MAY 2021

SCIENTIFICAMERICAN.COM

SCIENTIFIC AMERICAN

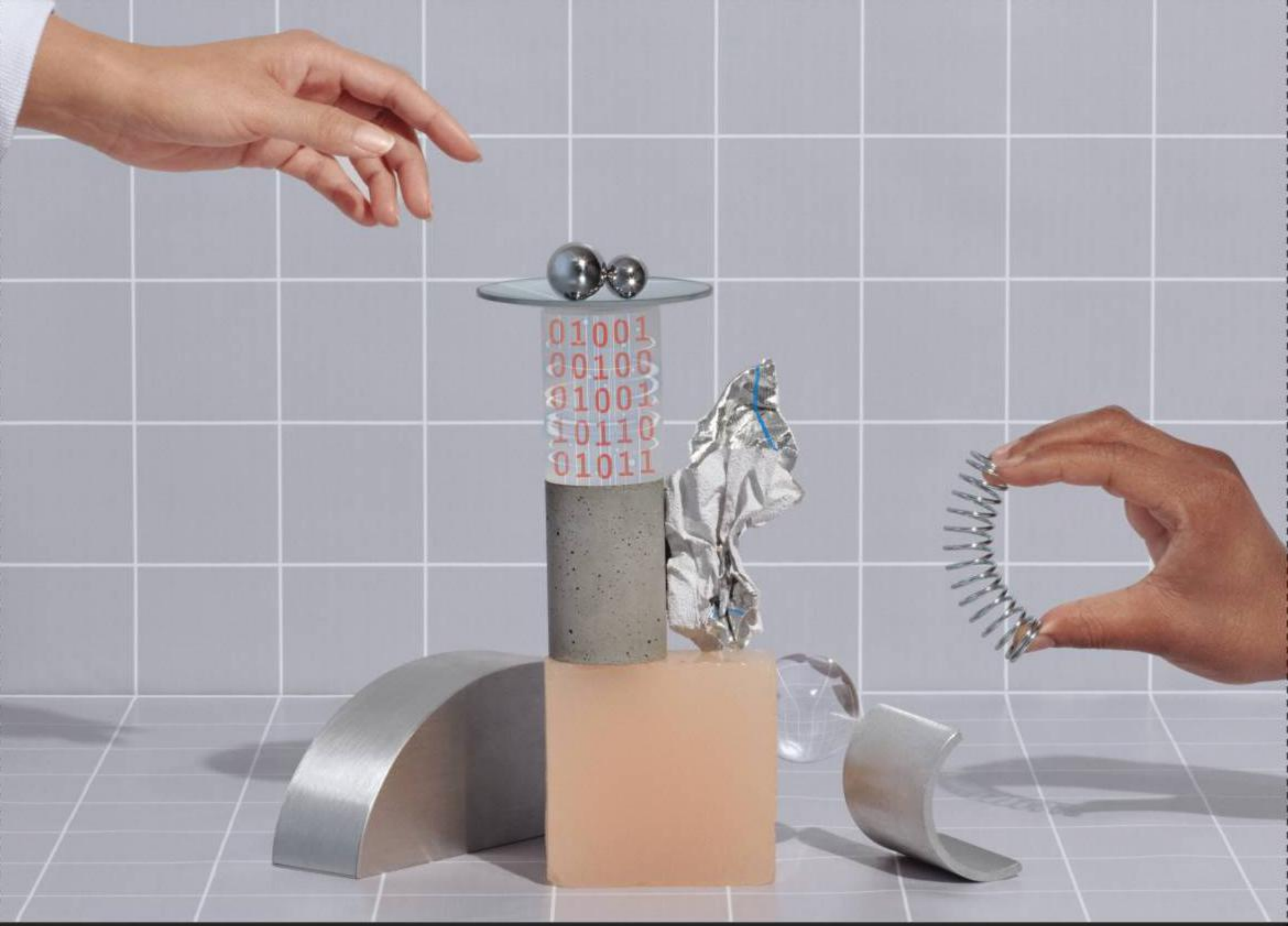
A New Map of the Universe

Alzheimer's and the Blood-Brain Barrier

How to Help Adolescents Flourish

JOURNEY INTO THE AMERICAS

Genetic and archaeological discoveries tell a new story about how the continents were populated


01001
00100
01001
10110
01011

MAY 2021

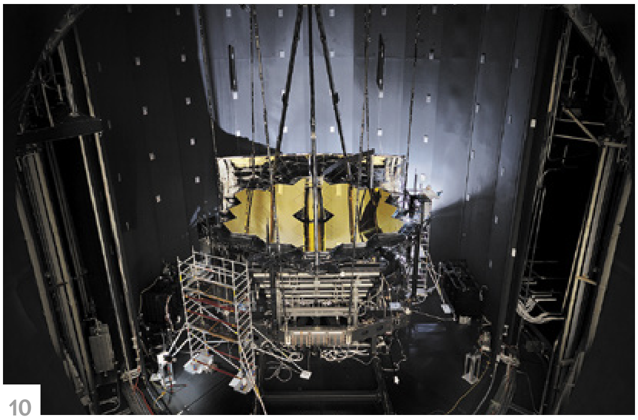
VOLUME 324, NUMBER 5

SCIENTIFIC AMERICAN

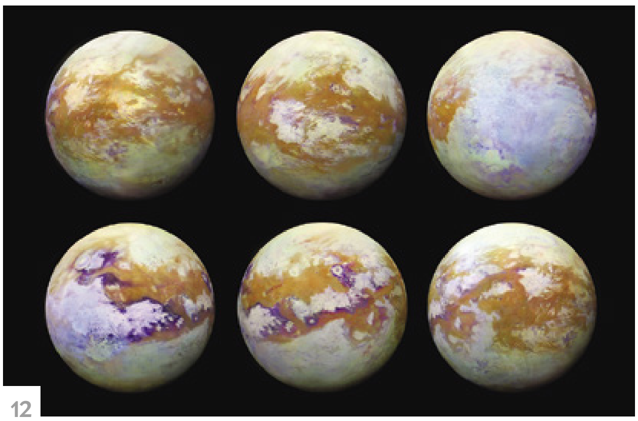
MICHAEL BERUMEN AND MORGAN BENNETT-SMITH

ON THE COVER
The peopling of the Americas was once thought to be a simple process: a group of hunters migrated from East Asia in pursuit of game animals around 13,000 years ago and gave rise to the Indigenous peoples who live on these continents today. Recent genetic and archaeological finds have upended this tidy story. Illustration by Winona Nelson.

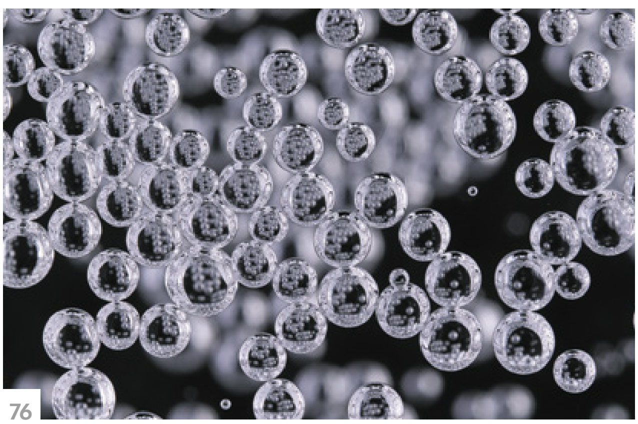
SCIENTIFIC AMERICAN



10



12



76

Scientific American (ISSN 0036-8733), Volume 324, Number 5, May 2021, published monthly by Scientific American, a division of Springer Nature America, Inc., 1 New York Plaza, Suite 4600, New York, N.Y. 10004-1562. Periodicals postage paid at New York, N.Y., and at additional mailing offices. Canada Post International Publications Mail (Canadian Distribution) Sales Agreement No. 40012504. Canadian BN No. 127387652RT; TVQ1218059275 TQ0001. Publication Mail Agreement #40012504. Return undeliverable mail to Scientific American, P.O. Box 819, Stn Main, Markham, ON L3P 8A2. **Individual Subscription rates:** 1 year $49.99 (USD), Canada $59.99 (USD), International $69.99 (USD). **Institutional Subscription rates:** Schools and Public Libraries: 1 year $84 (USD), Canada $89 (USD), International $96 (USD). Businesses and Colleges/Universities: 1 year $399 (USD), Canada $405 (USD), International $411 (USD). Postmaster: Send address changes to Scientific American, Box 3187, Harlan, Iowa 51537. **Reprints inquiries: RandP@sciam.com. To request single copies or back issues, call (800) 333-1199.**
Subscription inquiries: U.S. and Canada (800) 333-1199; other (515) 248-7684. Send e-mail to scacustserv@cdsfulfillment.com.

Laura Helmuth is editor in chief of *Scientific American.*
Follow her on Twitter @laurahelmuth

Appreciation

It seems like every conversation these days quickly turns to COVID vaccines: Which of your dear ones have gotten a shot, when are you due for your booster, did you have any side effects? Social media is filling up with selfies of people showing off their "I got vaccinated" stickers in the post-vax observation rooms, bursting with a mix of joy and relief and gratitude that you can see in their eyes above their masks. (Another newly relevant pandemic word: "smizing," or smiling in a way that's visible in your eyes.) Our *Scientific American* publisher, Jeremy Abbate, asked his mom if she felt any side effects from her second shot, and she said, "An acute appreciation for science." He shared the exchange on Twitter, and about a quarter of a million people hit the heart-shaped "like" button. I'm sure I'm not the only one who would like to safely elbow-bump Jeremy's mom and every single scientist who worked on the vaccines, as well as everyone who produced, transported and delivered them, all the volunteers who are helping with outreach and recruitment, and everyone who has socially distanced and masked up and abided by the latest research and public health recommendations. Thanks to you, people are alive today who would have died.

Some of the people who have sacrificed the most during the pandemic are schoolkids and college students. Their COVID isolation has hit while they are developing social and emotional intelligence, finding a sense of purpose and understanding their place in the world. New research on the adolescent brain, shared by writer and *Scientific American* contributing editor Lydia Denworth on page 56, emphasizes that this is a time of opportunity for helping young people flourish, despite the challenges.

Our photo-essay on page 66 may make you recall the smell of classroom chalk dust. Photographer Jessica Wynne has traveled the world (at least until COVID) to document mathematicians' blackboards, which, as space and physics editor Clara Moskowitz narrates, attempt to "reveal universal truth."

The universe, by the way, is big. "Vastly, hugely, mind-bogglingly big," as sci-fi humorist Douglas Adams wrote and astronomers Kyle Dawson and Will Percival have shown with their work on the largest map of the cosmos ever made, starting on page 34. It's a three-dimensional map of four million galaxies over billions of light-years that may help solve the mysteries of dark energy and the shape of the universe (which is big).

For another mind bender, turn to page 62 to find out from researcher Kelly Jaakkola whether dolphins are left- or right-handed (even though they don't have hands) and why it's been so tricky for people to agree on which direction they're spinning.

Dolphins and about a quarter of all ocean species spend part of their lives near coral reefs, which are suffering. Marine scientists led by Raquel Peixoto are trying to find beneficial microbes that can help reefs withstand heat, disease and other pressures, and the work is now being tested in open waters. It's a risky strategy, but as science writer Elizabeth Svoboda explains on page 48, some experts say it's time to start taking risks.

The blood-brain barrier is basically a filter that lets sugar and oxygen in blood vessels into the brain but keeps proteins and pathogens out. Neuroscientists Daniela Kaufer and Alon Friedman (*page 42*) have found that the barrier breaks down under various kinds of stress, and its leaks could be a sign or possibly a contributing cause of Alzheimer's disease and other pathologies. If so, reversing the damage could protect people from brain disorders.

In our cover story beginning on page 26, anthropological geneticist Jennifer Raff shares new discoveries about who the first people were to reach the Americas and how and when they arrived. (And do take a second look at the opening illustration of the aurora borealis.) SA

Illustration by Nick Higgins

January 2021

"As young adults, my peers and I felt that society had the motive and ability to take care of us. I don't see that now."

PETER DYRHAUG *McMINNVILLE, ORE.*

BIG OLD GALAXIES

Arianna S. Long's "Too Big for the Universe" describes ancient galaxy clusters that are surprisingly massive for their early age. Could this observation be related to how supermassive black holes in the centers of some galaxies have grown so big so quickly that their size is also difficult to explain?

K. CYRUS ROBINSON *Tampa, Fla.*

While I was reading Long's article, I happened to be twirling a glass of iced tea and noticed that the bubbles on top had centered in a cluster that looked very much like the image of the Distant Red Core protocluster in the accompanying graphic. I wonder if there might be more of an influence from dark matter on the gases involved. What if the dark matter is also spinning while the gases are forming galaxy clusters?

DON STARBUCK *Bandon, Ore.*

LONG REPLIES: Robinson is correct: The growth of galaxies and that of supermassive black holes are intimately linked. And in general, we know that the more massive the galaxy, the more massive its central supermassive black hole. Thus, it's no surprise that some of the biggest black holes in the universe reside in these massive galaxy clusters. Some scientists think that their incredible sizes are the result of massive galaxy mergers in which the respective black holes also merge. Others think that just by being at the node of intersecting filaments, the cluster galaxies and their supermassive black holes receive more gas and matter to consume than other, more isolated galaxies. The cause is likely a combination of these effects, plus maybe some other, unknown physical processes still to be discovered.

Starbuck wouldn't be the first person to find physics in their tea! Check out the tea leaf paradox. We do know that both the dark matter halo and the baryonic matter (for example, stars, gas and dust) of a galaxy have spin—that is, angular momentum. It is believed that angular momentum was first introduced in the universe by gravitational tugs-of-war between competing overdense pockets of matter. As galaxies form and slam into one another, the spin can change in speed and direction. There is some evidence that cluster galaxies spin faster than noncluster galaxies (and that spin may therefore play a role in cluster formation). But it's not quite definitive, and astrophysicists have competing results and theories. We hope future telescopes and technology will help us answer this question.

FALSE COVID RUMORS

In "The Very Real Death Toll of COVID-19," Christie Aschwanden debunks the falsehood that counts of those who have died of the illness are inflated. One claim that is circulated as a reason to believe COVID death figures are exaggerated is that supposedly hospitals receive better reimbursement for treating COVID patients. As a result, the claim asserts, when they bill for payment, all patients with a positive COVID test result get classified as a COVID case regardless of cause of death or degree of illness.

To combat such rumors, it would be interesting to hear the author's findings, if indeed this issue has been researched.

PAUL KELSCH *Centreville, Md.*

THE EDITORS REPLY: Hospitals listing COVID as the cause of death cite positive laboratory tests, along with the reasons that COVID was the primary cause, and there are legal penalties for falsifying hospital records. There is no evidence of any overcount. The false rumor was spun out of one fact: under the CARES Act, hospitals can get an additional 20 percent reimbursement for confirmed COVID patients who are covered by Medicare. This is for the extra costs of severe and prolonged illness. Hospitals and health systems have not financially benefited from COVID: the American Hospital Association reports that they lost at least $323 billion last year because of the pandemic.

SOCIETY AND MENTAL HEALTH

"The Mental Toll of COVID-19," by Claudia Wallis [The Science of Health; December 2020], includes insights about the current psychological well-being of young adults. There is another important element to the rise in depression and anxiety among young people: the degraded state of our society.

We no longer have a cultural center—which a healthy society needs more than anything else. Born in 1949, I experienced the turmoil of the Vietnam War era. But as young adults, and as kids as well, my peers and I felt that society had its stuff together, with the motive and ability to take care of us. I don't see that now.

Myriad windows on the world compete for attention with spectacles that, ultimately, exacerbate the dissolution of reasonable expectations. Institutions prey on confused people at ever younger ages. This is not about some personal nostalgia. It is about knowing the difference between a fairly healthy society and one on the way out.

PETER DYRHAUG *McMinnville, Ore.*

COVID PATHOLOGY

Reading Akiko Iwasaki and Patrick Wong's "The Immune Havoc of COVID-19" reinforced my thoughts that researchers are dancing around the real pathology of COVID-19. This is a pathology in which an infection triggers an autoimmune reaction in some people. That scenario is not new. An example is rheumatic fever, which can be triggered by *Streptococcus* bacteria in the form of strep throat or scarlet fever. The ideal treatment would have to be two-pronged, treating first the infection and then the autoimmune reaction in severe cases.

Bruce Howard *Western Springs, Ill.*

HAND TRANSPLANTS

In "New Connections" [December 2020], Scott H. Frey describes how the brain may compensate for loss of nerves in transplanted hands. Another aspect to this story is that as important as central nervous system adaptation is for improved outcomes, coaxing greater success in peripheral nerves to regrow is a parallel goal.

Patients with transplanted or even reimplanted hands have dramatic long-term deficits in their recovery of skin sensation. Some studies indicate that only 10 percent of transected axons may ever successfully navigate to their targets. The goal of promising new work in peripheral neurobiology is the manipulation of neurons to pursue a plastic, regenerating growth state rather than maintenance of stable "wiring."

The response of peripheral nerves to injury is unique and elegant. For example, neurons retain proteins that act as "brakes" to their growth, and their inhibition can substantially improve the capacity for regrowth. Manipulating these intracellular signals, combined with the addition of a widening field of neuron growth factors, offers hope to ramp up the extent, speed and accuracy of regeneration. Moreover, new forms of support for peripheral nerve glial cells known as Schwann cells may also help persuade reluctant nerves to regrow.

Douglas W. Zochodne
Director, Neuroscience and Mental Health Institute, and division director of neurology, University of Alberta

ERRATA

"Clues to Collapse," by Karen Kwon [Advances], incorrectly says that the queen bee requires viable sperm to lay eggs. Without it, the queen can lay eggs that will hatch into drones but not worker bees.

"100 Years of Bird Banding," by Kate Wong, Jan Willem Tulp and Liz Wahid [March 2021], gave the wrong URL for reporting sightings of banded birds. The correct URL is www.reportband.gov

Coroners Should Be Abolished

These elected laypeople should be replaced by appointed medical experts

By the Editors

How many people in the U.S. have died from COVID? We know it is more than half a million, but the official count could miss tens of thousands of deaths. In TV police procedurals, the people who investigate premature deaths are depicted as highly trained, objective experts. In reality, the system in the U.S. is far less rigorous. The majority of states rely at least in part on coroners to rule on the circumstances surrounding unexpected or suspicious deaths—and contrary to what most of us probably believe, coroners are often laypeople without training in medicine. What is more, they are frequently elected officials, which makes them susceptible to political pressure from people or organizations looking to influence their conclusions. This system needs to be abolished.

The office of the coroner traces its origin to medieval England, where it was first established to help protect the financial interests of the crown. Death investigations were important because coroners collected the associated taxes, among other responsibilities.

Today most probes of the deaths of people who are not in the care of a doctor—including those who die at home or in police custody—are carried out by medical examiners and coroners. Medical examiners are physicians who are often board-certified in forensic pathology. Coroners are usually not physicians. In fact, in many states, coroners need only be of legal age with no felony convictions to qualify for the job. Yet they often have the final say on how someone died. There is no federal oversight of death investigation systems and no national standard to uphold. Instead states decide whether they use medical examiners or coroners, or a combination of the two—and determine the qualifications for the job. Most states have coroners in some or all counties.

To make matters worse, nearly 80 percent of the nation's coroners are elected to the office. This arrangement exposes investigations to corruption and political influence. Elected coroners are beholden to voters, after all.

This relationship can have serious consequences for public health. Take, for example, the current coronavirus pandemic. SARS-CoV-2, the virus responsible for the disease, is a leading cause of pneumonia. When someone dies without having had a COVID test, a coroner may attribute the fatality to a direct cause, such as pneumonia, without mentioning COVID as the underlying cause on the death certificate. A recent analysis carried out for science news service STAT found that tens of thousands of deaths from COVID are going unreported, mostly in counties that supported former president Donald Trump. It also found that counties that use elected coroners had higher rates of uncounted COVID deaths than counties that use appointed medical examiners. "The figures suggest that political leanings have helped suppress the true scale of deaths," STAT observed.

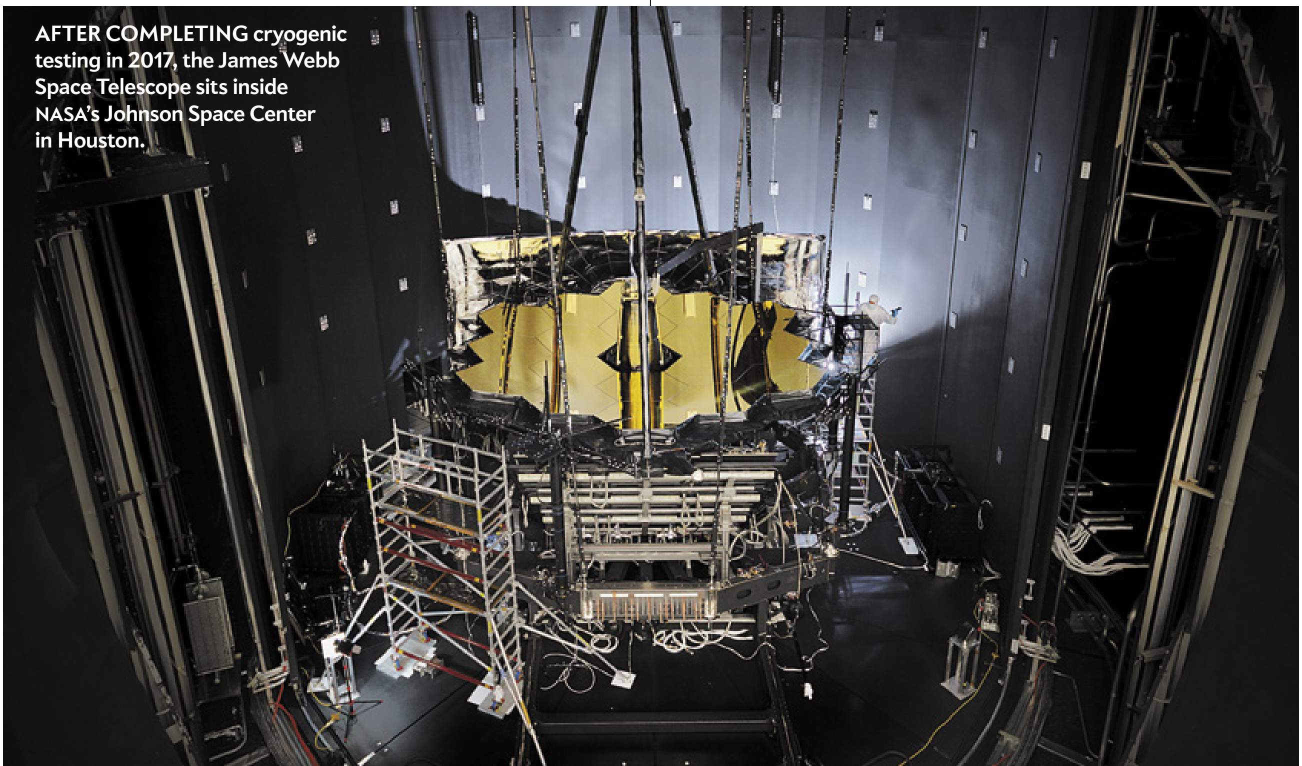
Voters are not the only source of influence on coroners. Death investigation has strong ties to law enforcement. Indeed, in many counties, the sheriff *is* the coroner. This arrangement poses obvious conflicts of interest. For instance, in 2017 public radio station KQED reported on the resignations of two forensic pathologists in San Joaquin County, California, who alleged that the sheriff-coroner interfered with their investigations into deaths that occurred during police arrest or custody to protect the officers involved. The sheriff assumes the duties of the coroner in 41 of California's 58 counties, according to the California State Association of Counties.

Leading medical and scientific organizations have long criticized the coroner system. As early as 1857, a committee of the American Medical Association recommended replacing elected coroners with court-appointed medical officials. In 1928 the National Academy of Sciences called for giving the medical duties of the coroner's office over to the medical examiner's office, which, the organization further argued, should be headed by a pathologist. The academy reiterated the need to move toward a medical examiner system in 2009. But the Centers for Disease Control and Prevention reports that just 16 states and Washington, D.C., have centralized medical examiner systems.

It is well past time to heed the experts' advice. Adopting a medical examiner system is not without challenges. For one, there are not enough medical examiners to go around. But with some of society's most pressing issues at stake, it has never been more important for states to lay the archaic coroner system to rest.

JOIN THE CONVERSATION ONLINE
Visit *Scientific American* on Facebook and Twitter
or send a letter to the editor: editors@sciam.com

Illustration by Taylor Callery



AFTER COMPLETING cryogenic testing in 2017, the James Webb Space Telescope sits inside NASA's Johnson Space Center in Houston.

Rename the James Webb Space Telescope

It shouldn't honor someone who helped enforce homophobic policies

By Chanda Prescod-Weinstein, Sarah Tuttle, Lucianne Walkowicz and Brian Nord

Because of its ability to see more deeply into spacetime than any instrument before it, the Hubble Space Telescope has completely transformed the way we see the universe—and ourselves. The James Webb Space Telescope (JWST), often called "the next Hubble," promises to do even better. Slated to launch later this year, JWST will peer farther into the universe than any optical or infrared telescope before it and could show us galaxies in their infancy, probe potentially habitable worlds and explore the mysteries of dark energy. These kinds of data not only provide insight into the universe but also help us humans situate our earthly concerns in context.

It is unfortunate, therefore, that NASA's current plan is to launch this incredible instrument into space carrying the name of a man whose legacy at best is complicated and at worst reflects complicity in homophobic discrimination in the federal government.

James Webb, who died in 1992, was a career civil servant whose time at the U.S. Department of State under President Harry S. Truman included advancing the development of psychological warfare as a cold war tool. He later oversaw the Apollo program as NASA administrator. When he arrived at NASA in 1961, his leadership role meant he was in part responsible for implementing what was by then federal policy: the purging of LGBT individuals from the workforce. When he was at State, this policy was enforced by those who worked under him. As early as 1950, he was aware of this policy, which was a forerunner to the antigay witch hunt known today as the lavender scare. Historian David K. Johnson's 2004 book on the subject, *The Lavender Scare,* discusses archival evidence indicating that Webb, along with others in State Department leadership, was involved in Senate discussions that ultimately kicked off a devastating series of federal policies.

Many astronomers feel a debt of gratitude for Webb's work as NASA administrator and are appreciative of and nostalgic for the time during the Apollo program when the space agency thrived. But while appreciation and nostalgia are important, they are not sufficient. Webb might have played a positive role at NASA, but his greater legacy beyond the agency is also relevant. Now that we know of Webb's silence at State and his actions at NASA, we think it is time to rename JWST. The name of such an important mission, which promises to live in the popular and scientific psyche for decades, should be a reflection of our highest values.

The allegations of Webb's complicity in persecution received broader public attention about six years ago. Although some astron-

CHRIS GUNN NASA

omers reacted with dismay at the time, many in the community believed the opportunity to rename the telescope had passed. More recently, an astronomer attempted to refute Webb's negative image in an unreviewed blog post, including by highlighting the fact that a homophobic quote was misattributed to Webb on his Wikipedia page. Astronomers on social media began to argue that in the absence of this specific quote, there was little to prove that Webb was responsible for homophobic policies.

But that correction changes nothing. Webb was in leadership as the lavender scare unfolded. Additional archival evidence, easily found by Columbia University astronomer Adrian Lucy, underlines Webb's role as a facilitator of homophobic policy discussions with members of the Senate. In particular, in 1950 assistant secretary of state Carlisle Humelsine submitted a set of memos to Webb that included "objectives and methods of operation of the Senate Committee established to look into the problem," which Webb then shared during a meeting with Senator Clyde Hoey of North Carolina. The records clearly show that Webb planned and participated in meetings during which he handed over homophobic material. There is no record of him choosing to stand up for the humanity of those being persecuted.

As someone in management, Webb bore responsibility for policies enacted under his leadership, including homophobic ones that were in place when he became NASA administrator. Some argue that if Webb was complicit, so was everyone working in the agency's administration at the time. We agree. But NASA is not launching a telescope named after its entire administration.

Some might be tempted to see the proposal to rename JWST as an attempt to litigate decades-old history. In fact, discrimination against queer people, including scientists, still affects their lives and careers. In 2016 the American Physical Society released the LGBT Climate in Physics report. Its core conclusion was that many queer scientists fundamentally do not feel safe in their workplaces. The climate is exclusionary, and physicists who identify as more than one minority, including LGBT+ physicists of color, experience the most harassment and exclusion. Astrophysicists who are LGBTQIA+ (lesbian, gay, bisexual, transgender, queer, intersex and asexual and/or ally, plus nonstraight identities not explicitly listed) exist and are marginalized. A 2021 study published in *Science Advances* found similar outcomes.

These practices are a continuation of history that dates back to Webb's era. Frank Kameny was an astronomer who was hired by the U.S. Army Map Service in 1957. When he was unwilling to provide information about his sexual orientation, he was investigated and subsequently fired. He could not find justice through the courts at that time, but he did spend the rest of his life as an activist. Kameny's case is a clear example of homophobic injustice during the era when Webb was active.

The same hypermasculinist fears that characterized the lavender scare and other ideological purges during the cold war continue to animate the incarnation of far-right movements across the globe. So what signal does it send to current and future generations of scientists when we prioritize the legacies of complicit government officials over the dreams of the next generation? With the launch of JWST just a few months away and a new presidential administration (and new NASA administrator) taking the helm, NASA has an opportunity to choose a new namesake that will embrace a future of freedom and inspiration for all.

This struggle is not limited to science or to the past: Just a few months ago Representative Joaquin Castro of Texas introduced the LOVE Act of 2020, which "requires the State Department to set up an independent commission to review the cases of individuals who were fired since the 1950s as a result of their sexual orientation, receive testimony, and correct employment records." Passage of the act would not only prompt an apology from Congress for its past complicity in the lavender scare but also provide protections for queer diplomats at home and abroad.

James Webb's legacy is the antithesis of the dreaming and sense of freedom inspired by the exploration of deep time and distant space. We will use this new telescope to learn about the origins of galaxies, the atmospheres of exoplanets and the nature of dark energy, which will offer insight into the fate the universe holds for us. We hope we have already learned some lessons about how humanity will move toward the future here on Earth rather than repeating mistakes of the past. There will always be complications in naming monuments or facilities after individuals. No hero is perfect.

Yet we can honor the incredible heroes who worked tirelessly to liberate others. Before she became a conductor on the Underground Railroad, a disabled and enslaved Harriet Tubman almost certainly used the North Star, just as it is documented that others did, to navigate her way to freedom. Naming the next Hubble the Harriet Tubman Space Telescope (HTST) would ensure that her memory lives always in the heavens that gave her and so many others hope. It could also serve as a reminder that the night sky is a shared heritage that belongs to all of us, including LGBTQIA+ people. The time for lionizing leaders who acquiesced in a history of harm is over. We should name telescopes out of love for those who came before us and led the way to freedom—and out of love for those who are coming up after. SA

Chanda Prescod-Weinstein is an assistant professor of physics and core faculty in women's and gender studies at the University of New Hampshire. She is author of *The Disordered Cosmos: A Journey into Dark Matter, Spacetime, and Dreams Deferred.*

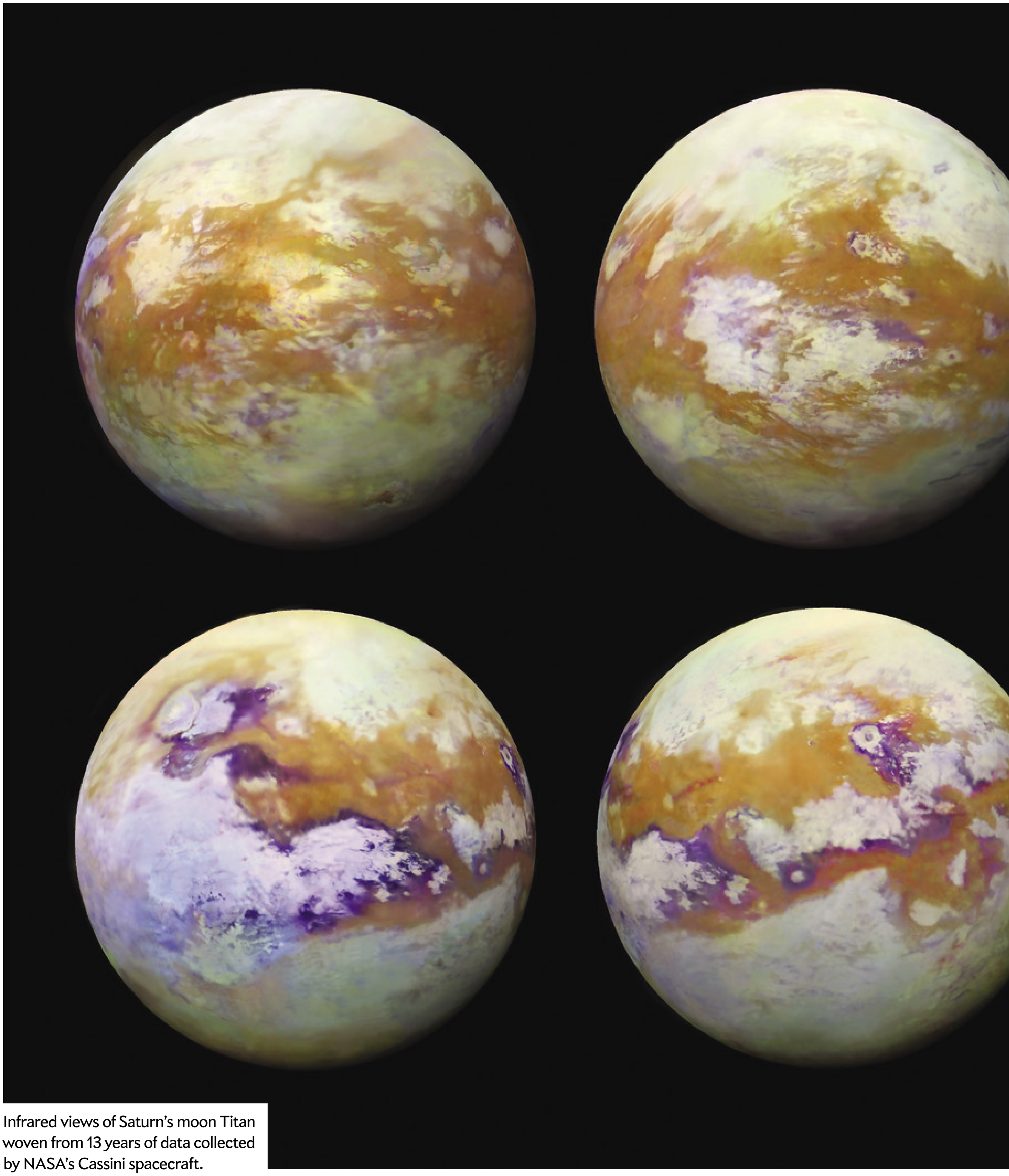
Sarah Tuttle is an assistant professor of astronomy at the University of Washington.

Lucianne Walkowicz is an astronomer at the Adler Planetarium in Chicago and co-founder of the JustSpace Alliance.

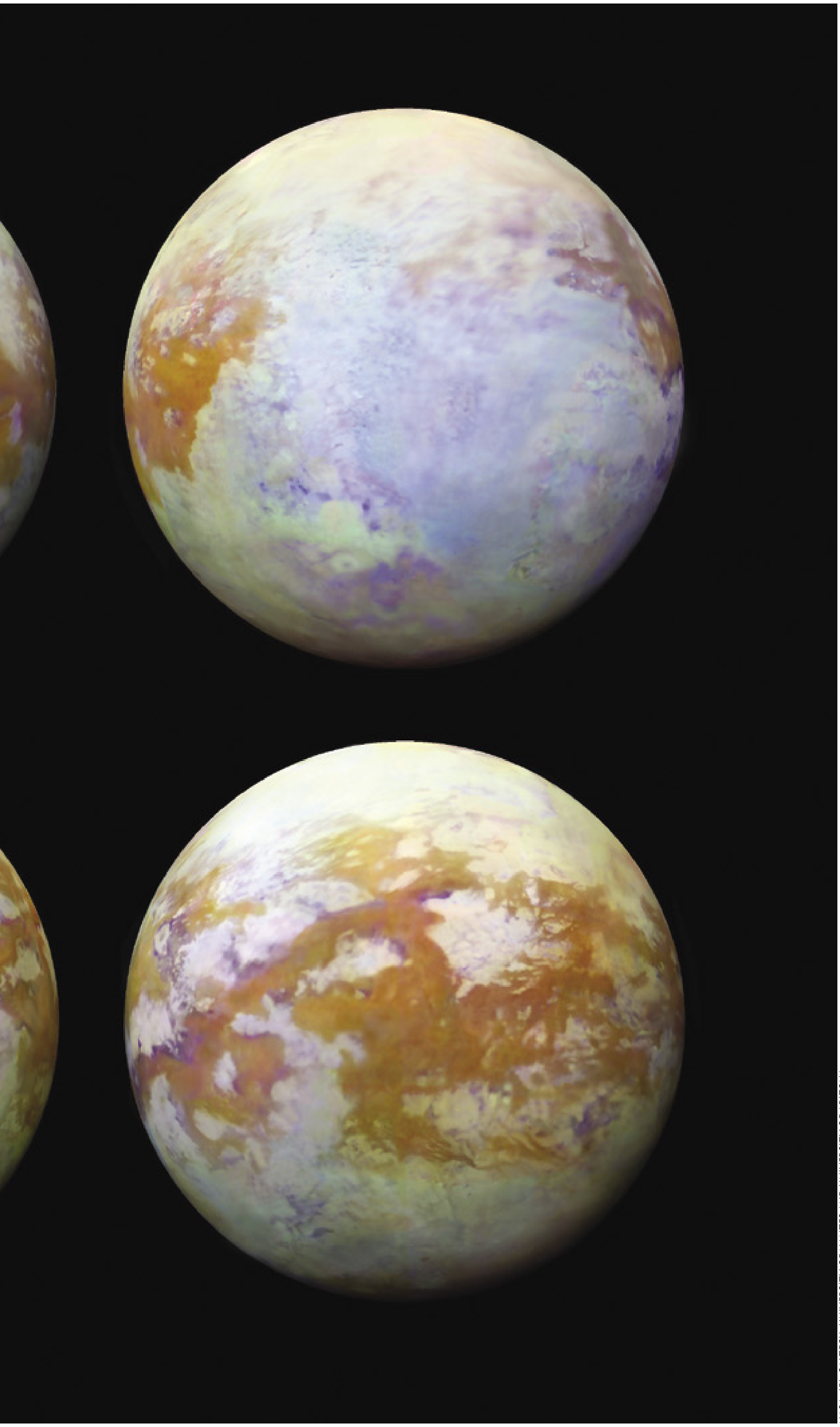
Brian Nord is a scientist at Fermi National Accelerator Laboratory and the University of Chicago.

JOIN THE CONVERSATION ONLINE
Visit *Scientific American* on Facebook and Twitter or send a letter to the editor: **editors@sciam.com**

ADVANCES



Infrared views of Saturn's moon Titan woven from 13 years of data collected by NASA's Cassini spacecraft.



NASA, JPL-CALTECH, UNIVERSITY OF NANTES AND UNIVERSITY OF ARIZONA

INSIDE

PLANETARY SCIENCE

Alien Depths

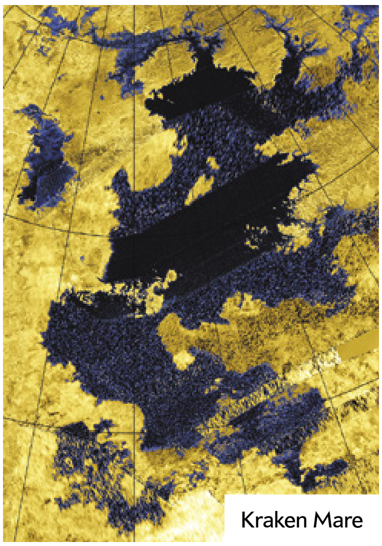
Titan's largest sea could be deep enough to swallow skyscrapers

Saturn's moon Titan is the only known place in our solar system, other than Earth, where liquid lakes and seas persist on a world's surface. Scientists are fiercely curious about these features, and now new calculations plumb the impressive depths of Titan's largest sea, Kraken Mare—a frigid blend of methane, ethane and nitrogen.

The finding comes from a fresh analysis of radar scans performed by the Cassini probe as it passed haze-shrouded Titan in August 2014. Using the scans, researchers estimated the depth in a part of Kraken Mare where it was possible to detect a seafloor and in others where it was not. Where a bottom was found, in a large northern estuary, some signals bounced back from the surface while others penetrated the liquid and echoed off the seafloor, says planetary scientist Valerio Poggiali of Cornell University. The echoes indicated this part of the estuary is up to 85 meters deep, Poggiali and his colleagues report in the *Journal of Geophysical Research: Planets*. But the central and western parts of the sea produced no seafloor echoes, suggesting that central Kraken Mare could be at least 100 meters deep—or even 300 or more.

"The idea that you can do bathymetry [measure depth] on a moon in the outer solar system is exciting," says Elizabeth Turtle, a planetary scientist at Johns Hopkins University Applied Physics Laboratory, who was not involved in the new study. The results "are so informative in terms of providing data to understand Titan and to help plan missions there."

The researchers caution that future work might indicate some signals failed to bounce back not because of great depth but because the liquid absorbed more radar energy than they calculated it would. That would suggest their working estimates about composition are off. Based on their calculations, the sea appears to comprise about 70 percent liquid methane, 16 percent liquid nitrogen and 14 percent liquid ethane at



Kraken Mare

a temperature of –182 degrees Celsius. When Cassini swept by, Kraken Mare's surface waves measured just a few millimeters high.

Depth and composition data are vital for engineers designing robotic submarines and other equipment to eventually journey through Titan's lakes and seas, says Steven Oleson, an astronautical engineer at NASA's Glenn Research Center in Ohio, who was also not involved in the study. He and other engineers have put together preliminary designs for such a craft, even though a robotic sub is not currently part of NASA's mission lineup. Understanding Kraken Mare is critical to understanding Titan overall: the sea holds about 80 percent of the moon's surface liquid and covers about 500,000 square kilometers—roughly twice the area of North America's Great Lakes combined. *—Sid Perkins*

NASA, JPL-CALTECH, AGENZIA SPAZIALE ITALIANA AND USGS

LANGUAGE

Signs of the Times

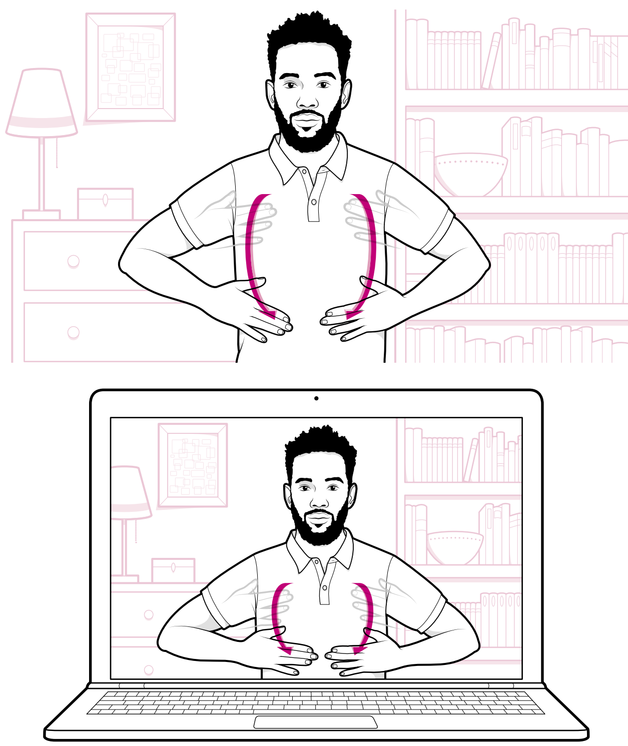
Pandemic videoconferencing is changing the way people use sign language to communicate

American Sign Language (ASL) users are no strangers to video chatting. The technology—which has been around since 1927, when AT&T experimented with the first rudimentary videophones—lets deaf and hard-of-hearing people sign via the airwaves. But after the coronavirus pandemic began confining people to their homes early last year, the use of platforms such as Zoom, Microsoft Teams and Google Meet exploded. This increased reliance on videoconferencing is altering some common elements of sign language.

Some adaptations arise as a result of a video meeting's limited window size. "The signing space is expansive," says Michael Skyer, a senior lecturer of deaf education at the Rochester Institute of Technology. "Even if many signs are produced easily or normally in the 'Zoom screen' dimensions, many are not." The sign for "body," for example, is usually produced by making a modified "B" hand shape and moving it from the shoulders to the hips. But to fit the reduced signing space demanded by videoconferencing, many signers have been ending it at the chest.

Signs that take up a lot of space may be harder to convey on video, but so are smaller ones with finer differences. Fingerspelled words, for example, as well as numbers and colors, all involve relatively small details formed with a single hand—which can make them harder to see clearly on a tiny conference screen. Skyer says signers must go slower and repeat themselves more often to fill in such gaps.

Signers communicating through video must also consider how they angle their bodies to convey meaning clearly. If two people face each other in person, each can easily see whether the other's hands are moving toward or away from them. This can be crucial for grammatical reasons; for example, signs representing future tense are usually made with a forward motion away from the signer's body, whereas past tense signs move the opposite way. Such nuances are sometimes difficult to detect on a video screen. Skyer is deaf and uses American Sign Language to teach in a bilingual ASL-English environment, in



In an in-person conversation, the sign for "body" involves moving the hands from the shoulders down toward the hips. But virtual communication tools often limit the field of view to the head and upper torso, so the signer may modify the movement to end higher up.

Illustrations by Brown Bird Design

which a teacher typically signs in ASL and also shares content in written English. When using videoconferencing in class, he says, he sometimes has to sign with his body turned to present himself in a three-quarters view, so that signs usually seen head-on are easier to understand.

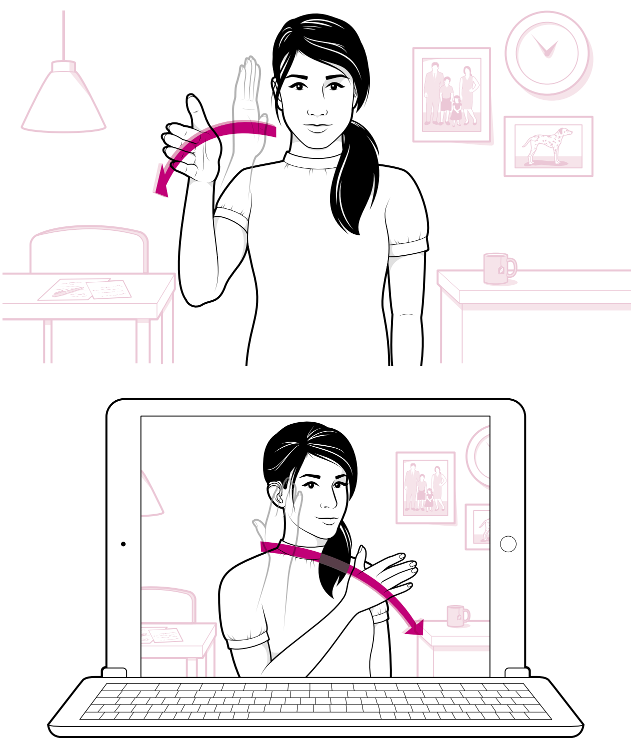
Some signs require a shared space for their meanings to be clear. Ones that involve indicating or pointing at another person simply do not work in a typical videoconferencing "room," where multiple speakers may appear in different arrangements on each participant's screen. Julie Hochgesang, an associate professor of linguistics at Gallaudet University, says some people using videoconferencing have begun making signs such as "ask" or "give" (which require indicating an individual person) more explicit by adding a referent, a sign that clarifies the subject of a statement.

Will such changes fade after people return to in-person interactions? They might—but some experts say linguistic shifts are still inevitable. Because sign languages often involve their specific physical environment and are impossible to separate from it, Skyer and Hochgesang both suggest people should not necessarily think of each sign language as having a defined identity. "Instead I like to say there are ASL communities with varying practices and lexicons," Hochgesang says. "Yes, undoubtedly, the long-term use of Zoom and other videoconferencing platforms (including FaceTime, videophones, and so on) will shape and constrain our language practices. But that's true for anything in our lives.… Our tools, people we interact with, and other aspects of our environment will always be a factor in our language and communicative practices."

Despite the limitations they place on American Sign Language, videoconferencing platforms can also be empowering for deaf people. Skyer says the multimodal features of these tools—which enable both video and text chat—give his students multiple avenues for learning. Instead of being constrained to one way of communicating, they can now type in written English using the chat feature or sign in ASL using the video feature, or do a combination of both—all from home.

"ASL is defined by how it is used," Skyer says. "How it is used is not static, and the Zoom changes show us this. Words, concepts and pragmatics [the use of language in social contexts] themselves evolve and shift given new mediums of expression."

—Sarah Katz



The sign indicating future tense, in which the signer moves one hand directly forward, can be hard to read on camera. Turning to a three-quarter orientation can help to capture the movement more clearly.

SEISMOLOGY

Imaging Calls

Sound waves from fin whales help scientists probe the earth's crust

Scientists have an unlikely new ally in their quest to map the structure of the planet deep below the ocean. Fin whales are 18- to 27-meter-long behemoths whose songs can be heard underwater up to 1,000 kilometers away, booming through the seas as loudly as a ship's engine does. New research in *Science* finds these calls can help create images of the seafloor subsurface down to 2.5 kilometers.

Seafloor-imaging systems typically send blasts of sound downward using large air guns. The sound waves penetrate the crust and bounce back to seafloor instruments, revealing the structures they travel through. But such surveys are expensive, and the guns' concussive noise can disturb marine mammals. The new study illustrates how the imaging process might sometimes use fin whale songs instead.

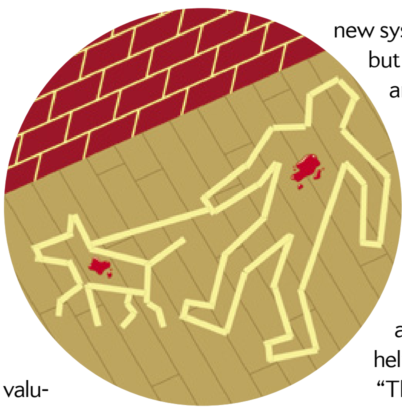
"It's actually quite cool to have another source of information," says study co-author Václav Kuna, a seismologist at the Institute of Geophysics of the Czech Academy of Sciences.

Kuna, then at Oregon State University, was studying earthquakes off the Oregon

FORENSICS

In the Blood

New system could provide fast results at a crime scene



A sleepy driver on a dark road hears a loud "thump!" and later finds a speck of blood on the front bumper. Or police spot a tiny but suspicious bloodstain at a crime scene. Quickly determining whether such traces come from humans or animals is crucial, but the necessary tests can be time-consuming—and may destroy valuable evidence. Researchers say a new technique could help.

To develop a rapid, nondestructive way to identify human blood, State University of New York at Albany forensic chemists Igor Lednev and Ewelina Mistek-Morabito combined spectroscopy and statistics. They shined infrared light on dried samples of human blood and on those of 10 animal species, including common pets such as dogs, cats and ferrets, as well as deer and elk (both of which are often struck by vehicles). The researchers recorded the reflected light, the spectrum of which changes based on blood's composition. They then used these data to train a machine-learning algorithm to quickly and accurately distinguish human from animal sources.

"Our technique could really help narrow down samples that are relevant to the case, before they are sent to a lab for DNA analysis," Mistek-Morabito says. Forensic scientists currently use destructive biochemical tests for differentiating human and animal blood—and these tests sometimes return incorrect results. The new system's accuracy has yet to be tested in the field, but Mistek-Morabito says that the initial results are encouraging.

In their study, published in *Communications Chemistry*, the researchers used a desktop lab instrument. Lednev is working to adapt the technology for use in a portable, handheld device. He envisions a handy, all-in-one spectroscopic tool that could one day characterize body fluid traces on the spot. "Portable instruments are the future," Mistek-Morabito says. "It would help us bring the lab to the crime scene."

"The study is a proof-of-concept for a nondestructive method to analyze samples," says University of South Florida forensic scientist Peter Massey, who was not involved in the project. To be of practical use in the field, the instrument must be small, easy-to-use and affordable, he adds.

Spectroscopy-based techniques are promising because they can potentially be as compact as a cell phone, says Matthieu Baudelet, a forensic chemist at the University of Central Florida, who was also not part of the research. But because the machine-learning process does not reveal specific physiological reasons for differences in spectra, Baudelet wonders if the results would hold up for blood from wild animals with wide-ranging diets and health.

To prepare the technology for practical forensics, the researchers will test and calibrate it with increasingly varied samples; Lednev is collaborating with forensic scientists from the New York State Police Crime Laboratory System to validate the technique under real crime-scene conditions. —*Harini Barath*

Illustration by Thomas Fuchs

WILDESTANIMAL Getty Images

Fin whales' powerful calls can help investigate structures underneath the seafloor.

coast when he noticed strange readings on the seafloor seismic instruments—and found they matched fin whale call frequencies. Whale vocalizations often appear in such instruments' records, says University of Washington marine seismologist Emily Roland, who was not involved with the study. Seismologists usually see these signals as a nuisance. Kuna, however, noticed that some vocalizations appeared on seafloor instruments' seismometers but not their audio microphones. This measurement suggested the signals were not coming directly from whales but were echoes bouncing back from within the crust.

Kuna first had to determine the whales' approximate locations, which were needed to use the signals for imaging. To do this, he timed two sets of waves emanating from each call: one that traveled directly to the ocean floor seismic station and another that bounced between the ocean floor and surface before hitting the same station.

Fin whales sing in loud, one-second pulses, an imaging-friendly pattern that is easier to analyze than continuous noise, says University of Washington marine geophysicist William Wilcock, who was not involved in the study. These whales are found almost everywhere except the ice-covered sections of the Arctic, he notes—so their calls "could potentially be used in a lot of regions."

The new technique does have limitations, Kuna says. Fin whale songs use a narrow set of frequencies that provide less crisp subsurface images than air gun blasts do. Additionally, a relatively flat seafloor is needed to triangulate the whales' positions and use their sounds for data analysis with just a single seismic station; multiple stations would be necessary in sloping or mountainous regions.

Nevertheless, whale calls' prevalence means they could provide new insight into old seismic data sets, Roland says. Measuring them could aid such fields as climatology (to better estimate seafloor sediments' carbon storage) and seismology (to precisely pinpoint earthquake locations and monitor fault zones).

"If we use the whale songs at least as a complement to other sources of signals, they are free and they are always there," Kuna says. "It's a win-win."

—Stephanie Pappas

The volatile Lokbatan mud volcano

ANDREY SHEVCHENKO *Alamy Stock Photo*

VOLCANOLOGY

Mud Blast

Scientists examine an ultraexplosive mud volcano

Not all volcanoes belch lava. Some erupt mud—lots of it. Most mud volcanoes just gurgle up bits of muck from time to time, but one is particularly known for frequent, powerful explosions. New research explains what powers these intense eruptions and just how strong they can get.

University of Oslo mud volcanologist Adriano Mazzini and his colleagues studied Lokbatan, a mud volcano in Azerbaijan. Mazzini calls this small country just north of Iran "the kingdom of mud volcanoes." It has hundreds, but Lokbatan is exceptional.

The volcano's first recorded eruption occurred in 1829. Roughly every five years since then it has launched plumes of mud, sometimes higher than 100 meters. Oil and methane deposits near Lokbatan tend to self-ignite during eruptions, so flames and smoke often accompany the skyrocketing mud. The sight rivals that of a traditional magma-fed volcano, Mazzini says: "They can be equally spectacular and powerful."

To investigate Lokbatan's impressive eruptions, Mazzini and his colleagues placed 30 gas monitors on the volcano's flanks to sniff for escaping methane and carbon dioxide. The team hypothesized that gases were building up more quickly underneath Lokbatan than under other mud volcanoes, which continuously vent gas into the atmosphere.

Lokbatan "degasses" at less than one-hundredth the rate of another nearby mud volcano, the researchers found. So when it does erupt, they concluded, gas escapes violently, and mud then falls back into the volcano's vent and effectively seals it. The mud "collapses back in and compacts, forming a plug," Mazzini says, which traps gas that accumulates until it triggers the next explosive eruption.

The researchers also found that Lokbatan's eruptions have likely been violent enough to rip apart its crater rim. They observed three enormous chunks of sediment—the largest topping 300 train cars in volume—to the west of Lokbatan, where portions of the main crater rim are conspicuously missing. These "mega blocks" are probably pieces of crater that broke off in an eruption; the researchers used computer models to show the massive fragments could have surfed kilometers downhill atop a thick layer of flowing mud. Historical records suggest this probably happened during an 1887 eruption, according to the team's study results, detailed in *Earth and Planetary Science Letters*.

Understanding mud volcano dynamics can inform ideas about what happens on other planets, including Mars, says astrobiologist Shirin Haque of the University of the West Indies at St. Augustine, Trinidad and Tobago, who was not involved in the research. The Red Planet has several possible mud volcanoes, she says, and "mudflows could have affected the present-day landscape we see on Mars." —*Katherine Kornei*

MEDICINE

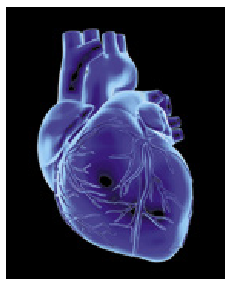
Heart Smarts

DNA-based test tracks transplant rejection

Having heart transplant surgery is daunting enough. But in the months afterward the body's immune system sometimes attacks the donor organ, which can have deadly consequences. To check for inflammation (a sign of organ rejection), doctors have to snip and analyze a sliver of tissue from the recipient's new heart—typically about 16 times in the first year. "There is a risk of damage during the procedure, and the results are far from reliable, yet [such] biopsies are the current gold standard," says cardiovascular medicine researcher Hannah Valantine of Stanford University.

But a new DNA-based blood test could give doctors crucial time to prevent sudden, early rejection of transplanted hearts. It would reduce the number of required invasive biopsies by about 80 percent, according to a study published in *Circulation*.

For each transplant in the study, co-author Valantine and her colleagues used blood samples to identify small genetic differences between heart donors and recipients. After the transplant, the researchers measured the percentage of donor-derived DNA in the recipients' blood plasma. Injured or dying cells from a transplanted heart release more donor DNA fragments than healthy cells do, so higher amounts of donor DNA imply a higher risk of rejection. With early warning doctors can start medical treatment to reverse the situation. The study analyzed blood samples from 171 recent transplant recipients and found rejection is likely when more than 0.25 percent of detected DNA is from the donor. The test provided a clearer signal and picked up rejection signs earlier than tissue biopsies did. It also revealed much earlier signs of a pernicious type of rejection, called antibody-mediated rejection, that biopsies can miss.



ANGELHELL *Getty Images*

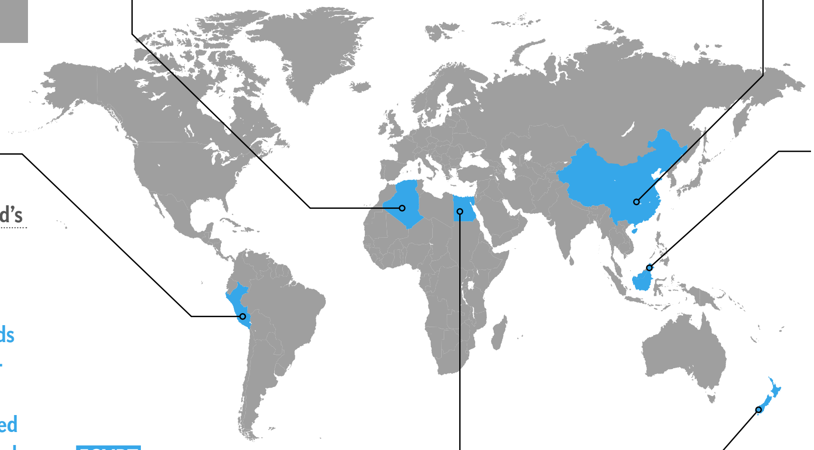
About 44 percent of the recipients in the study were Black. This was particularly important, Valantine says, because multiple studies have established that African-Americans have a high risk of rejecting donor organs of all kinds.

The test looks promising, but long-term clinical utility studies are needed to evaluate how treatments based on test results fare, says University of British Columbia medical researcher Scott Tebbutt, who was not part of the study. Noninvasive tests are invaluable, Tebbutt says, and "reducing the number of biopsies even by half is a significant improvement to the quality of the patients' lives." —*Harini Barath*

IN THE NEWS

Quick Hits

By Sarah Lewin Frasier



ALGERIA

Analysis suggests a meteorite from the Sahara Desert contains material as old as, or older than, Earth itself. The meteorite holds the oldest-known sample of magma from space and most likely came from a protoplanet forming in the early solar system.

CHINA

Researchers tested a new soft-body swimming robot first in a lake, next in the South China Sea, and finally in the Mariana Trench—almost 11,000 meters down—to prove it can flap its fins in extreme pressure as it explores the depths.

PERU

Scientists declared a *Liolaemus* lizard the world's highest-altitude reptile after a population was spotted at 5,400 meters in the Andes. These lizards must endure frigid temperatures, a particular challenge for cold-blooded animals, as well as reduced oxygen and increased ultraviolet radiation.

BORNEO

Scientists captured dung beetles in a forest in Sabah, dissected them, then sequenced the DNA in their guts to find matches with nearby wildlife. Because dung lasts within the beetles for about 48 hours, this method can reveal a location's recent visitors and inhabitants.

EGYPT

An excavation on the Red Sea coast revealed what seems to be a pet cemetery from nearly 2,000 years ago, the earliest yet identified. Nearly 600 cats, dogs and monkeys—mostly cats—were carefully buried, many with textiles, pottery or ornate collars.

NEW ZEALAND

Conservation rangers worked with hundreds of volunteers to "refloat" 40 stranded long-finned pilot whales, returning them to open water. Nine more of the beached whales died.

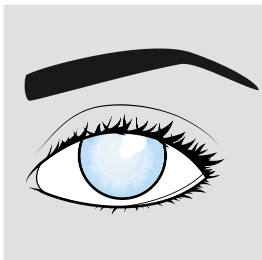
For more details, visit www.ScientificAmerican.com/may2021/advances

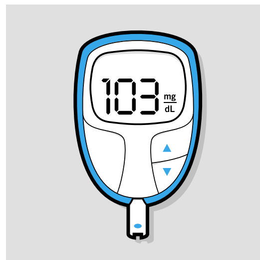
BIOENGINEERING

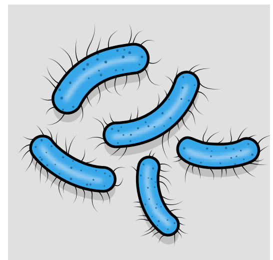
Better in a Flash

Light-activated cells hold wide therapeutic potential

Optogenetics is revolutionizing neuroscience. The technique involves genetically altering particular cell types to make them produce light-sensitive proteins; scientists can then activate the cells using light pulses delivered to the brain via fiber-optic cable. This has already given researchers an unparalleled ability to probe the circuitry underlying animal brain functions. But some have moved beyond the brain, working toward human medical applications. —*Simon Makin*







Treating blindness

Optogenetics offers a flexible approach to treating, and possibly curing, blindness. The retina's photoreceptor cells use light-sensitive proteins, called opsins, to convert light entering the eye into electrical signals. If these cells fail (a common cause of vision loss), researchers can use viruses to deliver opsin-producing genes to targeted cells—either to restore light sensitivity to photoreceptors or to make other cell types in the retina sensitive to light. This process can potentially treat blindness with many different causes and levels of retinal degeneration. It works in the laboratory, and multiple clinical trials of such systems in people are already underway. Setups sometimes use cameras and special goggles to project light wavelengths and intensity optimized for the opsin being used, but scientists are also testing opsins that respond to direct light.

Regulating glucose levels in diabetes

A team led by bioengineer Martin Fussenegger of ETH Zürich is optogenetically manipulating gene expression to regulate blood glucose levels in diabetic mice. In a 2011 study, the team engineered cells to respond to blue light by expressing a protein known to modulate blood glucose. Controlling genes in this way was a dramatic step forward, Fussenegger says: "It was a direct link between light and gene expression." The group's experiments showed increased insulin levels and reduced glucose sensitivity in mice that were implanted with the engineered cells and then treated with light. In 2017 Fussenegger and his colleagues described implanting wirelessly powered LEDs along with the engineered cells to create a smartphone-controlled semiautomatic system. They have since continued refining the technique.

Controlling gut microbes

The gut microbiome is immensely complex and includes trillions of individual microbes, most of whose functions are not understood. Baylor College geneticist Meng Wang and her colleagues recently described in *eLife* how they used optogenetics to literally shine light on the link between gut microbes and health. They altered *Escherichia coli* bacteria to turn on and off colanic acid production using green and red light, respectively. Wang's group previously showed that the acid protects cells against stress, promoting longevity—at least in worms. In the new experiments, worms with the altered bacteria lived longer when exposed to green light. But therapeutic applications are a long way off. "The major bottleneck is the delivery of light," Wang says. "Currently it's more a research tool for putting the microbiome under precise control" to study its links with health.

Illustrations by Brown Bird Design

GENETICS

Shape-Shifters

How did cichlids evolve to be so different—and so quickly?

Darwin's finches are perhaps the best-known examples of adaptive radiation—the evolutionary phenomenon in which one ancestral species rapidly diversifies into several new ones, each with unique adaptations for surviving in its own environment. But these Galápagos birds have nothing on the cichlids of East Africa. In the same two or three million years it took for 14 finch species to evolve, more than 1,000 cichlid species diverged from common ancestors in Lake Malawi alone. New research is now revealing the genetic mechanisms behind such rapid and dramatic biodiversity.

Cichlids exhibit a wild variety of body shapes, coloration patterns, mouth structures, behaviors, diets, and more. "When you look at them, they look so starkly different," says Earlham Institute evolutionary biologist Tarang Mehta. "But when you compare the [protein-coding] genes of these species, you see very little diversity."

Protein-coding genes influence an organism's major traits. Previous research had already indicated that cichlids' "non-coding" or "regulatory" stretches of DNA—which determine how, when and where the coding genes are turned on and off—evolved more rapidly than their coding genes. These regulatory spans let the same set of genetic puzzle pieces fit together in thousands of different configurations, a phenomenon Mehta refers to as "tinkering." But scientists were unsure whether this tinkering could drive the evolution of new species.

For a study published in *Genome Biology*, Mehta and his colleagues analyzed gene expression in the brain, eye, heart, kidney, muscle tissue and testis of five cichlid species from East African rivers and lakes. Using a computational model they developed, the researchers found that changes in the genomes' noncoding regions contributed a "substantial portion of the evolutionary substrate in adaptations" that led to divergence, says study senior author and University of East Anglia biologist Federica Di Palma. For example, the team found that regulatory changes altered certain coding genes' expression to let cichlids see better in various specific conditions. When species shared similar diets or habitats, they were more likely to evolve similar changes to these regulatory networks.

Many biologists worry about the accelerating loss of Earth's biodiversity—but science still does not fully understand how biodiversity evolves in the first place, says University of Basel zoologist Walter Salzburger, who was not involved with the study. The cichlids in Lakes Malawi, Tanganyika and Victoria offer researchers a unique opportunity to peer into that process, he adds.

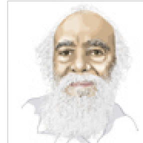
Mehta's team is now applying the same kind of analysis to tilapia, a cichlid group that includes the world's second-most farmed fish. If the researchers can identify the genomic tinkering associated with traits such as adaptation to extreme salinity or temperature, Mehta says, this could guide the selective breeding of tilapia to more efficiently feed a hungry world.

—Jason G. Goldman

East African cichlid species

JAVIER MILLÁN PHOTOGRAPHY *Getty Images*

Richard A. Jones, a philosopher and former professor at Howard University, has published poetry for 60 years. His latest volume is *Footnotes for a New Universe* (Atmosphere Press, 2021).



String Theory

Of herald wings came whispering
Like music down the vibrant string
—from *Renascence,* Edna St. Vincent Millay (1892–1950)

The
Geo-
metry
of
small
hid-
den
Dimen-
sions
by
Schwarz
and
Green
and
Brian

Violin
&
Nambu
Dr.
1988
in
it
about
Read
first
I
When
and
Greene

Strings
I
Thought
of
the
Rubber
bands
I'd
held
out
moving
Cars
Ed Witten

to
Stretch
them
& relax
them
to
Tones
musical
windows
wind

Play*ing*
&
Musing
Pythag-
oras
&
Kepler
&

Mech-
anics
double
dot
har
monics

Now
Spr-
Ing
Walk-
ing
down
Mul-
Pus
Street
&
stoop-
ing
to
tie
my
shoestr*ing*

an
inverse
Bessel
funct-
ion
&
then
again
loop-
ing
back
up
the

knot
vibrat-
ing
with
my
repeat-
ing
sinu-
soidal
stepp-
ing
&
loose 𝄞

Whether 𝄞
loops
or
Monster
Moonshine
groups
or
ding
ping
ring

Down
26
dimen-
sional
Vibrat-
ing
M
Branes 𝄞

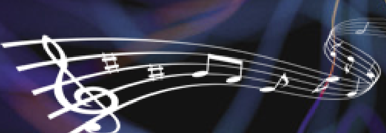
or
en-
fold-
ed
Calabi
Yau

s(*ing*)
p ♫
a ♫
c ♫
e ♪
s(*ing*)

I
wonder
how
strings
within
everything
can
cause
rubber
bands
removed
from
my
morning
newspapers
to make
treble
clefs
when
I
drop
them
on
my
table
and

tie my sneakers again to remind me that the universe is sneaky (and freaky) and always
untied and that I need to allow them to complete their patterned gestalts by holding them
out a speed*ing* car window or go wiggle-waggle or something like spaghettified str*ing* cheese

再次綁我的運動鞋提醒我, 宇宙是鬼鬼祟祟 (和怪異), 總是解開,
我需要讓他們完成他們的嗒嗒完型通過舉行他們一個超速的汽車視窗或去擺動-
搖擺或類似 spaghettified 串乳酪



AUTHOR'S NOTE: Few of us poets comprehend the complex mathematical ideas behind string theory, but at human scales we perceive many stringlike vibrations—including those of spoken languages (like the Mandarin my eight-year-old twin grandchildren are mastering). This poem invites the eye to go up and down in a sinusoidal oscillation (like colors, like rubber bands, like music, like strings). The Chinese characters represent the poem's last stanza as interpreted by Google Translate. ("Spaghettified" stumped the app.)

KOTO_FEJA *Getty Images (lines)*; LINEARCURVES *Getty Images (music)*

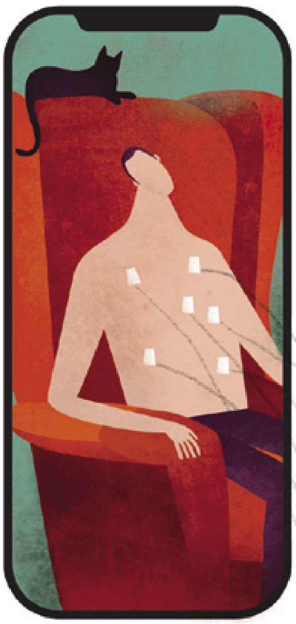
Claudia Wallis is an award-winning science journalist whose work has appeared in the *New York Times, Time, Fortune* and the *New Republic*. She was science editor at *Time* and managing editor of *Scientific American Mind*.

Making Research Less of a Trial

COVID has sparked changes to improve participation in medical studies

By Claudia Wallis

After her teenage daughter tested positive for the novel coronavirus this past January, Jennifer Scruggs got to work disinfecting surfaces in their home in Bethpage, N.Y. Then she noticed that she couldn't smell the Lysol she was spraying. "Uh-oh—this wasn't a good sign," she recalls thinking. "So I got tested, and sure enough, I was positive for COVID."



Scruggs, an administrative employee at Northwell Health, a network of hospitals and clinics based in Long Island, N.Y., heard that her employer was recruiting nonhospitalized COVID patients for a clinical trial. The goal was to find out whether famotidine, the active ingredient in the heartburn drug Pepcid, could reduce the severity of the infection. Eager to contribute to science, Scruggs was thrilled to learn she could participate without leaving home. Everything needed for the monthlong study—pills, instruments to measure her respiratory capacity and oxygen levels, a scale, a fitness tracker and an iPad—was delivered to her doorstep. Readings from the devices were transmitted via Bluetooth to the iPad, which conveyed them to the research team. Once a week a phlebotomist wearing protective garb arrived at her home to take blood samples. "Honestly," Scruggs says, "they made it very easy."

In the early months of the pandemic, medical research was radically disrupted for safety reasons. Nearly 6,000 clinical trials unrelated to COVID were stopped during the first five months of 2020, about twice the usual number, according to one analysis. But the outbreak has also accelerated a shift toward digital and remote research methods that make participation easier for patients and make data collection more efficient for scientists. Across diverse disciplines, study designs are being revamped to bring the trial to the patient rather than vice versa. Scientists also hope to show that sluggish processes that have long discouraged people from participating in cutting-edge research can be safely streamlined for a postpandemic era. "One lesson of COVID is that fast is possible," says cardiologist John H. Alexander, a senior faculty member and researcher at Duke University's Clinical Research Institute.

Trials begun in the past year already reflect changing practices. The original plan for the famotidine study was to have participants come into a clinic. "But we knew that when patients are recovering from COVID at home, the last thing they want to do is to come out for blood work or any kind of follow-up. So we completely revised our protocol," says Christina Brennan, vice president of clinical research at Northwell's Feinstein Institutes.

Alexander is co-directing a much larger, all-virtual trial comparing two anticoagulant drugs in people who have an artificial aortic valve. Patients are enrolled and followed entirely at a distance by researchers at 56 sites. "Everything is done over the phone," he says.

At MD Anderson Cancer Center in Houston, thousands of studies were underway when the pandemic hit. It was not possible to alter the approved protocols, but participant enrollment and some research-related visits have moved to phone or video conferencing, says Jennifer Keating Litton, vice president for clinical research. "The big thing that we had been dying to do for years was to establish remote consenting. Now patients can do it on their phone and sign all the consent forms."

José Baselga, who heads oncology research for pharmaceutical company AstraZeneca, sees COVID as a catalyst for far-reaching changes in cancer research. Studies often call for superfluous hospital visits and tests, he says. For example, "there is nothing written anywhere that you have to do lab work every three weeks," yet it is the norm. Baselga believes that relying more on remote monitoring of heart rate, respiration and other physical functions, along with reports transmitted daily by patients on their pain, appetite and symptoms, will be not only more convenient but safer. "Instead of waiting for them to show up in the emergency room sick and in pain, we can intervene ahead of that," he says.

Alexander has pushed for these kinds of updates to medical research as co-chair of the Clinical Trials Transformation Initiative, a public-private partnership aiming to improve the quality of medical research. "If we could make it easier and less duplicative to be in trials, we would have more participation," he says. Why, for example, do patients have to come in for separate research-related visits; why not collect research data when they come for ordinary care? But making big changes means confronting an entrenched infrastructure, and he worries that progress will fade when the pandemic ends. Baselga is more sanguine: "There is no way we'll go back to the 'good old days.'" ■

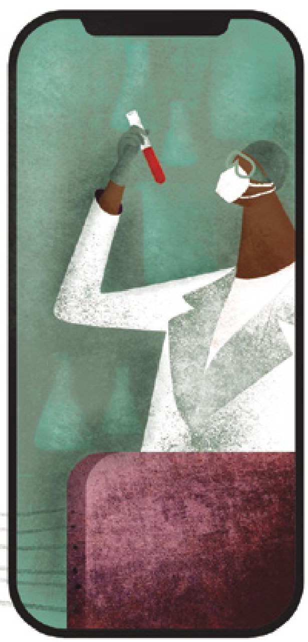
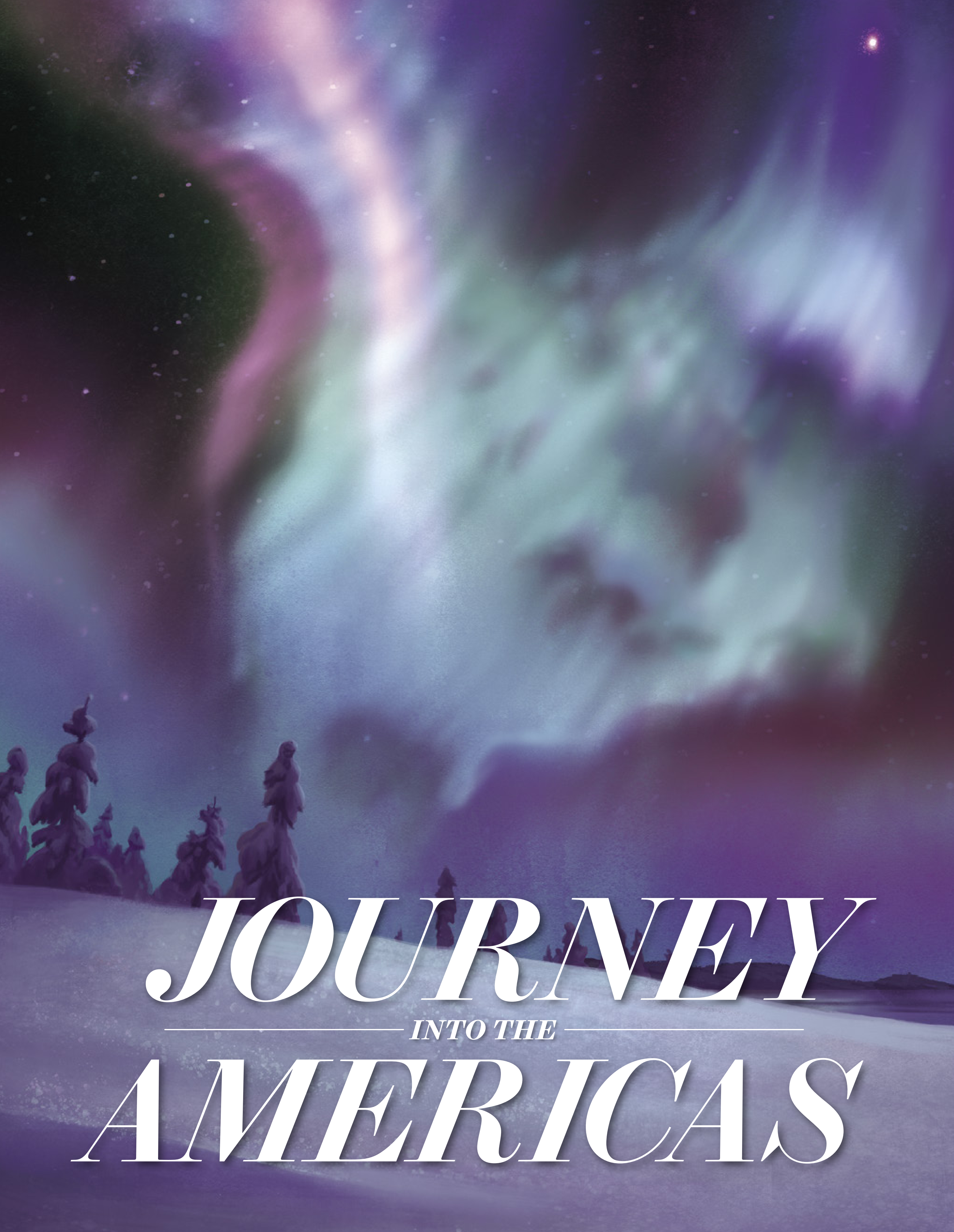


Illustration by Fatinha Ramos



JOURNEY INTO THE AMERICAS

ANTHROPOLOGY

The peopling of the American continents was a vastly more complex process than previously thought, involving the isolation and merging of multiple populations over tens of thousands of years

By Jennifer Raff

Illustration by Winona Nelson

Jennifer Raff is an anthropological geneticist at the University of Kansas. She studies genomes of contemporary humans and their ancestors for insights into prehistory, with a focus on the initial peopling of North America.

OUR SPECIES, *HOMO SAPIENS,* EMERGED IN AFRICA HUNDREDS OF THOUSANDS OF YEARS ago. From there modern humans followed in the steps of other kinds of humans—*Homo erectus,* Neandertals, Denisovans, and others—as they slowly spread across the planet. But the first *H. sapiens* who entered the Americas went somewhere no member of the human family had ever gone before. The process by which people explored, populated and adapted to the many different environments found across these continents was a momentous undertaking, one which began the rich and complex histories of thousands of different nations and communities.

In their journey into the Americas, the ancestors of present-day Indigenous peoples overcame extraordinary challenges. They survived the bitter cold and arid conditions of a global climatic event between 26,000 and 20,000 years ago known as the Last Glacial Maximum (LGM). They developed relationships with unfamiliar lands and their flora and fauna.

There are many perspectives that aim to explain these events. Indigenous peoples have numerous oral histories of their origins. Passed down from one generation to the next, such traditional knowledge conveys important lessons about the emergence of each group's identity as a people and their relationship with their lands and nonhuman relatives. Some of these histories include migration from another place as part of their origins; others do not. The framework that most Western scientists use in understanding the history of population movements is different. This article will focus on their models for the peopling of the Americas, while respecting and acknowledging that these models stand alongside diverse and ancient oral histories with which they may or may not be congruent.

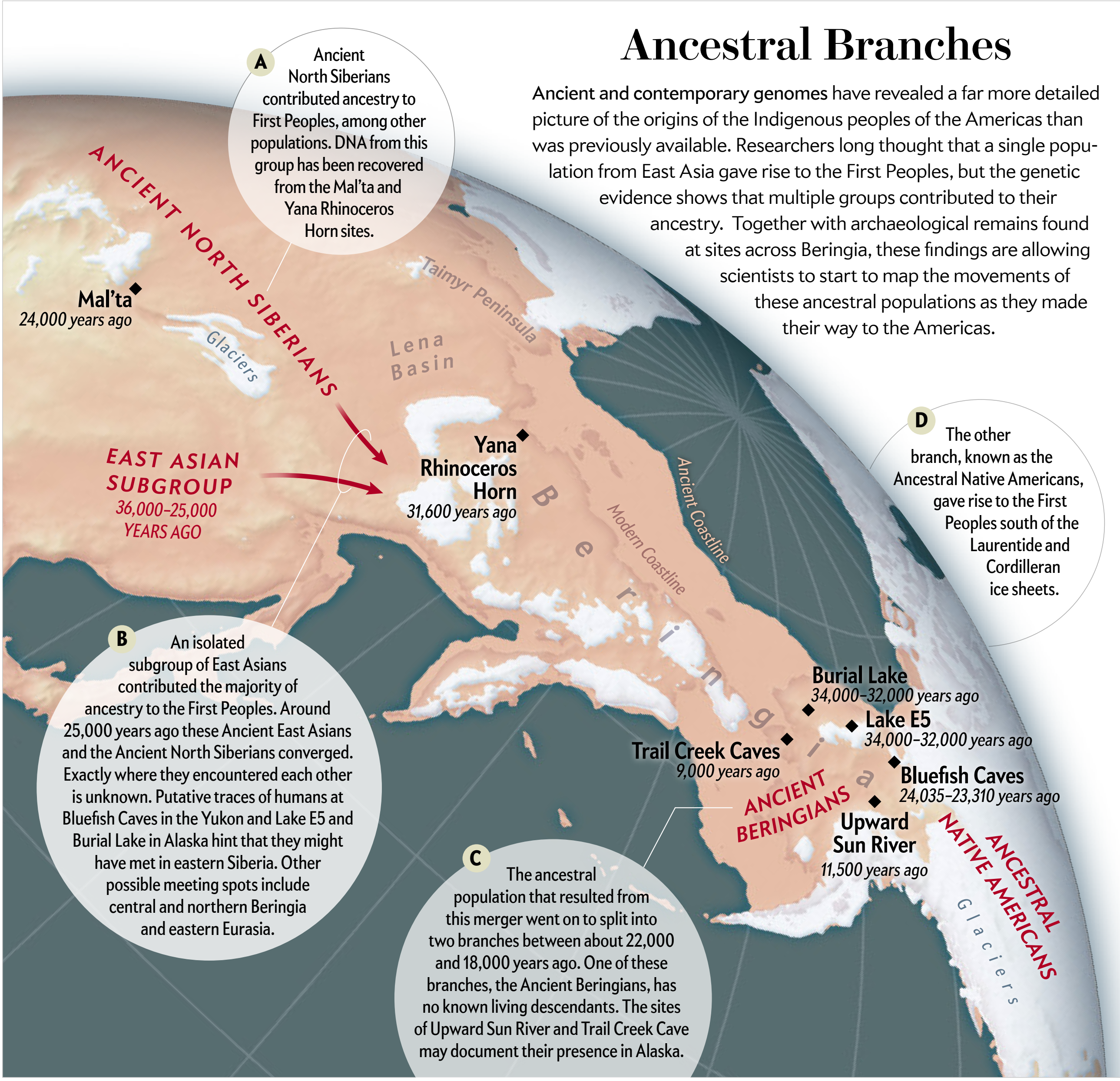
Archaeologists, biological anthropologists, linguists and paleoclimatologists have long sought to understand humanity's dispersal into the American continents. Their efforts have generated various hypotheses about the origins of Indigenous peoples, not only in terms of who their ancestors were but also when and how they established themselves in these lands. The one that prevailed for decades held that a single group of hunters from East Asia swept into the Americas after the LGM on the trail of big game animals and gave rise to all Indigenous peoples in this part of the world today.

But in the past few decades genetics has also been brought to bear on this chapter of the human story. It is no exaggeration to say that insights from genome studies have revolutionized our understanding. Although many gaps remain in our knowledge, these genetic findings, along with recent archaeological discoveries, have shown that the process of populating the Americas was far more complex than previously understood. Significantly, we now know that multiple ancient populations contributed to the ancestry of Indigenous peoples, not just one.

BEFORE CLOVIS

FOR MUCH OF THE 20TH CENTURY, the so-called Clovis First model of Indigenous origins dominated the field of archaeology. The hypothesis rested on the assumption that distinctive stone tools called Clovis points, found at archaeological sites across North America, marked the first appearance of humans on the continents. These fluted spearpoints appeared abruptly south of where the ice sheets were around 13,000 years ago, during the Late Pleistocene epoch, sometimes in association with the remains of megafauna such as mastodons, mammoths and bison. From the dates and geographical distribution of Clovis sites, archaeologists inferred that people migrated from Siberia to North America across the now submerged Bering Land Bridge after the LGM, moving swiftly down a corridor along the eastern Canadian Rocky Mountains that had opened up into interior North America as the ice sheets melted. These hunter-gatherers, who lived in small bands and ranged far in pursuit of big game, then spread rapidly southward to populate South America in about 1,000 years.

Eventually archaeological sites predating the first appearance of Clovis tools came to light. One such site is Monte Verde in southern Chile, which dates to 14,200 years ago. The artifacts found there—tools made of stone, wood and bone—are nothing like the



Clovis toolkit. They indicated that more than a millennium before the Clovis technology appeared in North America, other people had made it all the way to the southern tip of South America.

A revolution in molecular biology in the late 20th century enabled scientists to bring new approaches, including the ability to retrieve DNA from ancestral remains, to the question of when humans first populated the American continents. Researchers were able to directly sequence and analyze maternally inherited mitochondrial DNA and paternally inherited Y chromosomes from both contemporary and Ancient Indigenous populations. From these genetic data, they could estimate the timing of major demographic events. The broad outlines of population history emerged: ancestors in Asia, a period of isolation of the ancestors of Indigenous peoples during the peak of the LGM, followed by a rapid population expansion that predated Clovis and Monte Verde by several thousand years. But the picture was only a rough sketch, based on just a couple pieces of the genome. Complete genomes provide many orders of magnitude more information about a person's ancestry than mitochondrial DNA or Y chromosomes do.

It is now relatively easy to sequence complete genomes from living people. Genomes from some contemporary Indigenous peoples reveal genetic variation attributable to contact with Europeans following their arrival in the Americas in 1492. Portions of genomes that are inherited from the First Peoples—Indigenous ancestors who predate European contact—reveal histories extending tens of thousands of years backward in time.

Recovering genomes from the remains of these ancestors can be extremely difficult. The majority of DNA extracted from an ancient bone or tooth will come from soil microorganisms,

Map by Daniel P. Huffman

plants, animals and contemporary humans; the ancient DNA fragments will themselves be scarce and damaged. But recent advances have allowed scientists to retrieve and analyze DNA from even very poorly preserved sources. These developments have greatly increased the number of genomes from ancient peoples, and new methods for analyzing ancient genomes have helped us better understand the stories they tell. Together the ancient and contemporary genomes paint a far more detailed picture of the origins of the First Peoples than the one sketched by the mitochondrial and Y chromosome evidence, showing where different branches of their ancestors came from and when they met up.

AN ANCIENT CONVERGENCE

SINGLING OUT ANY SPECIFIC MOMENT as the "origin" of "a people" is arbitrary and oversimplified to the point of absurdity. Throughout time, human populations have been composed of people with complex mixtures of different ancestries, each with their own histories. But we have to start this genetic story somewhere, so we will begin it in the Upper Paleolithic period. Approximately 36,000 years ago, a group of people living in what is now East Asia became increasingly isolated from the broader population living in the region. It was a very slow process: they continued to exchange mates with their parent population for more than 11,000 years. By about 25,000 years ago, however, they were genetically distinguishable from the ancestors of contemporary East Asians. This isolated group of Ancient East Asians contributed the majority of ancestry to the First Peoples of the Americas.

All genomic studies rule out the possibility that the First Peoples mixed with Europeans or Africans or any other populations before 1492.

Another ancestral branch emerged around 39,000 years ago and lived at the Yana Rhinoceros Horn site in what is now northeastern Siberia 31,600 years ago. This area is situated in the western part of Beringia—the name given to the region spanning eastern Siberia, western Alaska and the land bridge that once connected them, which now lies under the Bering Strait. Two baby teeth found at Yana give us extraordinary insights into this population, which geneticists refer to as the Ancient North Siberians. The Ancient North Siberians at Yana were hunter-gatherers who lived in this high-latitude area year-round. The baby teeth came from two boys at Yana who lost them when they were 10 to 12 years old as their permanent molars and canines were emerging. The teeth themselves show that the boys had survived the dangers of infancy. Genomes recovered from the teeth, described by Martin Sikora of the University of Copenhagen and his colleagues in 2019, show that the boys were not close relatives and belonged to a sizable population comprising around 500 breeding individuals. Unlike Neandertals, whose genomes indicate that they had small populations and experienced periodic local extinctions, the Ancient North Siberians appear to have thrived in extremely challenging environments.

The Ancient North Siberians spread throughout northern and central Siberia. Remains of a child who lived at a site known as Mal'ta document their presence in south-central Siberia 24,000 years ago, during the Upper Paleolithic period. DNA recovered from these remains shows that many geographically dispersed populations, including present-day West Eurasians (a group that encompasses Europeans) and the First Peoples of the Americas, have ancestry from the Ancient North Siberians.

The two main branches of the First Peoples' ancestry—the Ancient East Asians and the Ancient North Siberians—converged around 25,000 to 20,000 years ago and interbred. The resulting ancestral population formed shortly after the start of the LGM, during which Siberia had an exceedingly cold climate with limited plants and animals. Humans would have found it very difficult, if not impossible, to live in this environment, and indeed there is essentially no archaeological record in northeastern Siberia between around 29,000 and 15,000 years ago. Many archaeologists infer from this absence that people sought refuge in other regions with more resources and better climates. We do not know exactly what happened, but it seems likely that the meeting of people from the Ancient East Asian and Ancient North Siberian groups occurred as part of a migration from Siberia in response to this environmental change. The question is: Where did they encounter each other?

They probably did not cross paths in western Beringia: that region appears to have been depopulated after around 29,000 years ago. This leaves eastern Eurasia, central or eastern Beringia, and northern Beringia as possible meeting spots. Genetics does not readily settle this geographical question. The genomes of Indigenous peoples indicate that their ancestors were isolated for several thousand years during the LGM starting shortly after the Ancient East Asians and Ancient North Siberians intermarried. This isolation strongly suggests that the encounter did not take place in eastern Eurasia, where the proximity of other groups would almost certainly have resulted in additional mixing, because that is what humans do. Still, some archaeologists argue that eastern Eurasia is the only region that has extensive and unambiguous archaeological evidence of human presence during this cold period.

Perhaps instead the ancestors of Indigenous peoples rode out the LGM on the southern coast of what would have been central Beringia. Paleoenvironmental reconstructions have shown that it would have had a mild climate, possibly resembling a wetland, because of the proximity of ocean currents. It would have been a relatively comfortable place for people and animals to live when the ice sheets were at their maximum extent. But central Beringia is now underwater and inaccessible, so archaeologists have been unable to look for direct evidence of people there. There are some intriguing hints of a human presence in eastern Beringia, however. Sites in the Yukon and on Alaska's North Slope have yielded putative traces of humans during the LGM. The evidence is not sufficient to convince most archaeologists, but it does call for more attention to be paid to this region.

The Siberian Arctic zone, a region above latitude 66 degrees North that lies north and west of western Beringia, has only recently emerged as another plausible candidate for a refugium during the LGM and thus a place where people from the Ancient East Asian and Ancient North Siberian groups might have come together. Today large parts of this area are underwater, but throughout the LGM it would have been a vast steppe-tundra plain that supported big populations of mammoths, woolly rhinoceros, bison and horses. It would have been a challenging environment for humans. Yet we know from the archaeological and genetic evidence at Yana that they were already well adapted for such Arctic conditions long before the LGM began. Still, as with all other potential refugia besides eastern Eurasia, there is currently very little direct archaeological evidence of humans in this part of the world.

Although we do not know exactly where the Ancient North Siberians and Ancient East Asians joined up, we can infer from genetics what happened next. Immediately after the two groups exchanged genes and while they were isolated from other human groups, a series of complex demographic events occurred very close in time that would ultimately give rise to peoples in the Americas and Siberia. The ancestral population split into at least two branches between about 22,000 and 18,100 years ago. One branch, named the Ancient Beringians, has no known living descendants. The other, known as the Ancestral Native Americans, gave rise to First Peoples south of the Laurentide and Cordilleran ice sheets.

This branch of Ancestral Native Americans was probably itself subdivided into multiple distinctive groups during the LGM. One of these groups, referred to as Unsampled Population A, has no known archaeological remains to define it, but the present-day Mixe people, who live in Oaxaca, Mexico, seem to have some of its DNA.

A few present-day populations in the Amazon appear to have additional ancestry from a group related to Australasians called Population Y. This link is one of the most puzzling ancestry findings of recent years. Traces of this genetic signal have also turned up in a 40,000-year-old individual from Tianyuan Cave in China. Thus far the evidence suggests that there was once an ancient group widespread throughout Asia that ultimately contributed this ancestry to contemporary Pacific peoples and some Amazonian populations. Researchers are still trying to pin down how many ancient and present-day peoples have this ancestry and where the source population lived.

More important, all genomic studies rule out the possibility that the First Peoples mixed with Europeans or Africans or any other populations before 1492. This conclusion runs contrary to stories of a trans-Atlantic migration promoted by popular television series, but the totality of genetic and archaeological evidence emphatically invalidates those notions.

SOUTHWARD BOUND

AFTER THE LGM, Ancestral Native Americans moved southward and split into at least three branches. The first branch to diverge is represented by a single genome from a woman who lived on the Fraser Plateau in British Columbia about 5,600 years ago. Not much else is known about this population. The other two branches encompass all the currently known genetic diversity of populations south of the ice sheets. The Northern Native Americans branch includes the ancestors of Algonquian, Na-Dené, Salishan and Tsimshian peoples. The Southern Native Americans branch includes the ancestors of Indigenous peoples distributed broadly throughout South America, Central America and much of North America. (Indigenous peoples of the Arctic have additional ancestry from subsequent migrations.) Experts disagree over when, where and how these populations dispersed into the continents. To date, there are three major competing scenarios for this process.

The most conservative archaeologists stand by what is essentially an updated version of the Clovis First model. In their view, the Swan Point site in central Alaska is the key to understanding the peopling of the Americas. Dated to about 14,100 years ago, it is the oldest uncontroversial site in eastern Beringia, and its stone tool technology is said to show clear links to the Diuktai culture in Siberia, as well as Clovis tools. These archaeologists argue that the ancestors of the First Peoples were in northeastern Asia or Siberia during the LGM and did not migrate across the Bering Land Bridge into Alaska until between 16,000 and 14,000 years ago. They maintain that Clovis represents the first successful establishment of humans in the Americas, with people traveling down the so-called ice-free corridor that formed as glaciers retreated, possibly followed by other waves of migration from Siberia. Under this model, sites predating Clovis are either rejected as invalid or attributed to people who did not contribute culturally or biologically to subsequent Indigenous populations.

Other archaeologists emphasize the importance of pre-Clovis evidence, including remains found half a world away from central Alaska at the Page-Ladson site in northern Florida. Described by Jessi Halligan of Florida State University, Michael Waters of Texas A&M University and their colleagues in 2016, this site contains stone artifacts, including a broken knife found in association with 14,450-year-old mastodon bones. The Page-Ladson site is significant to these researchers precisely because of how *insignificant* it would have been at the time: a small watering hole located much farther from the coastline than it is today, with no distinctive features to flag it on the landscape. Humans butchered a mastodon there and carried away its meat and one of its tusks, leaving behind some of its bones, the other tusk and the broken knife. Their visit to the site was evidently brief and purposeful, however; there are no traces of habitation, toolmaking or any other activities. This quick, targeted stop suggests that people had adapted to the landscape well enough to have been familiar with this obscure place and the likelihood of finding food and mastodon tusks for toolmaking there.

Learning the geography of a place, where resources such as watering holes that attract prey could be reliably found—a process that archaeologists call settling in—takes time. To some experts, Page-Ladson is clear evidence that people were settled in by at least 14,450 years ago, meaning that they would have been in the Americas much earlier. But how much earlier?

There are a number of sites throughout the Americas well below the southernmost margin of the continental ice sheets that date to between about 14,000 and 16,000 years ago. Explaining these sites requires an entirely different paradigm from the late peopling scenario described earlier. For one thing, their antiquity constrains the routes that people could have taken into the Americas. The ice-free corridor between the Laurentide and Cordilleran glaciers did not open until sometime after 14,000 years ago. If people were occupying sites by 14,450 years ago or

Dispersal Scenarios

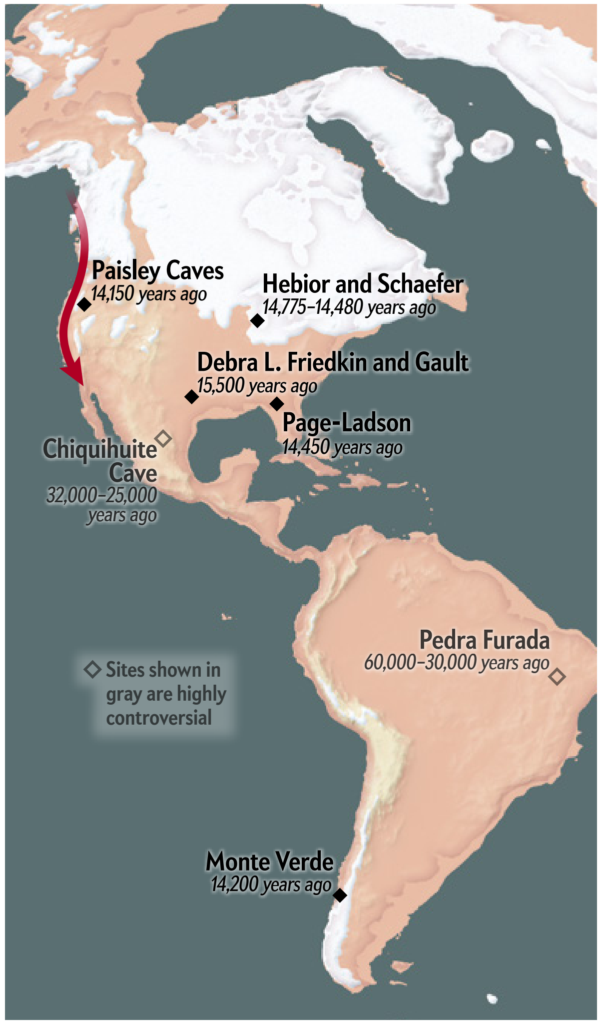
Experts disagree over when, where and how the ancestors of Indigenous peoples dispersed into the American continents. The current debate revolves around three major competing models for this process.

Scenario 1: A Late Peopling

Some archaeologists maintain that the people who made distinctive spearheads initially found in Clovis, N.M., and later discovered at sites such as Anzick in Montana were the first humans to establish themselves successfully in the Americas. The Swan Point site in Alaska figures importantly in their argument because it contains stone tools that appear to link the older Diuktai culture in Siberia to the Clovis culture in North America. Proponents of this so-called Clovis First model hold that people entered the Americas well after the Last Glacial Maximum, traveling down the ice-free corridor that formed as glaciers retreated. These researchers reject pre-Clovis sites as invalid or unrelated to contemporary First Peoples.

Scenario 2: An Early Coastal Peopling

Other archaeologists place great importance on pre-Clovis sites, arguing that they document human presence throughout the Americas well before Clovis technology appeared and before the ice-free corridor opened up. These scholars contend that people probably instead traveled by boat along the western coast starting around 17,000 years ago or possibly as early as 20,000 to 30,000 years ago, if the controversial claims for evidence of such ancient human activity at Pedra Furada and Chiquihuite Cave are to be believed.



Scenario 3: An Extremely Early Peopling

A small number of researchers believe that humans reached the Americas far earlier. They point to the Cerutti Mastodon site, which is said to preserve butchered mastodon bones and stone tools from 130,000 years ago. If these remains really are the result of such ancient human activity, they would indicate that the first people to arrive in this part of the world were probably *Homo erectus* rather than *Homo sapiens*. Most scholars reject this claim.

Maps by Daniel P. Huffman, Illustration by Jen Christiansen (artifacts) even earlier, it seems exceedingly unlikely that they could have taken this route. Furthermore, environmental DNA found in lake sediment cores from the middle of the ice-free corridor shows that it would not have been populated by plants or animals until around 12,600 years ago—long after people were already in the Americas. And the earliest direct archaeological evidence of humans within the corridor region itself dates to 12,400 years ago. On balance, the evidence suggests that the first humans to enter the Americas did not take the ice-free corridor in.

The most likely alternative route is via boat along the western coast, which would have become accessible about 17,000 to 16,000 years ago. A coastal route also fits genetic evidence for the Southern Native American expansion better. The best-supported models for population history currently show that the Southern Native American group diversified rapidly into regional populations throughout North, South and Central America between about 17,000 and 13,000 years ago. Travel by water along the coast would better explain the speed and timing of these population splits than the slower overland route would.

One variant of this early coastal peopling scenario allows that humans may have been present in the Americas during or even slightly before the LGM, perhaps as early as 20,000 to 30,000 years ago. Putative evidence of pre-LGM occupation comes from several sites in Mexico and South America, including Pedra Furada in northeastern Brazil. But most of the archaeological community remains skeptical about these sites, questioning whether they have been dated accurately and whether their supposed artifacts were shaped by humans or natural processes.

This skepticism does not rule out the presence of people in the Americas before the LGM. It simply means that more evidence is needed for confirmation. If people were in the Americas during or just prior to that time, their numbers would probably have been very small, so they would have left a very light archaeological footprint on the landscape. Intriguingly, an early presence might explain the puzzling signal of Population Y ancestry in some Amazonian groups: it could be the result of admixture between peoples dispersing into the Americas after the ice sheets retreated and those already in South America.

The third major scenario is radically different. A small group of scholars believes that people reached this part of the world at an extremely early date. This claim rests in large part on 130,000-year-old mastodon remains excavated from the Cerutti Mastodon site in California. In an analysis published in 2017, Steven Holen of the San Diego Natural History Museum and his colleagues concluded that damage patterns on the bones were the result of butchering. Stones found at the site were interpreted to be manufactured tools. *H. sapiens* is not thought to have begun spreading out of Africa in significant numbers until perhaps 70,000 to 80,000 years ago. If the Cerutti remains really are the product of ancient human activity, they would show not only that humans made their way to the American continents far earlier than previously thought but also that the first people to arrive were probably *Homo erectus* rather than *H. sapiens.*

Most archaeologists reject this argument for multiple reasons, including the possibility that modern construction equipment, rather than early human butchers, smashed the mastodon remains, which were discovered during a road-building project. Furthermore, patterns of variation in contemporary Indigenous genomes do not show separate descent of First Peoples from other humans, nor do they indicate admixture among anatomically modern *H. sapiens* and other kinds of humans in the Americas. If *H. erectus* made it to this corner of the planet, it left neither fossils nor genetic contributions to First Peoples.

As things stand in 2021, most archaeologists and geneticists agree that humans were established in the Americas by at least 14,000 to 15,000 years ago, but they disagree on exactly which pre-Clovis sites are legitimate and therefore how early people may have entered the continents. This diversity of opinions reflects the challenges of working with the archaeological and genetic records, which contain large gaps. Of the three scenarios described here, the second one comes closest to reconciling the archaeological and genetic evidence. But even that model cannot completely account for all the available data.

EMBRACING UNCERTAINTY

As we move forward in studying the peopling of the Americas, we can expect the story to grow even more complicated. At the time of this writing, there are perhaps several dozen publicly available complete genomes from contemporary and ancient Indigenous peoples. These genomes are unevenly distributed; most are from Central and South America and the northern parts of North America. There are few complete genomes from the present-day U.S., the result of Indigenous peoples' justified distrust in researchers. This lack of trust is rooted in the exploitation of Indigenous peoples by physicians and anthropologists who, starting in the earliest days of anthropology, looted ancestors' remains from their resting places. Many used the remains to posit racial classifications that have since been debunked. It is important that geneticists work with Indigenous communities to ensure that the quest for genetic knowledge does not perpetuate further harms.

This geographical gap in our understanding of genetic variation means that we are now in a dynamic period of research in this field. Every new genome sequenced adds tremendously to our knowledge. Investigators are also looking beyond human genomes to DNA from alternative sources such as the bacteria and viruses that are associated with people, as well as human prey and companion species, for clues. This use of nonhuman DNA can potentially illuminate human population movements while respecting the sacredness of Indigenous remains.

There is a good chance that fresh details will emerge that change the models discussed here. This article provides a framework for understanding the significance of these future discoveries. Scientists working within this field have learned to be comfortable with ambiguity and accept that our models are provisional, subject to revision in light of changing evidence. With new tools for DNA analysis and new questions to ask of the data, the future is exciting for studies of the First Peoples and how they triumphed on this last, arduous leg of our species' millennia-long march across the globe. SA

FROM OUR ARCHIVES

The First Americans. Heather Pringle; November 2011.

scientificamerican.com/magazine/sa

ASTROPHYSICS

A NEW MAP OF THE UNIVERSE

A chart of millions of galaxies across 11 billion years of cosmic history helps to answer some of the biggest cosmological questions

By Kyle Dawson and Will Percival

Illustration by Mark Ross Studios

Kyle Dawson is a professor of physics and astronomy at the University of Utah. He was principal investigator for the extended Baryon Oscillation Spectroscopic Survey (eBOSS) and is co-spokesperson for the upcoming Dark Energy Spectroscopic Instrument (DESI).

Will Percival is director of the Waterloo Center for Astrophysics at the University of Waterloo in Ontario and an associate member of the Perimeter Institute for Theoretical Physics. He was the survey scientist for eBOSS and is a primary science coordinator for the future satellite mission Euclid.

AS DOUGLAS ADAMS WROTE IN *THE HITCHHIKER'S GUIDE TO THE GALAXY,* "Space is big.… You just won't believe how vastly, hugely, mind-bogglingly big it is." We and many other astronomers have dedicated our careers to creating maps of the universe on the largest scales possible—to discovering just how big the cosmos really is and how it works.

The maps we create are crucial for studying the physics that drives cosmic history. In July 2020, a 20-year project we worked on called the Sloan Digital Sky Survey produced the largest map of the cosmos ever made. It includes our immediate surroundings, the farthest reaches of space, and everything in between. This three-dimensional chart contains the positions of four million galaxies laid out like signposts over many billions of light-years, stretching back in time to some of the earliest epochs of the universe.

The map shows that galaxies are not distributed randomly. Instead they cluster in patterns: long filaments and two-dimensional sheets of galaxies in some areas; dark voids containing few galaxies in others. Scientists believe these patterns emerged before the galaxies were born, starting less than one billion years after the big bang. By mapping as much of cosmic history as possible, we can record the growth of these patterns and deduce the fundamental laws that guided their evolution. This atlas of galaxies provides crucial information in the quest to understand some of the biggest mysteries in physics, such as the geometry of the universe and the nature of the dark energy driving the accelerating expansion of space.

CORES AND SHELLS

THE SLOAN DIGITAL SKY SURVEY, which uses the Sloan Foundation Telescope at Apache Point Observatory in New Mexico, included the extended Baryon Oscillation Spectroscopic Survey (eBOSS) project and its predecessor, BOSS. These efforts based their measurements on a pattern in the arrangement of galaxies throughout space called baryon acoustic oscillations (BAO). To understand this pattern, we must consider the evolution of the universe during the first 300,000 years, starting with the first fraction of a second after the big bang. At that time the universe underwent a period of rapid expansion called inflation in which the universe grew so fast that subatomic scales became the size of a golf ball in 10^{-32} second. During the expansion, minuscule quantum fluctuations in the distribution of energy in the universe became macroscopic in size. Regions of greater energy density gradually attracted more and more matter, leaving other areas empty. Over the next 13.7 billion years these dense spots formed the filaments, sheets and clusters of galaxies that we observe today. Astronomers call this process the growth of structure.

The BAO patterns arise because of the way light and matter interact and affect structure formation. The universe contains two kinds of matter: one that interacts with light—the regular material that we are used to dealing with in our everyday lives—and one that does not, called dark matter. In the hot and dense early universe, ordinary matter particles and particles of light (photons) bumped into one another so often that they were essentially stuck together, whereas dark matter was free to move independently. Gravity caused dark matter to cluster in the centers of dense regions, but pressure from light trying to travel outward dragged the normal matter away.

Regular matter and light went their separate ways about 300,000 years after the big bang, when the universe had expanded and cooled enough that particles spread out and photons could travel freely. That first release of light is still visible in the sky as the cosmic microwave background. Once light and matter were no longer bound, an excess of the normal matter was left in spherical shells around the overdensities of dark matter. Gravity drew both normal matter and dark matter to these structures, but the process imprinted a pattern of overly dense cores surrounded by spherical shells on the universe's matter. This pattern, known as the baryon acoustic oscillation feature, has a size called the co-moving sound horizon and is visible in our map of galaxies.

We can use this feature as what we call a standard ruler—a handy way to measure cosmic distances. Because the patterns were all created at nearly the same time and in the same way, the cores and shells are all about the same intrinsic size—approximately 500 million light-years separate each core from its shell. But when we see these shapes in our maps, they appear smaller or larger depending on how far away they are. So if we measure their apparent size on the night sky and compare it with what we know to be their intrinsic size, we can determine their distance from Earth.

SPREADING OUT THE LIGHT

THESE STANDARD-RULER distance calculations allow us to measure the average distance to a set of galaxies, but they do not by themselves provide cosmological information. For this we need additional information about the speed at which galaxies are moving away from us. The Sloan survey was well equipped to provide that information. In addition to capturing deep images of one third of the sky, Sloan targeted two million galaxies and quasars (galaxies dominated by a bright central black hole) through spectroscopy, a technique used to isolate the different wavelengths of light coming from an object. These spectral measurements reveal how quickly galaxies are traveling away from us, which depends on how much the universe has expanded between the time the light was emitted and when it was observed. Because this expansion stretches the wavelengths, the light becomes redder—a phenomenon called redshift.

Every BOSS and eBOSS observation captured the light spectra from 1,000 objects simultaneously, using a dedicated fiber-optic cable for each. One end of each cable was supported by an aluminum plate positioned at the focal plane of the telescope. In preparation for a night's observation, teams prepared eight of these plates in purpose-built cartridges, with a fiber plugged by hand into each of the 1,000 holes. It took about half an hour for two technical staffers to plug a single plate. The most productive month in the history of the Sloan survey was March 2012, when we observed 103,000 spectra using these plates.

We selected the target galaxies from imaging data previously obtained by telescopes around the world. Technicians drilled holes in the aluminum plates using a computer-controlled machine at the University of Washington so that when the telescope pointed at a particular patch of the sky for its one-hour exposure, the end of a fiber inside each hole lined up perfectly with the center of its target galaxy or quasar.

Because the light from distant galaxies takes a long time to reach the telescope, the maps show us 11 billion years of cosmological time, covering most of the history of the universe.

Every night between December 2009 and March 2019 that the moon was not overly bright, the telescope tracked a patch of sky, and the fibers fed the light that fell onto the focal plane into two spectrographs. These modern detector cameras digitally measured the light's intensity as a function of wavelength. With these data we could calculate each galaxy's redshift.

During the almost 10 years that eBOSS and its predecessor BOSS collected data, we measured the locations and redshifts of more than four million galaxies. Because the light from distant galaxies takes a long time to reach the telescope, the maps from BOSS and eBOSS show us 11 billion years of cosmological time, covering most of the history of the universe.

PROBING DARK ENERGY

BY COMBINING OUR REDSHIFT measurements with our distance estimates from the BAO standard ruler, we were able to study the relation between distance and redshift—in other words, how much the universe has expanded and stretched light given the distance traveled. This information shows us how the expansion of space has changed over the past 11 billion years, giving us insight into one of the biggest enigmas in physics today: dark energy.

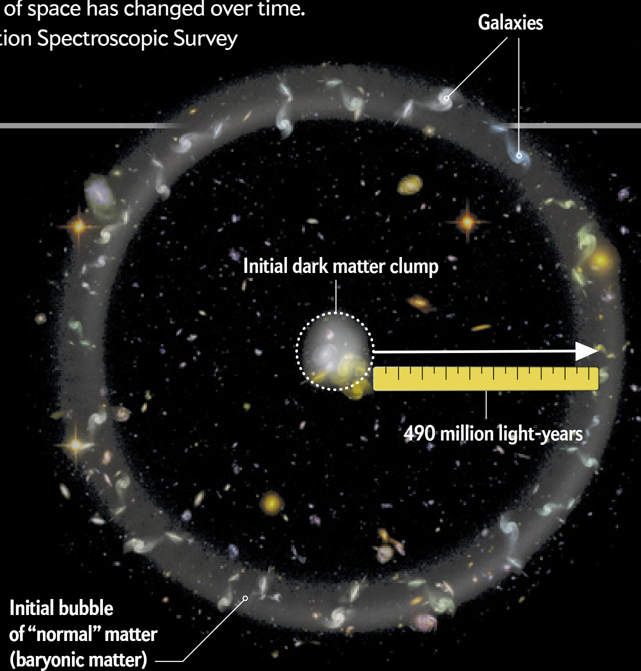
Dark energy is the mysterious force that seems to be accelerating the expansion of the universe—a surprising phenomenon discovered in 1998. The simplest mathematical model for dark energy is the so-called cosmological constant, lambda, a term in

How Fast Is Space Expanding?

Dark energy is the mysterious force driving the universe to expand faster and faster. To understand dark energy, astronomers working on the two-decade Sloan Digital Sky Survey created the largest-ever cosmic map to see how the expansion rate of space has changed over time. The final map was released by the extended Baryon Oscillation Spectroscopic Survey (eBOSS), part of Sloan that ran from 2014 to 2019.

1 START WITH A PATTERN IN SPACE

The eBOSS survey targeted an arrangement seen in galaxies across the universe called baryon acoustic oscillations (BAO). This imprint started with minute fluctuations in the energy throughout spacetime right after the big bang. Because of the way light and matter interacted in the early universe, these fluctuations caused dark matter to form clumps surrounded by spheres of regular matter and light, separated from the dark matter by some 500 million light-years. Over time gravity pulled both types of matter into the clumps of dark matter as well as the spheres of normal matter, leading to a relatively even mixing of dark and normal matter throughout the universe. Eventually galaxies formed everywhere there was matter, resulting in a pattern of cores and shells still seen in the spread of galaxies today.



2 USE THE PATTERN AS A RULER

The pattern will appear smaller or larger depending on the distance astronomers are looking at—faraway cores and shells will seem small, and those nearby will appear big. But scientists know all the shells are actually 500 million light-years from their cores. By comparing the apparent size of a BAO pattern with its known intrinsic size, researchers can deduce its distance. Thus, the imprint is a handy "standard ruler" to measure cosmic lengths.

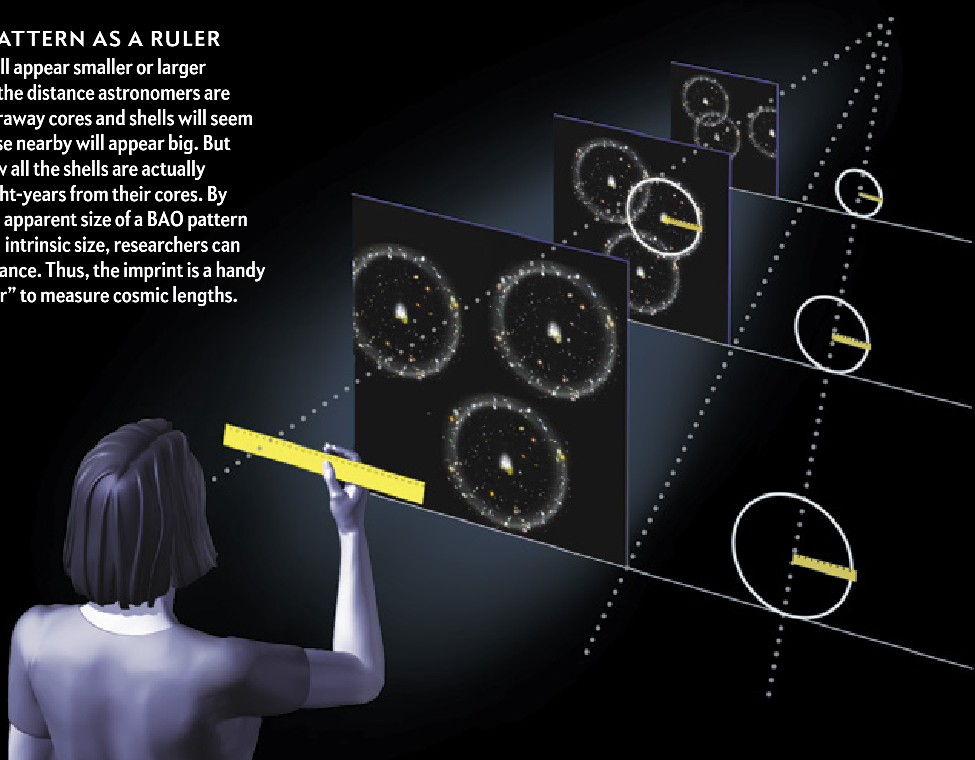
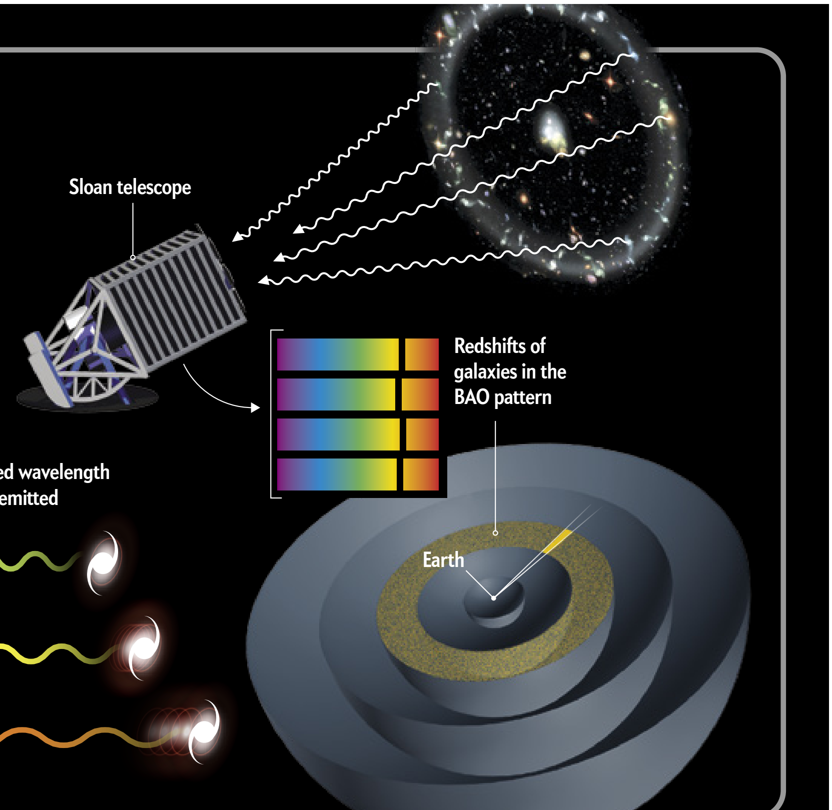
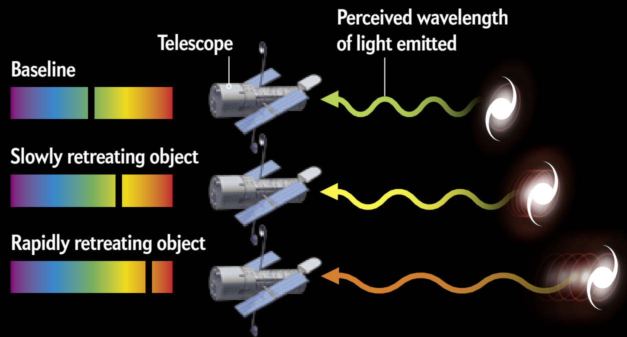


Illustration by George Retseck

3 MEASURE SPEEDS

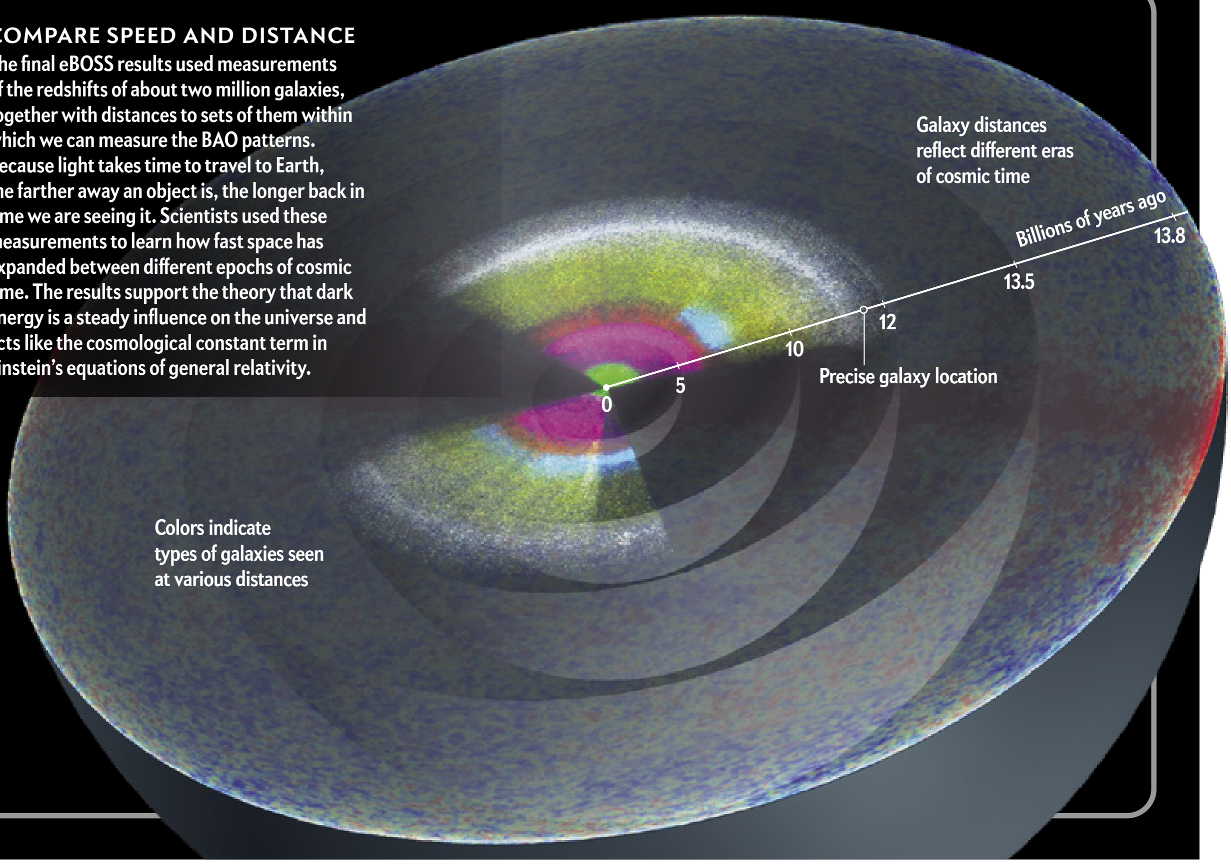
The next step toward understanding dark energy is to measure how fast the galaxies forming the BAO patterns are moving away from us. Because space is expanding, everything seems to be receding. This motion causes objects to appear redder the faster they are moving away—a phenomenon closely related to the Doppler shift. Astronomers can measure a galaxy's "redshift"—the amount its light has shifted toward the red end of the spectrum—to discover its speed away from us.





4 COMPARE SPEED AND DISTANCE

The final eBOSS results used measurements of the redshifts of about two million galaxies, together with distances to sets of them within which we can measure the BAO patterns. Because light takes time to travel to Earth, the farther away an object is, the longer back in time we are seeing it. Scientists used these measurements to learn how fast space has expanded between different epochs of cosmic time. The results support the theory that dark energy is a steady influence on the universe and acts like the cosmological constant term in Einstein's equations of general relativity.



ANAND RAICHOOR *Swiss Federal Institute of Technology Lausanne/Lawrence Berkeley National Laboratory* (step 4 map overlay)

IN 2000 the Sloan Foundation 2.5-meter Telescope in New Mexico began the Sloan Digital Sky Survey's two-decade mapping effort.

ENRICO SACCHETTI *Science Source*

the field equations for Einstein's general theory of relativity that describes the energy present in empty space. This energy can act as a repelling force, pushing against the inward pull of gravity to speed up the universe's outward expansion. Over the past 20 years this cosmological model, referred to as Lambda Cold Dark Matter (Lambda-CDM), has survived many tests; although we do not fully understand it, it is our best model.

Lambda-CDM has problems, however. Three recent observations show hints of discordance between the model and reality. The first is that measurements of the local expansion rate of space do not match up with Lambda-CDM predictions based on observations of the distant universe. The second is that observations of the cosmic microwave background suggest space might be slightly more curved than predicted by the theory of inflation. Finally, the distortion of light from distant galaxies by intervening matter seems to be weaker than expected in the Lambda-CDM model. Time will tell whether these tensions are the first signs that a new cosmological model is required or simply reflect problems with the measurements. Either way, eBOSS observations are helping to point us in the right direction.

They show, for instance, that a transition occurred when the universe was 60 percent of its current size: the expansion of space stopped decelerating and started speeding up. These findings agree with the Lambda-CDM model, which suggests that this point is when dark energy won out over the gravitational effect of matter, thereby decelerating the expansion rate.

Another crucial part of the cosmological model is the geometry of space. The theory of inflation predicts a universe whose geometry is very close to flat. But some earlier cosmic background studies suggest that space is slightly curved. Using the eBOSS maps, we were able to improve the precision of spatial geometry measurements by a factor of 10 compared with previous observations. We found no evidence that the universe is curved, giving a boost to the standard inflation picture.

We were also able to test cosmological models by looking at how quickly structures—clusters and filaments of galaxies—formed. The redshifts we measured in our survey record the relative velocity of galaxies with respect to us, the observers, but not the cause of that movement. Most of the redshift arises because of cosmological expansion—the fact that all objects in space are moving away from one another—but it is also partly caused by the growth of structure. As galaxies fall into clusters and away from voids, their velocities, and therefore their redshifts, change.

The velocities affected by structure growth, called redshift-space distortions, are apparent when we compare the patterns seen along and across the line of sight with the galaxies. The size of the redshift-space distortions tells us the rate at which structures grow. Using data from eBOSS and its predecessors, we calculated this rate to a precision of about 3.5 percent. Our result matches the predictions of general relativity, which is important because several previous measurements that relied on different methods have values that are about 10 percent lower.

Overall there is no evidence from our measurements that the standard cosmological model with lambda, the cosmological constant, is wrong. We see no surprises in structure growth, the nature of dark energy or the geometry of space. We do, however, see the same discrepancy we mentioned earlier between the expansion rate of space based on data from the local universe and that derived from the cosmic microwave background. Measurements based on the latter, for example, find an expansion rate of 67.28 ± 0.61 kilometers per second per megaparsec (a measurement of distance in space), whereas local measurements of supernovae lead to values 10 percent higher. Using our BAO measurements, we estimate an expansion rate of about 67 km/s/Mpc—both when we combine our numbers with cosmic background data and when we do not. The difference between this value and the rate astronomers get when they look only at the nearby universe is getting significant enough to call into question the basic assumptions of our cosmological model. There may still be a problem with one or more of the measurements that feed into these calculations, but it is at least equally likely that we need to revise the model for the early expansion of the universe and the co-moving sound horizon. We may need to introduce a new kind of particle, field or interaction to explain the dissonance we see.

We may need to introduce a new kind of particle, field or interaction to explain the dissonance we see.

BIGGER AND BETTER

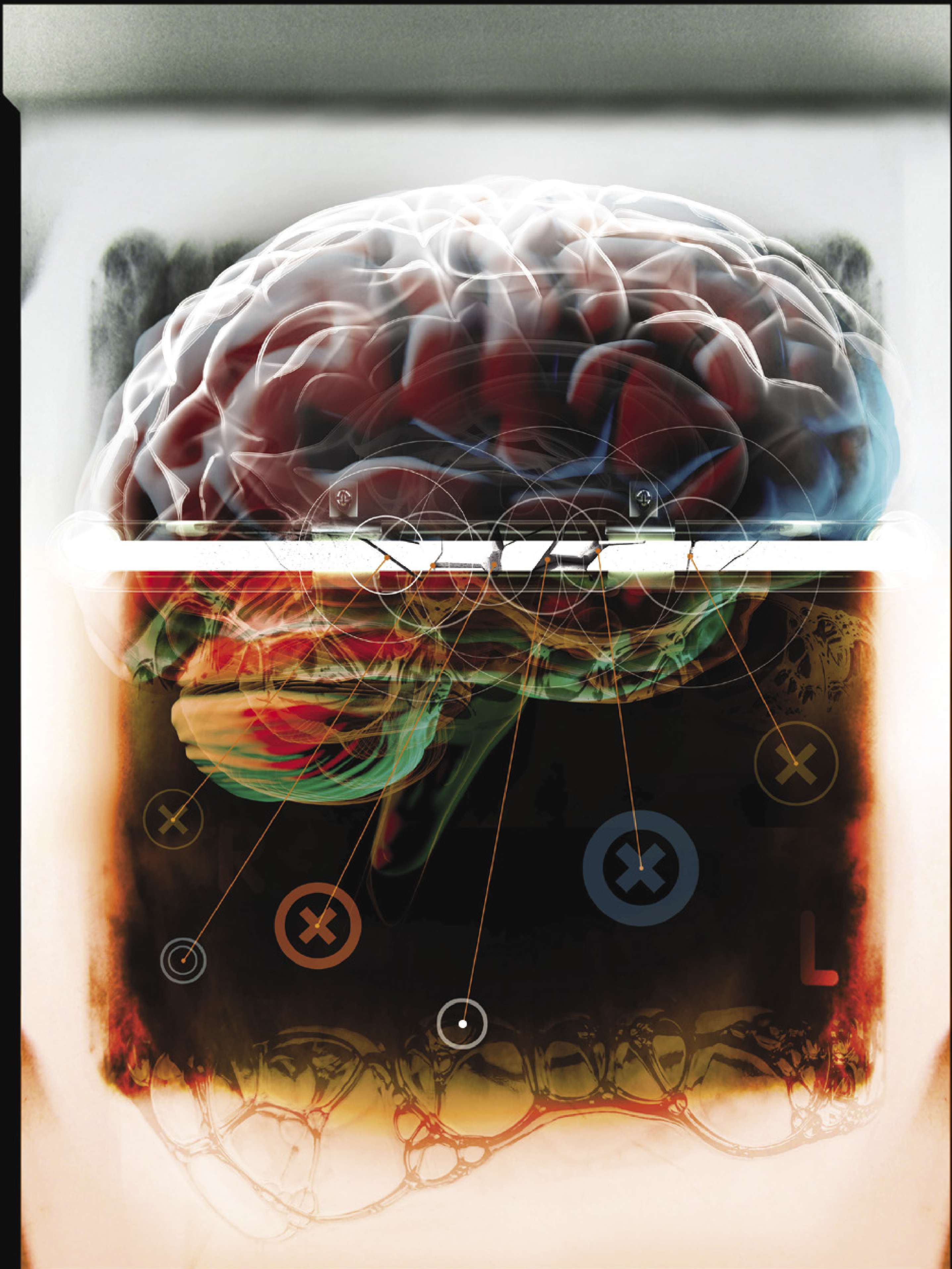
OVER THE PAST 20 YEARS the Sloan telescope and spectrographs have led the world in performing galaxy redshift surveys, culminating in eBOSS. The Sloan survey will continue with new maps of stars and quasars, and our success has inspired astronomers to plan even larger galaxy surveys covering a wider range of cosmic history. One such project, which has begun early science operations, is called the Dark Energy Spectroscopic Instrument (DESI). This survey will use a 5,000-fiber multiobject spectrograph located on the Mayall Telescope at Kitt Peak National Observatory in Arizona to create a deeper and denser map of the universe. The new spectrograph is capable of observing 5,000 targets simultaneously and is positioned on a telescope that has a primary mirror with a diameter approximately twice that of the Sloan telescope's. Rather than relying on humans, each of the 5,000 fibers will be placed into position by a dedicated robot. In five years DESI will create a galaxy survey that is more than 10 times larger than Sloan's.

Set to launch in 2022, the satellite mission Euclid, led by the European Space Agency, will also perform a large galaxy redshift survey. Using its space-based perspective to avoid the fuzziness introduced by Earth's atmosphere, Euclid will look at higher redshifts—that is, greater distances—than can be seen clearly from the ground. It will measure redshifts for approximately 25 million galaxies. In addition to DESI and Euclid, plans are afoot to build larger multiobject spectrographs on grander, 10-meter-class telescopes, which should enable a significant leap forward in our understanding of the universe. SA

FROM OUR ARCHIVES

Seeing in the Dark. Joshua Frieman; November 2015.

scientificamerican.com/magazine/sa


L

Daniela Kaufer is a professor in the department of integrative biology, an investigator at the Helen Wills Neuroscience Institute and associate dean of biological sciences at the University of California, Berkeley.

Alon Friedman is a professor in the department of medical neuroscience and William Dennis Chair in Epilepsy Research at Dalhousie University in Nova Scotia. He is also a professor in the department of cognitive and brain sciences and Dr. Helena Rachmanska-Putzman Chair in Neurology at Ben-Gurion University of the Negev in Israel.

NEUROSCIENCE

HOLES IN THE SHIELD

Leaks in a protective filter called the blood-brain barrier may lead to Alzheimer's and other dementias. Reversing the effects makes aging animal brains look young and healthy

By Daniela Kaufer and Alon Friedman

IT WAS THE MIDDLE OF THE NIGHT IN JERUSALEM, AND WE WERE WATCHING MICE SWIM. THE YEAR WAS 1994, and the two of us were crouching over a pool of cold water in a laboratory at the Hebrew University. The room was chilly, our hunched backs ached, and we had been repeating this routine over many nights, so we were tired and uncomfortable. So were the mice. Mice really dislike swimming, especially in cold water—but we wanted to stress them out.

We humans were on the night shift because both of us had other things to do during the day. Kaufer was working on a doctorate in molecular neurobiology, and Friedman was an Israel Defense Forces physician and was often on call. What brought us together with the mice every evening was an attempt to understand a medical mystery: Gulf War syndrome. After the conflict ended in 1991, there were an increasing number of reports of soldiers from the U.S.-led coalition who were afflicted with chronic fatigue, muscle pain, sleep problems and cognitive deterioration, and those soldiers were hospitalized at higher rates than nondeployed veterans. Some doctors suspected that pyridostigmine, a drug that had been given to soldiers to protect them from chemical weapons, could cause these ailments if it made it into their brains.

There was a big problem with this theory, however: pyridostigmine in the bloodstream was not supposed to reach the brain. Blood vessels that course through this vital organ have walls made of specialized cells, packed very closely and with abilities to control what can get in and out. They form a shield that keeps toxins, pathogens such as bacteria, and most drugs safely within the vessels. This structure is called the blood-brain barrier, or BBB for short, and the drug should not have been able to pass through it.

Unless, however, the barrier was not intact. We wondered whether the physical and mental stress of combat might somehow trigger leaks in the shield. The swimming mice were our way of testing whether stress led to damage. When the swim session was done, we pulled each mouse from the pool and injected a drop of blue dye into one of its veins. Then we waited as the dye passed through its body, gradually turning the mouse blue. If the BBB was intact, the brain should have remained its normal pinkish-white color. We euthanized the mice so we could take a look at their brains under a dissecting microscope. Over several nights we had tried various lengths of swim time, but we had not seen any changes.

But on this night, after two dips in slightly colder water, things looked different: the brains had a strong blue tint! Lab work is usually tedious, and success is often subtle, but this time we were jumping up and down and hugging each other, giddy with excitement. Our weird experiment had worked. Stressful situations could make the BBB spring leaks. With our mentor, neuroscientist Hermona Soreq, we went on to show that such changes let in pyridostigmine and altered brain cell activity. We published these results in 1996 in *Nature Medicine* and in 1998 in *Nature*.

A quarter of a century later we can say that looking at these blue brains turned out to be a defining moment for both our careers, as well as the beginning of a lifelong friendship and scientific collaboration. Discovering the telltale blue tinge was the first step on a path that, over many years, led us to probe more and more deeply into the connection between other brain diseases and flaws in the organ's protective shell. Today pyridostigmine penetration is an important hypothesis for the cause of Gulf War syndrome, although there are other candidates. And our investigations have linked BBB damage—caused by aging or injury in addition to acute stress—to several more familiar illnesses: Alzheimer's and related dementias, epilepsy and traumatic brain injury. In two papers published in 2019 in *Science Translational Medicine,* we demonstrated that as people get older, this shield loses integrity and starts leaking, allowing blood proteins into the brain that normally do not get there. These proteins in turn activate a cascade of events among brain cells that can produce some of the most notable and widely seen changes associated with aging and illness: inflammation, abnormal neuron activity and cognitive impairment.

The cause-and-effect connection looks especially strong because stopping the reactions set off by these leaks actually reverses signs of disease, at least in rodents. In older mice, we can abolish the inflammatory fog with a targeted drug that protects brain cells from being irritated by blood proteins or by making genetic modifications that prevent those cells from releasing inflammatory molecules. Within days of the treatment the aged brains of these mice started to function more like young brains. Abnormal electrical activity subsided. Markers of inflammation dropped to low levels. When placed in mazes, the animals made their way through as quickly and accurately as young mice did. We cannot try the same experimental brain modifications in humans; it is not ethical. But we have been able to use imaging techniques to compare the brains of people with Alzheimer's with those of healthy people. The images show excessive and progressive BBB leaking in those with the disease, as well as other features of the illness-related cascade.

We do not yet know whether a damaged barrier is truly responsible for Alzheimer's or other brain illnesses. It could play a contributing role along with other causes, including genetics and a variety of cellular problems that have been observed in aging brains. Or it could be collateral damage. And experiments in mice often do not pan out in people. But right now the long-standing dominant theory for Alzheimer's—that it is triggered by a buildup of a protein called beta-amyloid in the brain—is looking less convincing than ever. Numerous experiments have reduced levels of this protein in the brain, yet the disease and associated mental decline in people remained unaffected. Drugs that target beta-amyloid have failed to help. Given that there are now 50 million people worldwide with dementia and another 10 million diagnosed every year, according to the World Health Organization, many scientists say it is high time to consider alternative explanations. If flaws in the brain's protective shield start a chain of events that leads to disease—a chain that experiments suggest can be blocked to restore brain health—it is a path of investigation worth pursuing.

FLAWS IN THE WALL

WITH "BARRIER" IN ITS NAME, the BBB sounds like a wall around the brain, but it is really more like a distributed filter. Our body's control center gets 15 to 20 percent of the oxygen-rich blood pumped out by the heart, delivered by an intricate mesh of blood vessels. They look different than vessels in the rest of the body, with walls made of tightly packed cells with specific molecular transport systems that form a semipermeable filter. Networks of brain cells need a carefully controlled environment to function, so this filter lets molecules such as oxygen and glucose get through but blocks blood proteins, certain ions, immune system cells and pathogens. This protective mesh extends throughout most areas of the brain, from the outer layers of the cortex, where higher-order cognition occurs, to deep places such as the hippocampus, which regulates memory storage. Problems with the filter can therefore lead to all kinds of neurological difficulties.

Back in the 1990s, as we were completing our initial work on Gulf War syndrome, we knew that other researchers had noted BBB damage in some brain disorders, including Alzheimer's. But we did not know whether this problem was a cause or an effect or how leaks in the shield get started and what they might do to alter brain function. We did, however, want to find out.

After our time working in Jerusalem, Kaufer went to Stanford University for her postdoctoral fellowship, and Friedman continued his medical training in Israel, specializing in neurosurgery. But time and distance did not let us forget. On a vacation together with our families, sailing between Greek islands, we caught up.

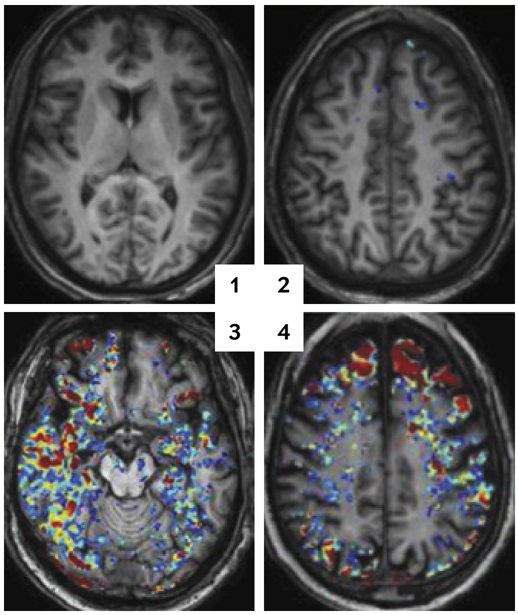
Kaufer was learning more about how stress affects the brains of mice in work at Stanford. Friedman, in his own practice, was reaffirming the early observations from other researchers who saw flawed BBBs in many patients suffering from very different neurological conditions. Just what was the damaged barrier doing?

We began to figure out the answer to this question in the mid-2000s, when we got the chance to work in Berlin with the late neuroscientist Uwe Heinemann of the Institute for Neurophysiology, part of the Charité Center for Basic Medicine. Heinemann opened his lab to our next key experiment. We wanted to observe brain function directly after the BBB started to malfunction, so we gave rats a chemical that essentially poked holes in the barrier and then dissected their brains. We kept the brain slices alive in nourishing fluid and used an electrode to record the electrical signals that the cells used to communicate with one another.

The first few days were boring. The neurons were giving off signals one after another in staccato, irregular patterns, "talking" as if nothing unusual had happened. We almost decided to give up. Then, on the fifth day, the cells' chatter patterns changed. More and more neurons started to pulse together in synchrony. After a full week we nudged them with a small signal from an electrode, mimicking a brief electrical message within the cerebral cortex. This nudge produced a storm of cells firing together, similar to what is observed in people and animals with epilepsy.

We think what happened with these cells is analogous to generating a Twitter storm. Imagine that you created a Twitter account today and tweeted some sensational statement. You would probably get a very small response because you would not have many followers. If in the next few days you built a bigger network of followers and tweeted again, however, the same statement would be likely to be retweeted, recruiting more followers who would also retweet it, eventually leading to a storm of tweets on the social media platform. Similarly, when we disrupted the BBB, neurons in the brain were not discombobulated right away, but after they had spent a week building a new network of connections, a small jolt prompted a big electrical storm. These patterns, which we call paroxysmal slow-wave events, are similar to activity seen by other scientists in the brains of people diagnosed with Alzheimer's and with epilepsy.

This storm happened only after we mimicked a BBB leak. Without one, our brain slices were untroubled by any electrical tempests. So we hypothesized that there was some element from the blood that was reaching these neurons to trigger the brain reaction. We tested this theory in a young, healthy rat with a normal BBB by injecting blood directly into its brain—bypassing the barrier—and monitoring electrical activity. It took several days, but again the storm built and exploded. Clearly, it had something to do with the blood. But blood is a complex fluid containing many different kinds of cells and proteins, so we set off on a painstaking filter-and-trap expedition to isolate the culprit. Eventually we found one blood protein that created the disturbances: albumin.



AGING BARRICADE: Brain scans, highlighting a colored tracer molecule in the blood, show more leaks in the blood-brain barrier as people age. A 30-year-old looks clear (*1*). At age 42, blue spots indicate small seeps (*2*). By age 65, red and yellow spots show bigger flows (*3*). At age 76, the pattern continues (*4*).

ALON FRIEDMAN AND DANIELA KAUFER

THE START OF TROUBLE

WE WERE NOT THRILLED with our catch. Albumin is very common and is involved in many bodily functions, so it was hard to isolate what it was doing in this situation. We would have preferred a rarer component. But albumin was what we got, so we dug in. Kaufer moved to the University of California, Berkeley, to run her own lab, and Friedman started his, first at Ben-Gurion University of the Negev in Israel and later at Dalhousie University in Nova Scotia. We planned a joint, long-distance series of experiments over several years to delineate the steps from BBB disruption and albumin leakage to the appearance of neurological disorders.

The first thing we learned was that when albumin gets into the brain, it appears to stimulate astrocytes, key brain cells that provide structural and chemical support for neurons and their connections. When albumin contacts an astrocyte, it binds to receptors that usually serve as docking stations for a molecule called transforming growth factor beta (TGFβ). Among other things, TGFβ activates astrocytes and sentinel cells called microglia to start inflammation. Normally, localized inflammation is the brain's way of limiting damage by destroying malfunctioning cells in a targeted assault. But if albumin continues to seep in, the astrocytes and microglia get hyperstimulated, and too many damaging chemicals get released, including an overabundance of TGFβ. Lots of brain cells get hurt, and key neural circuits are modified or weakened, so their functions deteriorate. Often doctors have observed this same destructive cascade in patients after traumatic brain injury; sometimes it leads to epileptic seizures.

The sequence shows up in the aging brain as well, as we learned by looking for it in mice. The animals typically live a bit more than two years on average. We allowed a colony of mice to age peacefully and looked inside their brains at various points. Albumin, we saw, was not in the brain at all in younger mice, but it began to show up in middle age. The effect was modest at first, but there was a clear decline in the integrity of the barrier, and it got worse as the mice got older. The affected mice also had more trouble remembering their way through mazes than did their younger and relatively albumin-free counterparts.

When the albumin showed up, other experiments showed us, TGFβ started to get active. We stained the brains in ways that

Mind the Gaps

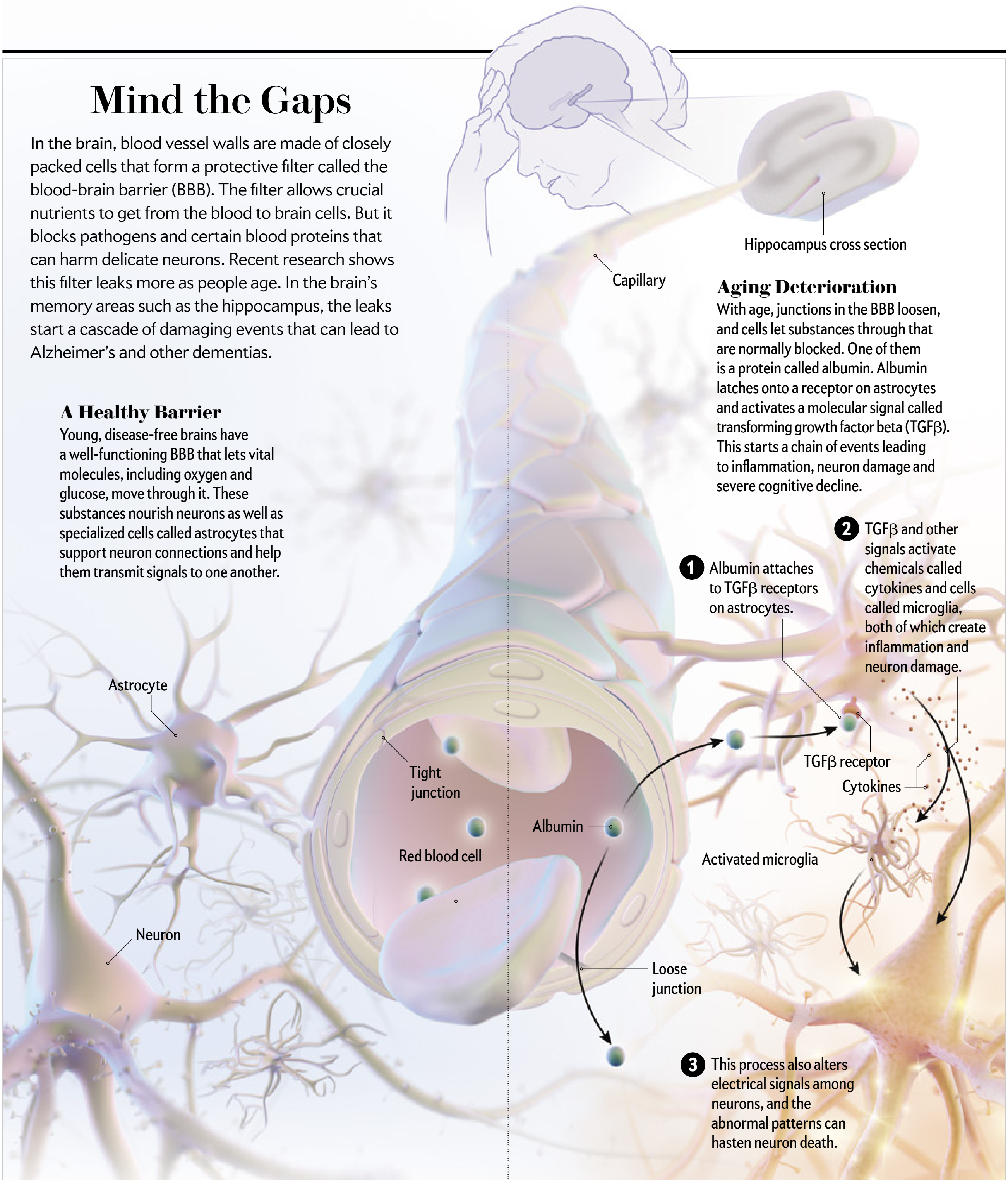
In the brain, blood vessel walls are made of closely packed cells that form a protective filter called the blood-brain barrier (BBB). The filter allows crucial nutrients to get from the blood to brain cells. But it blocks pathogens and certain blood proteins that can harm delicate neurons. Recent research shows this filter leaks more as people age. In the brain's memory areas such as the hippocampus, the leaks start a cascade of damaging events that can lead to Alzheimer's and other dementias.

A Healthy Barrier

Young, disease-free brains have a well-functioning BBB that lets vital molecules, including oxygen and glucose, move through it. These substances nourish neurons as well as specialized cells called astrocytes that support neuron connections and help them transmit signals to one another.

Aging Deterioration

With age, junctions in the BBB loosen, and cells let substances through that are normally blocked. One of them is a protein called albumin. Albumin latches onto a receptor on astrocytes and activates a molecular signal called transforming growth factor beta (TGFβ). This starts a chain of events leading to inflammation, neuron damage and severe cognitive decline.



Plugging the Leaks

Because albumin that gets through the barrier appears to start a sequence that ends in disease, scientists would like to stop this cascade. One approach would be to plug the initial breaches in the shield, but researchers have not yet demonstrated an effective way to do so (A). Scientists have interrupted the sequence later on, when albumin contacts astrocytes. In mice, an experimental drug called IPW blocks TGFβ receptors on those cells, so albumin cannot latch on (B). Researchers also have genetically altered animals so their astrocytes do not produce these receptors. Both approaches have made aged, damaged mouse brains look healthy again.

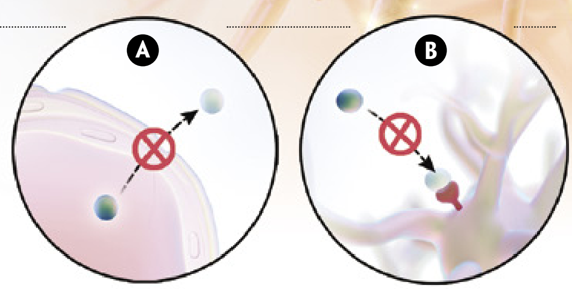


Illustration by Now Medical Studios

highlighted the activated form of the growth factor as well as the astrocytes that produced it. The inflammation related to TGFβ always started after albumin appeared, and it got worse as more of the protein leaked in. This pairing was especially abundant in the hippocampus, a brain area that is a key component in memory regulation.

Within the past five years or so we have been able to provide good evidence that this same process happens in people. We used tracer molecules to tag signals of barrier leakage in people in their mid-20s to mid-70s. With magnetic resonance imaging, we could see that the degree of these drips increased as people got older. Other researchers, such as Berislav V. Zlokovic of the University of Southern California Keck School of Medicine and his colleagues, used slightly different imaging methods to show barrier deterioration in aging people with cognitive impairment. In our work, we added autopsies of a separate group of people and showed that heightened albumin levels accompanied greater amounts of TGFβ, always in astrocytes. These concentrations were higher in older people and heightened as well in people who had died of Alzheimer's when compared with those without the disease.

BRAIN REJUVENATION

THEN WE REVERSED the deterioration in mice. We could not stop albumin from starting to seep through the BBB, but we could block the TGFβ cascade that came after the leaks. We developed a group of mice in which we genetically cut out the portion of DNA that tells astrocytes to produce TGFβ receptors, eliminating that feature from the cells. When the mice were still relatively young, we implanted a tiny pump in their brains that injected albumin. We did the same thing to a group of young, normal mice. Then we put both groups into a tricky water maze. (Watching mice swim seems to be a recurring theme with us.) The mice with receptors had a lot of trouble. But the animals without receptors swam the maze like young, healthy mice—speedily and accurately—and when we changed the maze configuration, they learned the new route, too. When we looked at their brains, we saw low levels of both inflammation and abnormal electrical activity.

This was really very encouraging. But for people, the option of knocking out a gene for a brain feature will not be available therapy any day soon. There is, however, another form of medicine. Barry Hart, a medicinal chemist at Innovation Pathways, a start-up drug company in Palo Alto, Calif., had designed an anticancer drug that specifically blocked the activity of the TGFβ receptor. Hart contacted us and suggested that we try the drug, called IPW, on our mice. (The three of us have since formed a company to further develop the medication.)

When we gave the drug to middle-aged mice—the ones that were starting to show albumin leakage—we learned that it made their brains look young again. TGFβ activity dropped to levels seen in youthful mice, markers of inflammation went way down, and abnormal electrical activity and seizure susceptibility diminished.

But the big surprise came when we tested actual behavior and cognition. We set up another maze, and this time we ran older mice through it. Some of the aged animals were treated with IPW, and some were not. We did not predict a lot of improvement, because we thought irreversible damage had already been done. (Our mice without the TGFβ gene had been spared the long months of deterioration inflicted by the inflammatory cascade, but these animals had not.) Within days, however, the treated mice were almost as good at learning the maze as rodents half their age. The untreated mice just shambled along as usual. Moreover, the mice that got IPW showed no sign of the "Twitter storm" effect that we typically see in humans with Alzheimer's or epilepsy and not much evidence of inflammation. It was as if an inflammatory fog had lifted, allowing the brain to regain its youthful abilities. These, along with the studies of human brains, are the results we published in 2019 in *Science Translational Medicine*.

The maze outcome was so unexpected, even to us, because, like most people, we had considered aging damage as a one-way trip—deterioration that cannot be undone. That is probably the case for major brain trouble, such as the havoc that occurs in Parkinson's disease or in advanced Alzheimer's after so much beta-amyloid has accumulated that it kills off swaths of neurons and other cells. But our intervention research may indicate that in the absence of a lot of cell death, the aging brain has a hidden capacity to rebound from some types of insults.

And our findings have implications for acute injuries as well, not just gradual deterioration. Treating rodents with IPW after concussions or traumatic brain injury alleviated the inflammation, seizures and cognitive decline that they developed. Animals that got a neutral placebo drug were not helped.

FIXING THE DAMAGE

THE WORLD POPULATION IS AGING, and the number of people with dementias and Alzheimer's is on the rise. We are aging, too, so this is personal. Both of us are about 50 years old, and our dinner conversations with friends often revolve around our concerns with our aging bodies (some of us used to run marathons and now cannot even finish a Zumba class) and brains (Kaufer cannot remember the names of the parents in her daughter's class at school). Neuroscientists have a poor understanding of the early triggers of this transition from a young, healthy brain to an old, dysfunctional one. Alzheimer's and other neurological diseases of aging are complex and can have many causes.

Now a leaky BBB has to be considered as one of them. This barrier-breach theory provides a remarkably intuitive and straightforward new model to understand why the brain declines with age. And it is a model that gives us optimism: the results of our work strongly hint that the aging brain retains a capacity for reshaping and restoring itself, an ability that may be suppressed, but not irreversibly lost, by persistent leakiness and the ensuing chain of events.

The next step for us and for other scientists is to look for strategies and therapies to reduce barrier leakage. In the past, pharmaceutical research into the barrier focused on ways to increase permeability, not limit it, to get more drugs across it to treat brain tumors or infections. Our results show that it is time to flip the question: Can we come up with ways to stop the shield from degrading, stop harmful substances from getting across, or at least interrupt the fall of molecular dominoes if they do? There is a chance to do a lot of good for a lot of people if we can figure these things out. SA

FROM OUR ARCHIVES

The Way Forward. Kenneth S. Kosik; May 2020.

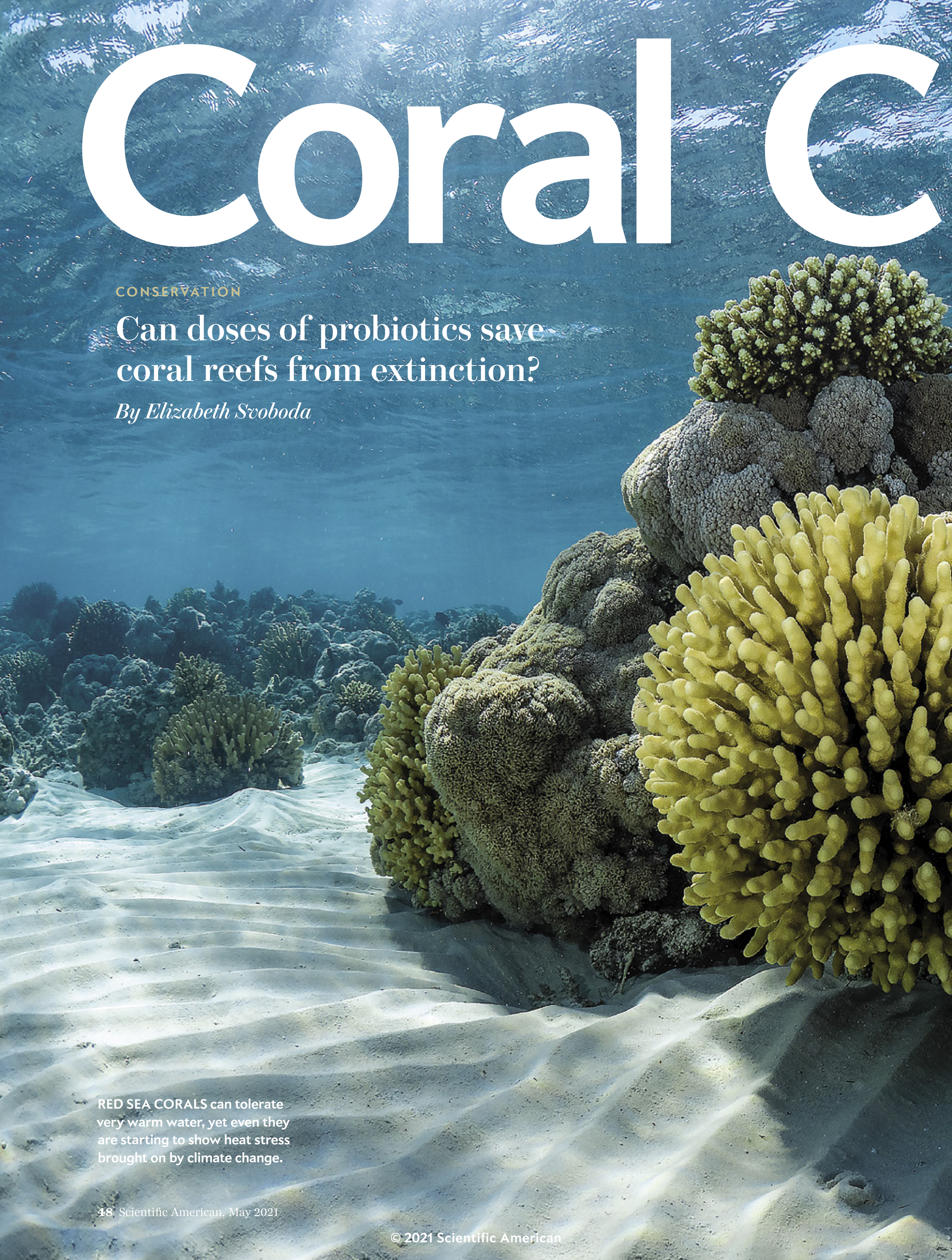
scientificamerican.com/magazine/sa

Coral C

CONSERVATION

Can doses of probiotics save coral reefs from extinction?

By Elizabeth Svoboda



RED SEA CORALS can tolerate very warm water, yet even they are starting to show heat stress brought on by climate change.

ocktails

Elizabeth Svoboda is a science writer in San Jose, Calif., and author of *What Makes a Hero?: The Surprising Science of Selflessness* (Penguin Group, 2013).

Manta rays and whitetip reef sharks glide past socially distanced visitors

at Rio de Janeiro's hangar-sized AquaRio aquarium. In a laboratory upstairs, above the main gallery, a new experiment is underway, one that marine scientists hope will enhance the survival prospects of the world's coral reefs.

Twenty rectangular aquarium tanks, each about 20 centimeters wide, are arranged in a grid on the fourth floor. Each one houses a colorful assortment of coral fragments. The researchers will treat some tanks with cocktails of probiotics, a mix of bacteria designed to promote resilience under tough conditions.

Researcher João Rosado draws murky liquid into a pipette, then stands over the first tank and carefully depresses the plunger, squirting the mixture into the seawater. "Can you see that, like smoke?" says Rosado's colleague Pedro Cardoso of the Federal University of Rio de Janeiro, through his face mask. "Those are the bacteria." Cardoso is talking to me over a live video feed the team set up so I could witness the proceedings remotely. The gray bacterial cloud surrounds the coral like a shroud, settling on it. Later, Rosado will treat other tanks with probiotic-filled rotifers—microscopic marine animals that corals eat with their tiny mouths. Corals in a third set of tanks will get both treatments, and those in a fourth set will get none. The investigators will probe the various corals over the coming weeks to see if any of the regimens improve coral health.

The use of rotifers is a new attempt to get "good bacteria" to corals in distress. The results from the December 2020 experiment will help inform biologists' intention to apply probiotics to reefs in the wild in hopes of improving their chances of surviving the high temperatures and disease outbreaks that are overwhelming them. Rosado and Cardoso's trial—led by marine biologist Gustavo Duarte—builds on work by their mentor, Raquel Peixoto, who published the first probiotics experiments in 2015. She is a leader of the audacious and controversial rescue plan to administer probiotics in the ocean, which could change the ecosystem. Peixoto will apply probiotics in the Red Sea later this year, and conservation groups are eagerly exploring the concept. Although Peixoto and her contemporaries have conducted many lab experiments and will carefully restrict the first open-ocean tests, she says corals are so threatened it is "time for us to take some risks."

Coral reefs cover nearly 285,000 square kilometers of ocean floor worldwide. They are largely concentrated into a dozen major chains, but they exert a global influence on marine and human life. Almost a quarter of marine species spend at least some part of their lives there. The reefs dampen storm surges and waves that can tear apart shorelines. They feed millions of people and account for almost $20 billion annually in global tourism.

Yet the world's corals are in a state of possibly terminal decline. Scientists first observed mass coral bleaching—a sign of starvation—in 1983, and by the 1990s they had started to link bleaching to changing sea temperatures. Between 1987 and 2019, oceans warmed 450 percent more than they did between 1955 and 1986. Since 1980, 94 percent of coral reefs have experienced at least one episode of severe bleaching. The Great Barrier Reef has suffered three such events in the past five years. A report from the United Nations Environment Program estimates that largely because of ocean warming, most of the planet's reefs will suffer annual severe bleaching by 2034 and, without intervention, will be gone entirely by 2100. Global reef death most likely will continue even if countries begin to get their carbon emissions under control. To reverse the trend, "we have a very narrow window of time—basically a decade," says Carlos M. Duarte, a marine ecologist at King Abdullah University of Science and Technology (KAUST) in Saudi Arabia. "The window is rapidly closing."

Scientists developing probiotics see the treatments as more than a stopgap to postpone reef death. They think probiotics have a real chance to reverse some damage that has already been done, enabling once threatened corals to flourish and strengthening new human-bred corals that are transplanted onto ailing reefs. "It sounds so radical," says Rebecca Vega Thurber, a marine microbial ecologist at Oregon State University. But, she adds, "with proper experimental design and application, it could be helpful."

Big questions still need answers. When applied at sea, will probiotics wash away? Would the labor-intensive techniques cost huge sums of money when tried across reefs hundreds of kilometers long? And even the most avid backers acknowledge the risk they are running. In some ways, reef treatments sound a bit like geoengineering—sprinkling iron into the sea to

PRECEDING PAGES: MICHAEL BERUMEN AND MORGAN BENNETT-SMITH

BLEACHED CORALS, such as these on the Great Barrier Reef outside Cairns, Australia, are vulnerable to starvation and disease that can lead to death.

BRETT MONROE GARNER *Getty Images*

encourage growth of algae that soak up carbon dioxide or spraying aerosols into the air to reflect the sun's rays back to space, lessening global warming. Seeding reefs with bacteria might alter the ocean ecosystem at a fundamental level.

Some experts worry that certain bacteria could accidentally spawn new coral disease outbreaks, a possibility that arose in a recent lab test. And no one knows exactly how the treatments will affect ocean life further up the food chain, such as fish and crabs that feed on coral polyps.

As with climate change, however, the global prospects for reefs have become so dire that many conservationists think extreme fixes are needed. "It's not a good position for scientists to be [in]," says Peixoto, now a marine microbiologist at KAUST. But she says the decision is clear. "We have to act. Otherwise, it's going to be too late."

REEF REPAIR

RESEARCHERS HAVE BEEN TRYING to restore damaged reefs since the 1970s. In 2000 Baruch Rinkevich of Israel's National Institute of Oceanography started one of the first nurseries to raise young corals and transplant them onto reefs that had suffered damage from fishing, diving or storms.

Scientists started looking into specific fixes for bleaching a few years after that. In 2010 researchers at Florida's Mote Marine Laboratory showed that by chipping fragments off of healthy corals in lab tanks they could trigger a Herculean growth response that promptly turns those fragments into full-fledged baby corals. (Corals can reproduce sexually by releasing eggs and sperm into the ocean or asexually by budding—essentially, cloning.) In 2018 and 2019 researchers in Mexico and Israel used the Mote team's strategy to generate coral fragments and transplant them onto reefs just off Mexico's Pacific coast. The new corals that grew from them showed an impressive survival rate of about 60 percent, despite the damaging effects of Hurricane Willa. On Florida's reefs, corals the Mote team has grown from fragments merged into larger colonies that in 2020 began successfully spawning in the wild.

Breeding is another strategy. Since at least 2015 researchers at the Australian Institute of Marine Science (AIMS) and elsewhere have been trying in labs to selectively breed so-called super corals, which carry genes that help the animals withstand stress. Teams at the institute and the University of Hawaii's Gates Coral Lab are creating these ultraresilient corals using "assisted evolution," which involves selecting wild corals with desirable genetic traits, such as the ability to survive high ocean temperatures, then cross-breeding them to yield offspring with an abundance of the traits. In a 2020 lab study at AIMS, temperature-tolerant corals created this way proved up to 26 times more likely to survive extreme heat than other corals.

Yet another approach to helping corals is to enhance reproduction. In 2017 a team at the California Academy of Sciences, the Nature Conservancy and SECORE International, a conservation organization, began catching the eggs and sperm that

RESEARCHER Kelly Pitts applies a paste laden with a single probiotic onto corals off the Florida coast in hopes of helping the animals fight stony coral tissue-loss disease (*1*). On a different dive she pumps a liquid form onto corals nearby (*2*).

healthy spawning corals release in the wild on rare but predictable nights. The researchers complete the fertilization in the lab, then transplant larvae onto needy reefs.

These techniques share a daunting drawback: restoration workers have to manipulate corals in a lab and refine ways to transplant them onto struggling reefs, a slow and costly process. It could be quicker and more affordable if a therapeutic could be administered directly to ailing corals in the wild. That prospect helped to lead researchers such as Peixoto to probiotics. And, theoretically at least, selectively bred lab corals, or chipped fragments, could also be treated with probiotics to make them more resistant to heat and disease before they are transplanted in the sea.

Coral formations are constellations of thousands of animals called polyps, each often smaller than a pinky fingernail. Every polyp hosts a variety of bacteria, algae, fungi and other microorganisms, collectively known as its microbiome. Like microbes in the human gut, these tiny residents carry out tasks that keep the whole system functioning. In recent years metagenomic analysis—sequencing the genes of the microbes on a polyp—has supplied a clearer picture of which tasks the microbes are performing. Scientists at the Massachusetts Institute of Technology, the Woods Hole Oceanographic Institute, and elsewhere have isolated bacteria that consume excess nitrogen, preventing nearby algal blooms that starve coral of nutrients. Other microorganisms degrade reactive oxygen species—molecules that damage coral cells—or help corals capture carbon for energy. Much as microbes in the human gut help to break down food, contributing to our nutrition and health, researchers theorize that beneficial coral microbes make the hosts more resilient to environmental stresses by supporting their overall health and warding off polyp disease and tissue loss.

As ocean temperatures rise, however, the microbial relationships within corals start to break down. Scientists at Oregon State University have found that bacterial communities on stressed corals often become unstable, potentially giving disease-causing microbes a chance to spread. Warming oceans, together with ocean acidification caused by higher carbon dioxide levels, also disrupt the microbe-aided calcification process that gives corals their structure, making it harder for them to repair damage. At the same time, stressed polyps expel their *Symbiodinium* algae, which turn sunlight into food for polyps, leaving them without a food source. This gives corals a characteristic bleached appearance that biologists recognize as a sign of doom because bleached polyps are also more vulnerable to disease. Peixoto has witnessed this alarming transformation firsthand.

HUNTER NOREN, NSU, GIS AND SPATIAL ECOLOGY LABORATORY (*1*, *2*)

2

aquarium temperatures and resist disease.

One of Peixoto's newest experiments, being reviewed by journals, goes deeper, appearing to show distinct mechanisms that probiotics may use to enhance corals' health. Her team in Brazil placed four finger-length coral segments in each of 20 small tanks and assembled a cocktail of six bacterial strains from healthy *Mussismilia hispida,* a common South Atlantic coral. Every few days they removed a few segments, dripped a dot of probiotics onto their surfaces, and returned them to the tanks. Next they raised the water temperature on half the tanks.

The results weeks later were dramatic: more than a third of the control corals had died, but almost all the treated corals were alive. Detailed analysis revealed multiple ways the probiotics appeared to promote health. The treated corals less strongly expressed genes linked to inflammation. They also showed less gene activity related to cell death. That means corals "can even bleach, but it's not to the extent that they lose tissue," Peixoto says. "The probiotics provide them with this kind of buffer." That buffer could give other restoration measures—such as super-coral breeding or spawning baby corals from fragments—a better chance to work. The right probiotics applied in the lab before transplantation could potentially increase the corals' odds of survival.

A DISINTEGRATING UNIVERSE

AS A KID ON VACATION, Peixoto snorkeled the Brazilian reefs near Bahia, entranced by the vivid universe beneath her. On dives as an adult, she saw that universe disintegrating. Corals were turning into lifeless skeletons; the ones that were hanging on looked wan and sickly. "Every year is getting worse," she says. "You dive and see 90 percent of the species dead." Peixoto resolved to do something transformative, something that could revive wild corals. "We want to protect the diversity already there in the reef," she says, "to make sure colonies can survive."

She had a novel starting point in mind. In a 2010 experiment aimed at developing an alternative to the hazardous chemicals used to clean up oil spills in Brazilian mangroves, her team demonstrated that oil-sucking bacteria could break down the oil and promote plant health and growth. What if she could summon concentrated bacterial reinforcements to protect coral reefs? No one had tried probiotics, but she had a hunch they might work.

As a first move, Peixoto harvested tissue and seawater from the surfaces of local corals. Then she sequenced the bacterial genes in that mix to find species that carry out functions promoting survival. She grew the native microbes in culture and mixed bespoke cocktails for each reef environment. Her work paid off in late 2018, when she and her colleagues published a study showing that their tailored probiotic blend helped corals survive hot

THE FIRST FIELD TRIAL

ON A CRISP DAY in January 2020, scientists at Florida's Smithsonian Marine Station applied a probiotic to coral in the ocean, the first time that had been tried. The probiotic, which they had been developing for three years, wasn't a broad-spectrum blend like Peixoto's. It was designed to counter a specific threat, one of the gravest to Florida's reefs: stony coral tissue-loss disease. Researcher Kelly Pitts, who had joined the team in 2019 after working on antibiotic treatments at Nova Southeastern University, wanted to test probiotics as a more natural aid for coral health. She donned her oxygen tank and fins and descended from a small boat onto a reef ringing Florida's eastern coastline off of Fort Lauderdale. At roughly nine meters deep, as Pitts tells the story, a clear plastic bag about half a meter across and pinned to the seafloor came into view, enclosing a coral formation like a dome.

The target inside was a great star coral that was more than a decade old (colonies can thrive for decades or even centuries). Some of the polyps were still a vibrant orange, but others had faded to khaki, a sign they might have been ravaged by stony coral tissue-loss disease. Pitts snaked a flexible tube under the dome's edge, then attached a bacteria-filled syringe to her end of the tube. As she lowered the plunger, murky white liquid bloomed in the dome, thick enough to obscure the coral.

Pitts was excited but anxious. Her team had been testing its probiotics in tanks for months, but being out on the reef was completely different. What if the mixture escaped the bag? She felt the same apprehension during another test months later when she squeezed a probiotic gel, like toothpaste from a tube, onto a coral on the seafloor that was fully exposed to the water, no bag to encapsulate it. When the paste stuck fast to the coral despite surrounding water currents, her nervousness gave way to elation, and she laughed with joy, clapping her hands underwater.

Stony coral tissue-loss disease, which eats through polyps like acid, had laid waste to more than 96,000 acres of reef in Florida and the Caribbean since 2014. The disease—suspected to be bacterial—was spreading unchecked, killing large formations within weeks or months. By 2017 quelling the outbreak had zoomed to the top of the priority list for Florida conservationists. Using rapid gene sequencing, the Smithsonian Marine Station researchers identified a strain of *Pseudomonas* bacteria, present in small quantities on local corals, that produced the marine antibiotic korormicin. In aquarium tests, concentrated doses of the probiotic bacteria kept the disease at bay.

During lab tests the researchers applied the bacteria to a range of corals from the broader reef to be sure it would not harm any healthy species. In a rush to get the disease under control, Florida researchers had been dosing corals with antibiotics such as amoxicillin since 2018—a drastic measure that was also killing scads of beneficial bacteria. Pitts hoped probiotics could get around that indiscriminate injury.

In late 2019 the Smithsonian team secured the state permits needed to plunge into ocean trials. Researchers were cautious and were mindful of the need to start small, but the disease was spreading so fast local conservationists were in favor of the proposed test run.

During the January 2020 field trial and another in September 2020, Pitts and her colleagues treated 14 coral formations using the dome method and seven others with the paste. When the team did an initial survey of the reef two weeks after the January trial, the disease's progress had stopped in about 80 percent of the treated corals. Some of their patchy lesions were also beginning to heal. The growing COVID-19 pandemic, however, caused scientists to pause trials for a time.

Peixoto admits she gets impatient with people who call for too much caution: "If we don't do anything, the corals will die."

UNINTENDED CONSEQUENCES

ALL MICROBIOLOGY IS CONTEXTUAL. Changing the concentrations of one "beneficial" type of coral bacteria can affect other key bacteria in the microbiome in ways that are hard to predict. For skeptics of coral probiotics, this complexity and unpredictability is a source of unease. "Maybe the function is temporarily good," Vega Thurber says. "But it could easily switch to be something that has a negative effect."

Hawaii Institute of Marine Biology molecular ecologist Ty Roach, who has done his own probiotic lab tests, worries about irreversibly changing a coral microbiome or an entire marine ecosystem. "The more I've tinkered with it, the more I'm concerned," he says. In one unpublished study of his involving about 130 finger-length *Porites* corals in a dozen three-gallon tanks, some of the corals died of disease after his team inoculated them with a dose of their own native bacteria (not a tailored cocktail like those Peixoto makes). The first trouble Roach noticed was that certain corals formed thick sheets of mucus on their surfaces, as if they were irritated. Then small patches of polyp tissue started to die, like spreading canker sores. Roach was alarmed but not surprised. The coral's natural bacterial mix includes microbes from the *Staphylococcus* genus, which is known to cause disease in humans.

Roach adds that there is scant peer-reviewed research that describes the exact biological mechanisms by which probiotics might protect coral hosts. "We've been able to make some corals withstand a little more heat," Roach says. "How that works is very unclear." And he wonders whether the treatments will affect other marine life. "A lot of other organisms are in direct interaction with these corals on the reef," he says, including fish, algae and crustaceans. University of Derby aquatic biologist Michael Sweet, a longtime colleague and friend of Peixoto's, supports probiotic methods if they can be proven safe. But he also echoes Roach's concerns: "I don't want to be the one responsible for releasing a superbug into the environment that becomes the next coral disease."

How often probiotic treatments should be applied is also unknown. Human probiotics for digestive disorders often need to be taken every day or even twice a day. Researchers can only guess if applications, say, once a week or once a month would be enough to create a resilient microbial equilibrium.

Risk is just one practical consideration. At this stage, the cost of applying cocktails across an entire reef is hard to calculate. Peixoto says a little of the mixes she has created goes a long way, but it might cost up to $600 to $700 to treat one square kilometer of reef, assuming trained divers apply the probiotics (and assuming they have a dive boat of their own). An application might protect corals from heat damage for up to a month. On a wide scale, robots built for applying the compounds would be less expensive than human divers, she says.

Sweet recently reported that creating lab-grown corals through assisted evolution—transplanting them on a reef and monitoring them—would cost between $49 and $227 for each coral colony. Reefs often have tens of thousands of colonies per square kilometer. If probiotic bacteria were added to the lab-grown corals before transplant, the added cost "would be low," Sweet says. But "if we need to redeploy the probiotics regularly, it could become an expensive method."

Yet Roach and Sweet also know that reefs are in such peril that conservation funders will likely forge ahead with probiotics in the wild. "If there's one thing we've learned," says marine biologist Crawford Drury, Roach's Hawaii colleague, it is that

MARINE SCIENTIST Raquel Peixoto tests probiotics in the lab. She plans to apply a multistrain bacterial cocktail in the Red Sea this year to help corals fend off bleaching.

“if we start losing reefs, the willingness to do something extreme skyrockets.”

Indeed, big organizations are embracing the idea. The World Wildlife Fund in Brazil, which is financing some of Peixoto’s research, is optimistic about the technique’s prospects. In Brazil, the massive reef bleaching event of 2019 “turned the key” to exploring newer conservation options such as probiotics, says Vinicius Nora, a WWF Brazil conservation analyst. Australia’s Great Barrier Reef Foundation, which has committed hundreds of thousands of dollars to probiotics research, also sees Peixoto’s treatments as a promising way to fortify lab-grown coral intended for transplant. Foundation officials are working with Peixoto and Australian scientists to include probiotics in future restoration projects if further small-scale tests go well. “It’s a catch-up that we’re having to do,” foundation biologist Ove Hoegh-Guldberg says. “You’ve got to jump in with boots on and test a few ideas.”

RADICAL DETERMINATION

PEIXOTO UNDERSTANDS her critics’ concerns. To help ease some minds, including her own, she is planning contained experiments this year at the 700-square-meter artificial ocean in the University of Arizona’s Biosphere 2. The tests will give a clearer look at how probiotic treatments might affect other ocean life. Still, she doesn’t spend a lot of time second-guessing her course. She admits she gets impatient with people who call for too much caution. She feels a moral obligation to use all means to save reefs. For Peixoto, that means deploying coral probiotics in oceans very soon. “If we don’t do anything,” she says, “they will die.”

Her next act will be staged at KAUST, which sits on a spit of Saudi Arabian coast that curls into the Red Sea like a lobster claw. From the docks, Peixoto can step into her dive boat and motor out to a shallow reef 10 minutes away, where schools of golden butterflyfish cruise over decades-old coral monoliths on the seafloor.

RAQUEL PEIXOTO KAUST

Because Red Sea reefs have thrived for years in high-temperature water, bacteria that limit heat damage here could help scientists learn how to confer heat resistance onto ailing corals elsewhere. The reef, Peixoto says, “is like my vault. I go there and get the gold.” Yet even stalwart Red Sea corals are starting to show signs of stress. A bleaching event devastated sections of reef in 2020, and experts fear worse is to come. Peixoto is fine-tuning a blend of bacteria she hopes to apply on the reef this year, while still ramping up experiments in Biosphere 2. The trial will be the first time she and her team test probiotics in the ocean.

Some Red Sea reef formations are separated by long stretches of empty seafloor. This will make it easier for Peixoto to apply probiotics to one formation while leaving the next-closest ones untouched. “These will be very small and well-controlled experiments,” she says.

Even so, the test will be a different approach than what the Smithsonian team used in Florida. The Smithsonian’s treatment was a single microbe deployed to treat a specific coral disease. Peixoto will dose corals with a multistrain cocktail that has a much broader aim—to fortify corals against bleaching and the ill health that follows. As in the past, Peixoto will isolate beneficial microbes from local corals and mix them into a custom slurry. She will exclude any groups of bacteria known to cause disease and will first conduct detailed risk assessments in tanks at the university to make sure the cocktail does not cause any adverse coral health effects in a small setting.

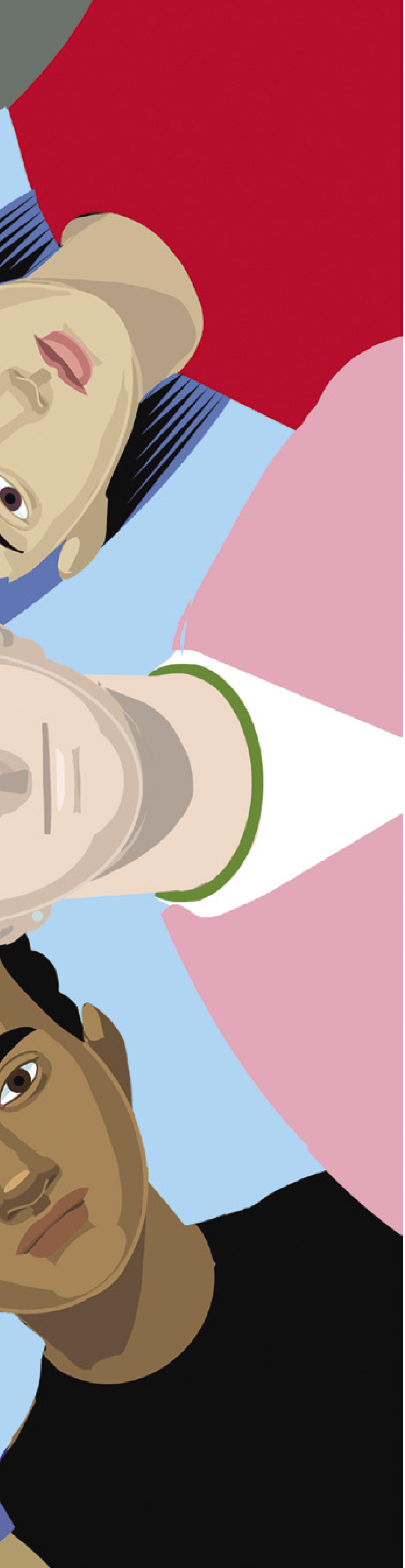
If that test goes smoothly, she will eventually apply her mix to several reef formations, about two square meters each. The microbes will be delivered via strips of time-release, water-resistant adhesive that sticks to the corals or to nearby sediment. After a few weeks Peixoto will assess how the health of treated corals compares with that of controls. Periodic checks will continue for a year, and throughout the process she will monitor nearby fish and other large organisms such as sponges for unintended bacterial effects.

Peixoto recognizes the magnitude of this next act, but the widening coral ghost towns she sees on her dives have strengthened her commitment to err on the side of radical intervention. She is an optimist, with an innovator’s faith in the power of bioremediation. She knows some people might call her hasty. Yet Peixoto and others think bold intervention is simply required now. “If we develop all the technologies, we can still have beautiful reefs,” she says, “rehabilitated reefs that can thrive.” Without that targeted assistance, she sees a long undersea dark ages ahead. SA

FROM OUR ARCHIVES

Diving in Coral Gardens. Roy Waldo Miner; September 1934.

scientificamerican.com/magazine/sa



MIND

age of oppor-tunity

A refined understanding of the adolescent brain could lead to improvements in education and mental health

By Lydia Denworth

Illustrations by Alison Seiffer

Lydia Denworth is a Brooklyn, N.Y.–based science writer, a contributing editor for *Scientific American,* and author of *Friendship: The Evolution, Biology, and Extraordinary Power of Life's Fundamental Bond* (W. W. Norton, 2020).

HERE IS A PARABLE FOR OUR TIME: THERE ONCE WAS AN ADULT WHO wanted to encourage eighth graders to eat healthier food. The adult designed a lesson plan full of nutritional information—why fruit and vegetables are good for you, why junk food is bad for you, and so on. A similar approach had worked with younger children. But the eighth graders declared the intervention—and, if we're being honest, the adult—boring. They carried on eating junk food, some of them in greater quantities than they had before.

Versions of that story play out in real life all the time, although the age of the adolescents varies, and the goal could be anything from reducing bullying or depression to increasing engagement with math. With discouraging regularity, researchers find that what works with younger children is no longer effective with adolescents. Eighth grade seems to be the inflection point.

If we thought more carefully about what it is to be an eighth grader, however, down to the level of changes in the brain, our parable could have a happier ending. Thirteen-year-olds are concerned with status and respect—these kids do not want to feel patronized by adults. In a study published in 2019 in *Nature Human Behaviour,* instead of nutritional information, researchers showed more than 300 eighth graders in Texas investigative reports revealing that food company executives use unhealthy ingredients, target young adolescents in their marketing, and won't let their own children eat their products. The students were outraged and began to see healthy eating as a way of taking a stand against being manipulated. For the next three months the students made healthier snack purchases in the cafeteria. And in a follow-up study, the researchers found that the students, especially boys, with higher levels of testosterone (a marker of pubertal maturation in both boys and girls) were most likely to respond well to the intervention.

Over the past 15 years neuroscience has dramatically changed our understanding of the structural and functional changes in the brain during adolescence, which runs from around the age of 10 all the way into the mid-20s. It is a time of rapid brain growth and neuronal fine-tuning when young people are especially sensitive to social cues and rewards. More recent research has focused on how the adolescent brain interacts with the social environment. It shows that social context and acceptance strongly influence behavior. Adolescence might even constitute a sensitive period for social and emotional learning, a window of time when the brain is uniquely primed by neurochemical changes to make use of social cues for learning.

A growing group of researchers and clinicians see these neuroscientific findings as a chance to do things differently. When a young brain is looking for experience, teachers, parents and other influential adults should seek to capitalize on the richness of learning and stave off negative experiences such as smoking or drug use. This was a central idea in the 2019 National Academies of Sciences, Engineering and Medicine report on the promise of adolescence, which called for investments in programs and interventions that use the brain's capacity to change during adolescence to promote beneficial shifts in young people's life trajectories.

A sensitive period for social and emotional processing also suggests that certain phases of adolescence may be more opportune than others for certain approaches. Early adolescence in particular—from roughly age nine to 11—could be an opportunity to launch kids on a positive path by buttressing their sense of self and motivation to learn. The nutrition experiment shows the benefits of fine-tuning interventions for middle adolescents, who have been through puberty. And no one wants to suggest that it's ever too late to help young people in trouble, especially given that the most serious behavioral and health problems of adolescence tend to occur at 16 and beyond.

To meaningfully compare the results of which interventions work best at age 10 or 14 or 18 requires extensive longitudinal studies, which have not yet been done. Even so, the advances in developmental science appear poised to lead to wiser, more effective approaches to supporting young people's education and physical and mental health. These new methods emphasize adolescents' concern with status and respect, their evolving sense of self in relation to the wider world, and their need to contribute and find purpose. Similar ideas already underpin the growing interest in social and emotional learning among educators. Rather than focusing on the storminess of the teenage years, these ideas offer a sunnier view of adolescence as a window of opportunity.

RETHINKING ADOLESCENCE

FOR DECADES much of the research on adolescence focused on its dark side. Although those years are the physically healthiest period in life, when strength, speed, reaction time, reasoning abilities and immune function all improve or peak, adolescence also brings alarming increases in rates of accidents, suicide, homicide, depression, alcohol and substance use, violence, reckless behaviors, eating disorders, obesity and sexually transmitted disease compared with the rates for younger children.

But a different interpretation of adolescence emerged in the 2000s, stemming from two important new findings. Neuroscientists showed that puberty ushers in a period of exuberant neuronal growth followed by a pruning of neural connections that is second only to the similar process that occurs in the first three years of life. They also showed that the maturation of the adolescent brain is not linear. The limbic system, a collection of brain areas that are sensitive to emotion, reward, novelty, threat and peer expectations, undergoes a growth spurt while the brain areas responsible for reasoning, judgment and executive function continue their slow, steady march toward adulthood. The resulting imbalance in the developmental forces helps to explain adolescent impulsivity, risk taking, and sensitivity to social reward and learning. From an evolutionary sense, much of adolescents' behavior pushes them to leave the safety of family to explore the larger social world—a step on the way to becoming independent adults.

Another line of research, from the human connectome project, shows that adult brains vary in their patterns of neural connections throughout the brain, whereas children's connectomes are less distinctive. Those differentiated patterns of connection emerge in adolescence—between the ages of 10 and 16, just when social values and cognition are developing quickly. And the changes in the connectome data show up on average a year to a year and a half earlier in girls than in boys, just like puberty does, which suggests that the two things are intertwined.

The idea that adolescence might constitute a sensitive period for social and emotional processing was put forward in 2014 by neuroscientists Sarah-Jayne Blakemore and Kathryn Mills, now at the University of Cambridge and the University of Oregon, respectively. Previous research had assumed that social-cognitive abilities such as theory of mind were mature by the middle of childhood, but Blakemore and Mills laid out the many continuing changes across adolescence in social cognition and the network of brain regions governing social behavior.

Sensitive, or critical, periods are windows of time when the brain is primed to make specific neural connections that depend on the input received. They are timed to when important information is available and most useful for development. For sensory processing such as vision and hearing, such periods are well defined with an opening, peak and closing. A brain deprived of sight or sound early in development will never be able to see or hear normally. Likewise, a sensitive period for language acquisition explains why people who learn a foreign language after puberty typically have an accent. Sensitive periods for social learning have been harder to pin down.

During adolescence the brain may be uniquely primed by neurochemical changes to make use of social cues for learning.

Animal research has identified some versions of sensitive periods for social learning. Songbirds can delay the closing of the sensitive period for vocal learning if they need more time to learn their songs, which usually happens in adolescence. "It's a gorgeous example of a sensitive period for learning that has social function," says Linda Wilbrecht of the University of California, Berkeley, who has studied sensitive periods in songbirds, mice and humans.

Neuroscientist Gül Dölen and her colleagues at Johns Hopkins University identified an adolescent critical period in mice for something called social conditioned place preference (social CPP). The research followed up on an observation by the late Estonian neuroscientist Jaak Panksepp. He presented mice with two different kinds of bedding—on one, the mice were alone; on the other, they were with friends. When the mice subsequently had a choice of bedding, adolescents, in particular, showed a preference for the bedding that carried a memory of friends.

Dölen ran similar experiments with roughly 900 mice at 14 different ages and mapped out exactly when this preference for place occurs. Triggered by changes in oxytocin that lead to increased synaptic plasticity, it peaks 42 days after birth (roughly age 14 in humans), when the mice become sexually mature. "It's a really important stage of their lives when they're leaving the nest and trying to create their own groups," Dölen says. "[In] that window of time, when they're really sensitive to what other members of their group are doing, when they're learning from their group, when they're forming attachments to the group—that's when that peaks." It seems the brain is suddenly alert to and rewarded by information that it had previously ignored. "There's information flowing by us all the time," Wilbrecht says. "Once puberty and hormones pass through the circuit, suddenly those cues have meaning. They don't have salience until you shift into the adolescent phase."

PRIMED FOR LEARNING

THESE WINDOWS of rapid change create both learning opportunities and vulnerabilities. What adolescents are learning is all-important. "The adolescent brain is primed for social and emotional learning, to explore, to interact, to take chances so they can learn, but it all depends on what we do to give them scaffolded opportunities in order to learn," says psychologist Andrew Fuligni of the University of California, Los Angeles. Harmful experiences may lead to negative spirals from which it's hard to recover. Research has shown that earlier experimentation with alcohol and drugs makes an adolescent more likely to become addicted.

Research shows that adolescents have a need to contribute to society, and doing so can safeguard against anxiety and depression.

"When your brain is going under rapid reorganization, that's probably not the best time to introduce external chemicals," says developmental psychologist Anthony Burrow of Cornell University. "Your body and brain are paying attention in a slightly different way. [Your brain is] going to organize itself around what you've done to it at that particular moment."

Protective factors in the adolescent's environment could support positive trajectories. What do protective factors look like? They include supportive relationships with family and caretakers and access to resources such as scaffolded opportunities to learn in positive ways. They also include some elements that have previously been underappreciated. Fuligni's research shows that adolescents have a need to contribute to society and that doing so makes them feel valued and can safeguard against anxiety and depression. "Part of what the brain is designed to do during the teenage years is to learn how to contribute to the social world," Fuligni says. This need is particularly significant in adolescence, he argues, because it's a time when the social world is expanding and young people are becoming capable of "making contributions of consequence." These contributions can occur within peer groups, the family, or at a larger societal level. It's no accident that recent social protest movements for gun control and against structural racism have been led in large part by young people.

The specifics of what today's adolescents are learning—and what they are not—may bear on the alarming rises in depression, anxiety and suicidal ideation at that age compared with earlier ages (as well as with previous generations). Some of the information they encounter about mental health may be amplifying their problems, says psychologist Nicholas Allen of the University of Oregon. He points to the controversial Netflix series *13 Reasons Why,* which included a detailed depiction of a character's suicide and which research suggests was associated with an increase in adolescent suicides. "Whether it's a supportive, solution-oriented discussion or whether it's a ruminative, hopeless discussion will have a big effect," Allen says. "Too often adolescents who are tending toward depression, anxiety or suicidal ideation have a tendency to ruminate, and they find friends—both online and offline—who feed that tendency rather than help the teenagers move beyond it."

EFFECTIVE INTERVENTIONS

THERE IS STILL DEBATE about how best to use the new neuroscientific knowledge to help adolescents. "We've learned an enormous amount about the brain, but the application of that knowledge is not straightforward," Allen says.

A big question is when to intervene. One argument for zeroing in on early adolescence is to act preemptively. Because so many of the problems of adolescence occur in the mid- to late teenage years, many interventions target that time. "If you're a developmentalist, that is too late," says Ronald Dahl, a pediatrician and developmental scientist and founder of the Center for the Developing Adolescent at U.C. Berkeley. "Smaller, more subtle, positive interventions earlier are probably a much more promising way to improve population health." The logic of that idea first struck Dahl when he was still practicing as a pediatrician. At conferences, he started mentioning the importance of reaching kids early and found educators nodding their heads. They introduced Dahl to the idea of the fifth grade slump and the eighth grade cliff, a phenomenon in which children's disengagement with education starts slowly with a dip in grades and participation around fifth grade, when most students are 10, and accelerates so that those same students are failing three years later.

The neuroscience also suggests that acting early could make sense. "What we're increasingly learning is that there's another node of new plasticity around the time puberty starts," Dahl said at a conference in early 2020. "We talk about this as a high-stakes pivotal transition in terms of patterns that are beginning to be

shaped." In a study in Tanzania, Dahl and his colleagues succeeded both quantitatively and qualitatively in reducing ideas of gender inequality among 10- and 11-year-olds with a series of technology lessons at which girls were as likely to shine as boys.

Others are wary of focusing too much on any one phase. They emphasize that what neuroscience contributes to the discussion is a reminder of what to prioritize. "What is the thing at this stage of life that is most plastic, that is open for input? That tells you where the risk is, but it also tells you where the opportunity is," Allen says. "What the brain science says is that you should be looking in this area: social and emotional learning."

It is not surprising then that those interventions that look most promising take into account adolescents' desire for status and respect, as well as their need to contribute and find a sense of purpose. According to Fuligni, the most successful volunteer programs give adolescents a say in what to work on and a chance to reflect on the work, and the projects also feel meaningful. Meaning seems to matter in other efforts, too. In a study of early adolescents participating in a 4-H program, Burrow found that those who were asked to write about their sense of purpose before engaging in an educational activity were more likely to engage with the activity and find it important and interesting. "Purpose is a pretty powerful form of identity capital because it's not just an answer to the question of who you are, but it's an answer to the question of who you're going to be and the direction you're heading in," Burrow says. "It's got legs."

Psychologist David Yeager of the University of Texas at Austin has been exploring how best to frame messages to teenagers and studying whether their effectiveness interacts with pubertal maturation, a sign that the neurochemical changes are playing a role. "You should be able to show that if you communicated respectfully to teenagers in a way that felt authentic and supported their autonomy and independence, you should have bigger effects for adolescents, especially if they're more mature in terms of their puberty," he says.

So far his research bears that out. One series of experiments showed that the way you frame a request to take medicine predicted different rates of compliance and furthermore that those rates varied with testosterone levels. Some 18- and 19-year-olds came into the lab and were given instructions in a condescending way: *I'm the expert, I know what's good for you, take this.* Another group of young adults were given instructions in a more respectful manner: *Let me explain the reasons this medicine can be useful.*

For ethical reasons, the medicine in question was actually a spoonful of Vegemite, a notoriously unpleasant-tasting vitamin supplement. Asked respectfully, people were twice as likely to take the Vegemite. Furthermore, participants with higher testosterone levels were significantly less likely to take the medicine in the disrespectful condition and more likely to comply in the respectful condition. When Yeager and his colleagues manipulated testosterone levels with a nasal inhaler, they found that doing so made individuals with naturally low testosterone levels behave just like those with naturally high testosterone levels.

While the medicine study was a nice test of how respectfulness might matter, Yeager says that the 2019 nutrition study informing eighth graders about unsavory food industry practices, which he helped lead, is even more promising. "That's the first direct evidence that these pubertal hormones sensitize you to status and respect and therefore change the way you respond to health messages," he says. "And not just how you respond in the moment but the way you internalize them and continue to keep acting on them after the treatment is over."

In other words, now we know more about what causes adolescents to put up a wall and resist attempts to change their habits, beliefs and ways of coping. That same knowledge offers ways to break down that wall. "It's only recently that we know how to work with those sensitivities and not against them," Yeager says. "I'd like it to be a wake-up call for adults who work with kids." ■

FROM OUR ARCHIVES

The Amazing Teen Brain. Jay N. Giedd; June 2015.

scientificamerican.com/magazine/sa

ANIMAL COGNITION

The Riddle of Dolphin Handedness

Studying the spinning preferences of dolphins identified a quirk of human perception

By Kelly Jaakkola

RIGHT OR LEFT? People have unwittingly disagreed about how to interpret a dolphin's three-dimensional spin.

Kelly Jaakkola is a cognitive psychologist and marine mammal scientist. She is director of research at the Dolphin Research Center in Grassy Key, Fla.

HUMANS DO NOT ACT SYMMETRICALLY. MOST OF US PREFER, AND ARE better at, using one hand rather than the other; balancing on one leg rather than the other; and for those of us who spin (gymnasts, dancers or divers, for example), spinning in one direction rather than the other.

Brains also do not function symmetrically. A version of this idea has long lived in pop psychology, where people are sometimes characterized as being either left-brained (analytical) or right-brained (creative). And although the pop-psych version of this may rest on questionable data, the underlying idea of asymmetrical brain function (what scientists call lateralization) is well established. For example, in humans, language is typically processed in the left hemisphere, and spatial information is processed in the right.

Because each side of the brain controls a different side of the body, studying asymmetrical behaviors can provide us with information about asymmetrical brain function. And if we study this in animals, it may give us insights into brain evolution.

HANDEDNESS WITHOUT HANDS

THE TYPE OF LATERALIZATION most familiar to people is undoubtedly handedness. This has been studied in animals by looking at things such as which hand monkeys use to grab something, which paw dogs use to knock food out of a container, and so on. But what do you do when the animal you're studying doesn't have hands (or paws)? How do you study lateralization in an animal like a dolphin?

It turns out that behavioral asymmetries come in various types, not just limb biases such as handedness and footedness but also sensory asymmetries, in which we do better on different types of tasks depending on which eye (or visual field) we use, and turning biases, where we prefer turning in one direction rather than the other.

Because different types of biases may come from different underlying causes, studying many different behavior types, across many different animals, can provide us with a fuller understanding of brain lateralization and its evolution.

A NEW SPIN ON SPINNING

THIS IS WHERE IT GETS TRICKY. When comparing across animals, we have to take into account the fact that body plans and typical ways of moving may be different. For example, if the animal walks upright (like humans and birds) the long axis of its body is vertical, but if it walks on all fours, the long axis of its body is horizontal. This means that "turning" can involve very different types of movements. For an animal on all fours, turning involves crunching the long axis of its body to one side or the other. For an animal on two legs, turning involves spinning around the long axis of its body, which is kept straight. And for an animal like a dolphin that locomotes in three-dimensional space, either type of turning is possible.

When we set out to study lateralization in dolphins, we were careful to separate these two different types of turning, but we ran into another problem when our researchers kept disagreeing about what counts as a spin "to the right" (or left). After a

PRECEDING PAGES: WW PICS UNIVERSAL IMAGE GROUP AND GETTY IMAGES

lot of discussion (and sometimes argument), we realized that we had stumbled on a weird quirk of human perception. Apparently humans interpret the direction of spinning in opposite ways depending on the orientation of the animal.

To get a feel for this, try the following: First, stand up and spin "right." Then lie down face-down on the floor and roll "right." If you are like most people, in the upright case your right shoulder moved toward your back, whereas in the horizontal case your right shoulder moved toward your chest, or front side. That is, you made the exact opposite rotation. (And in case you're wondering, no, you can't get around this by describing spins as clockwise/counterclockwise instead of right/left. You get the same results if you substitute "clockwise" for "right" in the examples above.)

Before this, almost all scientific studies of lateralization of turning or spinning motions had studied a single species in a single orientation, like a human turning (upright) or a whale breaching (horizontal)—so the issue had never come up. This meant, however, that published research studies had in fact been using opposite coding systems for different animals depending on their orientation. A spinning turn in which the animal's right side moved toward its front was typically coded as left/counterclockwise in studies of humans and walking birds but as right/clockwise in studies of dolphins and whales. Of course, if we want to look at turning lateralization across different species, we all need to agree on the direction of a turn, which meant we needed a new coding system.

The system we came up with was actually inspired by the "right-hand rule" of electromagnetism that many of us learned in high school or college physics. According to that rule, if you point your right thumb in the direction in which an electric current flows through a wire, the curve of your fingers shows you the direction of the magnetic field flowing around that wire. We adopted the general outline of this schematic model to create the right-fingered spin (RiFS) versus the left-fingered spin (LeFS) coding system. In this system, when a coder's outstretched thumb is oriented along the animal's long axis, pointed toward its head, the curled fingers of the relevant hand describe the direction of rotation. This allowed us to quickly and unambiguously code spinning/turning behaviors no matter the animal's orientation or direction of movement.

STUDYING the asymmetric behaviors of dolphins revealed the need for a new coding system for spinning direction.

TONY WU Nature Picture Library and Alamy

THE BENEFITS OF A FRESH PERSPECTIVE

SOME PREVIOUS SCIENTIFIC PAPERS had claimed that dolphins show strong rightward behavioral asymmetries, similar to human right-handedness and therefore had a left-hemisphere specialization for action. But because "right" didn't always mean the same thing in the earlier coding systems, it wasn't clear if this claim was really true. To test it, we examined different types of behavioral asymmetries in a group of 26 dolphins, such as "Which direction do they swim around a lagoon?," "Which side of their body do they touch things with?" and "Which direction do they spin if they dive up and to the side?" By making sure to separate out the different types of motion and using the unambiguous RiFS/LeFS coding system, we found that—contrary to previous claims—dolphins do not have a general rightward asymmetry after all.

People often think that scientific progress happens when we learn something new that we didn't know before. Another kind of scientific progress happens when we realize that there is a problem with the way we've been looking at things all along. In those cases, figuring out a different way of looking can lead to seeing things more clearly. And as science-fiction writer Isaac Asimov once pointed out, "The most exciting phrase to hear in science, the one that heralds new discoveries, is not "Eureka!' but 'That's funny…'" SA

FROM OUR ARCHIVES

Deception in the Wild. Barbara J. King; September 2019.

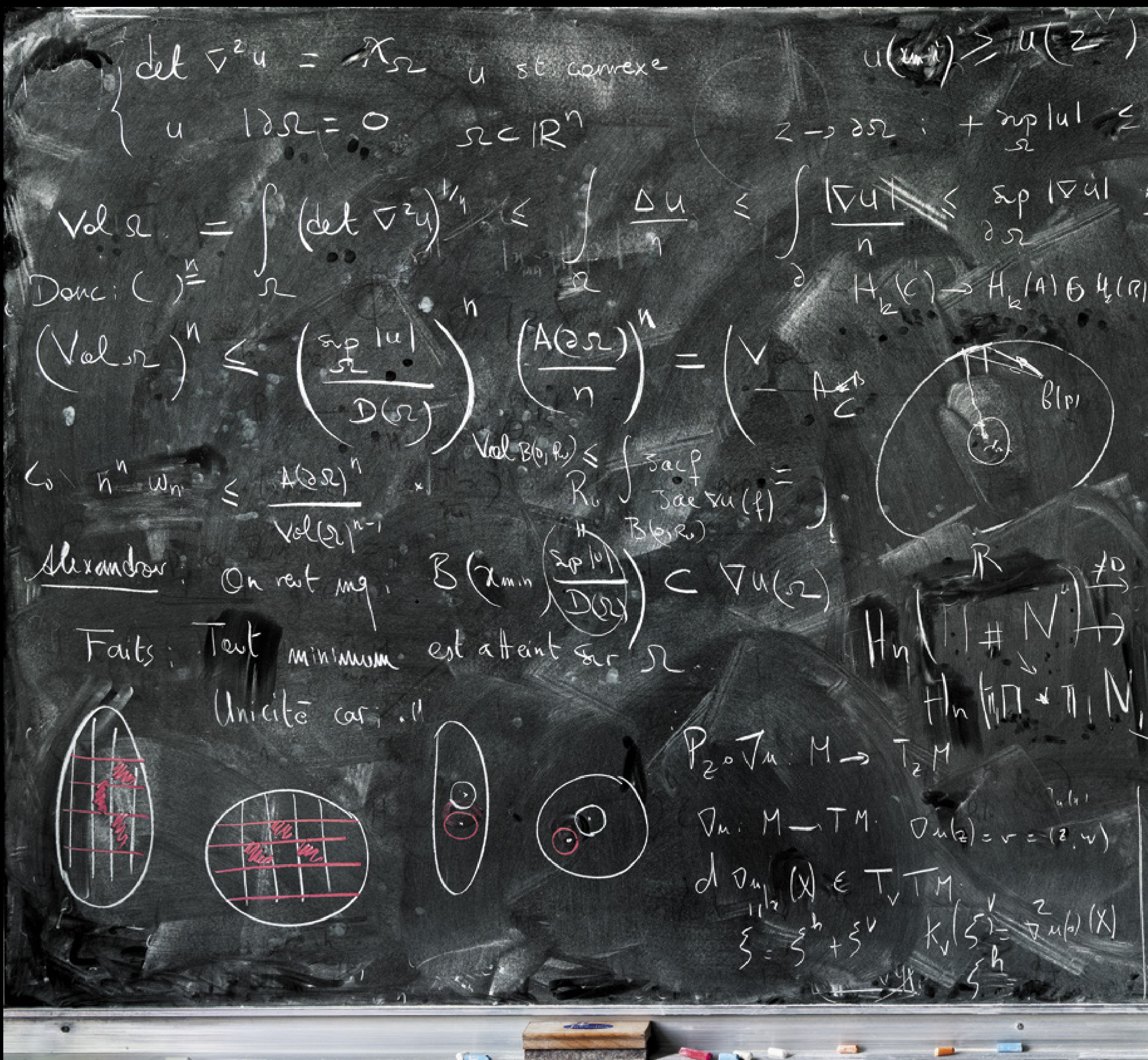
scientificamerican.com/magazine/sa

MATHEMATICS

Chalkbo

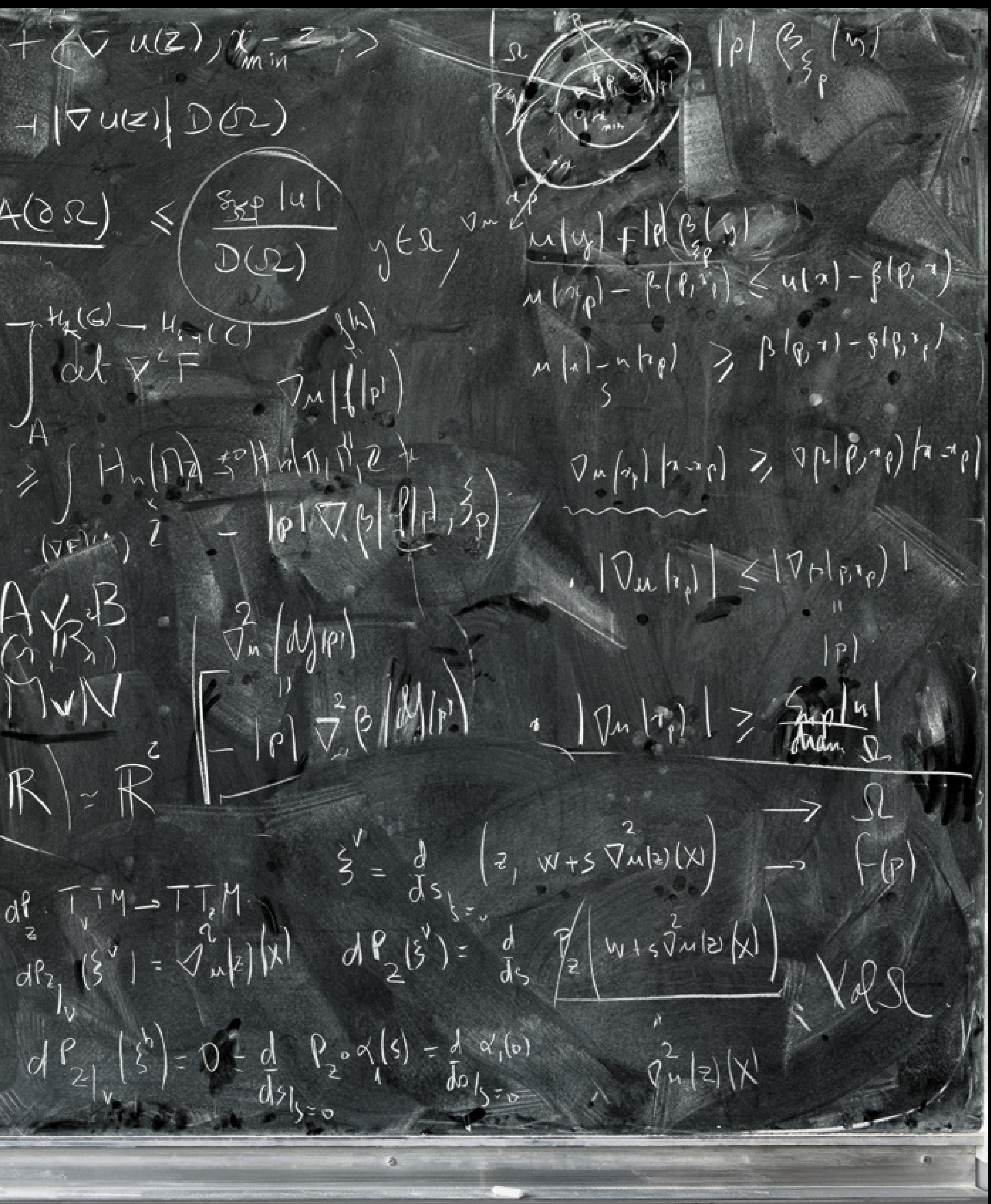
A photography project reveals the allure of topology, geometry and

By Clara Moskowitz *Photography by Jessica Wynne*



ard Art

mathematical theory

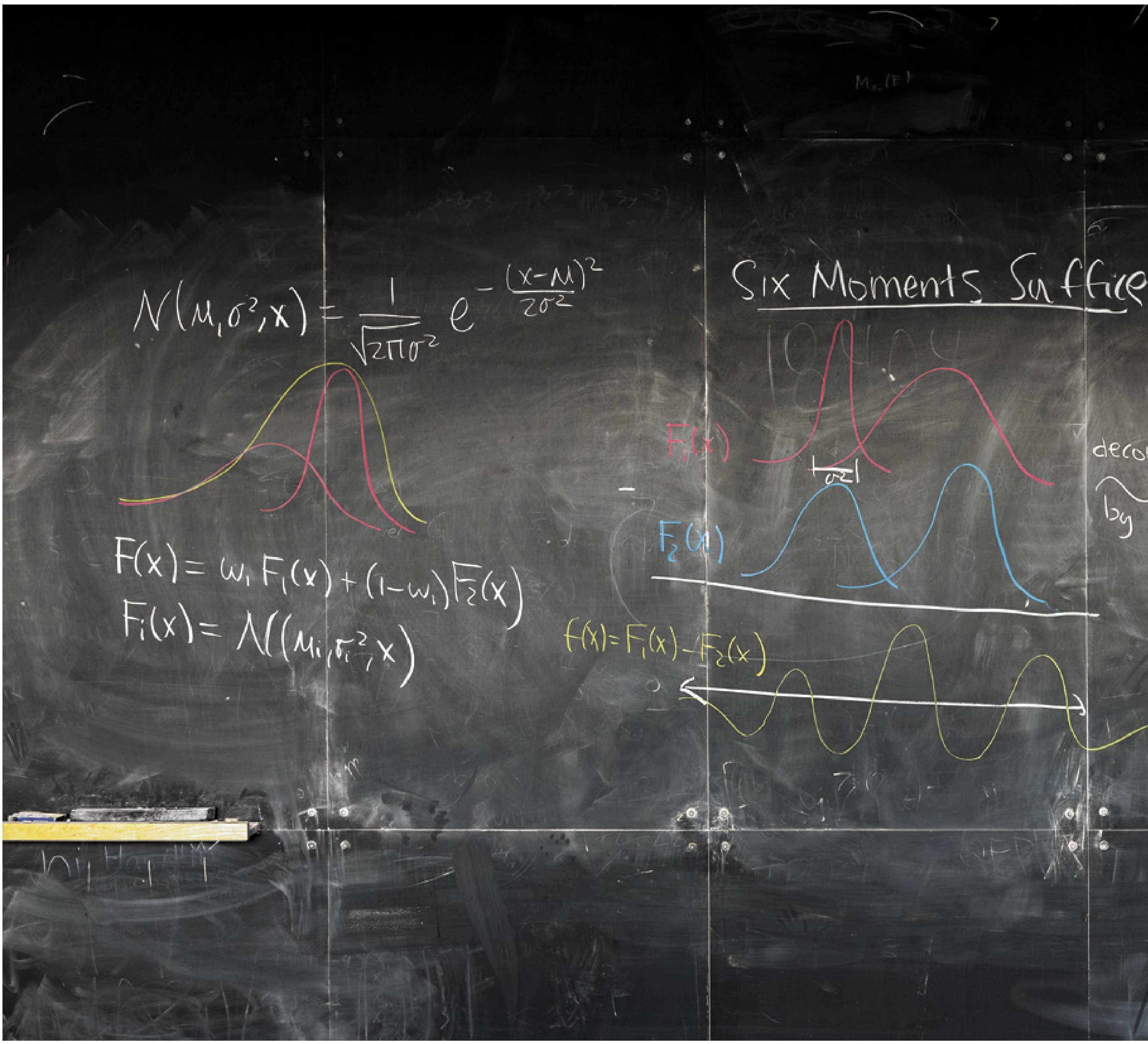


Isoperimetry

A conundrum dating back to the ancient Greeks called Dido's problem asks: Among all planar figures having the same perimeter, which one encloses the greatest area? The answer, the Greeks knew, is the circle, and it was finally proved in the 19th century. But a related problem persists in non-Euclidean geometry. Gilles Courtois, director of research at the Institute of Mathematics of Jussieu in France, was studying this question. "We thought that we had found a path toward a solution," he says. "The scheme was so simple that we were able to write it on the board." Unfortunately, the idea didn't pan out, and the project "remains a work in progress."

Clara Moskowitz is a senior editor at *Scientific American,* where she covers space and physics.

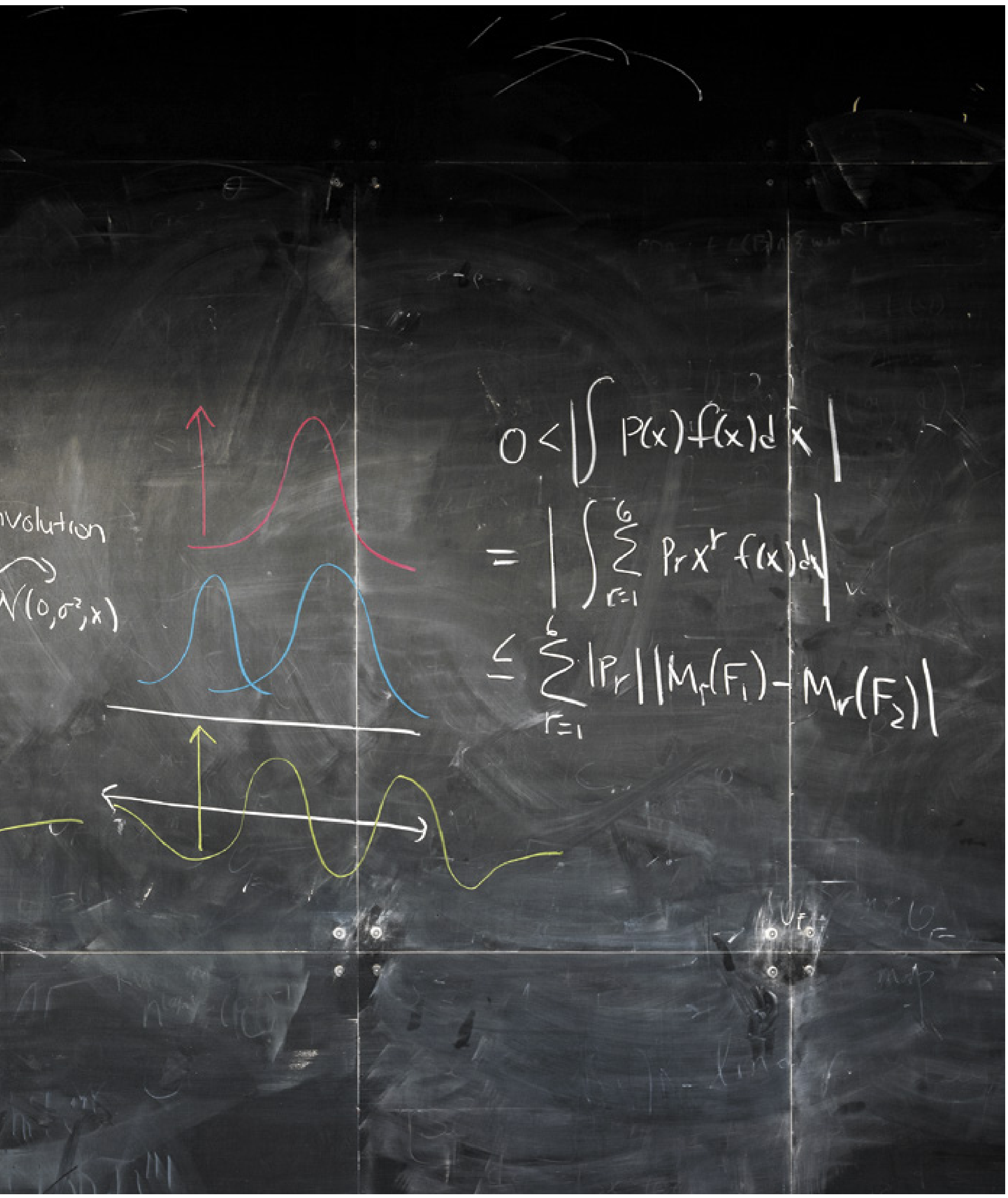
EVEN WHEN IT IS INSCRUTABLE, MATH IS BEAUTIFUL. PHOTOGRAPHER Jessica Wynne set out to capture this appeal when she began photographing mathematicians' chalkboards around the world in 2018. "I've always been interested in entering into worlds outside my realm of knowledge," Wynne says. Without comprehending what the math on the chalkboards represented, she was able to appreciate it on a purely aesthetic level. "It's a similar feeling as when I'm looking at an abstract painting. But it added more interest that beyond the surface there's great meaning and great depth, and they're trying to reveal universal truth."



Wynne was first drawn into the world of math when she befriended two mathematicians who vacationed near where she spent summers on Cape Cod. As she learned about their research, she found many parallels between the process of math and the process of art. “I was really surprised to witness how they work and how creative what they do is,” she says.

As Wynne began to travel to different universities to meet more mathematicians, she discovered how diverse their chalkboard styles are. “Some were very clean and neat and very carefully considered,” she recalls. “And some were just this explosion and chaos. The chalkboards almost felt like portraits of the person and depended on the personality of the mathematician.”

Many of the photographs will be collected in a book, *Do Not Erase: Mathematicians and Their Chalkboards,* forthcoming in June from Princeton University Press. Wynne intends to continue the project, especially because her travels were cut short by the pandemic. She had planned to visit the mathematics department of the University of Cambridge until she learned that their chalkboards had all been replaced by dry-erase and digital boards. “I’m very attracted to the whole analog nature of working on a chalkboard,” she says. “I noticed a lot of places were getting rid of their blackboards, and I felt an urgency to document this.” ■

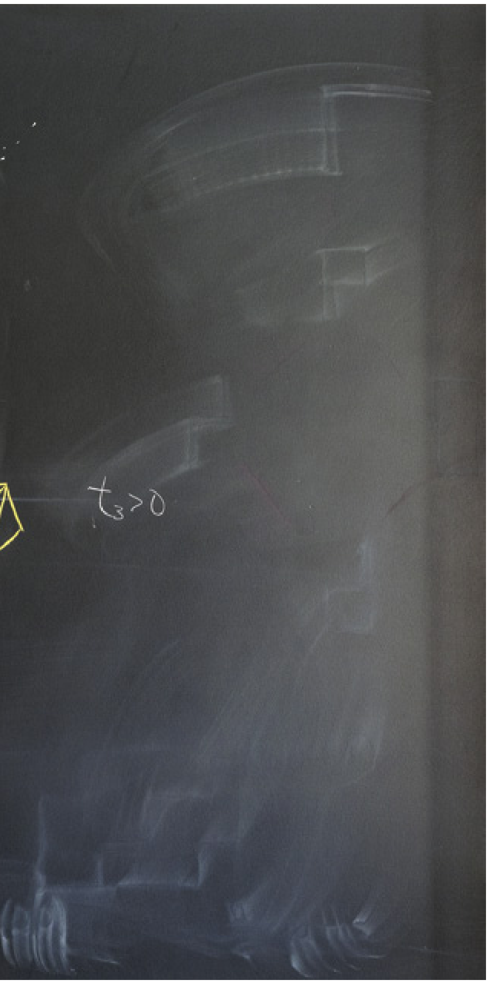


Mixed Gaussians

Physical measurements (such as the heights of women chosen randomly from a population) will commonly produce a distribution called a Gaussian, a plot that looks like a rounded mountain. Machine-learning algorithms are often given heterogeneous data (for instance, the heights of random women and men), and a challenging task is to disentangle the measurements into two or more components. Ankur Moitra of the Massachusetts Institute of Technology and his colleagues discovered a way to separate the curves that requires only the first six “moments”—special characteristics—of the mixture. “What I drew on the chalkboard is the key proof in our paper,” Moitra says. “It turns out that this is equivalent to being able to take two different mixtures, subtract them, and show that the resulting function crosses the zero axis at most six times.”

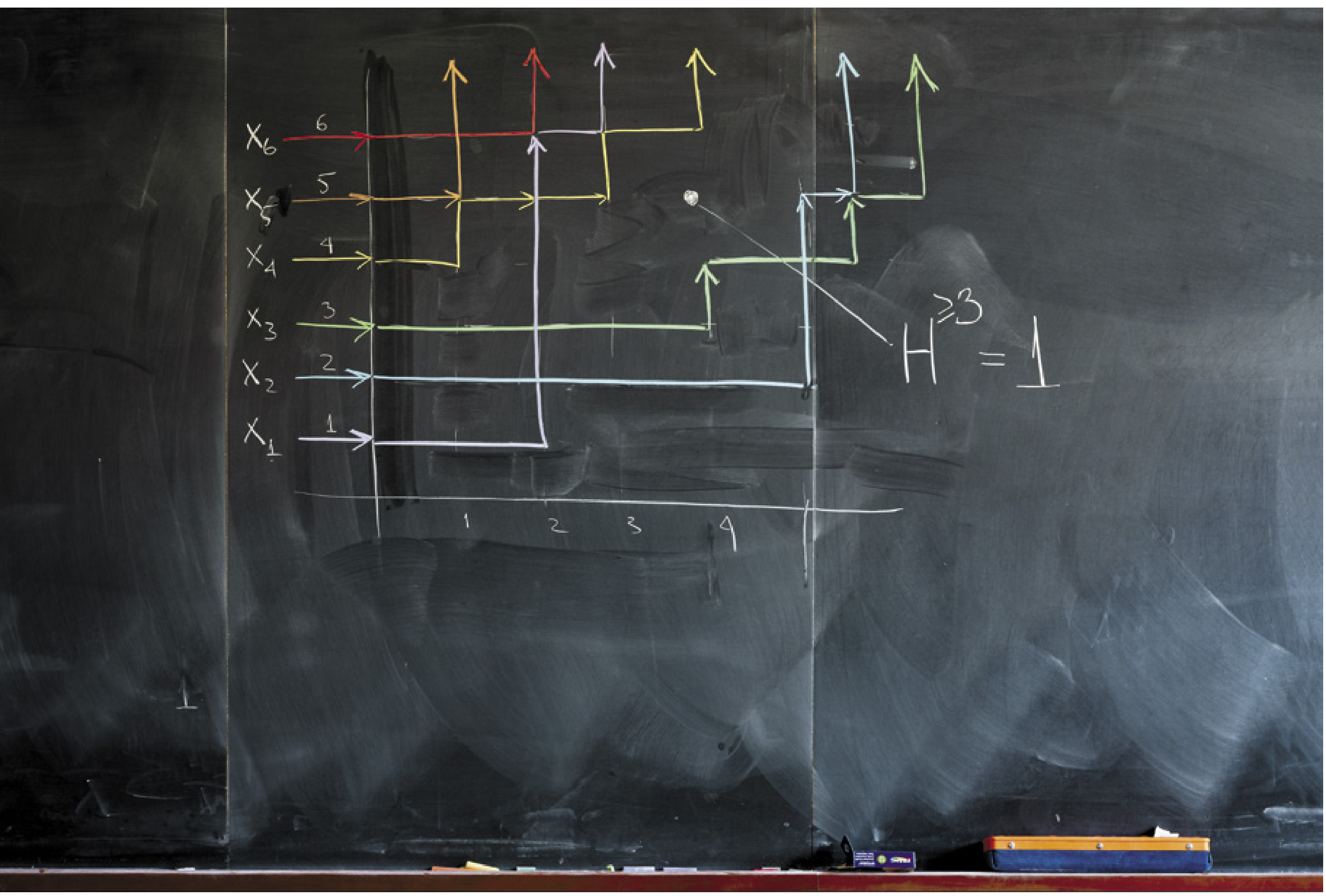
Branching Waves

Stick-figure-like diagrams represent snapshots of wave evolution. The white lines encode the locations of peaks for a configuration of shallow-water waves at a particular moment in time. “These waves have interesting interactions,” explains Harvard University mathematician Lauren K. Williams. “For example, two waves can meet and form just one wave coming out, and if one lets the time vary, one sees different patterns of wave interactions.” Williams and her collaborator Yuji Kodama of the Ohio State University used the diagrams to study solutions to the so-called Kadomtsev-Petviashvili (KP) equation describing wave behavior. They found that the wave patterns that arise from a certain class of solutions can be classified by triangulations of a polygon (*in yellow*). “If one changes the parameters of the solutions a bit, these wave patterns can degenerate and form, for example, the white ‘starfish’ pattern shown at the center,” she says. At the bottom left is what Kodama and Williams call a “Go-diagram,” named after the board game Go, played with black and white stones, which they use to study certain solutions to the KP equation.



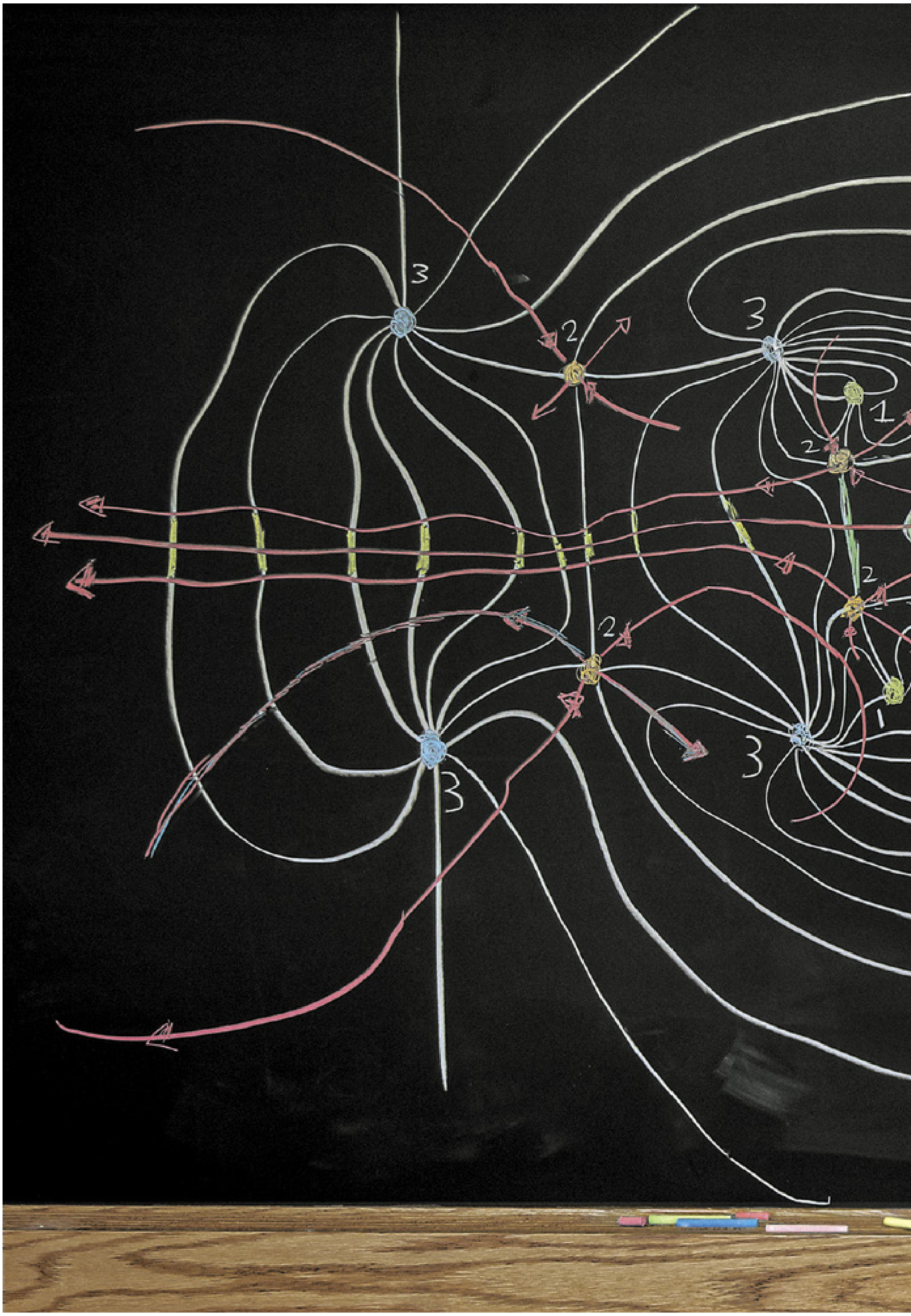
Out for a Walk

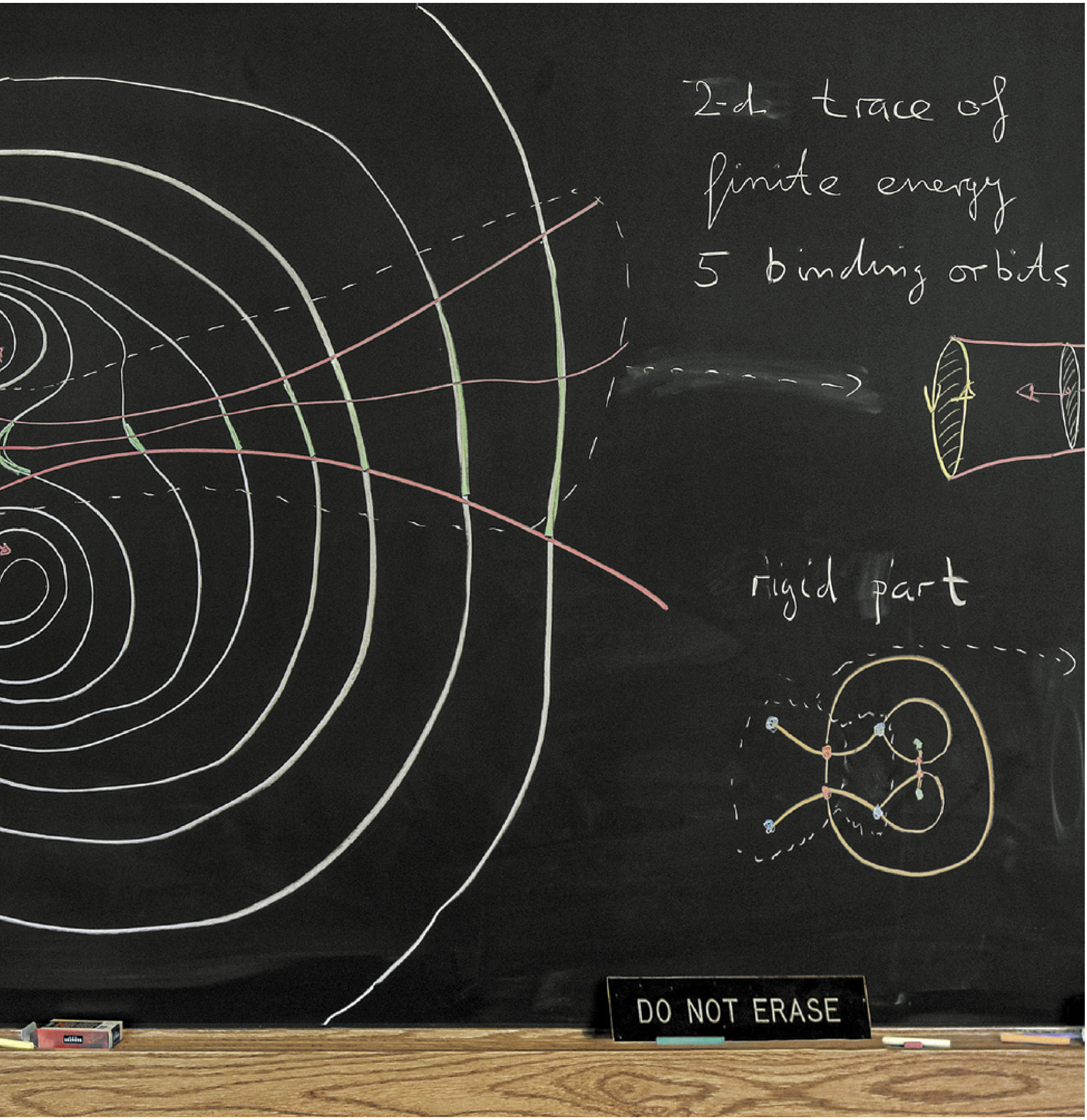
Each colored line shows the path a pedestrian takes through a square grid in this "vertex model." The walkers' paths cannot overlap, so whenever two meet they must decide which way each one will go. The decision might be biased—for instance, walkers of cooler colors may be more likely to go east than north compared with walkers of warmer colors. "In spite of its simple description, its large-scale behavior is intricate and closely related to a number of mathematical and physical phenomena," says Alexei Borodin, a mathematician at the Massachusetts Institute of Technology. Vertex models can be expanded to include many more walkers and many more colors. "A combination of deceptive simplicity, hidden depth, and efficacy of mathematics in the analysis makes this system attractive to me." Borodin also likes "the aesthetics factor," he adds.

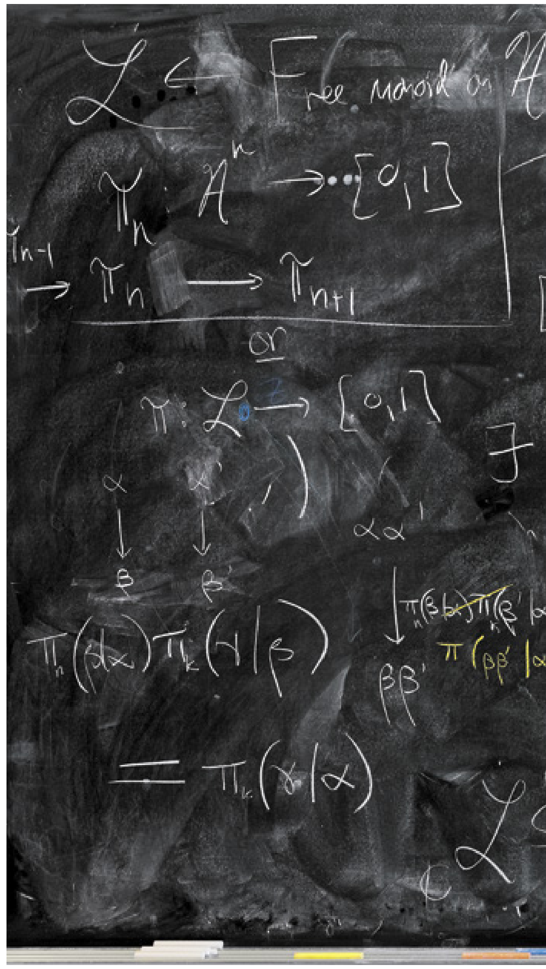


Organized Chaos

There can be order in chaos, it turns out. Between 1999 and 2003 Helmut Hofer of the Institute for Advanced Study in Princeton, N.J., and his colleagues developed a field to study this order, called symplectic dynamics. Hofer's board depicts "finite energy foliations" (*white lines*)—tools for characterizing the chaos in a dynamical system such as a satellite moving between Earth and the moon. This intricate system of surfaces relates to the evolution of a satellite's position and momentum as it interacts with the gravity from the two planetary bodies. Hofer hopes that "this much better understanding of the chaos will ultimately have applications in the design of space missions." For instance, earlier efforts used insights about chaos to preserve fuel during space exploration but at the expense of added travel time. Hofer suggests this new work could further boost fuel savings without lengthening a mission's duration.

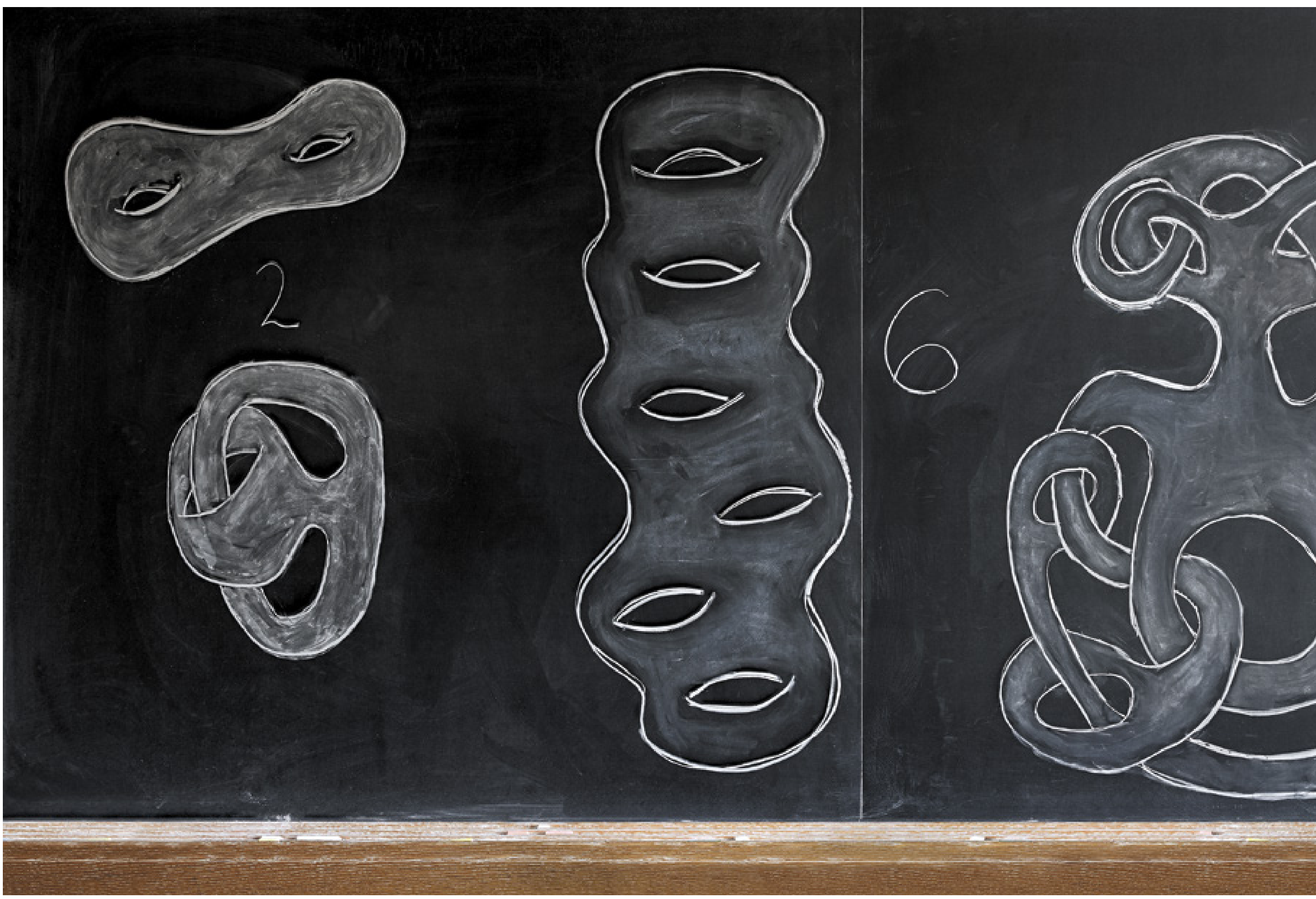


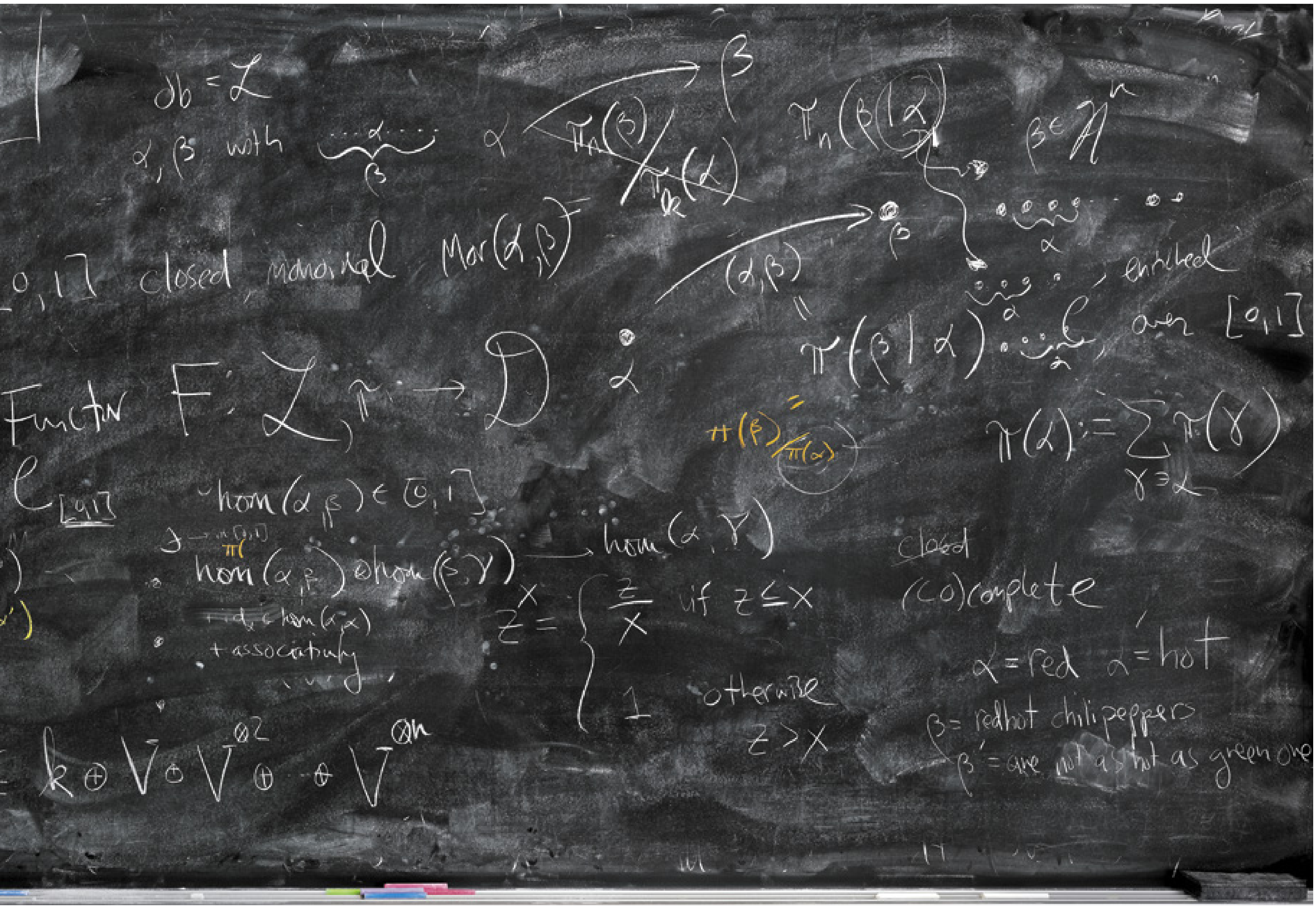

2-d trace of
finite energy
5 binding orbits
rigid part
DO NOT ERASE



Matching Shapes

A coffee cup and a doughnut are famously "the same" shape according to the mathematical field of topology, which categorizes surfaces by how many holes they contain. Because both the cup and the pastry have a single hole and could be bent and stretched into the same shape without making any cuts or perforations, they are topologically identical. Similarly, the two surfaces labeled "2," as well as the surfaces labeled "6," are fundamentally the same. "They are a lot of fun," says Nancy Hingston, a mathematician at the College of New Jersey, who studies paths on such shapes in her work on differential geometry.





A Collaboration

Chalkboards are often the best tools for mathematical collaborations—visual and tactile places to merge two people's ideas and instincts. Mathematicians John Terilla of Queens College and Tai-Danae Bradley of X, the Moonshot Factory, were attempting to understand the hidden mathematical structure at work in natural language. "That was the first time we spoke about formalizing that structure in a particular way," Terilla says. "Tai and I were working together at the board, and it shows both of our writing. The large 'There exists [denoted by ∃] a functor F,' for example, is mine; the 'hom(alpha, beta) in [0,1]' below that is Tai's." This research is part of a general quest of Terilla's to search for "what's at work behind the scenes to understand what's going on," he says. "Going up a level in abstraction to explain something is a bit like going out of your way to climb a hill and look around—useful in research since it can show the way forward in uncharted territory."

FROM OUR ARCHIVES

Math Is Beautiful, But Is It Art? Jen Christiansen; ScientificAmerican.com, January 27, 2015.

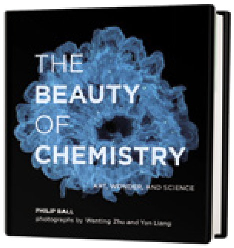
scientificamerican.com/magazine/sa

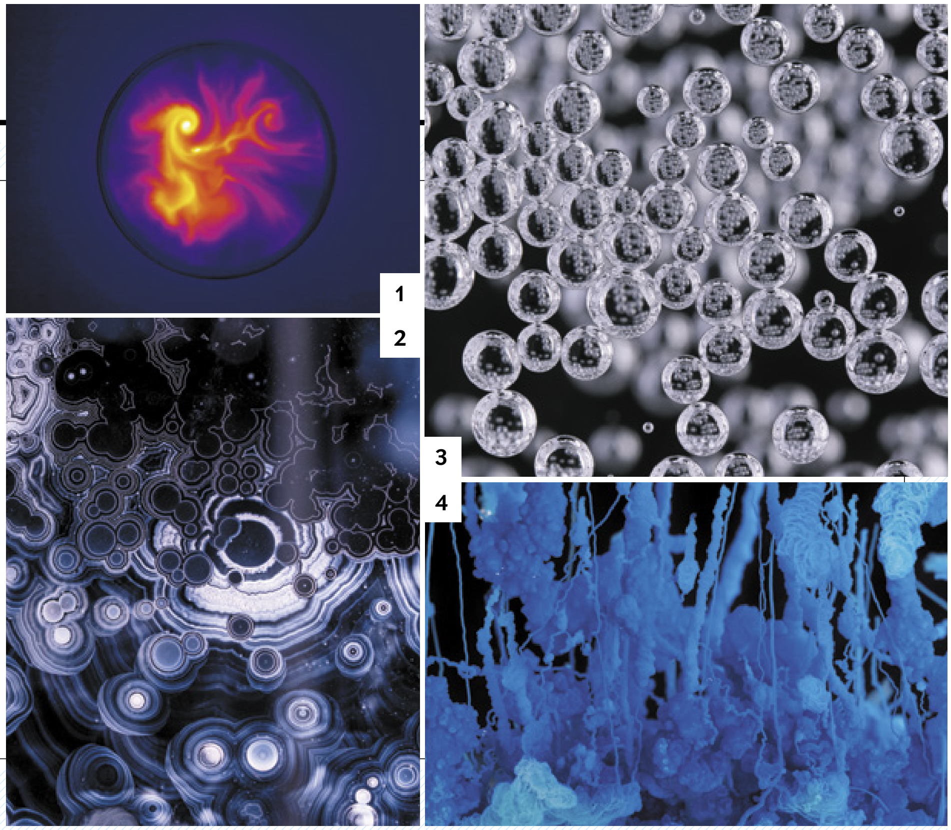
RECOMMENDED

By Andrea Gawrylewski

The Beauty of Chemistry: Art, Wonder, and Science

by Philip Ball. MIT Press, 2021 ($49.95)





Chemistry is perhaps the most sensual of the sciences, writer Ball posits in this absorbing collection of photographs from science artists Wenting Zhu and Yan Liang. Behind every smell, every worldly texture, even every emotional response, there is a chemical reaction. The wonder of those reactions is on display here, from the mesmerizing precipitation of heavy metals such as cobalt and nickel to the thermal heat map of sodium dissolving in plain water. The alien look of a copper nitrate "chemical garden" evolves through the action of ions and precipitation. Ball explains the science of these complex reactions and interweaves them with literary ideas and philosophical contexts. Far from portraying a routine lab procedure, this collection showcases chemistry's excitement and aesthetic allure.

THERMAL IMAGE of sulfuric acid mixing in water (*1*). Sodium silicate drying on glass (*2*). Bubbles of carbon dioxide in a soft drink (*3*). Chemical garden formed by copper nitrate in sodium silicate (*4*).

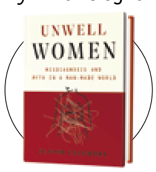
Helgoland: Making Sense of the Quantum Revolution

by Carlo Rovelli. Riverhead Books, 2021 ($20)

It is not just laypeople who find quantum mechanics inscrutable—the more physicists ponder it, the more perplexed they become, writes physicist Rovelli. The esoteric theory describing the behavior of particles on the submicroscopic scale rewrites the rules of normal reality we are accustomed to, substituting probability for certainty. Seriously considering its implications for understanding the world, he says, is "an almost psychedelic experience." This entertaining and legible guide paints the history of quantum theory and lays out its possible meanings, including the author's favorite—the "relational" interpretation—which posits that things exist only through their interactions with other things: there is no absolute reality. *—Clara Moskowitz*

Unwell Women: Misdiagnosis and Myth in a Man-Made World

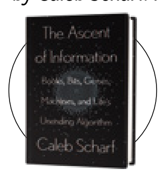
by Elinor Cleghorn. Dutton, 2021 ($27)



Researcher Cleghorn provides an essential history of misogyny in health care, beginning with the so-called father of medicine himself, Hippocrates, who wrote that female bodies were a weaker version of male bodies. That prejudice has carried through thousands of years, and its remnants are well preserved today: women's ailments have been an afterthought in research, and women are still underrepresented in clinical trials. Women of color are particularly underserved: Black women are up to five times as likely to die in childbirth as their white counterparts, and more than 20 percent experience discrimination when they visit doctors. This clear-eyed assessment is both a catalog of how medicine has been complicit in female oppression and a call to action for drastic reform.

The Ascent of Information: Books, Bits, Genes, Machines, and Life's Unending Algorithm

by Caleb Scharf. Riverhead Books, 2021 ($28)



According to some estimates, our global civilization now generates some 2.5 quintillion bytes of information. This data deluge—which astrobiologist Scharf dubs our "dataome"—has profound implications for our future, for good or ill. For instance, is it good or bad that the dataome places a heavy physical burden on the world in the form of energy-hungry computers, storage devices and telecommunications technologies? On such matters Scharf prefers to conservatively outline the limits of current knowledge rather than make pronouncements with false certitude, but the end result is no less audacious: a transformative new way of looking at our increasingly data-driven existence. *—Lee Billings*

WENTING ZHU AND YAN LIANG, IN COLLABORATION WITH THE CHINESE CHEMICAL SOCIETY

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 *Discerning Experts* (University of Chicago, 2019).

What Makes a Problem "Hard"?

The vaccination debacle shows that we need to rethink the term

By Naomi Oreskes

There is a saying in the field of artificial intelligence: "Hard things are easy; easy things are hard." Called Moravec's paradox, after Hans Moravec, founder of robotics company Seegrid, it is explained in detail in a recent book by computer science professor Melanie Mitchell entitled *Artificial Intelligence: A Guide for Thinking Humans*. Activities that most people find very hard, such as playing chess or doing higher mathematics, have yielded fairly readily to computation, yet many tasks that humans find easy or even trivial resist being conquered by machines.

Twenty-five years ago Garry Kasparov became the first chess grand master to lose to a computer. Today computer programs can beat the world's best players at poker and Go, write music and even pass the famous Turing test—fooling people into thinking they are talking to another human. Yet computers still struggle to do things most of us find easy, such as learning to speak our native tongue or predicting from body language whether a pedestrian is about to cross the street—something that human drivers do subconsciously but that can stymie even the most advanced self-driving cars.

AI researchers will tell you that chess turned out to be comparatively easy because it follows a set of rigid rules that create a finite (albeit large) number of possible plays. Predicting the intentions of a pedestrian, however, is a more complex and fluid task that is hard to reduce to rules. No doubt that is true, but I think there is a bigger lesson in the AI experience that applies to more urgent problems. Let's call it the vaccine-vaccination paradox.

Anyone familiar with biology is hugely impressed by the agile scientific work that in under a year yielded astonishingly effective vaccines to fight COVID-19. Both the Moderna and the Pfizer-BioNTech vaccines use messenger RNA (mRNA) to deliver instructions to cells to generate the spike protein found on the novel coronavirus, which prompts the body to make the antibodies needed to fight an actual infection. It is a brilliant piece of biotechnological work that bodes well for similar uses of mRNA in the future.

Yet even several months after those vaccines were cleared for use, it is extremely hard to get the American population fully vaccinated. In the U.S., the difficulties have included the vexed politics of the past year, but the logistical challenges turned out to be great as well. Before the vaccines were authorized, some health experts were concerned that there might not be enough vials and syringes or cold storage. Others noted the problem of vaccine hesitancy. And since the vaccines became available, a host of new problems, including such quotidian tasks as scheduling, have plagued the program. The hard task of creating a vaccine proved (relatively) easy; the easy task of vaccination has proved very hard.

Maybe it is time to rethink our categories. We view chess as hard because very few people can play it at a high level, and almost no one is a grand master. In contrast, there are nearly four million nurses in the U.S. alone, most of whom presumably know how to deliver inoculations. If we had to, nearly all of us could probably learn to drive a truck to deliver vaccines. But this perspective confuses difficulty with scarcity. As the AI example shows, many things that all of us can do are in some respects remarkably difficult. Or perhaps we are conflating what is difficult to *conceive* with what is a challenge to *do*. Quantum physics is conceptually hard; administering 600 million shots in a large, diverse country with a decentralized health system is a staggeringly difficult practicality.

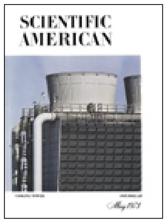
We call the physical sciences "hard" because they deal with issues that are mostly independent of the vagaries of human nature; they offer laws that (at least in the right circumstances) yield exact answers. But physics and chemistry will never tell us how to design an effective vaccination program or solve the problem of the crossing pedestrian, in part because they do not help us comprehend human behavior. The social sciences rarely yield exact answers. But that does not make them easy.

When it comes to solving real-life problems, it is the supposedly straightforward ones that seem to be tripping us up. The vaccine-vaccination paradox suggests that the truly hard sciences are those that involve human behavior. SA

JOIN THE CONVERSATION ONLINE
Visit *Scientific American* on Facebook and Twitter
or send a letter to the editor: editors@sciam.com

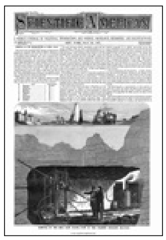
Illustration by Jay Bendt

MAY



1971

1921



1871

1971 When Time Began

"Specially designed equipment has been set up in two widely separated locations: my laboratory at the University of Maryland and the Argonne National Laboratory near Chicago. Within the past two years simultaneous increases in the output of detectors at these sites have provided evidence of bursts of gravitational radiation emanating from the center of our galaxy. These findings have stimulated much theorizing and a good deal of disagreement among astrophysicists. It is conceivable that the source might be an unusual object such as a pulsating neutron star. It is also conceivable that the mass at the galactic center is acting as a giant lens, focusing gravitational radiation from an earlier epoch of the universe. The relatively large intensity apparently being observed may be telling us when time began.—Joseph Weber"

1921 Science News

"On the ground that citizens ought to be in a position to avail themselves of what science teaches, and to estimate the work of the serious scientist as well as the claims of the faker, it is essential that the people understand modern science. Under the financial support of Mr. E. W. Scripps, whose name is familiar to the readers of several hundred newspapers that use his news service, a foundation has been laid for the Science Service. It will publish books and magazines, conduct lectures and conferences, produce motion pictures, and especially will extend the willingness and the ability of the average newspaper to deal with scientific news."

Radio at Home

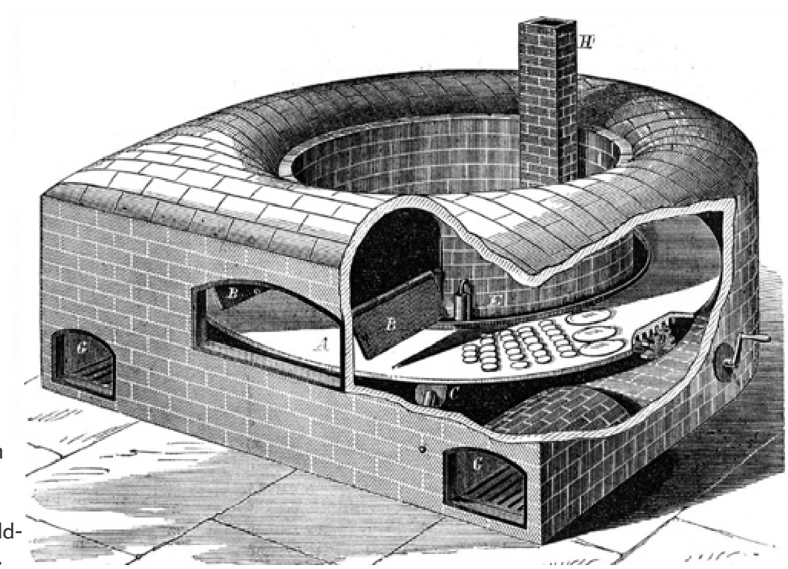
"We are on the verge of a new era in radio communication, namely, radiophone music for the home. The idea is to have radiophone stations at central points sending out concert music as well as speeches and lectures via radio, and compact receiving sets in various homes and clubs to intercept the waves. Already there are several radiophone stations in operation, and at least one wireless company has developed a receiving set made as a cabinet, incorporating a concealed loud-speaking telephone unit, so that the transmission can be heard throughout a room. It is believed that leading manufacturers of radio equipment will maintain radiophone concert and lecture services for their patrons."

1871 Superior Bread Baking

"Our engraving illustrates a newly invented baker's oven, which seeks to combine the advantages of the old fashioned brick oven with those of continuously acting mechanical ovens. The latter have failed to produce a sweet and wholesome bread. The dough is put in, and when brought around again by the rotating platform, is taken out at the door. Swinging damper doors prevent the escape of heat. It is claimed that this oven will bake anything in the superior manner accomplished by the brick oven. It is also said to excel in economy of fuel and labor."

Down in the Salt Mine

"The most productive salt mines in the world are those of Wieliczka, in Austrian Poland, ten miles from Cracow. The greatest depth is about eight hundred feet. They have seven different levels. The apparatus for letting us down was an iron basket, in which we sat, with our legs hanging outside, holding to ropes fastened above to a ring encircling an iron shaft. When we stopped, one of the torchbearers went before, and the other behind me, as we walked over a wooden bridge, and down a flight of stairs, and through several passages, all cut from the salt. Salt varies a great deal in quality. The green salt contains six or seven percent of clay, which destroys its transparency. Another sort, *spiza,* is crystalline, but mixed with sand; the perfectly pure, *szybik,* is found in large crystallized masses. The yield of the mine is about 500,000 tuns annually, valued at ten dollars per tun. When the mines were discovered is not known, though it is certain that they have been worked nearly nine centuries.—Junius Henri Browne"



1871: New oven bakes bread with modern efficiency but old-fashioned taste.

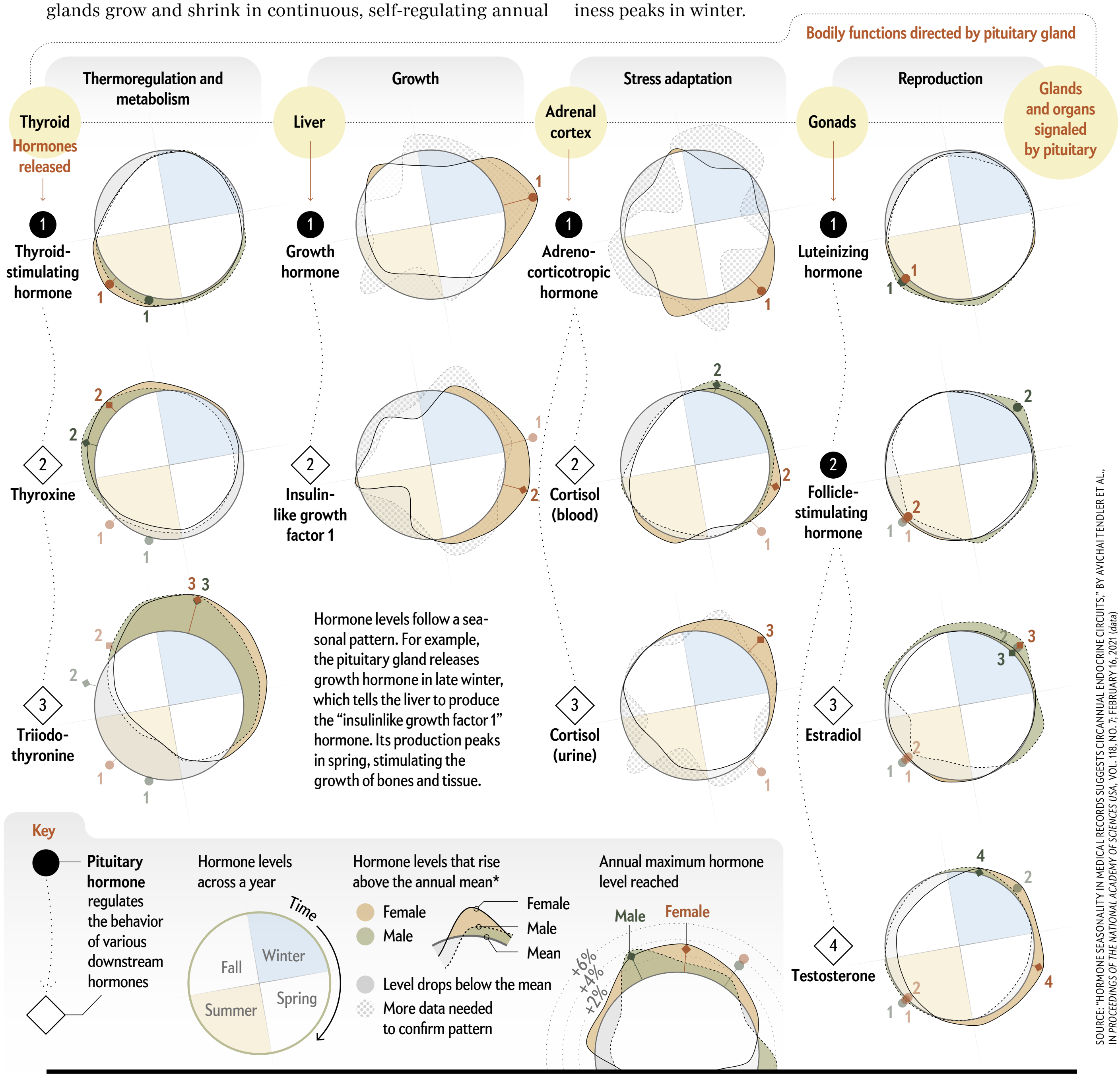
SCIENTIFIC AMERICAN, VOL. XXIV, NO. 21; MAY 20, 1871

Text by Mark Fischetti | Graphic by Accurat

Hormone Season

An internal body clock creates an annual cycle of hormone highs and lows

Hormones can surge and drop within minutes to direct many of our daily functions: sleep, digestion, reactions to stress. General hormone levels rise and fall slightly across the year as well. New work shows that the pattern has a seasonal memory of sorts, too, governed by a newly discovered internal clock. By studying millions of blood tests, researchers at the Weizmann Institute of Science in Rehovot, Israel, found that hormone-producing glands grow and shrink in continuous, self-regulating annual cycles. Each maximum or minimum causes hormone levels to rise or fall by several percent—small but significant—though often several months later. The cycles, and lag times, are evident in hormones released by the thyroid, liver, adrenal cortex and gonads, directed by the pituitary gland in the brain. The results support a growing body of work that shows that fertility tends to be higher in midwinter, kids grow faster in spring and moodiness peaks in winter.



*Curves connect mid-monthly mean values. All samples were normalized for age of the individual and time of day that the sample was taken. Analysis did not include a nonbinary category.

SOURCE: "HORMONE SEASONALITY IN MEDICAL RECORDS SUGGESTS CIRCANNUAL ENDOCRINE CIRCUITS," BY AVICHAI TENDLER ET AL., IN *PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES USA*, VOL. 118, NO. 7; FEBRUARY 16, 2021 (*data*)

ROLL UP YOUR SLEEVE

AND CRUSH THE VIRUS!

DON'T WAIT. VACCINATE.