

- Changes in blood flow to parts of the prefrontal cortex, substantia nigra and nucleus accumbens
- Reduced size of the striatum
- Changes in development of the nucleus accumbens
- Reduced volume, thickness and/or connectivity of the anterior cingulate cortex and orbitofrontal cortex

Source: "The Effects of Childhood Maltreatment on Brain Structure, Function and Connectivity," by Martin H. Teicher et al., in *Nature Reviews Neuroscience*, Vol. 17, September 2016 (*reference*)

Graphic by Body Scientific

Traumatic stress is most often what tips these traits and tendencies into pathologies or disabilities. Addiction often results from attempts to self-medicate the symptoms—which is why treating the underlying trauma can be essential to a cure.

MICHAEL, A VETERAN in his 30s who has struggled with both PTSD and addiction, understands all too well how they are connected. (Names have been changed for privacy.) Fortunately, he was able to get both treated simultaneously as part of a study led by Sudie Back, professor and director of addiction sciences at the Medical University of South Carolina.

The treatment included a psychotherapy called COPE, which stands for "concurrent treatment of PTSD and substance use disorders using prolonged exposure." On its own, COPE has been found to be safe and effective in multiple clinical trials. The study Michael enrolled in tested whether adding the social-bonding hormone oxytocin could improve outcomes. Such combined therapies for co-occurring disorders offer a glimpse of what better care could look like in the future.

Michael was raised on a prison farm, where his father worked in corrections. From an early age he was abused by an older relative who beat him and persistently threatened him with sexual assault. He joined the air force just after high school, and in Afghanistan he volunteered for risky assignments. "I was 18 and wanted stories to tell," he says. The first time his unit got attacked, though, he slept through the first few minutes, which led him to start taking stimulants: he never wanted to be caught off guard again.

Combat and witnessing so much suffering and death caused PTSD. (Childhood abuse seems to increase the risk of PTSD developing later in life in response to acute stressors.) At the time, Michael says, everything felt "surreal," and he wasn't really processing anything emotionally. He was also drinking and taking large quantities of "speed"—stimulants such as amphetamines that promote wakefulness and, in large doses, can cause paranoia. "People in my chain of command were noticing that I had a lot of issues with anger," he says. Recognizing his problem with stimulants, Michael quit taking them in 2007 and started counseling to deal with his intense rage, a common symptom of PTSD. Returning home after six years of service, he had difficulty adjusting and was drinking heavily. He enrolled in the trial in 2023.

COPE involves 12 weekly 90-minute sessions led by a trained therapist. Because drug cravings are often driven by stress, COPE teaches better emotional regulation and thereby addresses PTSD and addiction simultaneously. Participants in the program are asked to recount their traumatic experiences repeatedly in a safe place, which helps them manage stressful memories and stop avoiding environments and experiences that can trigger them. They are also gradually exposed to increasingly challenging situations that they would typically avoid, at a pace they control.

Brain changes induced by adversity can lead to a person prioritizing immediate relief over planning for an uncertain future.

"At the heart of trauma—and trauma-related issues—is avoidance," Lopez-Castro says. By replacing avoidance with approach, exposure therapy retrains the brain to recognize safety. Over time this strategy increases both the ability to tolerate stress and the capacity to stay calm in situations that evoke the fear, grief or anger associated with past traumas, which is essential to recovering from both PTSD and addiction. Because alcohol and other drugs are often craved during and used to cope with strong emotions, COPE also teaches alternative ways of managing distress such as breathing techniques and seeking support from others.

Further, because trauma is marked by a sense of helplessness in the face of potential annihilation, recovery from it requires maximizing the patient's sense of control, security and autonomy. Toward this end, therapy needs to be highly structured and predictable so the patient knows what to expect and can pull back if it becomes overwhelming. "We talk to them about the rationale, which is so important," Back says.

Many addiction-treatment programs, unfortunately, view questions about process as resistance to recovery. Newcomers to 12-step programs are often told to "shut up and listen" because "your best thinking got you here." This dismissive approach can generate mistrust, especially if patients perceive that counselors are being punitive rather than helpful when pushing them to confront their fears. In contrast, effective trauma and addiction therapists explain exactly why they are going to ask patients to face the painful situations they most seek to escape—and how this will diminish the power of these memories when done slowly and with a measured and controllable escalation of intensity.

Traumatic memories are often stored differently in the brain, which may account for why people with PTSD experience them as "flashbacks" and feel as though they are reexperiencing terror here and now. The therapeutic process in COPE can transform the patient's recollection of past traumas from fully reexperiencing them into simply telling a story of what happened—and may help the brain process these memories more typically. As Back has noted, the COPE program reduces PTSD symptoms—and that in turn cuts drug craving and use. Simply stopping the

drugs doesn't help the underlying issues and can, in fact, exacerbate symptoms.

Another prominent commonality between addiction and PTSD is that maintaining strong social connections is usually essential to lasting recovery because healthy relationships are physiologically fundamental to stress relief. This dynamic begins in infancy: babies literally cannot modulate their stress system without nurturing touch from caregivers, which releases endogenous opioids and oxytocin, creating a sense of comfort and safety. In normal development, oxytocin may link this stress relief in the presence of loved ones to the activation of the opioid system. Both substances are released when parents soothe their children, creating an association between the parent and comfort. Later, when Mom "kisses the boo-boo to make it better," this gesture triggers endorphins to relieve the pain and stop the tears.

In earlier research, Back and her colleagues found that the therapeutic bond between patient and therapist is a leading determinant of recovery—so they thought adding oxytocin might improve this connection. One study by the group of people who had PTSD without addiction showed that oxytocin accelerated positive change. The new study, which included those who had PTSD with addiction, hasn't been completed or unblinded, so Michael doesn't know whether he got the hormone or a placebo. But he does know that he got better.

"I think it was really just being able to get some things out that I had put to the side and then just the way the whole process went," Michael says, describing what helped him most. He stresses that his relationship with his therapist was crucial, calling her "very personable" and "very understanding." The repetition and emotional safety helped him make sense of his experiences and put them more firmly behind him. He is now able to use alcohol moderately without returning to his prior compulsive drinking.

Another promising approach that can be combined with addiction treatment is known as cognitive processing therapy (CPT). This treatment focuses on minimizing patients' distorted thoughts and self-concept rather than exposing and taming the traumatic memories themselves. It can be especially useful for people whose fear of their own traumatic memories prevents them from revisiting the experiences—the biggest obstacle to the success of COPE and other exposure therapies.

Sandra started drinking with friends when she was 15. "I remember feeling anxious from a really early age," she says. "It just alleviated that feeling for me." Over the next few years she became dependent on alcohol and, later, ketamine, which she began using at raves.

In her early 20s Sandra had just started treatment for her substance use disorder at a program in New York City called the Center for Motivation and Change when she was held hostage and sexually attacked by a boyfriend she was trying to break up with. She received CPT after a coach connected with that organization helped her have him arrested and get a restraining order.

Sandra says the treatment targeted "false beliefs or core ideas that you've had about the world and other people due to the trauma." She gives several examples: "A main one was, like, I'll never be a good girlfriend or, like, girlfriend material. I'll never find happiness. Or I'll never feel safe again."

Her ex had told her repeatedly that he was the only one who would ever want her. CPT helps patients reality-test these ideas and reject the overgeneralizations and catastrophic thinking they represent. When these hyperbolic thoughts are expressed in the safety of therapy, their power is diminished, and healthier ways of seeing can start to replace them. Sandra initially attempted to moderate her use of alcohol and other drugs but ultimately decided on abstinence.

She's now been sober for more than a year but has a mixed relationship with 12-step programs, which she had tried at various times and now uses selectively. She had to drop one AA sponsor, or mentor, who tried to engage her in a harmful version of the fourth step, in which people take "moral inventory" to look at the character defects the program sees as underlying addiction. The written version of this step asks participants to focus on accepting a role in major events in their lives so that they can take responsibility for their actions. In the course of this effort, Sandra's sponsor asked her to look for her part in having been assaulted. "I just did *not* agree," she says, and she fired the sponsor. For victims of trauma, believing that being raped or abused was somehow their fault is profoundly damaging—and is one of the beliefs that both COPE and CPT aim to change, not reinforce. These days Sandra attends certain AA meetings for social support but does not engage with those who push problematic ideas about the steps.

My own experience of the fourth step was much more positive, largely because the person I worked with recognized that like many other women struggling with addiction, I had a bigger problem with hating and blaming myself than I did with trying to avoid accountability.

Treatment providers have tried to move away from this "tough love" approach in recent years. But it is hard to eliminate it because many 12-steppers employed as counselors believe that what worked for them should work for everyone. Worse, many facilities, often called "therapeutic communities," are modeled on a defunct cult called Synanon that was seen as having found the first real cure for heroin addiction. Synanon's leadership believed that voluntarily working the steps was too soft and turned the method into a coercive one, using confrontation, humiliation and emotional attacks as

ways to force change. (AA—a voluntary, self-governed group—takes no official position on treatment policies and practice, so it cannot address misuse of its program.)

Nzinga Harrison is co-founder and chief medical officer of Eleanor Health, which provides evidence-based online and outpatient addiction and mental health care to around 30,000 people in seven U.S. states. The overwhelming majority of these patients have had prior negative experience with treatment, she says. "They experienced traumas in their early life, and then they go into treatment, and the treatment itself is traumatic, reinforcing abandonment, devaluing them."

Lopez-Castro adds that "the shaming that has been so much a part of their experience of being traumatized is then evoked in [treatment] settings where they're told, 'You are weak, worthless.'" She has conducted interviews with people with PTSD who were addicted to cocaine and heroin and were receiving clean needles from a program intended to reduce the health risks associated with syringe use. Many, especially the older ones, reported that their prior experience of treatment was being screamed at or being made to scrub floors with toothbrushes and wear dunce caps. "It has been really brutal for them," she says, "and these were their formative experiences of treatment."

Lopez-Castro is starting work on a study that will look at whether providing trauma-informed, empathetic care to people who inject drugs can help participants reduce harms associated with drug use. This effort is based on insight from harm-reduction therapists, who have found that some traumatized people cannot even start to change their drug use patterns without first learning alternative methods to manage trauma symptoms.

PTSD AND ADDICTION also can be addressed through approaches that increase neuroplasticity, which is the brain's ability to change and adapt in response to experience. Neuroplasticity varies over the lifetime. Early childhood and adolescence are known as sensitive or critical periods when the brain is most capable of learning rapidly and altering its trajectory in both positive and negative ways. If adverse experiences occur during these times, they can hardwire dysfunctional behavior patterns, making them difficult to change.

Treatments that alter plasticity are therefore likely to be helpful, as long as they are used under conditions where people can safely learn healthier strategies for organizing the way they think and act. Everything currently known to have antidepressant effects—from medications such as fluoxetine (Prozac) to exercise—increases plasticity as well and might augment other therapies for PTSD and addiction.

Intriguingly, psychedelic drugs such as LSD and psilocybin mushrooms have recently been found to rapidly increase plasticity and may act by restoring the plasticity associated with critical periods. Researchers are now studying these substances to separately treat PTSD and various addictions, and early clinical trials with MDMA, known colloquially as "ecstasy" or "molly," suggest promising results. MDMA not only increases neuroplasticity but also prompts the release of oxytocin, which may account for why people often describe their experience on the drug as one of feeling connected, empathetic and loving. This social specificity may make it especially helpful for people with PTSD and addictions.

Trauma is so prevalent among people with addiction that all treatment programs need to be prepared to address it.

One clinical trial of people with moderate to severe PTSD, published in 2023 in *Nature Medicine,* found that 46 percent of participants had complete remission of symptoms with therapy plus MDMA, compared with 21 percent in the group that received the same therapy plus a placebo. Researchers in Australia are now studying the combination of COPE and MDMA for people with PTSD and alcohol use disorder. Other studies of various psychedelics to treat addiction and PTSD, separately or simultaneously, are also underway. The U.S. Food and Drug Administration has designated MDMA, LSD and psilocybin as potential "breakthrough" medications, which puts them on a faster track toward approval. In early August, however, the FDA rejected MDMA-assisted therapy for PTSD, asking for another phase 3 trial to further assess benefits and safety.

Both addiction and PTSD are complex conditions, and it is unlikely that any single approach will work for everyone. But there are now more options than ever, which should bring greater odds of recovery. Evidence-based approaches such as COPE and CPT need to be made available more widely, and people with addiction must be empowered to choose the therapies that best align with their needs. Because traumatic experience is so prevalent among people with addiction, all treatment programs need to be prepared to address it—and to ensure that treatment at least does no harm.

I am lucky to have avoided the most traumatic types of treatment when I was desperate and vulnerable. Although I was still subjected to some questionable practices, such as being treated in an authoritarian setting, I was ultimately able, as one highly useful AA slogan puts it, to "take what I like and leave the rest." Making addiction treatment more trauma-informed and compassionate is not only the right thing to do, it's the easiest way to rapidly improve outcomes and to get people to welcome much needed care. ●

FROM OUR ARCHIVES
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Sara Reardon; July 12, 2023. Scientific American.com/archive

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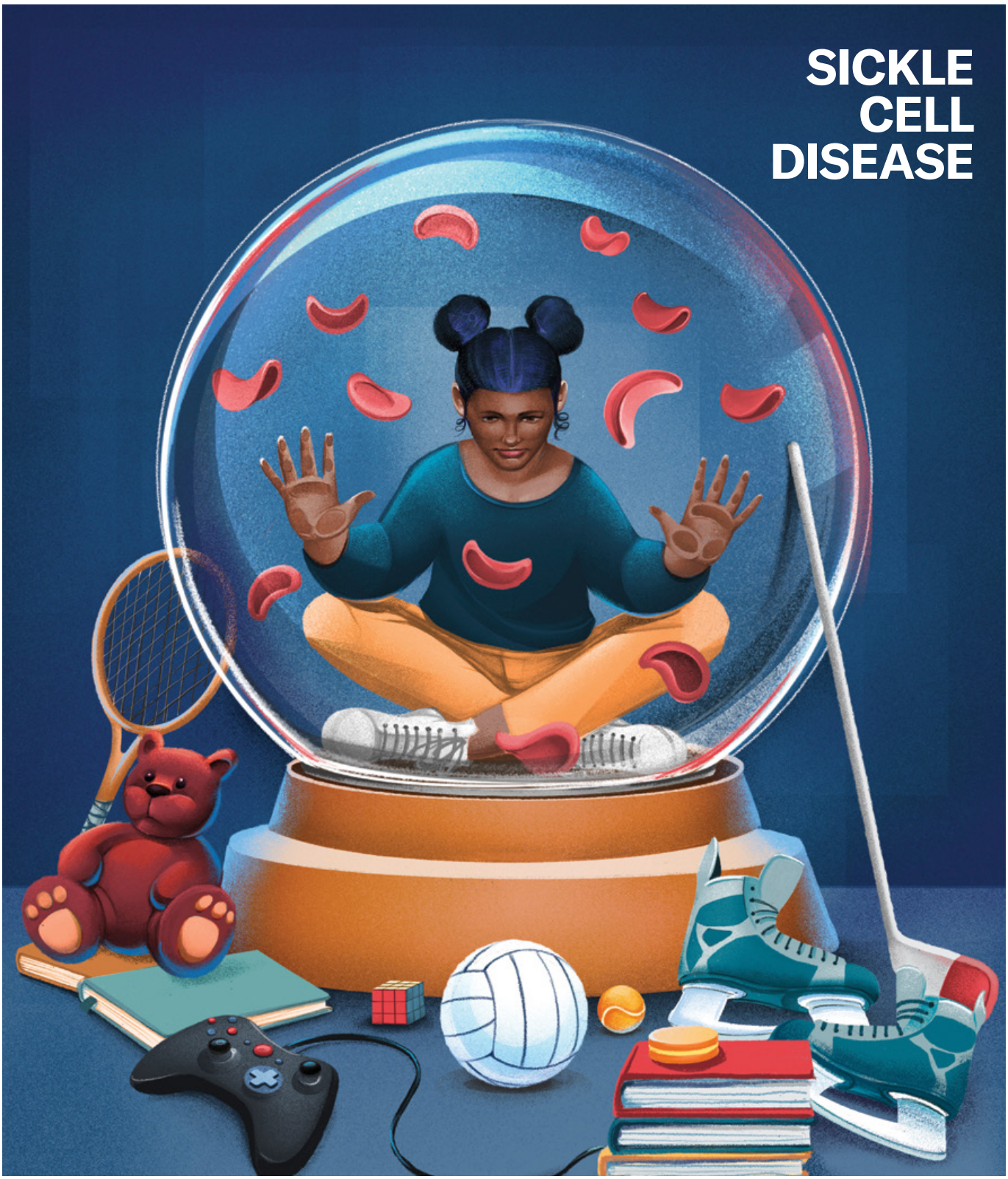

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SPECIAL REPORT

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New Attention and Hope for Sickle Cell

THE OLDEST KNOWN EVIDENCE OF SICKLE CELL DISEASE has been traced back more than 7,000 years, and the illness was first described in medical literature more than a century ago. It was the first molecular disease to be understood, a single mutation in a single gene that causes a heritable illness. When someone has one copy of the mutated gene, the trait is often asymptomatic, but when someone inherits a copy from each parent, the disease can become excruciating. The mutation results in abnormal hemoglobin, which causes red blood cells to curve into a characteristic sickle shape and to become stiff and sticky; ultimately the sickled cells fail to deliver oxygen efficiently to tissues throughout the body. Untreated, the disease can cause sepsis, pneumonia, strokes and heart attacks, and it brings on the punishing pain that occurs when blood vessels are blocked during vaso-occlusive episodes.

The disease affects millions of people across the world—some estimates suggest as many as 20 million—but despite its historical significance and widespread incidence it remains underfunded, understudied and undertreated. Those with the disease in the U.S. benefit from screening and treatment from birth, which over the past 50 years has extended the average patient's lifespan from 14 to 53 years. But people too often encounter a biased medical system that tends to mistrust their reports of extreme pain and accuse them of drug seeking. In the low-income countries where sickle cell is most prevalent and newborn screening for the disease is limited or nonexistent, too many children with sickle cell do not live past five years old.

Patients, physicians, researchers and advocates are pushing for change. Some are expanding screening and treatment options in places such as sub-Saharan Africa, as technology has allowed for more accurate, portable options. Others are illuminating patient experience, showing sickle cell pain to be some of the most intense ever experienced and seeking new ways to both prevent it and alleviate suffering once it sets in. They are pursuing increased funding and new public health policies to ease the burden on low-income nations, to improve patients' lives and to further genomic medicine research. And they are moving new therapeutics through the discovery pipeline and into clinics, where patients are just beginning to reap the benefits. Above all, they are lifting up the voices of people with sickle cell disease, who have been dismissed for far too long.

—LAUREN GRAVITZ,
CONTRIBUTING EDITOR

Reshaping a Disease

New therapies are changing the lives of sickle cell patients. Understanding their perspectives could improve all of medicine

BY MARYN MCKENNA

NATHAN WOOD IS 15, lanky and tall. He longs to play basketball; he lives in Yonkers, just outside New York City, and his high school and city parks provide plenty of opportunity for shooting hoops. But his body won't allow it. Nathan was born with sickle cell disease, an inherited condition that makes round red blood cells collapse into sticky crescents. The distorted cells clump inside blood vessels, depriving tissues of oxygen and inflicting excruciating pain. Exercise or stress or even just changes in routine can trigger a crisis, so Nathan's mother, Melissa Wood, has often homeschooled him and drives him everywhere—a rare thing in New York, where kids prize their independence.

But the caution is necessary because Nathan's sickle crises are so frequent. About twice a month, he estimates, he feels the first throbs in his hands or joints, signaling the approach of pain so intense that it forces him to lie flat in bed until it passes. And about twice

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a year the crises get bad enough to put him into Children's Hospital at Montefiore in the Bronx, where he's been a patient since he was a baby.

He would very much like his life to change. "Just get back into basketball, start going to school, and doing what I want to do as a kid," he said in a chat at Montefiore on a sunny June day when his family had brought him in for blood tests. "And not be separated from other people and not be different."

Nathan might soon have that chance. For the first time in the 114 years since sickle cell was originally described in a medical journal—although it existed, undefined, for millennia before then—therapies may end a disease that afflicts 100,000 Americans and millions more throughout the world. Last December the U.S. Food and Drug Administration approved two gene-editing treatments that compensate for the mutated DNA that causes sickling. In clinical trials, most patients who received the treatments had no pain episodes afterward, an indication their cells had ceased to sickle. In the wake of that success, several other gene therapies are moving through clinical trials, and Nathan is joining one.

Once he begins treatment this January in Nashville, Tenn., Nathan will face a grueling year of multiple procedures, including months of isolation in a hospital. But if the treatment succeeds, it will remake his life—and his family's. For Melissa, her fiancé and Nathan's two siblings, his illness has been a constant worry. "I got the call a few days after he was born," Melissa says. "I'm looking at this perfectly healthy child, and it just took all my happiness away in that instant. And from there I've had him in a bubble. So this will kind of ease me off of him a bit."

The approved new therapies and the ones likely to come after them hold the potential to alter the entire experience of sickle cell—and, some advocates hope, to change the way medicine treats people with many other conditions. Sickle cell history includes triumphant breakthroughs in science: Research on the illness signaled the dawn of the era of molecular medicine. Progress in testing and treatment involved dogged work by physicians who would not give up on their patients. Disseminating awareness of risk required ferocious activism by communities. Yet for more than 100 years medical research and practice have also illustrated the costs of racial disregard and a lack of commitment to disadvantaged communities. At the start of the second century of sickle cell science, all those factors will determine what the future of medicine may be.

AT ITS SIMPLEST, sickle cell disease is a problem caused by the smallest unit in genetics: a change in a single nucleotide—one of about three billion in the human genome—within a gene that directs the production of one part of hemoglobin, the protein that carries oxygen molecules through the blood. Hundreds of millions of hemoglobin molecules are packed into each red blood cell. The hemoglobin produced by the genetic variant can change shape as it gives up the oxygen it is transporting. That shift forces the enclosing cell to deform and turn rigid, taking on the sickled appearance that gives the disease its name. The distorted cells lodge in blood vessels instead of slipping smoothly through them as round red blood cells do.

The nucleotide substitution in the *HBB* gene—producing what's known as hemoglobin S, in contrast to normal hemoglobin A—is heritable. Someone who receives one altered gene from one parent is at risk of sickle cell trait, a condition in which few red blood cells are affected. Someone who receives two copies of the gene—a one-in-four chance if both parents carry it—will have the disease. That leaves them at risk for pain crises, anemia as the stiffened cells break down, organ damage because sickled cells carry less oxygen to tissues, a dangerous blockage of blood vessels in the lungs called acute chest syndrome, high blood pressure, and stroke.

Researchers working in western Africa have traced accounts of sickle cell crises back hundreds of years, noting that the symptoms had specific names in different languages and were understood to occur in generations of families. Sickled cells have been identified in modern studies of mummified tissue from Egypt dating to 3200 B.C.E. and skeletons from Kuwait that were buried in about 200 B.C.E. Scientists at the National Human Genome Research Institute, part of the National Institutes of Health, used a family-tree analysis of almost 3,000 genomes to estimate that the sickle cell mutation first arose in the Sahara approximately 7,300 years ago and was subsequently carried through the African continent by migrations.

At the time that mutation appeared, the Sahara was not a desert; it was green and wet, containing grasslands and forests and permanent lakes, along with the animal and insect life suited to those ecosystems. A type of malaria parasite has been identified in fossils that date back at least 20 million years, and the disease has been infecting humanity from our first emergence. And that seems to be a reason the mutation spread: A single copy of the gene—effectively, having sickle cell trait—conferred protection against severe malaria. It would have been a formidable advantage for people living in some of the most malarious places on the planet. This dynamic offers an explanation for why the sickle cell mutation persisted in sub-Saharan Africa, which still has the highest prevalence of sickle cell disease, and spread around the Mediterranean and into the Middle East.

Different strains of malaria arrived in South America, the Caribbean and the U.S. South in the 1600s. The disease devastated indentured European laborers and enslaved Native Americans. The observation that some African people—kidnapped and then enslaved in the New World—were protected from the worst effects of malaria was perceived as extra incentive for their captivity. Apologists for slavery argued it proved that Africans were intended by nature to be agricultural laborers. Economist Elena Esposito of the University of Lausanne in Switzerland has shown, using sale records incorporating places of origin, that planters paid a premium for enslaved Africans whom they assumed possessed resistance to the disease.

Although there have been many waves of migration from Africa and the Mediterranean to the U.S., historians say much of the sickle cell disease in people of African heritage in the Americas may be traced to the enslavement and transport of their ancestors. The link between sickle cell and a forcibly disadvantaged group set the pattern for how U.S. society would respond to the disease.

THE MODERN STUDY of sickle cell disease began with a descendant of that African diaspora after an unusual set of circumstances allowed him to bypass medicine's racial segregation. During the 1904 Christmas holidays a dental student in Chicago named Walter Clement Noel sought help for what felt like pneumonia. Noel was Black, but he was not a member of the post–Civil War Great Migration into northern cities. He was a member of an affluent family on the Caribbean island of Grenada and was studying at the Chicago College of Dental Surgery. Benefits available through that post made medical care affordable at four downtown hospitals that Noel otherwise would have been unlikely to approach for care. He crossed the street from his lodgings to what is now Rush University Medical Center and was treated by faculty physician James Herrick and his intern, Ernest Irons.

The two men did a thorough exam of Noel, noting a cough, fever, swollen lymph nodes, a slight heart murmur, and scars on his legs from recurrent ulcers. Nothing notable showed up in a urinalysis, but Irons noticed something odd about Noel's red blood cells under a microscope. When Herrick described Noel's case in a medical journal in 1910, he wrote that the blood contained "a large number of thin, elongated, sickle-shaped and crescent-shaped forms."

Noel stayed in the hospital for a month, receiving nourishing food and iron supplements but never a diagnosis. "We were at a loss to account for this peculiar complexus of symptoms," Herrick admitted in his write-up. The two doctors saw him a number of times until he graduated from dental school in 1907, and then they lost track of him. (They might never have known that he died in Grenada in 1916, ostensibly from pneumonia but probably from complications of sickle cell.) Three other patients with the same symptoms were reported in the next 12 years, in Virginia, Maryland and Missouri. But in 1923 physicians began to recognize the disease in dozens of people. In 1924 American medicine agreed that the constellation of disordered cells, symptoms and family history represented a unique disease rather than the effects of any known pathogen.

There would, of course, have been many more patients than those—but during this period the medical workforce most would have consulted was being eliminated. In 1910, the same year Herrick published his report on Noel, a so-called reform plan for U.S. medical education forced the closure of all but two historically Black medical schools, almost wiping out training for Black physicians because medical schools were otherwise largely segregated. That pushed Black people's participation in the medical workforce far below their representation in the population. The imbalance has persisted: in 2022 fewer than 6 percent of physicians in the U.S. identified as Black, although more than 13 percent of the population chose that identity in 2020 census data. Researchers say those closed schools would have trained several generations of Black physicians and mentors, an estimated 35,000 missing from the field.

"At the same time that you have this new disease being described, the workforce to take care of [patients] plummets," says James Taylor VI, director of the Center for Sickle Cell Disease at Howard University. The center at this prominent historically Black university is the oldest one in the U.S. The limits on Black people working as physicians and in other healthcare roles, he says, are "the root of so many of the disparities we still see today."

Restricting Black participation in the medical profession deprived sickle cell patients of health-care workers who would have best understood their needs and may have contributed to the maligning of people experiencing sickling crises as addicts faking pain to obtain opioids. It also might have enabled an enduring pattern in sickle cell research: biochemical discovery racing far ahead of improved patient care.

Chemist Linus Pauling, later a two-time winner of the Nobel Prize, identified the hemoglobin defect in 1949. Once he identified the cause of sickle cell as a mutant hemoglobin molecule, Pauling dubbed sickle cell anemia a "molecular disease." That framing effectively launched the biomedical era of newly powerful laboratory research. Mark T. Gladwin, a longtime sickle cell researcher who is dean of the University of Maryland School of Medicine, says "sickle cell disease has always led the cutting edge of science discovery, whether it's understanding the regulation of [genetic] promoter sequences or understanding protein biochemistry and folding. The concepts behind prion disease and amyloidosis, protein-folding diseases, those were predicted by sickle polymerization."

One of the first drugs to meaningfully help patients was not a novel antisickling agent. Instead it was penicillin, which became available in U.S. pharmacies in 1945. Sickling makes children more vulnerable to a variety of infections, but when child mortality was already high, deaths associated with sickle cell did not stand out from other childhood illness. Antibiotics made it possible to cure those infections, and by preventing death, they allowed the disease to be perceived in survivors. (Twice-daily doses of antibiotics are still routinely prescribed for children younger than five years who have sickle cell disease.)

The first drug that actually made an impact on the disease process of sickle cell was a compound called hydroxyurea. It was originally a cancer drug, but researchers showed it could also prompt production of a type of hemoglobin that is present before birth and in infants but fades after a few months of life. Cells with this kind of hemoglobin resist sickling—an explanation for why newborns with the illness do not experience sickle crises. Hydroxyurea reduces sickle crises and hospitalization by half. Yet it was not tested against the disease or approved by the FDA until the 1990s, nearly 50 years after Pauling's discovery of the sickle cell mutation.

The dearth of treatments created a kind of feedback loop. Sickle cell looked like a disease in which no progress could be made; because of that, new researchers were discouraged from entering the field, which de-

"I don't want to have sickle cell. I would jump through 18 hoops. But jumping through those hoops means risks."
—Melissa Creary *University of Michigan School of Public Health*

layed progress further. Vivien Sheehan, a hematologist and associate professor of pediatrics at Emory University School of Medicine, who leads a lab studying the genomics of sickle cell, recalls an esteemed faculty member telling her during her training not to pursue sickle cell as a career. "I can picture what he thought," she says. "We had one old drug; there was no pharma interest, no gene therapy. NIH funding was low compared with other genetic diseases."

WHAT CHANGED THE PICTURE was activism. In 1970 a physician named Robert B. Scott, Jr., was a faculty member at what was then a predominantly white medical institution that later became part of Virginia Commonwealth University. That year he wrote a blistering editorial in the *Journal of the American Medical Association*. He laid out how little funding sickle cell was receiving either from the government or from private donors compared with other genetic diseases. As an example, he estimated that research into cystic fibrosis, which occurred in one out of 2,940 children, received 65 NIH grants in 1968; sickle cell, affecting one in 500 children, received 22. And, highlighting the lack of generational wealth in the Black community, he also estimated that muscular dystrophy research benefited from $7.2 million in volunteer contributions, compared with just $50,000 for sickle cell, which had no national advocacy organization.

Scott did not say explicitly that race was the reason sickle cell had been neglected, but the conclusion was obvious. The following year the Black Panther Party announced it was making sickle cell one of its main priorities, creating a People's Sickle Cell Anemia Research Foundation and launching a massive educational campaign that included community events offering free screening for sickle cell trait and disease. To put both the editorial and the campaign into context: The Civil Rights Act had passed in 1964, and Martin Luther King, Jr., was assassinated in 1968. A national election was looming in 1972. Maybe to heal the nation—or maybe, more cynically, to attract Black votes—President Richard M. Nixon proposed a sickle cell research program. The National Sickle Cell Anemia Control Act passed in 1972, committing the NIH to creating 10 research and training centers around the country. But crucially, the bill allowed no new money for the effort; instead it was funded by other NIH programs' budgets. So within several years sickle cell research was back to depending on the energy of individual researchers.

To be clear, these efforts produced life-saving results. In 1997 researchers established that periodic transfusions could reduce the risk of stroke in children diagnosed with sickle cell. In 2007 researchers in France demonstrated that children with sickle cell could be cured with a bone marrow transplant from a donor who was an exact immunological match, such as a full sibling. In 2009 investigators in the U.S. established that a similar process could cure adults. A burst of innovation in the past decade brought three new drugs into sickle cell care: L-glutamine, approved in 2017, and crizanlizumab and voxelotor, both approved in 2019. But researchers say uptake of these new agents has been slow. And hydroxyurea, still the best drug, faces a major usage hurdle: it is contraindicated for pregnant people, based on animal studies and limited human data showing it can produce birth defects.

Sickle cell experts hope more treatments and cures are coming. "What we currently have approved for drug therapies is not adequate," says hematologist Modupe Idowu, medical director of the UT Physicians Comprehensive Adult Sickle Cell Center in Houston, which treats about 1,300 adults with sickle cell disease. "Hydroxyurea remains the gold standard, but some patients really have reservations about it. Patients must stay on these indefinitely, and they are not curative. And patients continue to have pain episodes, and they continue to have complications."

Until now, the only true cure for sickle cell has been a bone marrow transplant from a family member who is a perfect immunological match. But only a few patients—between 10 and 20 percent—can identify one. The seemingly benign therapy of periodic transfusions carries its own risks, including a toxic overload of iron that has to be scavenged from the body. And over time excruciating sickling crises rewire pain pathways in the body, leaving patients with chronic pain.

The new gene therapies are an extraordinary scientific achievement, but they are difficult to obtain. The two recent treatments, Casgevy and Lyfgenia, became two of the most expensive drugs on the U.S. market when they were approved, costing $2.2 million and $3.1 million, respectively. Those prices cover only the gene editing of a patient's own cells—"not the coverage of the hospital stays, or all their visits with me, or the transfusions they will need in preparation, or the central line they will need placed, or the fertility preservation they may want first," says Kerry Morrone, an assistant professor at Albert Einstein College of Medicine in New York City and director of the sickle cell program treating Nathan at Children's Hospital at Montefiore. (The clinical trial Nathan has entered will pay for his care.) Approval, in other words, may not equal access and may not meaningfully improve the lives of most people with the disease today.

THE GENE THERAPIES are built on the back of a stem cell transplant. A patient must receive transfusions to force down the number of sickled cells in their bloodstream, then growth factors to make sure they produce enough new stem cells; they need other drugs to move the cells out from their bone marrow. The stem cells are harvested in a procedure resembling an extended blood draw and sent to the drug companies for genetic editing. Once they are returned, the patient undergoes therapy to kill their disordered cells before the edited ones are infused. The entire process can take a year.

The length, complexity and expense can prompt deep uncertainty in people living with sickle cell disease. Melissa Creary is one of them. She is a social scientist at the University of Michigan School of Public Health who studies the ways science, culture and policy intersect in sickle cell. She is also a sickle cell patient, having been diagnosed at three years old, and for much of her life she experienced few complications. Then, six years ago, when she was 40, an unexpected complication turned her mild case extreme, inflicting severe pain crises and requiring a strict schedule of doctors' appointments every five weeks, as well as a complex medication regimen.

"I do not ever miss one of these appointments," Creary says. "I know what the schedule looks like almost a year in advance. I have my community signed up for

who's going to be my buddy because I'm kind of worthless for that day."

She is considering gene therapy. "I'm having conversations with my providers, people I know personally, people I know professionally," she says. Her mother wants to see her cured. Yet Creary's clinician colleagues urged her to wait. Creary cannot be sure what consequences the treatment might have for her career, finances and support network. If an adult treatment program is not set up in Michigan, she would have to be hospitalized in another state.

"I don't want to have sickle cell anymore, either, despite the ways in which it has literally crafted who I am as a person, as a scholar," Creary says. "If I could be untethered to the health-care system through gene therapy, I would jump through 18 hoops. But jumping through those hoops also means all kinds of risks, known and unknown."

Creary advises various groups on equity and antiracism in medicine, and she is also thinking about how the promise and uncertainties of the new therapies will be communicated to other patients. People with sickle cell come into contact with medicine when they are experiencing the worst pain of their lives, she points out; they may act out because of that or have difficulty expressing themselves. They are likely to encounter racism not only in the outside world but within medicine as well, making it challenging to navigate care and to have their concerns taken seriously. And now they may be confronting the possibility that a functional cure could be out of reach for them because of decisions made by insurance companies or by politicians refusing Medicaid expansion plans.

"At the end of the day, this is about trust and mistrust," Creary says. "We haven't done what we need to do in order to build the trust with this population, in order for the science to be as efficacious as it needs to be."

SICKLE CELL MEDICINE now has two goals. One is to imagine the next genetic therapies, perhaps developing gene edits that can be inserted into a patient without disrupting their immune system and blood cells first. The other, even more important, is to envision fair, thorough and accessible care. Patients and researchers agree that is what's most essential now.

Historian Keith Wailoo, a professor of history and public affairs at Princeton University and author of several books on sickle cell, says there has been an ongoing mismatch between what medicine has prioritized and what patients need. He cochaired a committee at the National Academies of Sciences, Engineering, and Medicine that, in 2023, published a report on whether equity can be a required part of innovation. "The core question was, Is it possible to have a society where equitable access to innovation is more than just an afterthought?" he says. "The moment that we're in right now should be an object lesson for how we need to innovate in a smarter way."

Across the U.S., medical centers that have transplant programs are evaluating whether they can deliver the new therapies. They also are scrutinizing who might pay for the procedures and associated care because the cost is beyond the reach of most families, and no one knows how insurance companies will respond.

The Centers for Medicare and Medicaid Services are currently negotiating to set prices; after that, state governments would have to opt in. The limitations of medical insurance are not a new story to Americans, but in this case, whether a patient is eligible for these therapies may depend on not just their age and the state of their disease but where they live.

Clinicians and patients did not have discussions about these things in the past, because the concept of transforming the disease was out of reach. But they are having them now. "Before this time, our conversations about disparities have been about making sure patients with sickle cell are getting clinical care," says Seethal A. Jacob, director of the pediatric sickle cell program at Indiana University and Riley Children's Health in Indianapolis, which is applying to offer gene therapy. "But now we need to talk about how we close the gap of disparities in access to these treatments."

Sickle cell medicine has reached a potentially transformative moment. The history of sickle cell is a tale of bravery and agony, effort and neglect, that mirrors the history of the Black experience in America. If these new therapies and the ones that come after them prove truly successful, individual lives will be completely changed. And perhaps a long-standing wound of inequity and injustice might begin to be healed.

Changing the Story

These sickle cell researchers and advocates are fighting for change at every level, from the laboratory to the clinic to the global stage, and their work is transforming lives

BY KAVIN SENAPATHY

OBIAGELI NNODU

CHAMPIONING NEWBORN SCREENING

After attending the first annual Global Sickle Cell Disease Congress in Accra, Ghana, in 2010, Obiageli Nnodu returned home to Nigeria with a deep resolve to combat the disease in her own country. Nigeria is estimated to have the world's largest population of people with sickle cell disease, and Nnodu, a clinical hematologist and sickle cell researcher at the University of Abuja, has been treating adults with the illness since 1985. She knew she would have had far more impact if she could have intervened when they were young. Most people who die from sickle cell disease in Africa are children who have never been diagnosed, so instituting widespread newborn screening would be the most effective way to help them survive.

At the time, the efforts to screen newborns in Nigeria were small and isolated, with little communication or collaboration among groups. Nnodu co-founded the Sickle Cell Support Society of Nigeria (SCSSN), a nongovernmental organization that brings together other NGOs, doctors, researchers, parents and patients. Her first goal: collect as much data as possible about the disease in her country.

Nnodu quickly learned that diagnostic tests in Nigeria required tedious sample collection, transportation to one of only six sickle cell centers across the nation, reliable power for the diagnostic machines at those centers, and highly trained personnel to collect and process the samples. In a country like Nigeria, with a largely rural population, scaling up this process was simply not feasible.

By 2017 more practical tests had been developed—ones with a low learning curve that didn't require electricity and could be conducted at the patient's location. Between September and December of that year Nnodu's team used those simple devices to test more than 1,000 newborns across Nigeria and proved they could reliably and accurately diagnose day-old babies. Shortly thereafter a study of infants at immunization clinics in the capital city of Abuja showed their approach could be integrated into a public health system.

Based on Nnodu's foundational studies, a health-care network, the Consortium on Newborn Screening in Africa, was created; by 2021 it included seven countries. It works to establish and expand newborn screening and early-intervention programs at medical centers and hospitals. Nnodu is also the principal Nigerian investigator for another multicountry collaboration, the Sickle Pan African Research Consortium, which is working to develop infrastructure for sickle cell disease research, care, education and training in sub-Saharan Africa.

In just 15 years "she has taught those working with her the power of networking, collaboration and attention to detail," says Adekunle Adekile, the previous chair of the SCSSN and a sickle cell researcher and professor of pediatric hematology at Kuwait University.

Nnodu acknowledges that it's unusual for a hematologist who works with adults to focus on newborn screening. She hopes that by identifying sickle cell disease early, she can get these tiny patients to pediatricians who will look after them so they can grow up, be educated, take on grown-up responsibilities "and come to me."

WALLY R. SMITH

MANAGING PAIN AND CARE FOR ADULTS

Wally R. Smith, a hematologist at Virginia Commonwealth University School of Medicine, has dedicated his career to understanding and championing the overlooked. His work on adults with sickle cell disease brought attention to a long-neglected group of patients. He was the first to show how their pain has been underestimated and undertreated.

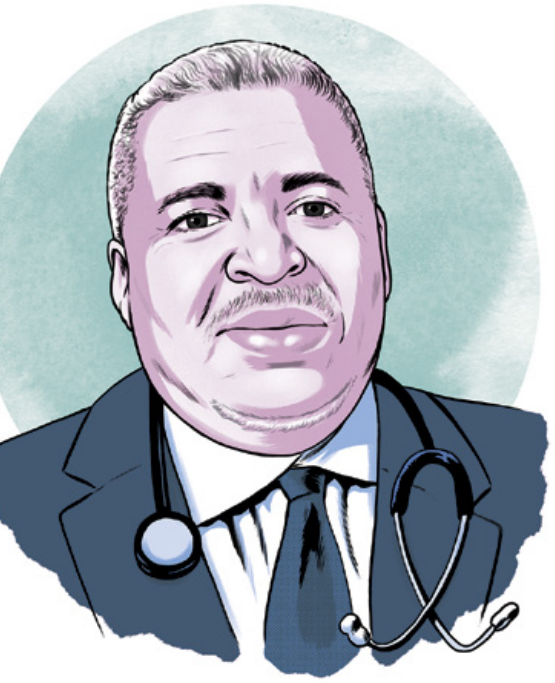
Until the 1980s life expectancy for a child with sickle cell in the U.S. was less than 20 years. They're now living into their 50s and beyond, but medical care has had a hard time catching up. A system originally built to serve pediatric patients with limited expectations of living to adulthood must now help them transition to adult care. That transition directly affects how people with the illness fare throughout the rest of their lives. Smith not only saw the problem but worked to build a health-care system to serve young adults with sickle cell disease.

Smith started at his own hospital, reaching out to 15-year-old patients at the medical center to ready them for the upcoming transition. He kept track of them, helping them transfer their care after high school and ensuring they made their first visit to an adult physician. From 2011 to 2013 the program roughly doubled the number of people who visited an adult sickle cell care provider within six months of finishing high school, from about 50 to 100 percent of graduates.

Smith helped to scale this effort up and is now an adviser to the Sickle Cell Trevor Thompson Transition Project, which ran a child-to-adult transition trial at 14 sites throughout the southern U.S. In 2023 interim results showed the program had improved quality of care, including in pain management, at all the project sites. That was "our shining moment," Smith says.

Smith is best known, however, for

Illustrations by Joel Kimmel



his work showing how drastically sickle cell pain had been underestimated in both frequency and intensity. As recently as 20 years ago, the field assumed patients sought clinical care at the onset of mild pain. This misunderstanding led to pain being minimized and left untreated. But Smith showed that people with sickle cell disease tend to deal with their mild to moderate pain at home until it's unbearable, at which point harm to their bodies has already occurred.

Smith's scientific rigor was integral to defining sickle cell pain, says Ify Osunkwo, chief patient officer at Novo Nordisk. His work has ensured that "the scientific community and the lay community alike understood that sickle cell disease pain is multidimensional."

STUART ORKIN

GENE THERAPY FOR FETAL HEMOGLOBIN

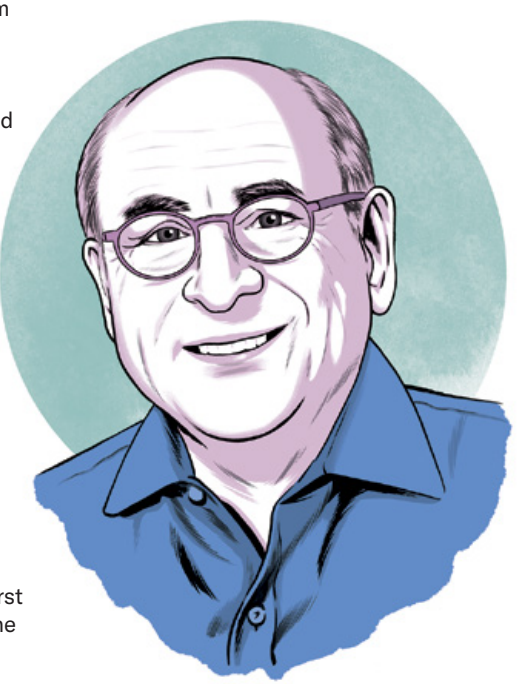
Infants with sickle cell disease don't start experiencing symptoms until three to six months of age, because up to that point their red blood cells retain the form of hemoglobin dominant in developing fetuses, hemoglobin F (HbF). This form prevents the clumping that is characteristic of the disease and keeps the cells round and flexible. Stuart Orkin, a hematologist and pediatrician at Harvard Medical School, has dedicated much of his career to figuring out how to get adult bone marrow to make more HbF.

For decades Orkin and his colleagues assumed there were multiple genetic variants involved in turning HbF production off and on. If someone had told him in 2000 that they'd have the solution a decade later, he says, "I would have said, 'No, you're crazy.'" But in 2008 genome-wide association studies linked HbF levels to certain genes, including one called *BCL11A*. Orkin's laboratory dug deeper and found that something in *BCL11A* switches off HbF production in infancy.

When Orkin's team moved its research into a mouse model of sickle cell, the scientists found that eliminating *BCL11A* in developing red blood cells cured the mice of the disease. That finding, published in 2011, transformed Orkin's perspective: one single cut in one gene could increase HbF production and unlock a cure. "That was the turning point," he says.

These discoveries led to one of the first sickle cell gene therapies approved by the U.S. Food and Drug Administration. The drug, marketed as Casgevy, is the first-ever approved treatment to use CRISPR gene-editing technology. Orkin wants to reach as many people as possible and is currently pursuing more accessible forms of sickle cell gene therapy. His goal is to learn everything there is to know about HbF so he can help design targeted remedies. It's a steep challenge, but, he says, "if nothing else, we're pretty persistent."

One of Orkin's collaborators, Douglas Higgs, says Orkin is not just persistent but visionary. "[He] has a great ability to see the best way forward and has recruited and directed many great young scientists to address these lines of inquiry," says Higgs, a blood geneticist at the University of Oxford. Today, he says, those scientists are leaders in the field.



LAKIEA BAILEY

ADVOCATING FOR THE ADVOCATES

Lakiea Bailey is an advocate, a sickle cell patient and a scientist who has worked to unravel the molecular mechanisms that underlie the disease. In these roles, she has unified her fellow advocates and improved patients' lives.

It's strange to learn how to live with pain, Bailey says. She was diagnosed with the disease at age three. When she turned 18, she saw that, practically overnight, her health-care providers stopped believing her pain was real. The child who had deserved compassion was suddenly treated like an unruly young adult with an attitude. It was an experience that deeply affected her approach, which includes urging institutions to "start with the premise that your patient knows their body." It might sound simplistic, but she says it's at the foundation of ensuring people with sickle cell disease receive the best possible treatment.

Bailey's view of the field was further influenced when she attended a 2014 gathering of government officials, patients, researchers and physicians who met to focus on the perspectives and needs of people with sickle cell disease. Bailey saw that because the disease had been systemically neglected, a slew of historically underresourced advocacy groups were working in isolation rather than collaborating as partners. So during that meeting Bailey convened a group that vowed to work together to build a nonprofit of community organizations, advocates, and medical and research advisers who would fight to put sickle cell patients first. This was the origin of the Sickle Cell Community Consortium. Between the advocacy and her lab research, however, Bailey's health was suffering. "It was getting harder and harder to keep cell cultures, my mice model and all the research I was doing going," she says.

After a break to recover, she took on the full-time executive director role at the

Sickle Cell Community Consortium. For too long, she says, people without sickle cell disease were in charge of what happened to patients, but they lack the necessary perspective. The consortium centers the voices of patients, including those with sickle cell trait (people who carry the sickle cell mutation but typically have few to no symptoms), as well as the needs of partner community organizations. In doing so, it uncovers unexpected, important issues. In response to a recent survey, which ranked coping with grief as a priority, the consortium is now working to support those experiencing emotional and financial fallout from the death of a loved one. The consortium is prioritizing patients' mental health and nutrition and helping them take control of their own well-being.

Bailey is now in yet another patient transition, "from adult to older adult." People with sickle cell disease are living longer than they used to, and she says aging with the disease is "its own sort of challenge." But she is using that knowledge to everyone's advantage. Bailey combines compassion, deep knowledge of patient needs, and a way of thinking that's both systematic and scientific, which makes her an absolute powerhouse, says Tomia Austin, executive director of the As One Foundation, a sickle cell education and advocacy organization. Austin says Bailey is an inspiration and someone the community looks up to, then points to one of her favorite interventions: Bailey outfits children with sickle cell in lab coats and helps them study their own disease.

To ensure the best possible treatment for sickle cell, institutions should start with the premise that your patient knows their body, Lakiea Bailey says.

JULIE MAKANI

EMPOWERING AFRICAN GENOMICS AND CURES

Julie Makani says improving the lives of people with sickle cell disease requires a unified effort, whether in her native Tanzania, across Africa or worldwide. In 2004 she helped to establish a sickle cell program at the Muhimbili University of Health and Allied Sciences and Muhimbili National Hospital, where she's a hematologist. By collecting clinical and demographic data from thousands of patients throughout Tanzania, the center has created one of the largest single-center sickle cell cohorts in the world and is helping transform patient care and policy.

Makani believes sickle cell disease offers a model for translating genomics research into treatments both for illnesses caused by single-gene mutations and for more complex conditions. She says there is a racist notion that genomics and gene therapy are too lofty for African scientists, so she and her colleagues are showing "that we can and will do genomic research." Through the Human Heredity and Health in Africa initiative, Makani is helping to advance genomics and biomedical research by Africans. For example, she is working to identify variants in multiple genes associated with how the body processes hydroxyurea, a drug that increases the amount of hemoglobin F in the blood and helps red blood cells maintain their shape, which may prevent clumping. But the medication works in only two thirds of patients with sickle cell, and Makani hopes to find ways to help the remaining third.

Makani and her collaborators also aim to ensure that Africans can access new cures such as gene therapy and bone marrow transplants. She and her colleagues are working to get such treatments to African patients, sending people abroad to India or the U.S. when the therapies aren't locally accessible.

When the Ministry of Health in Tanzania approached Makani to nominate her for a World Health Organization public health award in 2020, she insisted they nominate Tanzania's sickle cell consortium rather than any one individual. At the plenary meeting of the 73rd World Health Assembly that year, she accepted the award on the consortium's behalf.

Steven Okoli, a lecturer and hematologist at Imperial College London, says this humility and collective mindset is typical of Makani and lies at the core of her leadership. He says Makani creates change through her awareness that "we all need to be involved in making sure sickle cell's profile is increased so that we can get better treatments to our patients."

Kavin Senapathy is a journalist based in Madison, Wis. She is author of *The Progressive Parent: Harnessing the Power of Science and Social Justice to Raise Awesome Kids* (Hanover Square, 2024).

New Treatments for Sickle Cell Disease

After years of little progress, new therapies to treat or even cure the disease are reaching patients BY SARA REARDON

GRAPHICS BY NOW MEDICAL STUDIOS

SICKLE CELL DISEASE MIGHT seem simple enough: it's caused by a single mutation in a single gene. But the way it affects patients is remarkably complex—so complex that 70 years after that mutation was discovered, treatment remains difficult. In people with healthy red blood cells, hemoglobin proteins carry oxygen as the cells circulate throughout the body. In patients with sickle cell, the namesake cells form when mutant hemoglobin proteins clump together into fibers, deforming red blood cells' usual saucer shape into a curved sickle, which prevents them from effectively delivering oxygen to tissues. These sickle cells can get stuck inside blood vessels, interrupting blood flow and often prompting intense pain and a crisis so severe it sends people to the hospital and puts them at risk of cardiac failure and other life-threatening issues. Over the long term, disrupted blood flow, oxidative stress and inflammation combine to cause strokes and permanent damage to blood vessels and other organs.

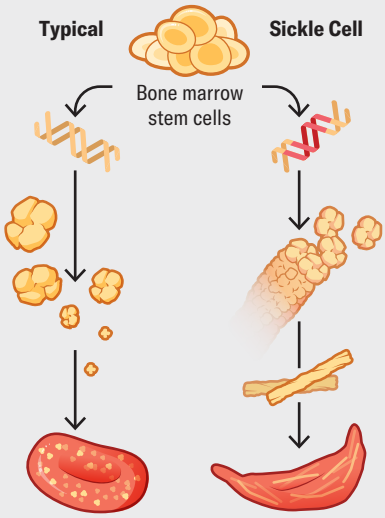
The disease strikes in so many ways that researchers are attacking the problem from multiple angles: at the source by preventing bone marrow from producing mutant red blood cells in the first place; at the

Sara Reardon is a freelance biomedical journalist based in Bozeman, Mont. She is a former staff reporter at *Nature*, *New Scientist* and *Science* and has a master's degree in molecular biology.

Understanding Sickle Cell Disease

Sickle cell disease originates in the bone marrow, where red blood cells are produced. Red blood cells carry hemoglobin, which allows them to transport oxygen to the body's cells. A faulty *HBB* gene changes hemoglobin's structure and leads to a cascade of events that can cause severe consequences for people with the condition.

1 FAULTY RED BLOOD CELL PRODUCTION



In people without sickle cell disease, the *HBB* gene encodes a normal hemoglobin protein.

Hemoglobin carries oxygen through the body. When oxygen molecules are onboard, the protein cannot bind to other hemoglobin proteins.

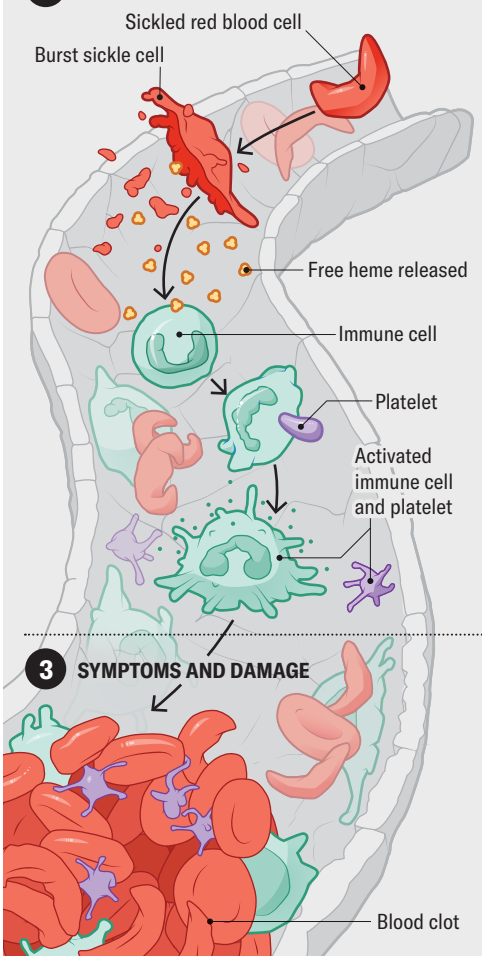
Healthy red blood cells are flexible, with a squished disk shape.

People with sickle cell disease have a mutation in the *HBB* gene and produce a faulty protein.

The misshapen hemoglobin is more likely to bind other hemoglobin proteins and form long fibers inside the cell.

The long fiber chains stretch and distort the cell, causing the distinctive sickle shape.

2 SICKLE CELL CASCADE OF EVENTS



Sickle cells are inefficient.
The long fiber chains make the cells rigid and likely to get stuck in blood vessels.

Sickle cells burst easily.
Sickle cells' membranes are fragile, and low-oxygen conditions can cause them to burst.

Burst cells cause inflammation.
When red blood cells split open, they release hemoglobin. One of its components, known as heme, triggers an immune response.

White blood cells and platelets are activated.
The inflammatory response draws white blood cells and platelets to the site. These cells release even more damaging inflammatory signals.

Sticky molecules are produced.
The inflammatory response prompts platelets and cells inside blood vessels to make adhesive proteins on their surfaces.

3 SYMPTOMS AND DAMAGE

Inflammation damages the blood vessel.
The immune reaction damages the endothelial cells along the vessel's walls. Chronic inflammation can cause long-term organ damage.

Clumping cells cause blockages.
The sticky proteins cause cells to get stuck in the blood vessels, obstructing the vessels and causing a pain crisis.

Source: Kelly Rose, chief scientific officer at American Society of Hematology (*consultant*)

cellular level by modifying the misshapen red blood cells' metabolism and protein structure; and at the immune level to prevent long-term organ damage. "The problem is [it's] all connected," says Marilyn Telen, a hematologist at Duke University. "So where do you build the dam?"

THE IDEAL PLACE TO HALT the disease is at its source: if bone marrow stem cells are generating the faulty red blood cells, replace them with ones that produce healthy cells. The most established method for this approach is a bone marrow transplant from a matched donor. The procedure requires eliminating the patient's original bone marrow cells pretransplant, using a course of strong chemotherapy, to create a niche for the introduced cells to grow in. The treatment can cause infertility and necessitates a long course of immunosuppressive drugs—often continued for years—to prevent the body from rejecting its transplant.

To try to improve on the success of bone marrow transplants, some companies have created gene-editing approaches that eliminate the need for immunosuppressive drugs. They remove patients' stem cells, modify the cells' DNA in a laboratory to prompt the production of healthy hemoglobin, then reintroduce them to the patient. A number of these gene-modifying approaches have already made their way to clinical trials or been approved by the U.S. Food and Drug Administration.

The form of hemoglobin that babies make at birth, called fetal hemoglobin (HbF), isn't affected by the sickle mutation. Typically HbF is mostly replaced by the adult version of hemoglobin within a few months after birth, leading several companies to focus on increasing the amount of HbF in the bloodstream. In 2023 the FDA approved Vertex Pharmaceuticals's exa-cel, which uses CRISPR-Cas9 gene editing to deactivate the gene that prevents production of HbF. The result is a higher fetal-to-adult hemoglobin ratio.

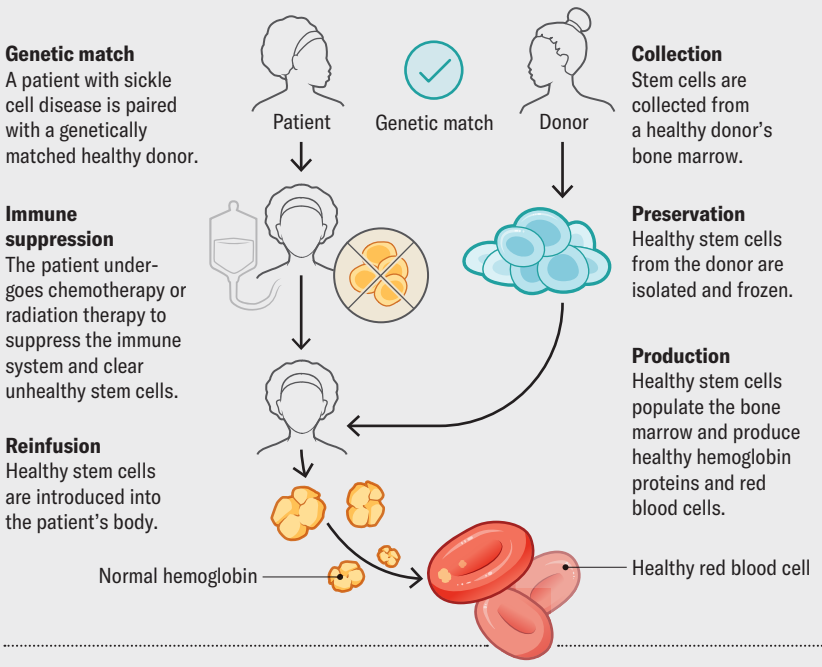
Editas Medicine is also enhancing HbF production, using a different CRISPR-related enzyme called Cas12a to do the editing. Whereas Cas9 edits DNA by breaking both strands of the double helix in the same place, Cas12a breaks them at different positions and results in more consistent edits. Beam Therapeutics is pursuing a similar method, using another form of CRISPR to swap single nucleotides in the genetic code that enhance HbF production. Both therapies are still in clinical trials.

Targeting the Source

Bone marrow stem cells express the faulty *HBB* gene that causes sickle cell disease. Therapies targeting these stem cells aim to have a curative effect, eliminating the sickle cell disease process altogether.

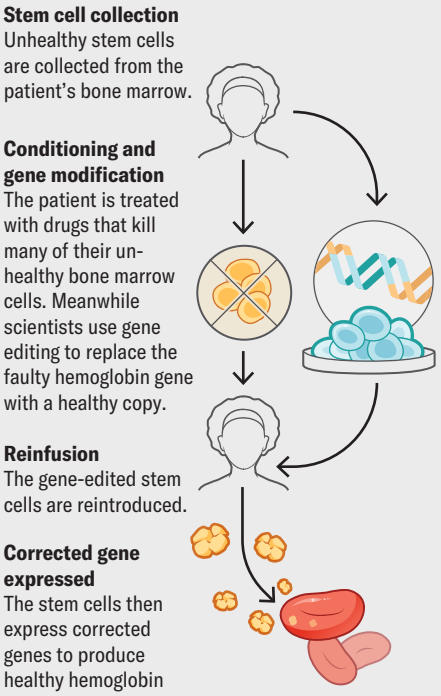
METHOD 1: BONE MARROW (STEM CELL)

Replacing a patient's bone marrow with that of a healthy donor can often effectively cure the disease, but this requires finding a genetically matched donor and using immunosuppressive drugs to prevent the body from rejecting the transplant.



METHOD 2: GENE THERAPIES

New treatments focus on using gene-editing technology to correct the faulty gene and increase the amount of healthy hemoglobin in the body.



Turning on other hemoglobin genes

Scientists are using CRISPR-Cas9 to edit patient stem cells, increasing fetal hemoglobin (HbF) production. HbF, which is active in fetuses but not adults, functions like normal hemoglobin. Gene editing reactivates HbF genes to produce healthy red blood cells.

FUTURE DEVELOPMENTS

Gene editing inside of your body

Scientists are researching how nanoparticles or viral transporters can carry gene-modifying drugs directly to the patient without first removing the stem cells. These treatments could reduce side effects.

Viral vehicles or nanoparticles carry new genes.

Gene editing occurs inside the patient to produce normal hemglobin and red blood cells.

A different strategy is to insert a more resilient version of the gene encoding adult hemoglobin rather than increasing HbF. Bluebird bio's lovo-cel, which also received FDA approval last year, uses a more classical gene therapy approach. Rather than editing a patient's DNA, it uses a modified virus to deliver a healthy, enhanced copy of the adult hemoglobin gene into bone marrow stem cells, where it integrates into the patient's DNA.

These new technologies, says Alexis Thompson, a pediatric hematologist at Children's Hospital of Philadelphia, are "an improvement over the many years and decades when we had very little to offer families."

A future approach might let doctors edit patients' bone marrow without removing it from the body. In a study published last year in *Science,* researchers described the development of nanoparticles that carry messenger RNA (mRNA) into stem cells in the bone marrow. When they used the particles in cells from people with sickle cell disease, the editing system encoded by the mRNA successfully modified the hemoglobin gene in those cells' genomes to produce more healthy hemoglobin protein.

It may be as many as 10 to 20 years before such in vivo technology is ready for large-scale human trials, Telen says. "We know the technology we need. We know a lot of the pieces. We just haven't been able to get it to all work together."

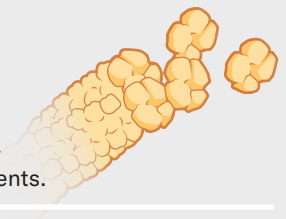
In the meantime current gene therapies remain expensive and challenging to scale up because each patient's batch of cells has to be edited individually. The treatments are out of reach for most people with the disease, particularly in sub-Saharan Africa, where 75 percent of all sickle cell cases occur.

All of this means that, for most people, the most accessible curative treatment is bone marrow transplantation from a donor with specific, genetically matched cellular markers. (Such matches are often but not always found among close family members.) And now a technique initially developed for treating blood cancers could make more transplants possible by expanding the donor pool. A strategy that includes a brief course of two chemotherapy drugs—thiotepa and cyclophosphamide—suppresses the immune systems of bone marrow recipients enough to allow them to receive transplants from almost any donor who shares half of their DNA, such as a parent, cousin or sibling without sickle cell disease.

In a 54-person trial, researchers found that

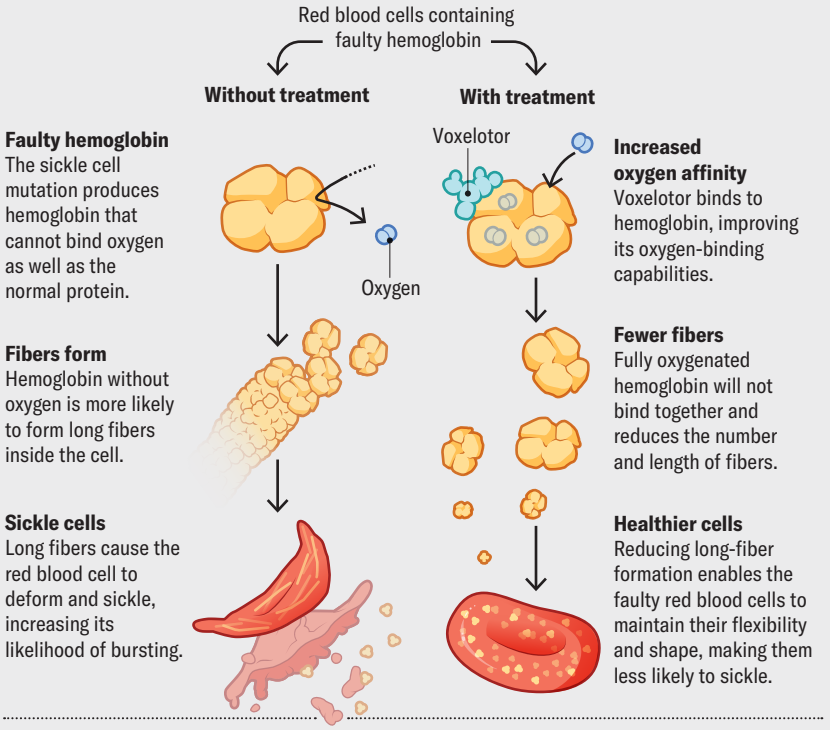
Targeting Cells and Proteins

Misshapen hemoglobin causes a cascade of events that lead to pain crises and organ damage. Drug therapies can intervene at various stages in this chain of events.



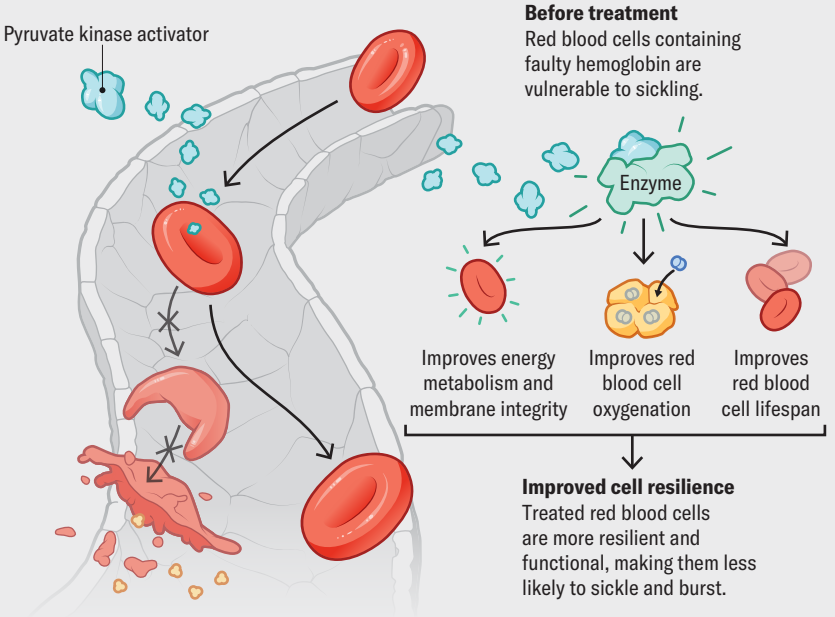
METHOD 1: IMPROVING THE HEMOGLOBIN INSIDE RED BLOOD CELLS

One treatment approach is to increase hemoglobin's affinity for oxygen. Drugs like voxelotor aim to reduce the formation of the long fibers that cause red blood cells to lose their shape and flexibility.



METHOD 2: IMPROVING METABOLISM IN RED BLOOD CELLS

Another promising class of drugs, known as pyruvate kinase activators, is still in clinical trials. The two leading candidates, mitapivat and etatopivat, stimulate an enzyme involved in red blood cell metabolism to increase the cells' energy and resilience, as well as improving hemoglobin's ability to carry oxygen.



around 90 percent of sickle cell patients treated with this technique who received transplants from half-matched donors went at least two years without rejection. Some patients appeared completely cured, says hematologist Adetola Kassim of Vanderbilt University, who led the study. And unlike gene therapy, this "haploidentical transplant" requires only a brief and far less toxic course of chemotherapy. Kassim says this approach may be a more affordable option: "The technique we use is exportable and scalable."

WHEN BONE MARROW TRANSPLANTS are out of reach, treatments that act further downstream can address physiological issues, such as hemoglobin clumping, and ameliorate symptoms. "The argument could be made that the vast majority of sickle cell patients in the world are unlikely to get curative treatment," Telen says. "So it behooves us to bring other drugs onto the market to improve their lives."

The FDA has approved three sickle cell drugs in recent years, and dozens more are in the pipeline. The first new drug, approved in 2017, was Emmaus Medicine's L-glutamine, an antioxidant that helps to maintain red blood cells' round shape. In a clinical trial, patients consuming L-glutamine powder mixed into food or drinks had 25 percent fewer pain crises than those in the placebo group.

Pfizer's voxelotor and osivelotor, the latter of which is in clinical trials, both bind directly to hemoglobin and increase its ability to hang on to oxygen. This action also prevents the protein from clumping and causing red blood cells to lose their shape. The FDA and European Commission approved voxelotor in 2019 and 2022, respectively, after data showed it could raise hemoglobin levels and protect against severe anemia. "When it works, it's amazing. It's somewhat of a miracle drug," says Jeffrey Glassberg, an emergency medicine physician specializing in sickle cell at the Icahn School of Medicine at Mount Sinai in New York City. But some patients don't respond, and a phase 3 clinical trial suggests it does not reduce the number of pain crises.

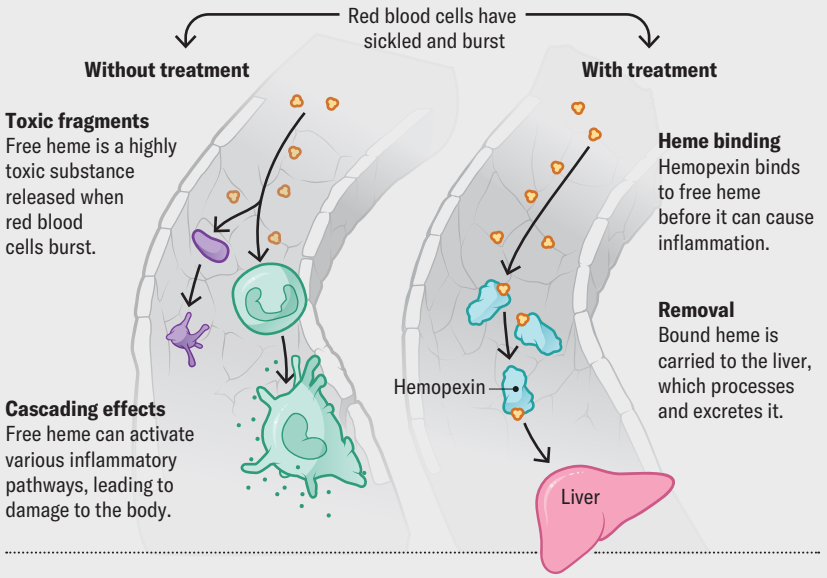
Another promising class of drugs, known as pyruvate kinase activators, stimulate an enzyme involved in cellular metabolism to both increase cells' energy and improve hemoglobin's ability to carry oxygen. The two leading candidates, Agios Pharmaceuticals's mitapivat and Novo Nordisk's etavopivat, are in clinical trials.

Managing Symptoms

Currently there are few targeted treatments available to ease symptoms for patients with sickle cell disease. These treatments look at preventing pain crises and reducing long-term damage to organs by targeting the immune system's response to damaged red blood cells.

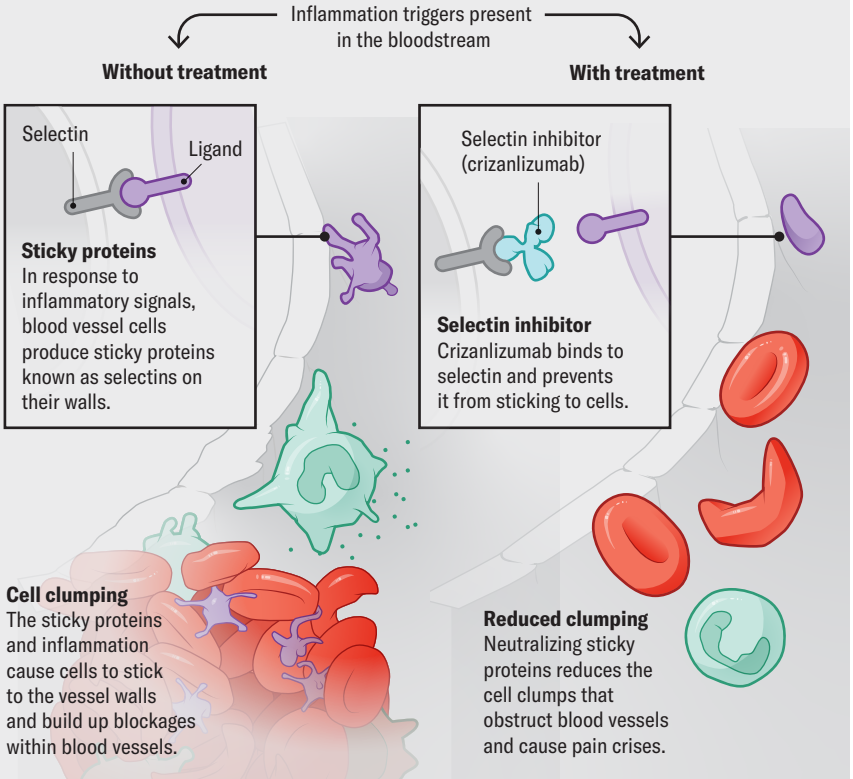
METHOD 1: CLEARING HEMOGLOBIN FRAGMENTS

Drugs such as hemopexin aim to clean up the loose heme that is released when red blood cells burst. The body can then safely process and excrete it, indirectly reducing the inflammatory response triggered by the free heme fragments.



METHOD 2: PREVENTING CLOGGED VESSELS

Selectin inhibitors aim to reduce the number of pain crises patients experience. These drugs attack the sticky proteins that allow cells and platelets to build up in blood vessels.



PHYSICIANS STILL HAVE FEW CHOICES for helping someone in the throes of an attack. Typically the only available options are pain medication and intravenous fluids. But new drugs that target something other than red blood cells might help with acute crises and reduce the immune reactions that contribute to pain and organ damage over time.

The third drug recently approved by the FDA, Novartis's crizanlizumab, attacks sticky proteins called selectins on blood vessels and platelet cells. Blocking those proteins prevents red blood cells from clumping together inside the vessels, supposedly preventing pain crises. But it may not be quite that simple. The European Medicines Agency revoked its approval of crizanlizumab in 2023 after a review committee found it didn't seem to reduce the number of crises people experienced. Glassberg thinks the drug is still useful—his unpublished research suggests that crizanlizumab and similar drugs currently in clinical trials could reduce long-term organ damage and chronic kidney disease.

Other approaches aim to diminish immune system activity. CSL Behring is conducting clinical trials of hemopexin, a drug that cleans up hemoglobin that has broken free of red blood cells. Loose hemoglobin causes cells to clump in blood vessels and contributes to inflammation, leading to long-term organ damage. Researchers elsewhere are investigating whether tamping the activity of certain immune-signaling molecules known as complement proteins might prevent the same inflammation-based injury.

Now Glassberg and others are trying to determine which of these drugs work best and whether certain combinations might work synergistically. He is currently running a trial at Mount Sinai called REAL Answers, in which 1,200 patients will receive the newly FDA-approved drugs, as well as an older one called hydroxyurea, alone or in combinations. Glassberg's team is assessing their effects on pain crises, monitoring for signs of organ injury and searching for genetic markers that could predict how well someone will respond.

It's too soon to know how most of these new therapies will fit into patient care. They might be most effective when started early in life. The drugs have not yet been extensively tested for safety and efficacy in children, but such an approach might prevent organ damage that can start early and then worsen over time.

Living with Sickle Cell Disease

AS TOLD TO ROXANNE SCOTT

TWENTY-FIVE YEARS AGO Yvonne Carroll spent much of her time delivering difficult medical news. It fell to her to call parents and tell them their newborns had sickle cell disease. If the infants weren't treated swiftly with prophylactic antibiotics to prevent sepsis, they could die from blood poisoning.

"People were barely taking penicillin at that point. We didn't have newborn screening in all 50 states, so you didn't even know who had sickle cell disease," says Carroll, who is now programs director in the department of hematology at St. Jude Children's Research Hospital in Memphis, Tenn. Life expectancy for an infant diagnosed with sickle cell in the U.S. was 20 years.

In the decades since, screening has become standard practice in the U.S., and it is on the rise in developing nations. Life expectancy for people with sickle cell disease in the U.S. has increased to around 50 years. But these patients, most of whom are Black, still face persistent racism, stigma, and other barriers when seeking medical care. SCIENTIFIC AMERICAN spoke with Carroll and with people living with sickle cell about their experience. Here they speak about how the disease has affected their lives.

The interviews have been edited for length and clarity.

IF YOU NEED HELP:
If you or someone you know is struggling or having thoughts of suicide, help is available.

Call the **988 Suicide & Crisis Lifeline at 988**

use the online **Lifeline Chat at 988lifeline.org/chat**

or contact the **Crisis Text Line by texting TALK to 741741.**

Photographs by Kholood Eid

JUANITA MCCLAIN,
PRESIDENT, SICKLE CELL WARRIORS OF BUFFALO, N.Y., AND EARTH SCIENCE EDUCATOR

Sometimes we know a pain crisis is coming on because of the yellowing of the eyes, or jaundice. Most of the time the pain starts in your joints because those are the places that are first affected by decreased oxygen in the blood. But you can get pain anywhere you have blood flowing through the body. And once the pain begins, there's no telling whether it will be excruciating or something you can deal with.

The pain of a crisis is indescribable. Minor pain is a six for me because I can deal with pain up until, like, about seven. And then once you see me crying or bent over, I'm at an eight or nine or 10 on the pain scale. But if I'm still moving even when I'm in pain, then I know I can manage on my own.

When a crisis starts, if I take medicine and the pain doesn't subside but instead continues to get worse—when I feel like I can't walk, I can't move, all I want to do is lie there and cry—that's it. I know it's time to go to the hospital.

When I arrive, it's sometimes hard for them to believe what type of pain I'm in, even if I'm crying, even if they see the tears coming down. I bring a health-care plan with me. Medical staff know they're supposed to give me two shots of morphine for the first round to see if that will help my pain, and if it doesn't, they should give me another one a couple of hours later. But I've had experiences where they've given me one or two doses and then they say, "Oh, your labs look fine. We're going to get your discharge papers ready." So then I'm fighting this battle, trying to get the pain medication that I need because they feel like I have been treated enough.

I have been diagnosed with depression and anxiety caused by my sickle cell disease, and it's because I find myself ready to give up when I'm in crisis. I feel like, if I have to live in this kind of pain and I can't get anyone to understand it, and if they can't help me, then what is the point of living? I don't want to go through another pain crisis. I don't want to be turned away from doctors anymore. So I'd rather just not be here. I've had suicidal thoughts quite often after times like that.

JASON ROBERT MOORE,
VICE PRESIDENT, SICKLE CELL WARRIORS OF BUFFALO, N.Y.

If I went to the hospital every time I was in pain, I would be there all the time. I'm at five out of 10 on the pain scale every single day. I only go to the hospital when my pain reaches an eight and lasts longer than about three hours. I can mostly fight that until morning—I try to only go to the hospital between 7:30 and 8:00 A.M., right after shift change. I'm pretty much one of the first people seen in the morning, so I can get in and get out.

Right now I'm on ketamine, which is a high tier of pain medication. But the last time I went to the hospital I noticed that my body's getting used to even that now. Going to the hospital four to five times a month is going to kill the efficacy of that, so I try to only go about once a month. I don't want to push past what I'm already at because I think the only thing left for me to take would be fentanyl.

My last job, I worked at a marijuana dispensary. I didn't use marijuana myself, because it didn't help my pain. But I knew what it was like to be down bad. I knew what it was like to go through pain and chronic issues and being in and out of the hospital. I could always relate to the patients. The job was a match made in heaven because I could really relate to these people and have heartfelt conversations. They felt seen and heard.

That job wasn't strenuous on my body: all I was doing was consulting with patients and cashing them out. Yet sickle cell played its part. I kept having to go back and forth to the hospital, and my body just ultimately broke down. I told my doctor, "I thought I had it this time, Doc." And she was like, "I thought you did, too. But look, you're still here." And she said, "I think it's time for you to hang it up. We've tried everything, and you still ended up here all the time." So she wrote me a note recommending full disability. That was it. That was my last job. December 2019. My last day was my birthday.

Jason Robert Moore

DOMINIQUE GOODSON,
SENIOR PROJECT MANAGER, SICKLE CELL CONSORTIUM AND PATIENT ADVOCATE, BROOKLYN, N.Y.

Imagine a really, really strong person, and they have this big sledgehammer, and they're hitting you with the sledgehammer with all their might: maybe on your leg, your thigh, your arm, your chest, your back. Over and over again, every second or two. But it leaves no marks, and you can't physically see it. That's what a pain crisis feels like.

One time I had a doctor tell me it was impossible for me to be having a pain crisis because I had sickle cell beta thalassemia. And I looked at him like, "What do you mean?" He's like, "You shouldn't be in physical pain. Sickle cell patients with beta thalassemia don't have crises." He didn't touch me, didn't put an order in my chart or anything.

So now I tell patients, learn to speak up for yourself. And if you're not able to, take someone to the emergency room with you. Take an advocate, a family member or a friend. Take someone with you because doctors and nurses will treat you better when they see someone else is there with you. The times I've taken my mentor or my best friend with me to the hospital, I was treated differently than when it was just me by myself. Even if it's just somebody on the telephone with you. Some sickle cell patients may be scared to speak up for themselves. And I tell them, "Your first advocate should be you. If you feel that someone is doing something wrong, you speak up on it and report it. There is nothing wrong with reporting doctors and nurses."

As far as gene therapy, I like it better than with the bone marrow transplant—because it's my own genes, it's less likely to be rejected. I would do gene therapy but only after having kids because the chemotherapy can cause infertility.

YVONNE CARROLL,
PROGRAMS DIRECTOR, HEMATOLOGY DEPARTMENT, ST. JUDE CHILDREN'S RESEARCH HOSPITAL, MEMPHIS, TENN.

When people with sickle cell disease go to the hospital, they have difficulty getting medication precisely because they know what drugs they need and how much of them. So when they go in and say, "I need X, Y and Z," and it's a really high dose, people are going to look at them like, "What's going on?"

Systemic racism exists in the healthcare system. And it exists especially for a


Yvonne Carroll

disease that affects mostly people of color in this country. When people with sickle cell disease go to the emergency room, they experience systemic racism combined with the opioid epidemic that is pushing health-care providers to not provide opioids anymore. These people have been taking opioids their entire life, so their tolerance level is high, but a lot of providers are very uncomfortable giving that level of opioids. So people wait to go to the emergency room. They don't want to go. And when they do, the opioids relieve the pain, but they also make them feel bad. They don't want to go, so they wait until the last minute when their pain is so high it takes multiple doses to bring them back to their normal level of chronic pain.

Part of my job includes developing educational material for patients with sickle cell disease and their families in collaboration with patients and providers. Once I asked a child, "Draw what your pain feels like," and they drew a shark biting them. I asked someone who was older, and they said, "Imagine you get your finger slammed in a car door, and then multiply that by 10." I told him, "I can't get past the car door thing, so I can't even go into the factor of 10." But what really struck me was when I talked to a mother with sickle cell trait [a condition, typically mild, that occurs when someone has one rather than two inherited sickle cell mutations]. She donated bone marrow for her child's transplant, and after they went through the process, she had a pain crisis—something that happens to people with sickle cell trait in rare circumstances. She said she was in so much pain that she had to apologize to her 10-year-old daughter because she had never imagined her daughter's pain was so severe.

Another part of my job has been working on a gene-therapy decision aid in conjunction with a team of patients, ethics experts, sickle cell advocates, hematologists and a genetic counselor to help patients and their families understand gene therapy and the other treatment options available.

There are a lot of logistics that go along with gene therapy: there's isolation, there's chemotherapy that suppresses your immune system. There's the fact that you have to be close to the center where you're getting the gene therapy. You won't be able to work, so you need someone to take care of you. But beyond that, the group that needs it most is the group that doesn't trust the medical system or clinical trials. We all know Tuskegee.

I tell people to hope and take the best care of themselves right now because 10 years from now the landscape will be different. When I started, children had pain crises all the time. Now it's rare. As a matter of fact, when they have one, they're like, "What the heck is going on?" It was commonplace to see sepsis, splenic sequestration and strokes in three-year-olds. It was devastating. That doesn't happen now. Sometimes it's still bleak, but things look much better than they did 25 years ago.

JUDITH MCCLELLAN, SOCIAL WORKER, SALISBURY, N.C., AND MOTHER OF A TEENAGER WITH SICKLE CELL

If this were oncology, the carpet would be rolled out for us. But sickle cell is the forgotten, frowned-upon, unimportant disease. And because we're Black people advocating for ourselves, people say we're being difficult.

I've worked in social work since 1997. My daughter, Kyarra, was born in 2006. When she was born, I was working in a doctor's office, and they weren't understanding. I've lost jobs because I was taking care of her. We've been faced with homelessness on several occasions because of job losses.

As far as treatments, I left all decisions up to Kyarra. Kyarra didn't want a bone marrow transplant. With the bone marrow transplant she said no, no, hard no. But with gene therapy she's 1,000 percent onboard. A hospital reached out to us. It's a clinical trial for kids aged 12 to 17. We're at the very beginning. She just did a bone marrow biopsy. Next is her cell collection. If they can get enough cells, we'll move forward. We don't know how soon, but we'll move forward. If they don't collect enough cells, we'll have to go back so they can collect some more. She's 17 years old, and the only thing she's worried about is if she's going to lose her hair. I'm worried about the chemo. And then there's the possibility that it just won't take.

If it works, she would be in the hospital less because she won't have as many pain crises. We are prayerful that she will have zero. I'm hopeful that we can have a normal life. At times, Kyarra misses 30 to 40 days of school. She just missed sickle cell camp. She wants to have a normal life as a teenager and stop missing out on school and social functions because she's in the hospital. I could maintain a job. So that would end our risk of homelessness, that would end struggle, that would end a whole lot of things. We're excited about it and hopeful it will work.

Roxanne Scott is a reporter in Queens, N.Y., covering health, science and the environment.

Ease the Pain

The excruciating pain of sickle cell disease is difficult to prevent or treat. Researchers are working on new ways to provide relief BY EMILY SOHN

KALPNA GUPTA WAS in a convention center banquet hall when a child changed the course of her career. As she recalls it, she had come to Ohio around 2008 for a conference on sickle cell disease because her laboratory was studying the misshapen red blood cells that define the ailment. Typically such conferences consist of one lecture after another, each full of slides on molecular mechanisms and chemical pathways, interspersed with talks from patient advocates and caregivers.

This time a 10-year-old boy described the bouts of debilitating pain he experienced as a result of his illness. Deeply moved by his words, Gupta imagined what it would be like if her own daughter were the one suffering. She turned to colleagues sitting next to her and asked, "Who works on pain in sickle cell disease?"

The answer at the time was hardly anyone. Gupta remembers only one presentation on pain at the meeting, a poster by Wally R. Smith of Virginia Common-

wealth University. This work was the field's first attempt to assess the extent of discomfort associated with the disease. Smith and his team discovered that sickle cell pain was more frequent and severe than researchers or physicians realized. In addition to the acute, excruciating attacks that are characteristic of the disease, they found that nearly a third of their study participants experienced chronic, sometimes daily pain, often in their back or joints.

It was a watershed result both for the field and for Gupta, who returned to her lab at the University of Minnesota and launched her own research program on sickle cell pain. In the 16 or so years since then, Gupta—who is now at the University of California, Irvine—has started, along with Smith and other researchers, to illuminate the complex processes involved in acute and chronic pain. This work has transformed the way scientists are understanding and developing treatments for sickle cell disease.

New medications target the underlying mechanisms of sickle cell [see "New Treatments for Sickle Cell Disease," by Sara Reardon, on page S11], sometimes reducing the frequency of acute attacks, but none is designed specifically to relieve pain once it starts. There is an urgent need to better address the illness's most prominent symptom: pain so agonizing it can harm people's careers, relationships and lives.

IN THE U.S., sickle cell disease is usually diagnosed through newborn screenings done shortly after birth. Screening is more inconsistent in other countries, particularly those in sub-Saharan Africa, where the disease is most common [see "Investing in Sickle Cell Disease," by Ambroise Wonkam, on page S24]. Early symptoms, which can include painful swelling in the hands and feet, generally begin when the patient is between six and nine months old, says Deepika Darbari, a hematologist at Children's National Hospital in Washington, D.C. As kids get older, they are struck with acute bouts of pain that last up to a week or more. These attacks happen an average of three times a year and account for 95 percent of hospital visits related to sickle cell disease. Known as vaso-occlusive crises (VOCs) or simply "crises," these events may be associated with the development of complications—such as liver and kidney issues, strokes, a pneumonialike lung disease called acute chest syndrome, and multiorgan failure—that can result in death.

Researchers have been stymied in their attempts to ease these patients' agony. In 1956 a University of Tennessee physician wrote, "The severe pain causes patients to grunt, groan, cry, twist and turn and to assume abnormal postures in the futile attempt to obtain relief." The pain most often occurs in the lower back, joints, arms, legs and core, and patients describe it in almost every possible form: sudden, throbbing, sharp, but also steady and gnawing like a toothache. In a Reddit forum dedicated to the disease, people compared the sensations to being stabbed repeatedly from the inside, to hitting a bruise with a needle-covered hammer, and to a knife being dug into them and then moved around. When asked to rate their pain on a scale from 1 to 10, Darbari says, people often say they can't give a number because it is too unyielding, but they rank it as worse than childbirth or postoperative pain. Sickle cell pain, Gupta says, "is thought to be the worst thing known to humankind."

Nearly a century passed between the first descriptions of the disease in Western medical literature and Smith's study, which refuted the long-held assumption that patients existed in one of only two states: pain-free or suffering from intermittent events. Instead the research—which relied on six months of daily diary entries from 232 people ages 16 and up—showed that 29 percent of study subjects had chronic pain more than 95 percent of the time, whereas just 14 percent experienced it rarely.

Additionally, although the reported pain intensity was higher than researchers had previously thought, Smith and his colleagues found that people typically went to the hospital only when they were in the middle of an acute attack. Overall, participants reported pain on 56 percent of the study days and acute crises on 13 percent but sought care on just 4 percent of them. The data made it crystal clear: physicians understood the disease based solely on what they saw in clinic, which had led them to vastly underestimate their patients' suffering. The researchers concluded that undertreatment was common, noting that "pain in adults with sickle cell disease is the rule rather than the exception."

These findings shifted the thinking about sickle cell. It is now recognized as a chronic disease in which repeated acute pain events transform the nervous system in ways that echo other conditions such as fibromyalgia, irritable bowel syndrome and phantom limb pain. "We have reconceptualized pain in sickle cell disease completely as a result," Smith says. "Sickle cell disease is a window into studying all chronic pain."

FOR DECADES EXPERTS assumed that because the misshapen red blood cells of sickle cell patients get stuck in blood vessels, blocked blood flow was causing pain wherever obstructions occurred. "In the past we thought it was a very simple thing—like, you have the vaso-occlusion, the person gets pain," Darbari says. "The vaso-occlusion gets resolved, and the pain goes away."

Growing evidence, however, suggests that pain sources are various and complex, leading some experts to push for a new description of attacks such as "acute pain events" or "acute pain episodes," says Amanda Brandow, a pediatric hematologist at the

Emily Sohn
is a freelance journalist in Minneapolis whose stories have appeared in *National Geographic*, the *New York Times*, *Nature*, and many other publications.

Medical College of Wisconsin in Milwaukee. Although many still call them "crises," such a linguistic shift reflects the idea that pain results from multiple causes, not just vaso-occlusion.

The nociceptive system, which registers pain, is one player. It's triggered by multiple processes in sickle cell disease, including aggregations of various cells—sickled red blood cells, white blood cells, platelets, and other types—that adhere to the lining of blood vessels. The clumped cells block blood flow, deprive tissues of oxygen and damage the vessel lining while activating inflammation-related cells such as platelets, macrophages and mast cells, as well as molecules such as cytokines.

Gupta has found in mouse models of sickle cell disease that acute attacks injure peripheral nerves and vessels in the skin, changing the signal transmission in the spinal cord in a vicious cycle that amplifies pain. These mice show hypersensitivity to cold, heat and even small amounts of pressure, mimicking the experience of people with the disease, who may find even a strong gust of wind unbearable.

Inflammation gets worse with each acute episode, according to studies done mostly in mice, leading to more serious complications. Eventually the cycle can alter the spinal cord and brain in ways that continue to amplify pain from the lightest touch. That can happen even when there is no ongoing vaso-occlusion, says Darbari, who studies brain-activation patterns to better understand this sensitization process. According to C. Patrick Carroll, director of psychiatric services at the Johns Hopkins University School of Medicine's Sickle Cell Center for Adults, sickle cell seems to change the nervous system in ways "that can amplify, facilitate, maybe even generate pain perception."

FOUR DISEASE-MODIFYING MEDICATIONS have been approved by the U.S. Food and Drug Administration for sickle cell, and some have shown modest benefit in preventing painful events. But they can't alleviate pain once it starts.

So far attempts to treat acute pain with pharmaceuticals have mostly fizzled. For example, in a placebo-controlled, randomized trial of L-glutamine, which can reduce adhesion, those in the test group experienced three painful events, compared with four in the placebo group. The pain of those acute attacks, however, was no less intense in the test group. "Trying to moderate the actual pain is something that I think we still need to do," Brandow says. "We need to target the pain source."

For now people typically have a home protocol they start at the onset of an acute event. It usually includes opioids (such as oxycodone), heat, and ibuprofen or other over-the-counter pain relievers, Darbari says. If those approaches fail, more intensive hospital care can include intravenous opioids and fluids, ketamine and local anesthesia, among other strategies. Yet even with those efforts, patients often remain in pain after discharge.

Opioids raise other concerns, too. Studies show that they might make things worse physiologically by increasing certain types of inflammation, including through the activation of immune cells called mast cells. Plus, sickle cell patients often require large opioid doses at regular intervals, which can leave them open to suspicion and accusations of drug seeking. With sickle cell in particular, Carroll says, providers accuse patients of faking or magnifying their pain to get drugs. "There's just a tremendous pall of suspicion that circles around sickle cell disease," he says.

The problem runs deep. "The pain that people have at home every day, silently, is slowly rotting their whole psychosocial milieu and causing stigma because nobody can see it. So they get accused of faking," Smith says.

Given opioids' reputation for causing addiction and overdose deaths, Darbari notes, families sometimes refuse the drugs even when their children are sobbing in pain. Whether sickle cell patients are more or less prone to addiction remains an unstudied question, Gupta says.

A number of medications for targeted, effective relief are now in various stages of investigation, including a drug known as rivipansel. This medication targets an adhesion molecule called E-selectin with the goal of preventing leukocytes from sticking to blood vessels. In a phase 3 trial, those who took rivipansel showed a 61 percent reduction of E-selectin levels in their blood. Patients who took the drug within 26 hours of an acute attack's onset had shorter hospital stays and spent half as long on IV opioids compared with those who took it after that window—two days instead of four. But because most study participants weren't dosed that early, the research team concluded that future trials must better assess treatment timing.

Another contender is imatinib, a cancer drug that appears to reduce inflammation. It inhibits a neuropeptide called substance P, which activates mast cells, causing inflammation and pain. Imatinib reduces VOC pain in mouse models of sickle cell disease and has shown potential to do the same in people. Studies show that adding imatinib to outpatients' treatment protocol reduced the number of VOCs and hospitalizations and shortened hospital stays. The drug also reduced the use of pain relievers significantly.

Given that so many pathways appear to lead to acute sickle cell pain, scientists are casting a wide net. "There are a lot of drugs in the pipeline," Brandow says.

CHRONIC PAIN in sickle cell patients generally emerges in adolescence or early adulthood. It affects up to half of all adults with the disease and can last for months,

becoming a part of daily life and manifesting in various ways: joint stiffness, bone pain, nerve pain, and more. Acute pain and chronic pain seem to involve different pathways; one clue, Brandow says, is that people whose sickle cell disease is cured by bone marrow transplants often continue to experience daily discomfort. It is too soon to know whether newly approved gene therapies will relieve chronic pain, she adds, because clinical trials didn't address that question.

Given the differences, researchers are investigating approaches that address both underlying mechanisms of chronic pain and patients' perception of that pain. On the pharmaceutical side, Gupta's work in mice suggests that cannabinoids may alleviate chronic pain by reducing inflammation and interrupting key pathways. There is also some promising evidence in results from studies on other debilitating pain conditions. In people with multiple sclerosis, for example, an oral cannabis spray called Sativex helps to alleviate neuropathic pain and muscle spasticity, both of which are also common symptoms of chronic sickle cell disease. Studies show that cannabinoids can act synergistically to improve the pain-relieving effects of opioids. And they ease ischemia-reperfusion injury, damage that occurs when blood flow is restored after a blockage, which can happen during or after a stroke but also is common in people with sickle cell disease. Anecdotally, many sickle cell patients report self-treating with—and achieving relief from—cannabinoid drugs. Gupta notes that research on these compounds specifically with sickle cell patients is needed but has been difficult to fund.

The microbiome is another intriguing target, Brandow says. She is wrapping up a large study, funded by the National Institutes of Health and the National Heart, Lung, and Blood Institute, assessing the differences in intestinal microbes between people with and without sickle cell. The project is also evaluating whether microbial communities change during acute events because prior studies suggested that certain gut microbes can upregulate specific immune pathways. And Brandow is investigating whether altering the microbiome to interfere with this process could reduce pain—something that has worked in sickle cell mice dosed with probiotics.

Another important approach, Smith says, will be interrupting pain signals in the nervous system. He believes it is particularly important to focus on children and adolescents before their brains develop a "nociplastic pain pattern," pain sensitivity that sets in after years of repetitive acute attacks. That won't necessarily require new drugs. Rather Smith suspects that doctors could prevent chronic pain, or at least diminish it, by providing better treatment to patients at younger ages.

Other factors that exacerbate chronic pain are loneliness, depression, malnutrition and social isolation, all common issues for people with sickle cell disease. Depression in particular affects between 20 and 60 percent of people with sickle cell, and studies suggest that treatment with antidepressants may reduce pain episodes. Companionship and a healthy diet might help, and those changes may also decrease the dose of opioids required to relieve pain, according to a mouse study by Gupta.

> "There's a tremendous pall of suspicion that circles around sickle cell disease." —C. Patrick Carroll
> *Johns Hopkins University School of Medicine's Sickle Cell Center for Adults*

Treating both acute and chronic pain will ultimately require addressing health-care disparities, Carroll says. In a study of 291 people with sickle cell disease, most of whom were Black, Carroll, Carlton Haywood, Jr., of the Johns Hopkins School of Medicine and their collaborators found that discrimination by health-care providers resulted in increased reports of chronic pain and higher pain severity. That study was published in 2014, but research continues to reveal high rates of stigma, racial bias and discrimination affecting this patient population, all of which can exacerbate pain. Haywood died of complications from sickle cell in 2021.

THE BEST TREATMENT will vary by individual, says Darbari, who advocates for a "whole-person approach." In her clinic, she aims to help children and families learn how to cope with the disease and manage their pain. Depending on a person's situation, they might benefit from a combination of medications; lifestyle changes that could include mindfulness exercises, massage, physical activity or stretching; and psychological interventions such as cognitive-behavioral therapy to address anxiety and catastrophizing, which can make pain worse.

In a trial published this year, adolescents with sickle cell disease who completed a 12-week, app-based program that taught them techniques for relaxation, goal setting and building a social community reported fewer pain days and less intense pain after six months, compared with nonparticipants.

Back in 2008, when Smith realized that he should ask people about their discomfort, he launched a new era of research into sickle cell pain. "We discovered this submerged part of the pain iceberg that is pain at home," he says. "We were only looking at the tip of the iceberg."

Sixteen years after Gupta heard a young boy talk about his pain and learned of Smith's study, she says, researchers are pushing the field forward, but pain remains mysterious in many ways. Eventually, experts hope, their science will ease the suffering.

Investing in Sickle Cell Disease

Global attention on and funding of disease research would benefit millions

BY AMBROISE WONKAM

SICKLE CELL DISEASE was first described in the scientific literature more than 100 years ago and affects more than seven million people. Cystic fibrosis was first described about 85 years ago and affects fewer than 175,000 people. Sickle cell results from a single mutation, whereas cystic fibrosis can be caused by nearly 2,000 different mutations, making it far more complex to diagnose and study. Yet cystic fibrosis has received considerably more attention, funding and research.

Those affected by sickle cell disease tend to be less affluent, live in places with fewer resources and mostly have darker skin. Despite the broad reach of the disease, it receives little attention in policy priority, medical research investment, advocacy and clinical-care funding. Such limited investments, relative to those for diseases such as cystic fibrosis that affect primarily lighter-skinned people in wealthier countries, are probably a consequence of the well-documented racism in society and in science over the past few centuries.

In 2021 sickle cell disease was one of the top three causes of death for children under the age of five in Portugal, Jamaica, Libya, Oman and San Marino. Researchers estimate that between 50 and 90 percent of children with the illness in Africa die before they turn five. In 2021 more than half a million babies worldwide were born with sickle cell disease, and more than 77 percent of them were in sub-Saharan Africa. According to those statistics, as many as 450,000 of those children will die. With better testing, treatments, and other resources, most of their deaths could have been prevented.

I was born in Cameroon and grew up witnessing the pain, challenges, social stigma, disability and early death caused by sickle cell disease among classmates, colleagues and family friends. This experience, coupled with the lack of health care and medications for those affected, led me to choose genetic medicine very early in my medical education, and I developed a strong commitment to researching the illness because I viewed it as a way to meet the greatest need of millions of people and have the greatest impact, particularly in Africa.

I introduced the idea of genetics-based prenatal diagnosis for early detection of sickle cell disease in Cameroon and South Africa in 2007 and 2010, respectively. Over the past 15 years I have published numerous papers on genetic variants associated with disease complications and longer survival in Africa. In 2017 I established the Sickle Africa Data Coordinating Center at the University of Cape Town, South Africa, which I continue to direct. The project is funded by the U.S. National Institutes of Health and aims to build significant infrastructure to support research activities in Africa within the Sickle in Africa consortium. A well-coordinated, multicenter, prospective longitudinal cohort study of sickle cell disease in Africa will improve our understanding of the pathophysiology, outcomes and determinants of the illness.

Sickle cell has so much to offer as a model disease for both science and medicine. But fully unlocking its potential and its treatments will take a concerted effort from high-, middle- and low-income nations alike. I believe there are three main areas where investment could accelerate equitable development of care and therapies.

ONE CRUCIAL AREA IS NEWBORN screening and comprehensive care. In high-income countries, treatments for newly diagnosed infants include penicillin to prevent pneumococcal infections and sepsis (the main causes of death in children under age five with sickle cell), hydroxyurea to increase fetal hemoglobin and reduce inflammation and vaso-occlusive episodes, and blood transfusions to treat anemia and prevent stroke. These interventions have reduced childhood mortality from sickle cell to nearly zero in countries where they are available.

In Africa, however, newborn screening has yet to become standard practice. It has been piloted in only a dozen countries across the continent, despite sickle cell's ever increasing numbers. A 2013 study in *PLoS Medicine* predicted that by 2050 the number of affected newborns would increase globally by about 100,000. That number was surpassed by 2021, almost 30 years earlier than expected, with the large majority of those babies born in sub-Saharan Africa.

Investment in sickle cell disease warrants critical support from international agencies. The effort to implement universal neonatal screening and comprehensive care in African nations should ideally be led primarily by those countries' governments. But the sums involved can be daunting: some studies have estimated that managing one person with sickle cell disease until age 50 could cost as much as $8 million. Four sickle cell drugs have been approved by the U.S. Food and Drug Administration, but they are not widely available, particularly in Africa.

We must establish sustainable global funding programs to improve care and longevity for people with the illness. Such investment would also benefit countries without large populations of sickle cell patients because the disease can be used to investigate how environmental factors modify a widespread, single-mutation illness and how other mutations affect complications such as stroke, cardiac problems and kidney disease. The research might reveal new targets for treatment not only in people with sickle cell but in the general population.

The World Health Organization recognized sickle cell disease as a major public health issue in 2006, and in 2018 the U.S. Congress officially designated September as Sickle Cell Disease Awareness Month. Although this kind of recognition doesn't provide money, it can raise awareness among governments and international organizations, leading to more policies and investments in prevention, care and research. In California, for instance, the 2024–2025 budget provides $5 million in funding to the state's Networking California for Sickle Cell Care initiative. The money is dedicated to comprehensive care for adults with sickle cell disease, including pain management and behavioral health services, as part of a larger, federally funded collaborative program that includes 13 states.

Moreover, significant funding from the NIH has helped the Sickle in Africa consortium develop its Sickle Africa Data Coordinating Center, which compiled the world's largest African registry of sickle cell patients. The consortium is also researching newborn screening with a pilot program in seven African nations (Tanzania, Nigeria, Mali, Uganda, Zimbabwe, Zambia and Ghana). Such initiatives are urgently needed in the continent's 47 other countries.

ANOTHER IMPORTANT AIM of sickle cell research should be better understanding of African genomes. In people with sickle cell disease, a protein in the blood called hemoglobin is abnormal and causes red blood cells to become distorted. Before birth a fetus with the disease has healthy red blood cells because fetal hemoglobin (HbF) is dominant at that point and is unaffected by the sickle cell mutation. After birth, adult hemoglobin progressively replaces HbF, and it typically makes up almost all circulating hemoglobin within four months. Some people, however, have variations in HbF-modulating genes, such as *BCL11A,* that allow them to continue producing that form of the protein at higher levels in adulthood. Sickle cell patients with these variations, who can have HbF levels above 8 percent, experience fewer disease complications and have longer life expectancies because they have enough HbF to prevent their mutant hemoglobin from sickling too many blood cells.

The main genetic mutation known to keep HbF levels higher after birth is within *BCL11A,* but that mutation accounts for only a small fraction of the genetic variation. Researchers estimate that in African populations, as many as 90 percent of such gene alterations are unknown. Only about 2.5 percent of all genome-wide association studies have been on people of African descent. By incorporating highly genetically diverse populations of African ancestry into genomic research, we could uncover HbF-promoting variants and provide new targets for drugs to enhance production of the protein.

THE THIRD KEY AREA for investment is research into the genomics of cardiovascular complications of the disease. Childhood mortality from sickle cell has decreased significantly in the U.S. over the past four decades, but adult mortality has not seen similar improvements. This is primarily because people who have lived with the disease for a long time experience acute and chronic cardiovascular complications—including stroke, heart failure, pulmonary hypertension and kidney disease. Genetic variations can increase the risk associated with these complications, but they are also therapeutic targets, so the better we understand them, the more effectively we can prevent and potentially cure the problems they cause.

As just one example, in people of African ancestry the gene *APOL1* has evolved common variants that confer resistance to trypanosome infections, which cause "sleeping sickness." But these variants are also frequently implicated in kidney disease in these same populations, including among people with sickle cell. Recent research has identified antisense oligonucleotide drugs that inhibit the protein produced by *APOL1,* and some of these drugs are now in preclinical or clinical phases of testing. Global medicine is already benefiting from sickle cell research.

To develop effective interventions and extend lifespans for people with sickle cell disease and to advance our understanding of cardiovascular complications both in sickle cell patients and in the general population, we must invest in multicenter, longitudinal, prospective studies in Africa and in wealthy countries, such as the U.S.

GIVEN THE EXTREME NEGLECT of sickle cell disease to date, the sheer number of people affected and all we could learn by studying the illness, we urgently need a global initiative to advance research and clinical trials for sickle cell patients, particularly in low-income settings. Our recent success in developing and deploying COVID vaccines has convinced me that such an effort is feasible. It must bring together various stakeholders, including international agencies, industry, national governments, patient support groups, and more. Investing now in sickle cell research and patient care would create the first model for understanding all other genetic conditions and could provide a blueprint for developing treatments for other diseases as well. Now is the time for global research to expand sickle cell disease programs so we can improve the millions of lives affected by this and other ailments.

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A Supreme Betrayal of Justice

Recent rulings of the Supreme Court undermine the role of evidence, expertise and honesty in American democracy

BY THE EDITORS

A **SAD BUT TELLING** coda to the Supreme Court's misrule came this summer, when the *Ohio v. EPA* decision blocked Environmental Protection Agency limits on pollution from Midwestern states affecting their downwind neighbors. In five instances, Justice Neil Gorsuch's opinion confused nitrogen oxide, a pollutant that contributes to ozone formation, with nitrous oxide, better known as laughing gas.

You can't make this stuff up. This repeated mistake in the 5–4 decision exemplifies a high court not just indifferent to facts but contemptuous of them.

As the first Monday in October dawns, starting another Supreme Court term, public trust in the justices, already at a historic low, is now understandably plunging. In the past four years a reliably conservative majority on the high court, led by Chief Justice John Roberts, has embarked on a remarkable spree against history and reality, ignoring or eliding facts in decisions involving school prayer, public health, homophobia, race, climate change, abortion and clean water, not to mention the "laughing gas" case.

This assault on expertise reached its crescendo in June, when the majority's *Chevron* decision arrogated to the courts regulatory calls that have been made by civil servant scientists, physicians and lawyers for the past 40 years. (With stunning understatement, the Associated Press called it "a far-reaching and potentially lucrative victory to business interests.") The decision enthrones the high court—an unelected majority—as a group of technically incompetent, in some cases corrupt, politicos in robes with power over matters that hinge on vital facts about pollution, medicine, employment, and much else. These matters govern our lives.

The 2022 *Kennedy v. Bremerton School District* school prayer decision hinged on a fable of a football coach offering "a quiet personal prayer," in the words of the opinion. In reality, this coach was holding overt postgame prayer meetings on the 50-yard line, ones that an atheist player felt compelled to attend if he wanted to stay off the bench. Last year's *303 Creative v. Elenis* decision, allowing a web designer to discriminate against gay people, revolved entirely around a request for a gay-wedding website that never got built, supposedly from a man who is straight and says he never made the request. Again, you can't make this stuff up—unless you are on the Supreme Court. Then it becomes law.

Summing up the court's term on July 1, legal writer Chris Geidner called attention to a more profound "disturbing reality" of the current majority's relationship with facts. "When it needs to decide a matter for the right, it can and does accept questionable, if not false, claims as facts. If the result would benefit the left, however, there are virtually never enough facts to reach a decision."

The "laughing gas" decision illustrates this nicely: The EPA had asked 23 states to submit state-based plans for reducing their downwind pollution. Of those, 21 proposed to do nothing to limit their nitrogen (not nitrous) oxide emissions. Two others didn't even respond to that extent. Instead of telling the states to cut their pollution as required by law, the court's majority invented a new theoretical responsibility for the EPA—to account for future court cases keeping a state out of its Clean Air Act purview—and sent the case back to an appeals court.

That means pollution that will cause an estimated 1,300 premature deaths in 2026

Illustration by Lehel Kovács

keeps on coming. Whereas fantasy prayers and fake websites tipped the scales of justice on one side, "an underdeveloped theory that is unlikely to succeed on the merits," as described in a rare dissent from Justice Amy Coney Barrett, swung things the other way for polluters. The decision seems aimed at hobbling the EPA by demanding it thoroughly respond to every inane public comment submitted by polluters in perpetuity before issuing a regulation, warns climate writer Robinson Meyer.

Climate change, in particular, seems to draw out the court's taste for fiction. The 2022 *West Virginia v. EPA* decision that halted efforts to limit greenhouse gas emissions from coal power plants, another 6–3 opinion, saw the majority enshrine a "major questions" doctrine. This legal theology, conjured from the penumbras and emanations of past antiregulatory decisions, insists that sizable regulations require patently-impossible-to-acquire congressional authorization. This is a "power grab" by a court anointing itself the economy's czar.

Science is dismissed and disdained in this war on reality. For example, a decision in late June upholding bans on unhoused people sleeping in public places criminalizes human biology, as the dissent noted. A frankly despicable decision this year to legalize bump stocks turned on gun fetishists' scholastic argument that holding your finger taut while a rifle bucks around it pumping bullets into men, women and children—the way more than 400 (400!) people were shot and 60 killed in Las Vegas in 2017—is not truly automatic weaponry. That's despite research showing a trend of greater fatalities in mass shootings, enabled by just such technology.

The 2022 vaccine-mandate decision, another 6–3 masterpiece, turned on sophistry that workplace rules cover only hazards found solely in the workplace (but somehow excluding, say, forced air sharing with infected employees) and ignored the deeper reality that vaccines save lives. The majority justices doubtless contributed to the hundreds of thousands of deaths of unvaccinated people in the U.S. from COVID with their decision.

A Clean Water Act case last year decreed wetlands environmentally protected only if their waters possess a "continuous surface connection" with a larger body of water. This invented requirement is wholly at odds with how water and wetlands actually work, leaving up to half of the country's protected wetlands now available for dredging.

The 2022 *Dobbs* case ended the right to abortion, an essential medical procedure that helps people manage their own health and bodies and has saved countless lives. The only arguments against abortion are not scientific but theological. The court waved away concerns about the very predictable health impacts of *Dobbs*. Two years later news reports abound of women facing dangerous pregnancies and people in states with stringent abortion restrictions reporting worse mental health. Infant mortality is up almost 13 percent in Texas.

The court's July 1 decision to immunize Donald Trump from prosecution for "official acts" undertaken in office while he was president means "it can never again be said that in America 'no man is above the law,'" retired federal judge J. Michael Luttig noted in response to the ruling. No evidence of an official act undertaken as part of a criminal unofficial one is permitted, the court added, nor is any inquiry into the chief executive's motives—both curious exclusions from criminal investigations that should rest on facts.

"Facts are stubborn things," observed John Adams in 1770, years ahead of the American Revolution and his later presidency. He was speaking at a murder trial of redcoats who fired into a crowd at the Boston Tea Party, before a judge sworn to serve a king. "Whatever may be our wishes, our inclinations, or the dictates of our passions, they cannot alter the state of facts and evidence: nor is the law less stable than the fact," Adams added.

Not so for our Supreme Court majority. Before taking office, justices must take an oath to "administer justice without respect to persons, and do equal right to the poor and to the rich, and that I will faithfully and impartially discharge and perform all the duties." In rejecting facts to please their political party—and their patrons—the justices of the court's majority have broken their oath, made to both the Constitution and the American people. ●

We Can't Turn Away from Reality

To resist complacency, we must understand how it operates

BY MARIANNE COOPER AND MAXIM VORONOV

OBJECTIVELY SPEAKING, we are living through a dumpster fire of a historical moment. Right now more than one million people are displaced and at risk of starvation in Gaza, as are millions more in Sudan. Wars are on the rise around the globe, and 2023 saw the most civilian casualties in almost 15 years.

H5N1 bird flu has jumped to cows, farmworkers have been infected, and scientists are warning about another potential pandemic. According to data from wastewater, the second biggest COVID surge occurred last winter. The Centers for Disease Control and Prevention estimated at least 28,000 people died of COVID in the U.S. between January and early August 2024.

Last year was the hottest ever and had the highest recorded number of billion-dollar weather and climate disasters. Not to mention that over the past few years, mass shootings have significantly increased, mental health issues have skyrocketed, and we've seen unparalleled attacks on democracy and science.

Truth be told, things were pretty bad even before the pandemic started four and a half years ago, with the Great Recession of 2008–2009, the 2009 swine flu pandemic and Brexit. Academics use terms such as "polycrisis" and "postnormal times" to describe the breadth and scale of the issues we now face.

Welcome to the new normal, an age where many things that we used to deem unusual or unacceptable have become just what we live with. Concerningly,

though, "living with it" means tolerating greater suffering and instability than we used to do, often without fully noticing or talking about it. When authorities tell us to resume normal activities after an on-campus shooting or give guidance on how to increase our heat tolerance in an ever hotter world, we may sense that something is awry even as we go along with it.

But what happens when overlooking and tolerating greater levels of harm becomes a shared cultural habit? Like the proverbial frog in boiling water, we acclimate to ignoring more and caring less at our own peril. In the short term, living in a state of peak denial helps us cope. In the long run, it will be our undoing. The danger here is desensitization: that we meet this unprecedented litany of complex problems, from climate change to the rise of fascism, with passive acceptance rather than urgent collective action.

How do we overlook and become hardened to bad things, especially in this scientific and technological age, when we've never been more capable of understanding and addressing them? To resist complacency, we must first understand how it operates.

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Social scientists have long investigated the social organization of denial, or how we collectively achieve reality-adjacent lives in which serious problems are not recognized or are made to seem normal. Research has found that a key factor leading us to "not see" social problems that should beg for our attention is the neutralization or evasion of disturbing or threatening information.

COVID is a good case study for illustrating the collective-denial playbook that underpins our new normal reality. A common strategy to neutralize a social problem is to make it difficult to know about—by scaling back COVID tracking, for instance. In April the CDC ended the requirement that hospitals report COVID admissions and occupancy data, removing one of the last tools we could use to monitor what's happening. "We now enter the blackout phase of epidemiology," wrote science journalist Laurie Garrett in May on X, adding: "There will be patients, but their numbers and whereabouts will be unknown. . . ."

Disappearing is also accomplished by not alerting the public. For example, during the winter COVID surge, the White House was silent. In fact, as COVID positivity and death rates rose, tweets from CDC director Mandy Cohen decreased. If the COVID situation is tracked and the public warned, things don't feel normal. But if we don't monitor or mention it, then things can feel back to normal.

Another tactic is minimization, which is why it's important to notice when neutralizing language enters the chat. For some time now, turns of phrase such as "endemic" and "during COVID" have been common vernacular. So have refrains such as "lower hospitalizations than last year." All of this language gives off an "it's just a cold," "mission accomplished" vibe, casting the disease into a worry-free zone safely behind us.

This minimization keeps the quiet part quiet: that the world is still in a pandemic per the World Health Organization and that more than 73,000 Americans died of COVID in 2023, a higher number than from car accidents or influenza. Among those who have been infected, about 10 percent have long COVID, a serious and often disabling condition with a disease burden comparable to that of cancer or heart disease and an economic cost rivaling that of the Great Recession, for which there are no approved treatments. What's more, each infection, no matter how mild, is associated with a substantially increased risk of health issues, including cognitive dysfunction, autoimmune disease and cardiovascular problems.

Prepandemic, these statistics would have been eye-popping. Now they constitute "back to normal." We think we no longer have a problem, when we've just changed the standard by which we deem something concerning.

Illustration by Donna Grethen

To shore up collective denial, we also rewrite the past. Not only do we repeat that we are better off now, we claim things were never that bad. Contesting the past to remove unwanted memories produces a cultural amnesia about the pandemic. And in burying the past, we sidestep accountability for what went wrong.

Truth tellers are the Achilles heel of collective denial because they call attention to what's being ignored. Thus, another playbook tactic is to hush them up, often by painting them as subversives or deviants. And so those who wear masks are ridiculed, scientists reporting on COVID risks are cast as fearmongers, and those with long COVID are dismissed as having anxiety disorders.

Time and again society pressures people not to see, hear or speak about the elephant in the room. To maintain our own peace of mind, we tune out, malign and shoot the messengers because they remind us of what we would rather disregard. Just look at physician Ignaz Semmelweis, environmentalist Rachel Carson, and NFL player and social justice advocate Colin Kaepernick. Indeed, people are regularly punished for being right.

So what do we do about our "ignore more, care less, everything is fine!" era? We need to stop enabling it. We can start by being more attuned to the everyday ways in which we ignore or otherwise fail to engage with troubling events—like that pinch we feel when we know we should click on a concerning headline but instead scroll past it.

We need to work harder to catch ourselves in the act of staying silent or avoiding uncomfortable information and do more real-time course correcting. We need to guard against lowering our standards for normalcy. When we mentally and emotionally recalibrate to the new normal, we also disassociate from our own humanity. We need to demand that our leaders give the full truth and hold them to account. We must stand up for the silenced and stand with the silence breakers. To counter the new normal's assault on normalcy, we must double down on our duty to know, to speak up and to remember. ●

Escaping the Chair Trap

Breaking up periods of prolonged sitting can improve your health

BY LYDIA DENWORTH

THERE IS A GOLDEN RULE for writers who hope to get any writing done: keep your butt in the chair. I try, sitting for much of the day at my computer. But I also sit at the kitchen table, in front of the TV, and sometimes in planes, trains or automobiles. "If you look at people's lives, what do they do? They just sit," says Neville Owen, a behavioral epidemiologist at the Center for Urban Transitions at Swinburne University of Technology in Melbourne. Many adults sit for more than half the time they are awake. Typically that's almost eight hours—and as many as 11.5—out of 16.

Lydia Denworth is an award-winning science journalist and contributing editor for *Scientific American*. She is author of *Friendship* (W. W. Norton, 2020).

According to a growing body of research, the health problems associated with sitting—heart disease and diabetes, to name two—aren't simply the result of these extensive periods on our keisters. The hazards are greatest when it is *uninterrupted* time: eight hours can be okay if people break it up by standing and moving around every hour—or if they exercise more vigorously when they are up.

Studies of sedentary behavior began decades ago by linking self-reported time spent watching television to a person's level of obesity. The research has progressed to include sophisticated devices capable of measuring not just steps but a lack of them. Those studies show that too much sedentary time, especially for prolonged uninterrupted periods, impairs glucose metabolism and is associated with a higher risk of type 2 diabetes. A 2024 study published in *JAMA Network Open* of nearly half a million people in Taiwan found a 16 percent higher risk of death from any cause and a 34 percent higher risk of cardiovascular disease for those who predominantly sit at work compared with those who don't. And a 2022 analysis in *JAMA Oncology* of 1,535 cancer survivors found that those who sat more than eight hours a day and reported no physical activity had the highest death risk both generally and from cancer specifically. (The researchers selected health characteristics to minimize the possibility that illness caused the sedentary behavior in the first place.)

In recent years overheated headlines have gone so far as to call sitting "the new smoking." It isn't quite, experts say. The risk of death from all causes is many times greater for people who smoke heavily than it is for those who sit the most. But sitting is a serious health concern, and public health institutions such as the World Health Organization have begun adding recommendations to spend less time sitting to their physical activity guidelines.

Those health guidelines also urge 150 to 300 minutes of moderate physical activity per week, which could include working out at the gym or going for a jog or a brisk walk. That raises an important point: even with other regular physical activity, too much sitting can still do harm. "It is possible to be both physically active and sedentary," says Lin Yang, a research scientist in the Department of Cancer Epidemiology and Prevention Research at Alberta Health Services in

People in the top 25 percent of exercisers can sit for more than eight hours per day without increasing risks.

Canada and co-author of the 2022 cancer study. Anyone who exercises regularly—as I do—but also sits for work has this risk.

Sedentary behavior is defined as a waking behavior that involves very low energy expenditure (sitting, lying, reclining). Scientists are still teasing out why it is so bad for us, but there are some likely reasons. Sitting—that is, a lack of movement—affects vascular function (particularly in the legs), blood pressure, blood glucose, cerebral blood flow and inflammation. "Patterns of being active or not being active are just so fundamental to our biology. You see them manifested in almost every system," Owen says.

One solution is to exercise even more overall, says physical activity epidemiologist Ulf Ekelund of the Norwegian School of Sport Sciences, who has studied the combined effects of sitting time and physical activity. "Physical activity can mitigate the effects of prolonged sitting," Ekelund says. "If you have to sit for long hours, you should try to be physically active above the recommended levels." Research indicates that people who rank among the top 25 percent in terms of time spent exercising can sit for more than eight hours a day without increasing their risk of premature mortality.

It is also important to break up time spent sitting with some movement, although scientists haven't yet pinpointed exactly how much is necessary. Our bodies work hard just to rise from a sitting position or vice versa. "Standing from sitting is so biologically active," Owen says. Experimental studies suggest a dose-response relation between time spent sitting and time spent moving. If you are going to stand up for only a minute, you should probably do so every half hour or so, Owen says. If you are going to walk around for a few minutes, then every hour would suffice.

Standing desks, not surprisingly, reduce sitting time for office workers, but the evidence for health benefits is limited and applies only to the workplace. Long periods spent standing can bring their own complications, such as varicose veins. "Really, it's about movement," Owen says.

The bottom line is to change your bottom time. This is far simpler than using fancy desks or ergonomic chairs and computer stands, although those things have their place. What the vast majority of adults and children need to do is move more and sit less. ●

The Paradox of 1 − 1 + 1 − 1 + 1 − 1 + 1 − 1 + …

How do we resolve a centuries-old paradox? The answer tells us as much about mathematicians as about their craft

BY JACK MURTAGH

HERE'S A MATH PROBLEM that everybody can solve: What is 1 − 1? 0. So far so good. If we then add a 1, the sum grows, but if we subtract yet another 1, we're back at 0. Let's say, we keep doing this forever:

$$1 - 1 + 1 - 1 + 1 - 1 + \dots$$

What is the resulting sum? The question seems simple, silly even, but it puzzled some of the greatest mathematicians of the 18th century. Paradoxes surround the problem because multiple seemingly sound arguments about the sum reach radically different conclusions. The first person to deeply investigate it thought it explained how God created the universe. Its resolution in modern terms illustrates that mathematics is a more human enterprise than sometimes appreciated.

Take a guess at what you think the infinite sum equals. I'll give you multiple choices:

A. 0
B. 1
C. ½
D. It does not equal anything.

The argument for 0 comes naturally if we include suggestive parentheses:

$$(1 - 1) + (1 - 1) + (1 - 1) + \dots$$

Recall that in mathematics the order of operations dictates that we evaluate those inside parentheses before evaluating those outside. Each $(1 - 1)$ cancels to 0, so the above works out to $0 + 0 + 0 + \dots$, which clearly amounts to nothing.

Illustration by Jay Bendt

Yet a slight shift of the brackets yields a different result. If we set aside the first 1, then the second and third terms also cancel, and the fourth and fifth cancel:

$$1 + (-1 + 1) + (-1 + 1) + (-1 + 1) + \ldots$$

Again, all the parentheticals add up to 0, but we have this extra positive 1 at the beginning, which suggests that the whole expression sums to 1.

Italian monk and mathematician Luigi Guido Grandi first investigated the series (the sum of infinitely many numbers) in 1703. Grandi, whom this particular series is now named after, observed that by merely shifting around parentheses he could make the series sum to 0 or 1. According to math historian Giorgio Bagni, this arithmetic inconsistency held theological significance for Grandi, who believed it showed that creation out of nothing was "perfectly plausible."

The series summing to both 0 and 1 seems paradoxical, but surely option C (½) is no less troubling. How could a sum of infinitely many integers ever yield a fraction? Yet ultimately Grandi and many prominent 18th-century mathematicians after him thought the answer was ½. Grandi argued for this with a parable: Imagine that two brothers inherit a single gem from their father, and each keeps it in their own museum on alternating years. If this tradition of passing the gem back and forth carried on with their descendants, then the two families would each have ½ ownership over the gem.

As proofs go, I wouldn't recommend putting the gem story on your next math test. German mathematician Gottfried Wilhelm Leibniz agreed with Grandi's conclusion, but he tried to support it with probabilistic reasoning. Leibniz argued that if you stop summing the series at a random point, then your sum up to that point will be either 0 or 1 with equal probability, so it makes sense to average them to ½. He thought the result was correct but acknowledged that his argument was more "metaphysical than mathematical."

Swiss mathematician Leonhard Euler employed more complicated methods to argue for ½ and addressed those who disagreed in a rather defensive paragraph in his 1760 paper *De seriebus divergentibus* (translation: "On Divergent Series"). Euler asserted that "no doubt can remain that in fact the series $1 - 1 + 1 - 1 + 1 - 1 +$ etc. and the fraction ½ are equivalent quantities and that it is always permitted to substitute one for the other without error." So a lot of smart people were strongly in favor of option C.

Infinite series like this one have flummoxed thinkers dating back at least to the ancient Greeks with Zeno of Elea's paradoxes of motion. In a well-known example, Zeno observed that to walk a path, one must first traverse half of it, then must traverse half of the remaining distance (¼ of the total path), and then half of the remaining distance (⅛), and so on. One can keep subdividing forever, which suggests that every time we walk a path we complete an infinite number of actions in a finite amount of time—a paradox.

While philosophers still debate the metaphysics of Zeno's paradoxes some 2,400 years later, mathematicians did make a substantial leap toward resolving them and the mystery of Grandi's series in the late 19th century. From the foundations of calculus emerged clarifying definitions about when infinite series sum to finite values. Finding the answer begins with looking at *partial sums*—add the first two terms, then the first three, then the first four, and so on. If these intermediate sums continue to get closer and closer to a fixed value, then we say the series "converges" to that value. Let's apply this to the series in Zeno's paradox, which sums half of a path plus a quarter of a path plus an eighth of a path, and so on.

$$½ + ¼ + ⅛ + 1/16 + \ldots$$

The first two terms sum to 0.75, the first three terms sum to 0.875, and the first four sum to 0.9375. If we summed the first 10 terms, we'd get 0.9990234375. The partial sums get closer and closer to 1, so the series converges to 1. Although we can conceive of a path as an infinite number of distances, calculus confirms that it still ultimately amounts to one path.

The partial sums of Grandi's series oscillate between 0 and 1 without ever homing in on a single value. So modern mathematicians would choose option D (Grandi's series does not sum to anything).

The resolution of Grandi's series raises a sociological question. Why does the mathematical community accept the partial-sum approach but not Leibniz's probabilistic argument or some other prescription for summing an infinite series? Although they may look alike and smell alike, summing an infinite series is not the same as addition. Addition does not change when you shift parentheses around—for example, $1 + (2 + 3) = (1 + 2) + 3$—but many series, including Grandi's, do. For convenience, mathematicians borrow words like "summing" and "equals" from addition to discuss series, but under the hood what they really *mean* when they say Zeno's series "sums to 1" or "equals 1" is that the partial sums converge to 1, no more and no less.

The partial-sum definition of convergence isn't arbitrary. The math community prefers it to alternatives for good reasons. It alleviates a lot of the paradoxes that beset earlier mathematicians who studied infinite sums, and it preserves many of the nice properties that finite addition enjoys. But other definitions of convergence are useful as well. For instance, rather than asking what number the partial sums approach, the Cesàro summation method takes the *average* of the first two partial sums, then the first three partial sums, and then the first four partial sums, and so on ad infinitum, and asks what those *averages* approach. If you apply this tweaked method to a convergent series like Zeno's, it will always give you the same answer. But it sometimes will give a different answer when applied to series that do not converge under the standard definition. In particular, Grandi's series has a Cesàro sum of ½.

Many other summation methods appear in the mathematical literature. In reality, we can't physically add an infinite number of things, so summation methods simply provide principled ways of assigning values to infinite series. The partial-sum definition holds deserved status as the default, but it occasionally helps to have other options.

Curiously, Grandi's series sums to ½ under most alternative methods. So a colloquial answer to our opening question might be: Grandi's series does not sum to anything, but *if it did* it would sum to ½. ●

Jack Murtagh is a freelance math writer and puzzle creator. He writes a column on mathematical curiosities for *Scientific American* and creates daily puzzles for the Morning Brew newsletter. He holds a Ph.D. in theoretical computer science from Harvard University. Follow him on X @JackPMurtagh

Hidden Battles, Heavy Costs

Health economics and outcomes research reveals the human impact of sickle cell disease

VERTEX

Sickle cell disease (SCD) is an inherited blood disorder affecting more than 120,000 people in the U.S. and at least 70,000 more across Europe and Canada. While SCD was one of the first genetic diseases to be biologically understood and clinically characterized, those characterizations have only scratched the surface of what it is like to live with this disease. For those touched by SCD, the true lived experiences and impacts on day-to-day life extend far beyond what can be found in a textbook.

As new therapies emerge, health-care decision-makers are seeking effective methods to evaluate their value. Robust data analysis and evidence synthesis are required to inform evidence-based decisions. That's where health economics and outcomes research (HEOR) plays a crucial role.

Vertex Pharmaceuticals

▲ Nick Li, global HEOR lead for hemoglobinopathies at Vertex Pharmaceuticals.

Nick Li is global HEOR lead for hemoglobinopathies at Vertex Pharmaceuticals. Below he explains why this type of research is essential to help understand the lived experience of SCD and ultimately to support modern health-care decision-making.

Why would a pharmaceutical company conduct health economics and outcomes research?

Health economics and outcomes research is a multidisciplinary field in which we use rigorous methodology to better understand and articulate the burden of disease. We can describe unmet needs and eventually communicate the value of a treatment. Embedding the patient perspective in our research and conducting studies to specifically document and quantify the patient experience is paramount to supporting patient communities. This way we can ensure these perspectives are considered in the evaluation of therapies.

How can HEOR help with sickle cell disease?

Over the past few years, we have been doing HEOR studies with the SCD community; gathering qualitative and quantitative data on the humanistic burden, health inequities, and economic burden of the disease. Our findings have been eye-opening: we learned about stigma, prejudice and systemic racism in SCD care and highlighted the multifaceted physical and mental toll on sickle cell warriors and their families. In-depth HEOR analyses can often help translate patients' experience into data that can inform health-care decision-making.

What is Vertex learning about sickle cell disease from HEOR?

While SCD can affect a person of any race or ethnicity, the disease disproportionately impacts non-Hispanic Black or African American people, comprising more than 90% of all those living with the disease. Systemic racism and stigma surrounding the disease further exacerbate these inequities.

For people with SCD, the struggle with excruciating pain is real and part of everyday life. As a result, individuals frequently visit the emergency department seeking relief from their pain. However, health-care providers do not always take these complaints seriously. Instead, they may suspect drug-seeking behaviour, label them as drug addicts and even deny them pain medication.

Besides the health inequities, we would say the next biggest challenge is the sheer magnitude of impact on a patient's day-to-day life. Even on a typical day, SCD symptoms can be unpredictable, and patients report limits on basic daily activities such as cooking, walking and showering.

> "SICKLE CELL DISEASE SYMPTOMS CAN BE UNPREDICTABLE, AND PATIENTS REPORT LIMITS ON BASIC DAILY ACTIVITIES SUCH AS COOKING, WALKING AND SHOWERING."

These challenges restrict participation in family and social life and can be detrimental to psychological well-being.

And the impacts go beyond health?

Unfortunately, yes. The need for ongoing medical care, including visits to the doctor, medications and specialized treatments, means costs can add up quickly. Emergency department visits

and hospitalizations are often unavoidable for individuals with SCD, and they can lead to unforeseen medical expenses and potential loss of income. This can become a vicious cycle: job pressure drives health issues and costs, but missed work reduces income and leads to financial instability.

What about school and higher education?

Managing a chronic disease such as SCD can severely interfere with a person's academic progress. This can lead to them falling behind in coursework and having difficulty keeping up with their peers, ultimately affecting educational attainment. The challenges only increase when pursuing higher education. The unpredictable nature of SCD can make it challenging to meet attendance requirements and sustain consistent academic performance. As a result, pursuing a degree may take longer or even be impossible, affecting career prospects and financial stability. The stress associated with all those challenges may also result in health issues and an increased likelihood of pain crises. So the vicious cycle continues.

"EMERGENCY DEPARTMENT VISITS AND HOSPITALIZATIONS ... LEAD TO UNFORESEEN MEDICAL EXPENSES AND POTENTIAL LOSS OF INCOME."

What more do we need to find out about life with SCD?

It's time to look at the adolescent and pediatric patient population and understand how the disease impacts them. Another important area is to bring in the caregivers' perspective, because they play an instrumental role in the day-to-day management of SCD.

Anything else?

The work of our HEOR team is only one small aspect of Vertex's commitment to the SCD community. We've committed $50 million through Vertex and the Vertex Foundation towards health equity initiatives, including support for the Massachusetts General Hospital Comprehensive SCD Treatment Center. We also provide support through grants and other funding opportunities that empower SCD advocacy groups globally, facilitate community gatherings, enhance medical education and support conferences. Our most recent funding supported a variety of programs and engagements, including community gatherings, disease awareness activities and continuing medical education. Together, we will work towards a more equitable future for every person living with this disease. ■

A Sickle Cell Warrior Battles for Equitable Healthcare

How a life-threatening health crisis drove one patient to advocate for sickle cell disease awareness

VERTEX

Kevin Wake lay on the bathroom floor of his Chicago apartment, immobile and unable to speak. The first responders arrived. As he listened, silent and helpless, Wake heard the care team diagnose the cause of his condition as an alcohol or drug overdose.

But they were wrong, and he knew his life depended on communicating that.

At the hospital, Wake fought desperately to be heard. After catching the attention of a nurse, he gathered enough strength to scribble three words on paper: "sickle cell stroke." The nurse presented Wake's note to the attending physician, who finally understood the true extent of his condition.

It was a simple act that would end up saving his life.

Wake, now 56, is the sole survivor of three brothers born with sickle cell disease. Each day is a struggle, as he battles both the debilitating effects of a disease that affects mostly Black and African American people and the prejudice that often accompanies it.

Like other people with SCD, whom he calls sickle cell warriors, Wake has red blood cells that are misshapen (or sickled) and rigid, unlike healthy red blood cells, which are soft and flexible. The sickled cells make it harder for blood to flow through the body, and can block blood flow to the tissues, causing episodes called vaso-occlusive crises, which can strike at any time and anywhere.

▲ **Kevin Wake, 56, lives with sickle cell disease, visiting his family's farm in Kansas.**

Courtesy of Vertex Pharmaceuticals

"It's a distinct and almost indescribable pain," Wake says. Left untreated, such crises can cause severe and even life-threatening complications, organ damage, blockages in the lungs called acute chest syndrome, and acute strokes.

And Wake was not alone in having his symptoms misunderstood.

"Unfortunately that's the kind of care that so many sickle cell warriors are faced with," he says. "They're not believed when they are in pain. It's not believed they have sickle cell."

Wake was treated effectively for his sickle cell stroke, but the incident still frustrates and angers him. He believes that getting proper care earlier in the episode could have changed the outcome and the severity of the symptoms he now suffers as a consequence. And he has no doubt about what was ultimately responsible for his poor experience with the healthcare system: racial prejudice.

"IT'S A DISTINCT AND ALMOST INDESCRIBABLE PAIN."

"It felt like a losing battle," he says. "I was seen one way and that's how I was treated. There wasn't a second thought that something else could be going on. They can see the color of your skin, but they can't see sickle cell."

Wake's experience is one reason why he now serves as president of the Uriel E Owens Sickle Cell Disease Association of the Midwest in Kansas City. He works directly with legislators and health-care providers to draw attention to the lack of awareness and education surrounding the disease.

These issues have affected Wake for his entire life. His mother had to leave her nursing job (and the healthcare it offered) to stay home and raise her sons with sickle cell disease. As his father was a farmer, the family had to buy their own

Kevin uses this room, created in honor of his brother, to meditate and reflect when he's having a difficult day.

Courtesy of Vertex Pharmaceuticals

health insurance, which meant significantly higher out-of-pocket costs.

"We would try to do whatever we could to survive without having to impact those insurance costs," he said. Growing up on a remote farm in Kansas, they also had to travel for more than an hour any time he or one of his brothers needed care or experienced a sickle-cell crisis, adding to the time and productivity lost to the disease.

Later in life, Wake recalls the challenge of keeping stable employment to pay his bills. "I used to try to avoid going to the doctor because I just didn't have the finances to pay for extra appointments," he says. "I only treated my SCD when it was absolutely necessary, when I was in crisis."

In his career, Wake felt under considerable pressure to overcompensate for his limitations, but this ultimately took a significant toll on his health. After working in the pharmaceutical industry for 23 years, overnight medical complications and a second stroke forced Wake into an early retirement on medical disability.

"That significantly impacted not only my income and my health insurance, but also it really affected me mentally and made me question what my purpose in life was," he says. "I went through a two-year period of deep depression and anxiety, not knowing how to make ends meet."

Wake knows he is not the only one. "I hear it from the community all too often. When a sickle cell warrior has to miss work due to their disease, they may lose pay or their job," he says. "They can't pay rent, or for their prescriptions or their groceries. We see a lot of patients who avoid getting care for their disease because of that."

"WHEN A SICKLE CELL WARRIOR HAS TO MISS WORK DUE TO THEIR DISEASE, THEY MAY LOSE PAY OR THEIR JOB."

When Wake was young, his doctors told him he wouldn't live past 25. Until he was in his 40s, he had never met anyone outside his family who lived with SCD, and he didn't know there were other people like him and his brothers. Until then, he felt burdened with the weight of his disease—the stress of balancing school, part-time jobs and doctor's appointments; the mental toll of managing the disease, and the belief that he needed to make the most of his potentially limited days.

After finally connecting with other people with SCD at a meeting of the organisation he now represents, Wake learned the skills he needed to look after himself. Now, he regularly sees a therapist, shares his story in support groups and benefits from music therapy.

"I always try to let people know that there are others out there going through this same thing," he says. ■

VERTEX

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Stefanie Worth
Mother of Winged Sickle Cell Warrior

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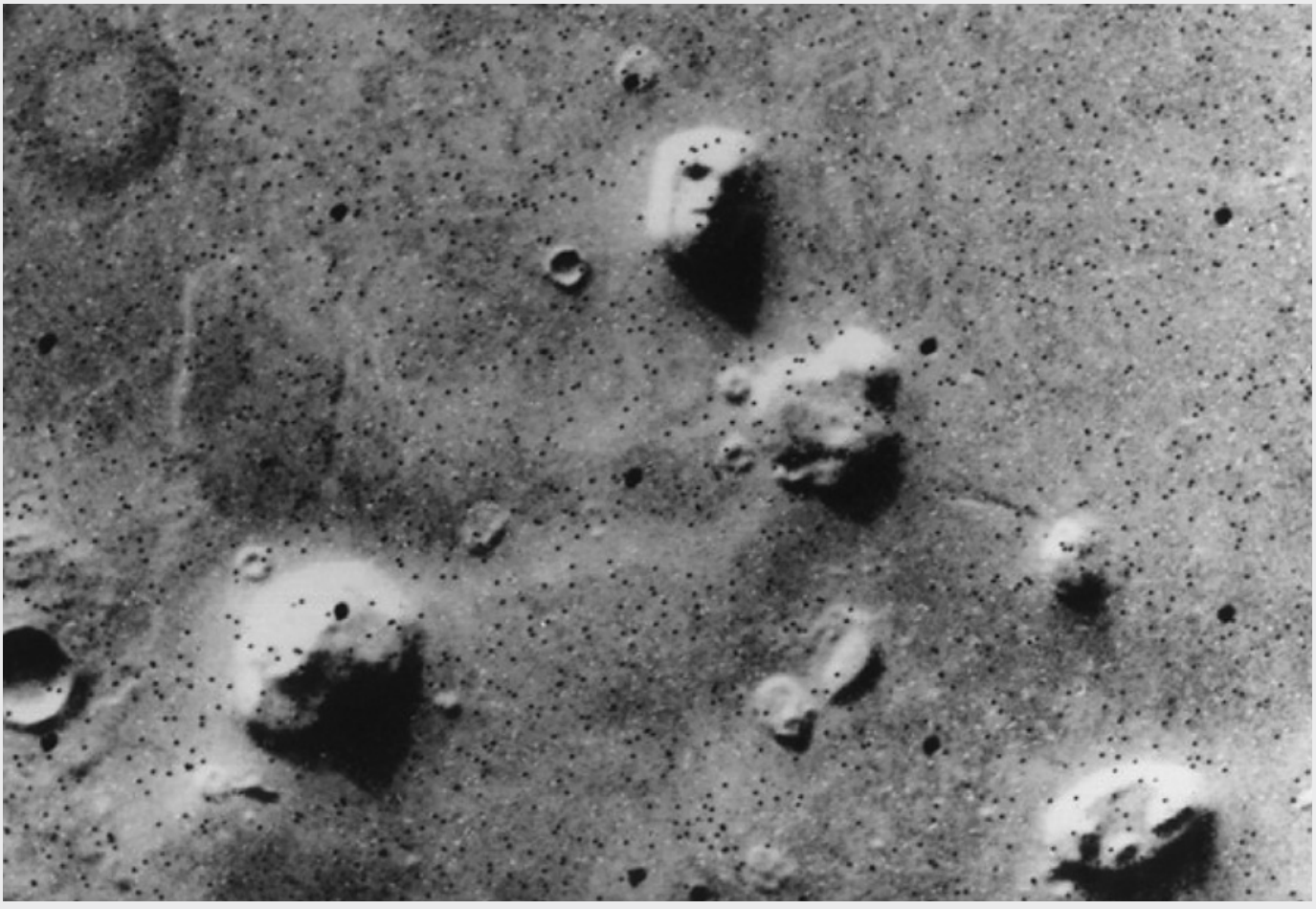

NASA/JPL/MSSS

NASA's Viking 1 orbiter photographed this region in the northern latitudes of Mars on July 25, 1976, while searching for a landing site for the Viking 2 lander. The image shows a mesa that resembles a human face (*center*), which helped to spawn a cottage industry of pseudoscientific claims about ancient Martian civilizations.

Cosmic Pareidolia

The human brain loves seeing patterns that aren't there

BY PHIL PLAIT

FOR GENERATIONS, the idea that Mars once harbored an advanced civilization has fostered a small but devoted community of true believers. These ancient Martians built canals and cities and other great works, so the general narrative goes, but for reasons unknown died out long ago. This belief was popularized by the eccentric American astronomer Percival Lowell as early as 1894, but the core idea had an Internet-fueled resurgence in the late 20th century. It spawned a cottage industry of conspiratorial books, credulous late-night radio interviews, questionable websites and even the big-budget (if disastrously confused) 2000 movie *Mission to Mars*.

The catalyst for that sudden, late-breaking burst of public interest was an image of the Martian surface taken by an orbiter as part of the NASA Viking 1 mission in 1976. In one of the orbiter's pictures of a region called Cydonia, scientists noticed a large mesa that bore an uncanny resemblance to a human face. Dubbed "the face on Mars," it soon attracted the attention of fringe pseudoscience enthusiasts (and, no doubt, grifters) who promoted it as some kind of monument made by extinct Martians.

To be fair, in the Viking image the landform really does look like a face, an eerie visage reminiscent of Easter Island *moai* or the Great Sphinx in Egypt. Could it be some ancient alien tribute to humanity, a memorial signifying the longing of an archaic extraterrestrial race?

Yeah, not so much—follow-up observations from later missions toting better tech, such as the High Resolution Imaging Science Experiment (HiRISE) camera on NASA's Mars Reconnaissance Orbiter, showed exactly what those of us familiar with such things expected: it was just a mesa, a big rock formation with a shape that, when viewed at low resolution from

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the right angle and with the illumination just so, looked somewhat like a face.

True believers in the face on Mars had fallen prey to a psychological phenomenon called pareidolia, our brain's tendency to impose a recognizable pattern on a visual stimulus. We all are subject to it; who hasn't lain on the ground looking up at clouds to see all kinds of things in them, such as animals, common objects, fantastic beasts and, yes, faces?

Faces are incredibly common outputs of pareidolia. We see them everywhere, including in wood-grain patterns, foods, and other everyday ephemera. For instance, I once saw the face of Vladimir Lenin in my shower curtain. That was a weird day.

Our brains are wired to see faces, which isn't too surprising, seeing as how they are the main way we recognize other people. But this trait has the unintended consequence of forcing us to see faces when they aren't really there. The simplest example is the classic smiley face: it's two dots over a curved line, just about as simple a geometric construction as can be, yet you cannot not see it as a smiling face. (Incidentally, we've seen smiley faces on Mars, too.)

Nebulous stimuli are fertile ground for pareidolia, and what better place for nebulous stimuli than an actual nebula? Astronomical objects are perfect for the phenomenon; gas clouds and galaxies have just enough structure to trigger our pattern-recognition ability. Even stars in the sky make patterns that look like recognizable shapes to us; that's why we have constellations. Ever since the telescope was invented, pareidolia has ruled the way we've named what we see.

The most iconic example of all is the Horsehead Nebula. Aptly named, it looks like a cosmic chess piece seen in profile, stoically waiting for its next move. The Horsehead is in the constellation Orion and is part of the immense Orion molecular cloud complex, a sprawling collection of cold, dense gas and dust. Such clouds are star-formation factories, spawning suns that light up the material all around them. The Horsehead is an extension of dark dust silhouetted against a bank of ruddily glowing hydrogen, lit up by the massive star Sigma Orionis not too far above the horse's "head."

Another one of my favorites is a Halloween twofer: officially designated IC 2218, it's an extended cloud of dust not far from the star Rigel, a brilliant blue supergiant marking Orion's knee. The cloud reflects the star's light, and seen one way it's called the Witch Head Nebula because of its uncanny resemblance to a stereotypical witch with a long nose and pointed chin cackling into the night. But amazingly, seen rotated 90 degrees (or with your head tilted), it looks more like a ghost floating menacingly with its arms upraised and its spectral tail trailing behind.

Not to be spookily outdone in Halloween pareidolia, in 2014 the sun decided to turn into a 1.4-million-kilometer-wide jack-o'-lantern, with a false-color composite image of solar active regions forming a grimacing gourdlike visage.

I vividly remember scanning the Milky Way along the constellation of Vulpecula with binoculars in my front yard when I was a kid. My mind was boggling at the sheer number of stars visible as I slowly panned across the sky, when suddenly several brighter stars slid by, aligned in a fairly decent row. I gasped, then exclaimed, "Oh, my God, it's a coat hanger!" I was right; the Coat Hanger cluster—or Brocchi's cluster, as it's officially called—is a collection of about 10 stars arranged in a shape that really does deserve the moniker. But it's just coincidence; the stars aren't all physically associated with one another and just happen to be aligned in our line of sight.

And that's not the weirdest stellar pareidolia in the sky. NGC 2169 is a pair of open clusters, two groups of stars each born together from the same cloud of nebular material. As seen from Earth, they appear to form the numerals 3 and 7; hence the nickname "the 37 cluster." The stars are about 3,500 light-years from Earth and young—only about 11 million years old. Come to think of it, I've never seen this one for myself in the actual sky. It's located near the top of Orion's upraised arm, so perhaps this winter I'll take a shot at it with my own telescope.

Of course, not all pareidolia is so esoteric. Planets and moons have their share of familiar shapes, too, usually in the form of craters. Besides the aforementioned smiley faces on Mars, there's also Mickey Mouse on Mercury and the iconic Tombaugh Regio, also known as the "heart" of Pluto.

The "man in the moon," however, is in my opinion a poser. I've seen various explanations for why people see a face in the moon's chaotic, giant-impact-sculpted mix of bright highlands and dark plains, but none are convincing to me. Still, around the first-quarter phase, a pair of letters appears on the moon: the Lunar X and V, shapes created by light and shadow as the sun rises over a pair of craters, illuminating their raised rims. Several other pareidolic features can be seen as well. I've always thought the huge impact crater Clavius looks like a cartoonishly surprised face.

The list goes on and on. It includes the Question Mark galaxy, the Space Invader galaxy, the Christmas Tree cluster, Rudolph the Red-Nosed Nebula, the seriously creepy MSH 15-52, which looks like a bony hand reaching across the cosmos, and the interacting galaxies Arp-Madore 2026-424, which look like an alien face. Not too many gas clouds look like geological features, but the North America Nebula is very well named.

I myself once discovered a pair of galaxies in a Hubble image that clearly appeared to look like a starship that had gone "where no one has gone before," although my attempts to name them the Enterprise Galaxies stalled out.

This all may seem like a lark, a silly bit of fun at the expense of astronomy. But it's not. Our brain is extraordinarily good at seeing patterns, and although some are fanciful and fantasy, in many cases those patterns are real, revealing fascinating physics underlying their beguiling appearance. Over the centuries we have uncovered a vast array of facts and observations about nature, and it's our ability to imagine that allowed us to make the leap, connecting many of these findings into the rules and laws of reality as we know it.

Science is imagination. We just have to be careful to not let it run away with us if we want to avoid the trap of seeing things that aren't really there. If you ever have to ask yourself whether you're seeing a gigantic sculpture of a human head or just a ragged hill on another planet, understanding pareidolia will help you face the face. ●

What Makes a Psychedelic Experience?

Is it chemical, empirical, or mental and subjective?

BY GARY STIX

A **DEBATE HAS LONG PERCOLATED** among researchers as to what happens after a person takes a psychedelic drug. The experience may stem at least in part from the placebo effect, which is rooted in the belief that taking psilocybin or ketamine will somehow be transformative. Boris D. Heifets, an associate professor of anesthesiology at the Stanford University School of Medicine, has been tackling this question amid his broader laboratory investigations of what exactly happens in mind and brain when someone takes a psychedelic. How much of their sometimes life-altering experience is chemical or empirical, and how much is mental and subjective? It turns out the effects may consist of a lot more than just a simple biochemical response to a drug activating, say, the brain's serotonin receptors.

Heifets recently had a conversation with SCIENTIFIC AMERICAN about his years-long quest to define the essence of the psychedelic experience.

An edited transcript of the interview follows.

Gary Stix
is senior editor covering mind and brain at *Scientific American*.

Are we coming any closer to understanding how psychedelics work, including in the context of therapy? Are we closer to using these transformational experiences to treat psychiatric disorders?

Having been in this field for a while, I still face this inescapable problem of how to study psychedelics. One framework that I find very useful is thinking about it in three categories.

There's the biochemical drug effect, which involves basic brain biology—chemicals interacting with receptors on cells. That happens whether or not you can "feel" the effect of the drug. Then there is the conscious experience related to changes in sensation and revelatory, hallucinatory and ecstatic feelings. These experiences are closely tied to taking the drug, and usually we think of them as caused by the drug. But it is quite difficult to say whether a lasting change in mood or outlook was a result of the drug—a biochemical effect—or of the trip itself, the experiential effect.

The third factor, then, is all those aspects of the overall drug experience that are independent of the drug or trip, the nondrug factors—what psychologist and psychedelics advocate Timothy Leary called the "set and setting." How much do your state of mind and the setting in which you take a drug influence the outcome? This category includes expectations about improvement in, say, your depression, expectations about the experience, the stress level in the environment. It would also include integration: making sense of these intense experiences afterward and integrating them into your life. And it's useful to put each of these things in its own box because I think each of them is somewhat isolated. The goal is to make each box smaller and smaller, to really deconstruct the pieces.

So how have you gone about examining all this?

One example of how we've used this framework in our research is an experiment in which we gave [participants with depression] ketamine during general anesthesia. The idea was to explore just the biochemical drug effect by blanking out conscious

Illustration by Shideh Ghandeharizadeh

experience to see whether people got better from their depression.

Our intention with this experiment was to get at this question that a lot of people have been asking: Is it the drug or the trip that is making someone better? You can address that question in a couple of different ways. One is to redesign the drug to eliminate the trip. But that is a very long process. As an anesthesiologist, my solution was of course to address the problem with the use of general anesthesia. We used the anesthetics to basically suppress conscious experience of the associated psychological effects of ketamine, which many people think may be relevant and even crucial to the antidepressant effects.

We collaborated closely with psychiatrists Laura Hack and Alan Schatzberg, both at Stanford Medicine, and we designed this study to look like every ketamine study in the past 15 years. We picked the same type of participants: people with moderate to severe major depressive disorder who had failed to improve with other treatments for moderate or severe depression. We administered the same questionnaires; we gave the same dose of ketamine.

The difference was these participants happened to be coming in for surgery for hips, knees, hernias, and while they were under general anesthesia, we gave them a standard antidepressant dose of ketamine. Because the patients were under anesthesia and couldn't tell whether they were on a drug or not, this may have been the first blinded study of ketamine.

What was surprising was that the placebo group [who received no ketamine] also got better, indistinguishably from those who received the drug. Almost 60 percent of the patients had their symptom load cut in half, and there was at least 30 percent remission from major depressive disorder. These were patients who had been sick for years, and that finding was a big surprise. In a sense, it was a failed trial in that we couldn't tell the difference between our two groups.

What I take from that is really that this doesn't say much about how ketamine works. What it does say is just how big a therapeutic effect you can attribute to nondrug factors. That's what people call the placebo effect. It's a word that describes everything from sugar pills to our surgeries. In our case, it may have had something to do with the preparation for the surgery. We messaged patients early; we engaged with them early. They weren't used to people being interested in their mental health.

What did you discuss?

We talked to them for hours; we heard about their histories; we got to know them. I think they felt seen and heard in a way that many patients don't going into surgery. I'm thinking about parallels with the preparation steps for psychedelic trials. Patients in both types of research are motivated to be in these studies. In our study, they were told that they were testing the therapeutic potential of a drug and that there was a 50–50 chance they might get it. And then there was the big event of actually having the surgery. In this case, it was similar to having a psychedelic trial—a big, stressful, life-impacting event.

The patients closed their eyes and opened them after the surgery, and in many cases, they had the sense that no time had passed. They knew they went through something because they had the bandages and scars to prove it. What I take from that is that these nondrug effects, such as expectations of a particular outcome, are almost certainly present in most psychedelic trials and are independently able to drive a big therapeutic effect.

It became obvious that people had powerful experiences. Most people don't spontaneously improve from years of depression. After surgery, they get worse. That's what the data show.

And the fact that we're able to make this degree of a positive impact after hours and hours of interpersonal contact and messaging, that's important. This was a very clear demonstration to me that nondrug factors, such as expectations and feelings of hope, contribute a substantial portion to the effects we've seen. And you would be foolish to disregard those components in designing a therapy. And, you know, the truth is that most clinicians make use of these techniques every day in building a rapport with patients, leveraging this placebo response.

Does that suggest in any way that the effects of psychedelics might be substantially—or perhaps entirely—placebo effects?

So this is where I think you have to ask the question: What do we mean by placebo? Characteristically, people use the word "placebo" in a kind of a dismissive way, right? If a person responds to placebo, the subtle implication is there was nothing wrong. And that's not what we're talking about here.

Think about everyday situations that bring about life changes. A heart attack or near-death experience may cause someone in a high-stress job to change their job and lifestyle habits—exercising and eating better. That all can be grouped under the label of a placebo effect.

Another possibility to achieve the same goal is having a transformational experience that you then use to make changes in your life. So the question is: How do you do this in a practical way? You can't exactly go out and give people heart attacks or even send them on life-changing experiences, such as skydiving or trips to the Riviera. But you can give them a psychedelic. That's a big, powerful experience. In many cases, that is unique in some people's lives and confers the opportunity to make changes for the better.

How does giving an actual psychedelic drug to someone in a clinical trial relate to the three categories you mentioned earlier?

Let's circle back to this idea that psychedelic transformation could rely on the biochemical effect, the experience of the trip itself or nondrug factors. Our study of ketamine during anesthesia really highlighted the role of nondrug factors such as expectation but didn't really get at the question of "Is it the drug or the trip?"

To answer that, some of my scientist colleagues are testing "nonpsychedelics," or nonhallucinogenic psychedelic derivatives, to see whether patients with depression, for example, get better after treatment with a drug that can cause some of the same biochemical changes as a classical psychedelic but doesn't have a "trip" associated with it. That's "taking the trip out of the drug." But what if you could "take the

drug out of the trip," meaning creating an experience that is reproducible across people that checks many of the same boxes as a classic psychedelic-induced trip but doesn't actually require the use of a psychedelic molecule? So what, in this context, you provide people with is a profound experience that can even be somewhat standardized so you can study it. And it would be powerful and vivid and revelatory, with a long-lasting impact. Do you get the same effects without a psychedelic?

That would not be definitive evidence. But it would strongly suggest that maybe there's nothing intrinsically special about the activity of a drug that activates a particular receptor that mediates the effects of psychedelics. What that would do is put front and center the role of human experience in psychological transformation.

So you might be able to bypass the need for a psychedelic drug if you can get the same result with a nonpsychoactive drug?

Maybe you can—we just don't know. That's an empirical question. To try to answer it, I've worked closely with Harrison Shong-Wen Chow, also an anesthesiologist at Stanford, on a protocol that we call "dreaming during anesthesia." It's really a state of consciousness that happens before emergence from anesthesia. When patients awaken from surgery, they progress from a state that is deeper than sleep. And they pass through a number of conscious states, some of which produce dreams. About 20 percent of patients will have some dream-memory imagery.

What we do is prolong that process and use EEG [electroencephalography] to home in on a specific biomarker of that state. We can hold someone in this preemergent state for 15 minutes. Participants wake up, and the stories they tell are very hard to ignore. These are some of the most vivid dreams they've ever had. They say things like "that was more real than real." The participants with physical trauma dream of reintegrating their body map, reimagining their body as once again whole. We had a participant who had been assigned male at birth and had gender-affirming surgery. She had been in the military and reimagined her life before her gender-affirming care. She saw herself doing high-intensity military training exercises, now with her body aligning with her gender.

These are intense experiences—vivid, emotionally salient, possibly hallucinatory. We published a couple of case reports where we actually have seen therapeutic effects on par with what we see in psychedelic medicine: powerful experiences followed by a resolution of symptoms in a psychiatric disorder.

What we're seeing is a shared physiology in terms of EEG results for these dream states and the EEGs for psychedelics. We see at least some shared phenomenology in terms of description of the experiences, and there are also similar therapeutic effects.

What are some of your next steps?

In addition to possibly producing a very compelling therapeutic using the common anesthetic propofol, we are working hard to develop experimental tools based on anesthesia, using our knowledge of how placebo works in the brain to separate these three factors: the drug effect, the experiential effect and nondrug factors. At least two of those big effects, neither of which depends on administering a psychedelic, appear to be capable of generating a profound therapeutic impact that certainly would be sufficient on its own to claim the outcomes seen in psychedelic trials. And that, to me, shows that maybe the emphasis is misplaced when we're focused on reengineering the drug to get rid of hallucinogenic effects. We should be focused on reengineering the experience.

But we're still working on number three, the drug effect. We have collaborations with David E. Olson, a chemist at the University of California, Davis, who has pioneered the use of nonhallucinogenic psychedelics. We are helping to characterize the profound neuroplastic effects of a drug he has developed that appears, at least in mice, not to trigger the same type of brain activation that classical psychedelics do. What I'm trying to convey is that, using these approaches, we are able to get some traction to experimentally define, isolate and identify the components of this very complex therapeutic package we call psychedelic therapy. ●

How to Reach a Creative "Flow State"

Both expertise and the ability to release one's control can help people enter a state of effortless attention

BY JOHN KOUNIOS AND DAVID S. ROSEN

LUDWIG VAN BEETHOVEN'S notebooks show that he spent countless hours laboriously developing and revising the musical ideas on which his great compositions were based. It was a torturous and all-consuming process. Beethoven was also the most gifted improviser of his time. He would sit at the piano and create, on demand, fleeting compositions so beautiful and imposing that they would reduce people to tears.

Beethoven illustrates two modes of creativity that can be used at different times by the same person. Most people are familiar with the arduous type—the creative struggle—from personal experience. Generating a stream of high-quality creative ideas is difficult. But the latter kind—the flow state, or the experience of being "in the zone"—is more elusive.

Since psychological scientist Mihály Csíkszentmihályi first identified flow and systematically studied it in the 1970s, this state of "effortless attention" has gained widespread interest. It is believed to enhance innovation, productivity, sense of purpose and joy. But until recently, all that was known about flow came from introspection and behavioral research. That body of work revealed important characteristics of the flow state but left some essential questions unanswered. In particular, researchers knew little about its inner mechanisms, and this lack of understanding hindered the development of tech-

niques for training or inducing flow to boost one's creative production.

In a study at Drexel University's Creativity Research Lab, we addressed this gap by posing a basic question about the nature of creative flow: Does it involve intense concentration and hyperfocused attention, or does it involve the release of attention and "letting go"?

Our study examined flow in the context of jazz improvisation. Jazz has been used in several previous studies of creative production because it requires the generation of a continuous, spontaneous stream of ideas that can be recorded in real time and rated after the fact for creativity and other characteristics. We recruited 32 jazz guitarists for the study. Some were relative novices, whereas others were highly experienced, as measured by the number of public performances that each had given. We directed them to improvise solos on six series of prespecified chords while listening to recorded jazz rhythm-section accompaniments. They also rated the intensity of the flow state they experienced during each performance. Expert judges later listened to recordings of these improvisations and rated them for creativity and other characteristics.

During the improvisations, we also recorded the musicians' brain activity using high-density electroencephalography (EEG). Because these recordings capture signals coming from electrical activity originating in the muscles, skin, eyes, and other areas, we took steps to remove this electrical noise and isolate improvisation-related brain activity. We then used sophisticated algorithms to map the sources of the neural signals in the musicians' brains.

Notably, the most experienced musicians reported, on average, greater intensity and frequency of flow states. Substantial experience with a task may therefore be a precondition for experiencing flow. This finding makes sense because it is hard to imagine feeling effortless attention while performing an unfamiliar task. Also unsurprising was that, on average, the judges rated the experts' improvisations as more creative than the novices' improvisations.

Next, to identify brain regions associated with the flow state, we compared brain activity during high-flow performances with that during low-flow performances. One striking finding was that high-flow performances were associated with reduced activity in the brain's frontal lobes, which are associated with executive function and cognitive control. This supports the idea that flow is a state of low cognitive control rather than hyperfocus.

Then we compared the most experienced musicians with the least experienced ones. The most experienced participants showed activity in a network of brain areas associated with hearing and vision during a flow state—sensory regions that were not activated in the low-experience musicians. Decades of practice and performance apparently led to the development of a specialized brain network for jazz guitar improvisation.

So it seems that creative flow can occur when two conditions are met. First, one has to gain expertise by practicing the task enough to develop, or "bake in," a specialized brain network for performing that task. Second, one must release conscious control so the specialized network can take over and produce ideas on autopilot, without the performer overthinking what they are doing or becoming overly self-conscious.

All too often people learning to compose music, play an instrument, write computer code or engage in any other creative activity become frustrated because it can, at first, be a grueling experience. Everyone knows that you must put in a great deal of practice before you can become fluent at something. The other key ingredient, however, is metacognition, or awareness of how you are thinking. Once you've put in the work, achieving flow relies on learning when to stop overthinking and micromanaging what you are doing and let your expertise take over.

The end result might not be like a Beethoven sonata. But if you can create it during a flow state, it will be your best work, and you will enjoy the process. ●

Illustration by Rudy Gutierrez

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David S. Rosen is a postdoctoral research fellow at the Center for Psychedelic and Consciousness Research at Johns Hopkins University. He studies music cognition, the neuroscience of creativity and flow, and psychedelics and is a lifelong and active rock musician and improviser (playing bass guitar and piano).

Parable of the Svalbard Seed Vault

An Arctic repository for agricultural plant diversity embodies the flawed logic of climate adaptation

BY NAOMI ORESKES

AT A LATITUDE of 78 degrees north lies the northernmost city in the world. It is an odd place. Way above the Arctic Circle—a mere 814 miles from the North Pole—Longyearbyen, in Norway's Svalbard archipelago, is home to only 2,400 people but more than 1.3 million seeds.

The Svalbard Global Seed Vault is an underground storage facility designed to secure seeds to "ensure that food crop varieties are not lost" in the event of a global crisis such as war, terrorism or climate change. Touted as "our insurance policy that we're going to be able to feed the world in 50 years," the vault has been situated at a location and depth in the Arctic intended to ensure that the seeds will not rot or sprout and will be available for use when needed. For further safety, the vault is refrigerated to zero degrees Fahrenheit and designed to withstand a magnitude 10 earthquake. (For comparison, the quake that produced the tsunami that devastated Fukushima, Japan, was magnitude 9.) On the surface, the seed repository sounds like a very solid idea. But it rests on shaky foundations.

The vault opened in 2008, following on an earlier iteration in which seeds were stored in a nearby coal mine. It is not specifically a response to the threat of climate change, but it is an epitome of climate-adaptation thinking. The logic behind it goes like this: Climate change is underway, and our political systems seem to be incapable of meaningful action to stop it, so we have little choice but to plan for a future when we will face serious climate disruption.

Naomi Oreskes is a professor of the history of science at Harvard University. She is author of *Why Trust Science?* (Princeton University Press, 2019) and co-author of *The Big Myth* (Bloomsbury, 2023).

Chief among the disturbances will be disruptions to the food supply as punishing droughts and heat waves lead to widespread seasonal crop failures and important individual food species become impossible to grow in the places where people are used to growing them. When that happens, a supply of diverse seeds—including some adapted to hotter, harsher climates—may be just the thing we need to protect our food systems and stave off disaster.

It's good to be realistic about the climate future we are facing, but the seed vault embeds a conceit common to many adaptation plans: we know what we are facing, so if we plan well, things will go well. But already chinks in the vault's armor have appeared. In 2017 the vault suffered a flood caused, ironically, by climate change. A very warm (but increasingly not exceptional) winter combined with heavy spring rain to thaw part of the surrounding permafrost, flooding the entrance and threatening the safety of the seeds. Changes have been made to the vault's entrance to lessen this particular risk, but the breach—less than a decade after the vault opened—shows that we humans are not very good at anticipating change, even in the short run.

Boosters of the seed vault sustain the logic of their effort in part by effacing the embarrassment of the flood. The timeline of the vault on the website of the vault's partner, CropTrust, does not mention it. When asked about the flood by a reporter for the *Guardian,* a representative of the Norwegian government, which owns and operates the vault, said: "It was not in our plans to think that the permafrost would not be there and that it would experience extreme weather like that … The question is whether this is just happening now, or will it escalate?"

You don't have to be a climate scientist to know the Arctic is losing permafrost; in Svalbard, the dislocation is obvious even to an untrained eye. And it's long been known that the Arctic would warm more rapidly than the rest of the globe: Princeton University geophysicist Syukuro Manabe predicted this effect—known as polar amplification—in the 1970s (he belatedly won a Nobel Prize in 2021 for this work). Today the Arctic is warming four times faster

Illustration by Scott Brundage

than the rest of the planet. Even if the entire world were to stop burning fossil fuels now, global temperatures would not return to normal for decades or centuries to come. Given the state of action (or inaction) on climate, we don't have to ask whether Arctic warming and permafrost loss will escalate. It is a near certainty.

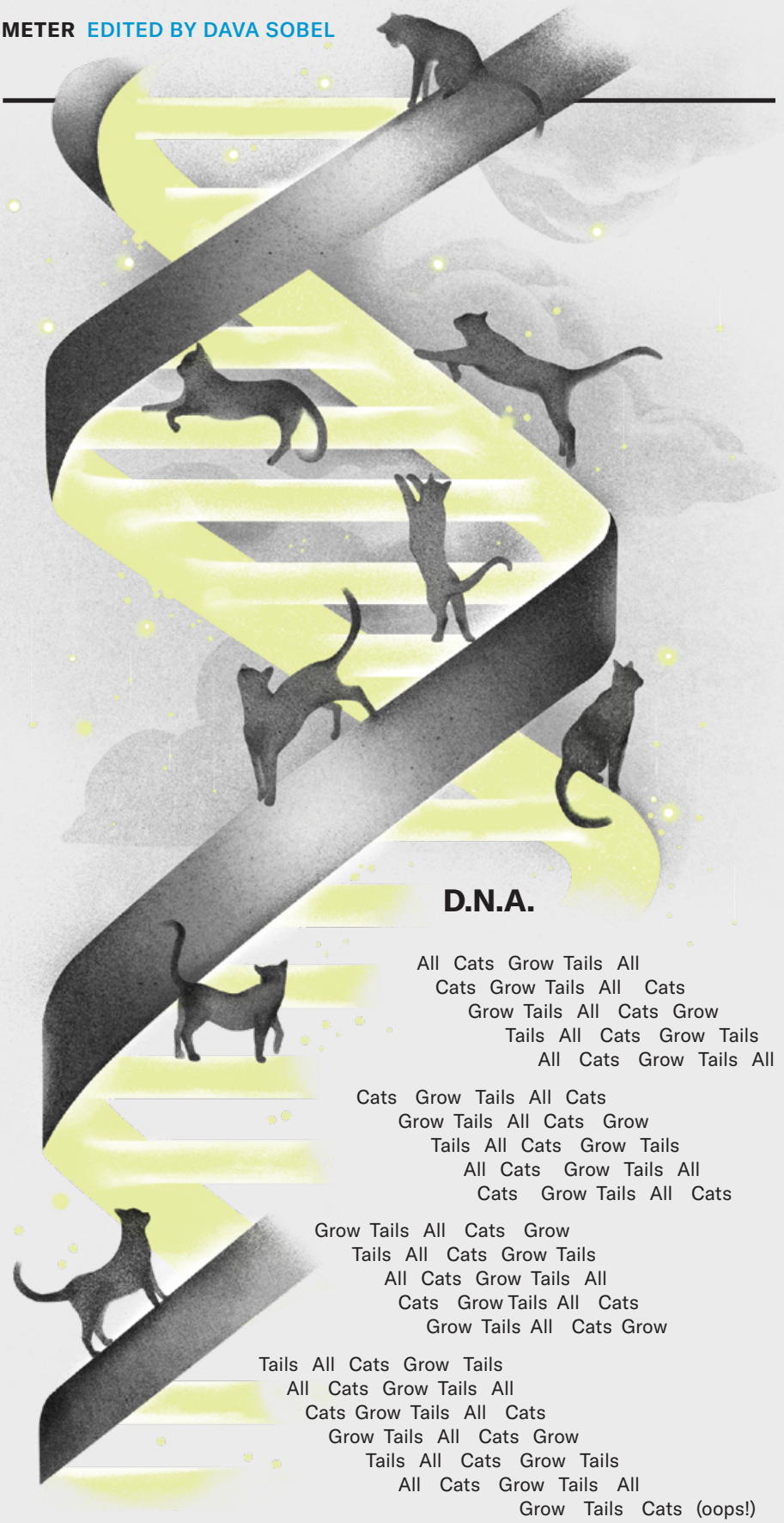
That is not the only problem with the thinking behind the seed vault. Proponents describe it as a "safeguard against catastrophic starvation," but there are reasons to doubt it would function that way. Scholars at the University of British Columbia noted that seeds isolated from the environment do not evolve, so if they are reintroduced decades from now, they may face a natural world to which they are no longer adapted. Because of this biological lag, Svalbard's diligently protected seeds might turn out to be useless, unable to grow or survive.

The vault's focus on seeds also neglects crucially important food crops such as cassava that are not typically propagated through seeds. And if we truly were threatened by global starvation, how likely is it that the seeds could be retrieved, distributed and sown and the crops reaped in time to feed the world?

The problem of biological lag could be addressed by regular updating of the stored seeds with new samples taken from nature, but that is expensive. Even without such updating, the expense of the vault—it cost €8.3 million to build, €20 million to upgrade and €1 million a year to maintain—makes one wonder if it is really a good use of conservation resources and scientific effort. And then there is its carbon footprint. Maintaining the vault at its chilly −0.4 degree F requires electricity from the public power plant in Longyearbyen, which runs on fossil fuel.

It's smart to plan for the future. But the seed vault assumes that we know enough to plan effectively and that people will pay attention to what we know. History shows this is often not the case.

The difficulties of the seed vault remind us that the most important thing we can do right now is not to plan to respond to climate disaster after it happens but to do everything in our power to prevent it while we still have that chance. ●



D.N.A.

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Jim Erhart has been writing poetry for most of his 96 years, and has published several collections, including, most recently, *Poetry With Pictures*. He lives in the hills of northern California, where he owns a historic gold mine.

Illustration by Masha Foya

The Population Bomb That Wasn't

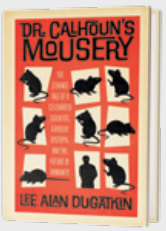
A biography of the rodent ecologist who tried to change the fate of humanity

BY BEN GOLDFARB

NONFICTION

In the 1960s and 1970s American society suffered a yearslong collective panic about the perceived threat of overpopulation. Biologist Paul Ehrlich appeared on *The Tonight Show* to tout *The Population Bomb,* his 1968 polemic about human numbers run amok. The 1973 film *Soylent Green* depicted a squalid hellscape in which surplus people would be processed into food. College students pledged to remain childless for the benefit of Earth.

This anxiety originated, in part, in the laboratory of John Bumpass Calhoun, an enigmatic ecologist who spent decades documenting the adverse effects of overcrowding on rodents in elaborate experimental "cities." Calhoun is largely obscure today, but few scientists in his time wielded more influence. He hobnobbed with science-fiction writer Arthur C. Clarke and was featured in books by naturalist E. O. Wilson and journalist Tom Wolfe—in the process spreading overpopulation angst far and wide. "The most profound impact of Calhoun's studies lies far from academic halls and ivory towers," writes Lee Alan Dugatkin in *Dr. Calhoun's Mousery,* a new biography nearly as quirky as its subject. Calhoun's work permanently "seeped into the public consciousness."



Dr. Calhoun's Mousery: The Strange Tale of a Celebrated Scientist, a Rodent Dystopia, and the Future of Humanity
by Lee Alan Dugatkin. University of Chicago Press, 2024 ($27.50)

Calhoun made for an unlikely prophet. A nature lover from Tennessee, he took a job in the 1940s leading a long-term study in Baltimore with the primary goal of controlling urban rats. Calhoun found that each city block was home to around 150 rats, a number he found low given the "abundant sources of food in open garbage cans." Rat populations, he suspected, were "self-regulating": when new rats tried to move in, residents kicked them out. But the unpredictability of Baltimore's streets—where humans were constantly killing rats or messing with the traps—frustrated Calhoun's analyses. To truly understand rat society, he decided, he needed to control their environment.

In the late 1950s the National Institute of Mental Health gave Calhoun the opportunity to manipulate rats in a remodeled Maryland barn. Calhoun, an endlessly inventive designer of experiments, built an enclosure outfitted with rat apartments and partitioned the pen into connected "neighborhoods," creating a murid arcadia that he could observe at his leisure.

This utopia soon turned nightmarish. As the rats multiplied, they fed and gathered in ever greater densities, leading to a social breakdown that Calhoun called a "behavioral sink." Packs of libidinous males relentlessly hounded females, who in turn ignored their offspring; in some neighborhoods, pup mortality hit 96 percent. The rats, Calhoun declared, suffered from "pathological togetherness" that could lead to collapse. In the years that followed, he shifted to mice, but his fundamental conclusions remained the same: rodents succumbed to chaos as their populations exploded.

Calhoun wasn't shy about extrapolating to our own species' fate. "Perhaps if population growth continues to grow unchecked in humans, we might one day see the human equivalent" of socially catatonic rodents, he told the *Washington Daily News* in one characteristic interview. His fears both channeled the zeitgeist and directed it.

Dugatkin—an evolutionary biologist, science historian and prolific author who sifted through thousands of pages at the Calhoun archive in Bethesda—is an admirably thorough researcher. But his granular chronology of Calhoun's activities sometimes slides too deep into a recitation of media coverage, conference talks and intricate experiments. Amid this blizzard of minutiae, *Mousery* occasionally loses sight of a question that should be central to any biography: Why does Calhoun matter *today*? Dugatkin acknowledges that the "lasting impact of [Calhoun's] work is nowhere near" that of pioneering behaviorists such as Ivan Pavlov. But he misses an opportunity to probe the social debates that his subject's work catalyzed. Did Calhoun's darker prognostications do harm? The population bomb, after all, failed to detonate.

Calhoun belonged to a generation of scientists who had no compunctions about straying from their disciplinary lane. He wrote poetry and sci-fi and consulted on humane prison design. Dugatkin captures the grand ambition of a man who gazed at rodents and saw the universe, even if the significance of his research is murky today. As Dugatkin notes, the disturbing dynamics that Calhoun produced in his micromanaged "universes" have never been observed in the wild. Calhoun didn't describe the world; he created his own.

Ben Goldfarb is author of *Crossings: How Road Ecology Is Shaping the Future of Our Planet* (W. W. Norton, 2023) and *Eager: The Surprising, Secret Life of Beavers and Why They Matter* (Chelsea Green, 2018).

Illustration by Frank Stockton

Adventures in Rewriting History

In a postapocalyptic world on the verge of its next crisis, the past is powerfully present

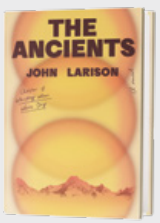
In *The Ancients,* an environmental disaster radically changes the landscape.

SENEZ/Getty Images

FICTION *The Ancients* opens with a bravura set piece of two sisters and their younger brother traversing a mountain range alone, on the brink of death. In author John Larison's depiction of a world that is both postapocalyptic and preapocalyptic, each sentence breaks as blunt as the stones the siblings must sleep on. Here, in this brisk, bold adventure of tribal migration, Larison confronts what it means to be human amid shifts in climate across millennia.

Some 230 generations after a great environmental disaster, villagers who have long fished or hunted elk find themselves once again forced to decamp from their homes in the face of a terrifying change. Deserts are swallowing lands that, readers soon learn, once were known as Alaska. On their journey the siblings encounter other tribes, other ways of living and thinking, and even a city that teems with all that's great and cruel in civilization.

As Larison examines the crucial role of storytelling in humanity's survival, the characters sing, chant, read, dance and even act on a stage, recalling the words of the ancients. These tales and warnings embody the practices, customs and rituals that have helped each far-flung group survive. They prove so powerful, in fact, that the plot turns on people's efforts to control passed-down narratives. They stage myths and fake scrolls to make it easier for the powerful to shape understanding of the present.



The Ancients: A Novel
by John Larison. Viking, 2024 ($30)

With themes of slavery, bloody vengeance and the greed of the civilized, Larison's own storytelling likewise draws on ancestral predecessors, including tribal origin stories and religious texts. The novel's imaginative sweep connects the ages of papyrus, pulp fiction and 20th-century epic potboilers such as Leon Uris's *Exodus.*

As survival fiction, the first chapters of *The Ancients* measure up to the work of Jack London and other greats of the genre in the attention paid to how much of what's human gets stripped away in the wild—and how much endures. But the story edges toward an action extravaganza as the novel barrels on, restlessly jumping among a host of storylines. Larison, who brought such welcome humanity to the outlaw Old West in *Whiskey When We're Dry,* here risks doing to readers what his great city does to his villagers: overwhelm them.

For all its warnings and violence, *The Ancients* still celebrates humanity's perseverance even as it asks what future societies that develop after ours might learn from the failings of our current one.

—Alan Scherstuhl

IN BRIEF

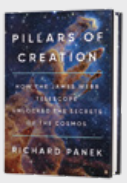
Absolution: A Southern Reach Novel
by Jeff VanderMeer. MCD, 2024 ($30)

Told in three ominous narratives, writer and critic Jeff VanderMeer's *Absolution* fills in the gaps from his enigmatic Southern Reach trilogy about the mysterious Area X. Old Jim, a reluctant and damaged agent with a secret government organization called Central, discovers 20-year-old archives of the first expedition to the area from biologists who encountered time dilations, animal mimics, a lighthouse emitting green energy and the enigmatic Rogue figure who terminated their research. Old Jim learns, among other things, that Central used brain augmentation and conditioning to control both scientists and animals. VanderMeer builds tension in these atmospheric and genuinely creepy tales that entertain as much as they disturb. *—Lorraine Savage*

Cryptography
by Panos Louridas. M.I.T. Press, 2024 (paperbound, $18.95)

Don't be misled by the straightforward title—this crash course is an engaging and perfectly paced introduction to cryptography, which computer scientist Panos Louridas mischievously describes as "the art and science of keeping and revealing secrets." Far from being a language just for hackers, cryptography is vital to the security technologies we use daily, from search histories to gym locker codes. The book covers both the history and principles of the field, complemented by well-designed diagrams that let you test your cryptography skills. In just five chapters, Louridas cracks the code on distilling an intimidating smorgasbord of topics into a digestible and delightful package. *—Lucy Tu*

Pillars of Creation: How the James Webb Telescope Unlocked the Secrets of the Cosmos
by Richard Panek. Little, Brown, 2024 ($29)



Having already chronicled a history of telescopes in his 1998 book *Seeing and Believing,* science writer Richard Panek boldly writes one of the first books about *the* telescope: the James Webb Space Telescope. Like any good profiler, Panek gets up close and personal with his subject, describing each layer of its sunshield as "the length of a long tennis lob and the width of a tissue." Woven into the narrative is the importance of the public in shaping the mission's trajectory, from electing leadership who fund the nation's space agency to bestowing Internet virality on JWST's first-released images of other worlds. *—Maddie Bender*

Nobel Connections

A deep dive into science's greatest prize

TEXT BY SARAH LEWIN FRASIER
GRAPHIC BY JEN CHRISTIANSEN

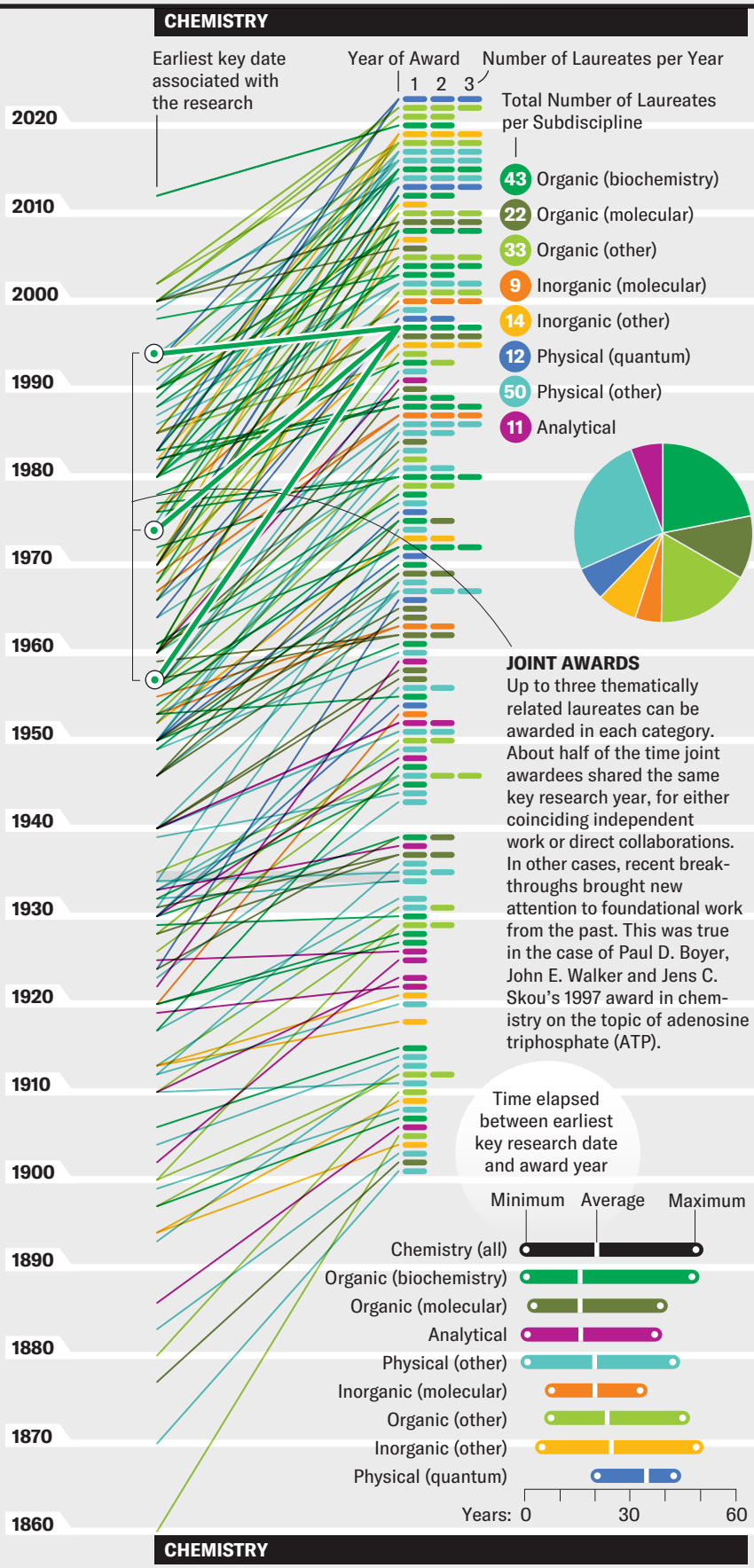
METEOROLOGIST Syukuro Manabe shared the 2021 Nobel Prize in Physics for his work modeling gases' movement through a column of atmospheric air—in the 1960s. His 60-year-old research had proved foundational for the computer models that scientists use today to interpret and predict our changing climate.

Manabe's wait was particularly long, but there is often a substantial gap between the awarding of a Nobel Prize and the earliest work it honors—an average of 20 years across categories, SCIENTIFIC AMERICAN found. "It takes time to prove that something has impact beyond just curiosity," says John Ioannidis, a Stanford University professor who has examined the Nobels' distribution and influence. Although the awards are not a representative look at all of science, they reveal the trends and incentives shaping key scientific fields.

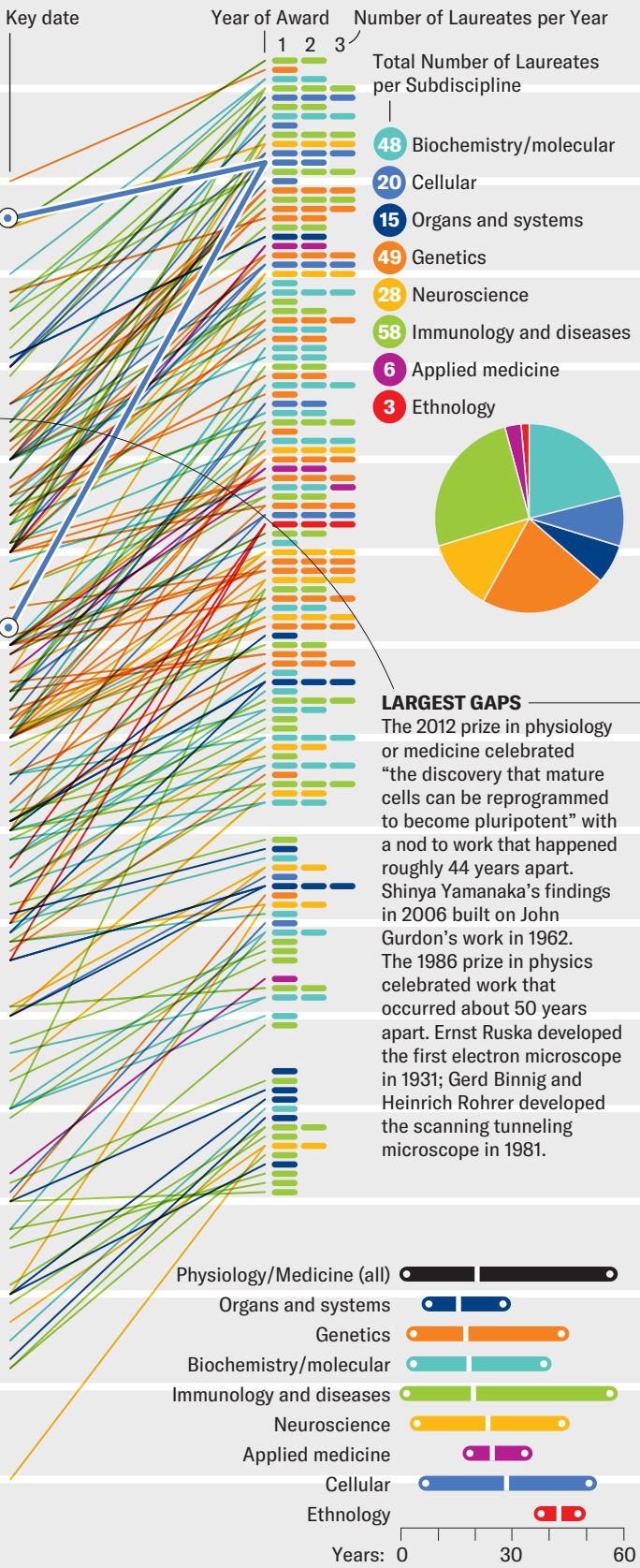
As Nobel season approaches, we at the magazine wondered what subfields of science have been most celebrated and whether there are visible patterns related to the amount of time between the research and the recognition. We used the official Nobel synopses and statements to sort the awards into our own subdiscipline categories and to inform research dates on a timeline that shows the trends.

One clear pattern is the increase in multiple laureates per prize. Each award can be split among a maximum of three living researchers, but that rule is increasingly constraining as science becomes more collaborative. This stipulation may even skew what gets highlighted as the most significant research going forward, Ioannidis suggests, if a Nobel Committee cannot pick only three individuals responsible for a result. "It's not easy to have someone who really stands out so separately from the rest of the world."

Source: https://www.nobelprize.org/prizes/lists/all-nobel-prizes/all/ (*primary reference*)

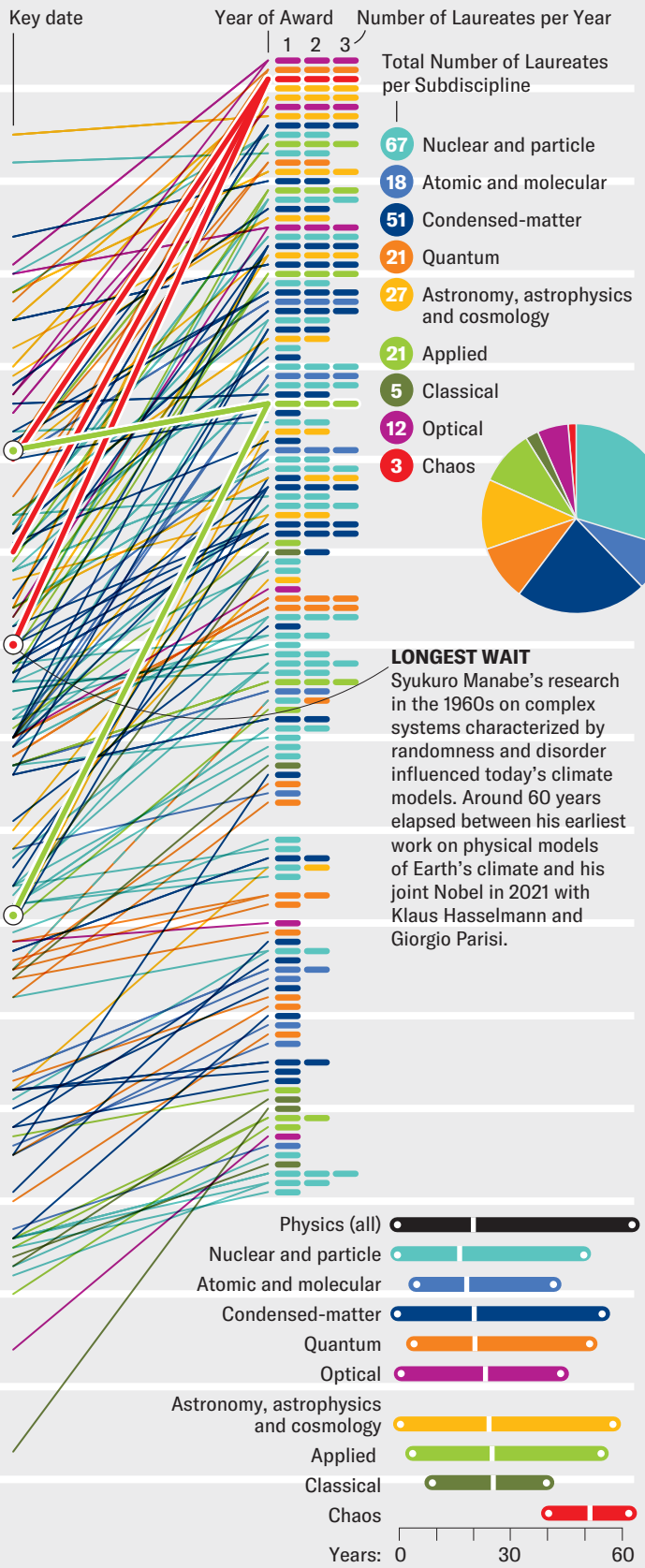


PHYSIOLOGY OR MEDICINE



LARGEST GAPS
The 2012 prize in physiology or medicine celebrated "the discovery that mature cells can be reprogrammed to become pluripotent" with a nod to work that happened roughly 44 years apart. Shinya Yamanaka's findings in 2006 built on John Gurdon's work in 1962. The 1986 prize in physics celebrated work that occurred about 50 years apart. Ernst Ruska developed the first electron microscope in 1931; Gerd Binnig and Heinrich Rohrer developed the scanning tunneling microscope in 1981.

PHYSICS



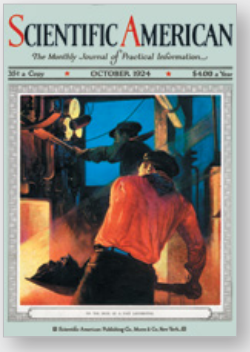
LONGEST WAIT
Syukuro Manabe's research in the 1960s on complex systems characterized by randomness and disorder influenced today's climate models. Around 60 years elapsed between his earliest work on physical models of Earth's climate and his joint Nobel in 2021 with Klaus Hasselmann and Giorgio Parisi.

PHYSIOLOGY OR MEDICINE
PHYSICS

50, 100 & 150 Years

BEST BASEBALL BATTING ORDER

1974 "Managers and baseball strategists give much thought to the batting order, following such precepts as putting a good runner first and a big hitter in the 'cleanup,' or fourth, spot. Does it make any difference? R. Allan Freeze of the University of British Columbia, writing in *Operations Research,* says 'the effect of using the best batting order rather than the worst is less than three extra wins per 162-game season.' Freeze conducted a computer simulation of some 200,000 baseball games, with teams in the traditional lineup, a second lineup of hitters in descending order of productivity, and a third lineup in ascending order."



LIFE AND LIMB FOR AIR MAIL

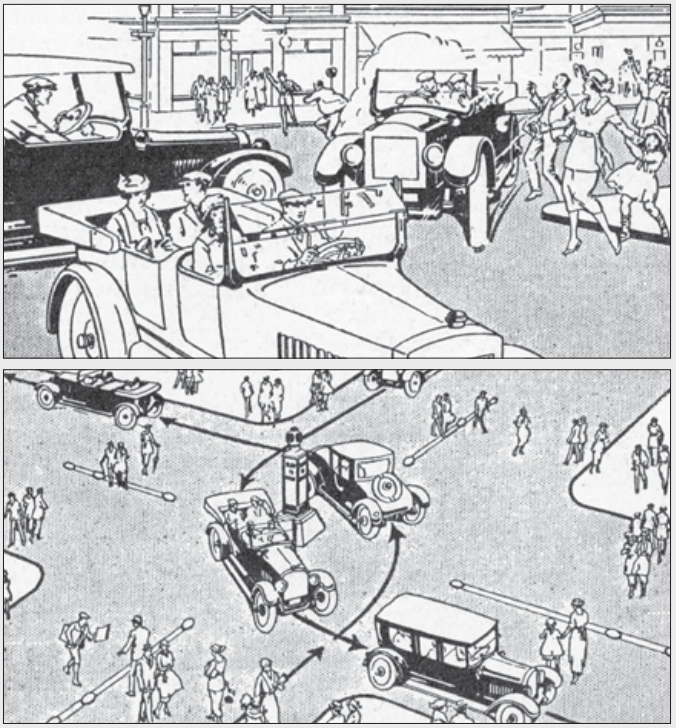
1924 "We pay tribute to the people of the Post Office Transcontinental Air Mail Service, the greatest single step ever taken to make commercial aviation a practical day-and-night reality. Very much to the point is the following quotation from a talk by Captain Hyde-Pearson, a veteran of the World War, shortly before he was killed in the air mail service: 'We risk our necks; we give our lives; we perfect a service for the benefit of the world at large.' While you sit in the safe shelter of your office or sleep in the secure comfort of your bed, these boys by day and by night may be sweeping through rain or snow or fog or the blackness of the night, with death ever at their shoulder, in the performance of a duty whose pay is small, whose risks are great, and whose only reward can be the gratitude and admiration of the American public."

MUMMIES DEMYSTIFIED

"At the Field Museum of Natural History in Chicago it was found possible to take X-ray photographs of a group of Peruvian mummy packs. To have unwrapped these mummy packs to ascertain whether they contained objects of special interest would have meant their destruction. By means of the X-ray pictures it is possible to learn what has been buried with the body. In the packs thus far examined have been found ears of corn, pottery, vessels of clay containing shells, bits of metal, gourd vessels, beads, clay figurines, cut-bone objects—or in some instances, nothing. It is also possible to gather something definite concerning the age, sex and condition of the bony structure of the body buried therein."

LADY EDISON, INVENTOR AND ENTREPRENEUR

"Lady Edison, as she is called, has 47 inventions to her credit and a diversity which is truly remarkable. The Lady Edison is Miss Beulah Louise Henry in New York. Here is a list of a few of her inventions: telephone call list; handbag with interchangeable covers; hair curler; ice cream freezer; pencil; electric fan shield; rubber reducing garment; 'Kiddie Klock' for teaching time; glove snaps and a roulette top. Miss Henry does not claim to have any special mechanical talent, and she torpedoed the idea that invention is the product of solitude. 'The solution of the snapper that fastens the corners of the umbrella to the frame came one day when I was preparing to go to a matinee with my mother,' she recalled. 'The biggest umbrella men in the country said it could not be done. Of course, I did not believe them. I have my inventions patented in four different countries, and I am president of two newly incorporated companies.'"



1924, Safer Traffic: "Idealistic sketch shows how the proper delineation of traffic lanes that bring all intersecting courses together at right angles will iron out the confusion of a busy corner. [And yet] the flashing beacon is vastly superior to mere marks on the pavement or signs at the curb."

CALL ME A SCIENT

1874 "Mr. Proctor recently asked for a single word which should convey the meaning of 'man of science.' Mr. Gosse has recently suggested the name 'scient'—a word which receives the support of Mr. A. J. Ellis, who, in the *Academy* for September 19, says: 'I beg leave formally to introduce a scient and to propose that this strictly formed disyllable should take the place of the American barbaric trisyllable scientist.' It will be seen, however, from the letter of a correspondent that the word is not entirely unobjectionable, as it may be confounded with Science when it is spoken in the plural. We suggest that our cousins call him the 'sci-ist,' which will be O.K., used in the singular or plural."

Scientific American, Vol. 131, No. 4; October 1924

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