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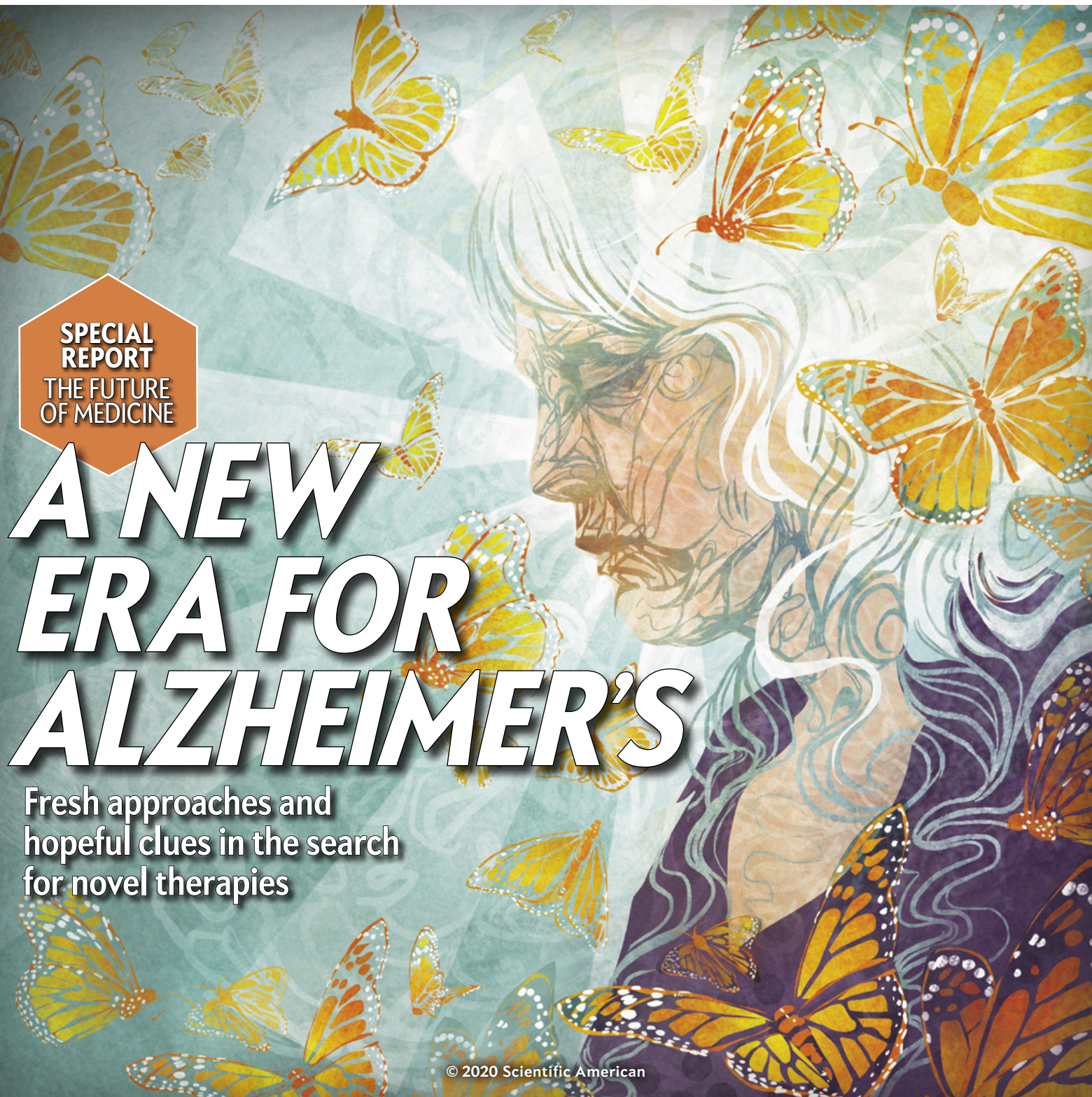

SPECIAL REPORT
THE FUTURE OF MEDICINE

A NEW ERA FOR ALZHEIMER'S

Fresh approaches and hopeful clues in the search for novel therapies

MAY 2020

VOLUME 322, NUMBER 5

SCIENTIFIC AMERICAN

ON THE COVER
After recent failed efforts to develop treatments for Alzheimer's disease, many scientists are taking a fresh look at causes of the illness. New research areas include the origins of abnormal proteins and wayward brain signals, the surprising role of air pollution, and factors that lead to higher risk for women.
Illustration by Galen Dara.

Photograph by Nico Lewis

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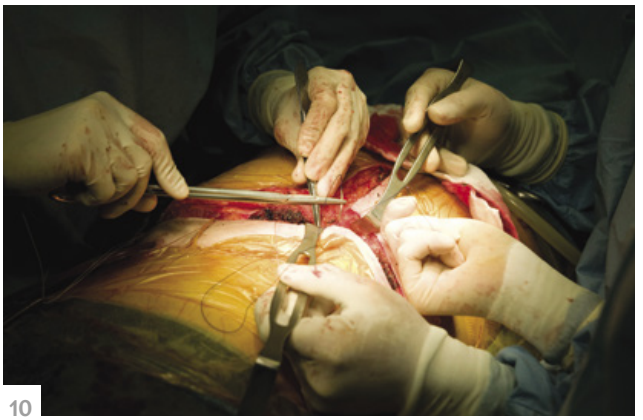

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Curtis Brainard is acting editor in chief of *Scientific American*. Follow him on Twitter @cbrainard

Diseases and Deadlines

Magazine issue closes are always hectic. We spend months working on each edition, but then for one week, roughly six weeks before publication, we have to triple-check each of the some 100 pages in the book and get them out the door in time to meet our monthly printer deadline. This close is different.

As I write this letter, it's 10 P.M. on Sunday, March 15. Last Tuesday our parent company, Springer Nature, told everyone in the New York City office that they could work from home because of the spread of coronavirus, and nearly everyone has availed themselves of the opportunity. On Wednesday the World Health Organization announced that the outbreak was a global pandemic. On Friday—the day we started sending pages for this issue to the printer—President Donald Trump declared a state of emergency in the U.S. And today New York Mayor Bill de Blasio said that public schools would close citywide.

So we're putting this issue to bed remotely—for many of us, with our kids running around wildly in the background. At the same time, we must keep up the daily news operation online, where you can find ongoing coverage of the coronavirus crisis, how it's impacting our lives and what's being done to stop it (visit sciam.com/coronavirusoutbreak for the latest). I'm not worried, because we have an amazing staff and because it's been done before. When Hurricane Sandy battered New York in 2012, our office building near the Holland Tunnel (we've since moved) was closed for a week.

Also, while coronavirus is the scourge of the moment, it's important to not lose sight of the perennial maladies that afflict us. Between 40 million and 50 million people around the world currently live with Alzheimer's and related dementias, with more than two million deaths annually. And unlike COVID-19 ("coronavirus disease, 2019"), there's no "flattening the curve" here. Therapies for Alzheimer's, let alone a cure, have proved elusive in the more than 100 years since the ailment was first recognized. But as we reveal in this year's Future of Medicine report, "A New Era for Alzheimer's," starting on page 26, scientists are at long last reassessing the basic physiology and biology of the disorder to find new paths forward (*page 30*). Along the way, they are taking a close look at the "amyloid hypothesis" that has dominated research in the field for decades (*page 34*) and paying more heed to underappreciated risk factors such as the ways that menopause may explain the higher prevalence of dementia in women (*page 37*) and the role of air pollution in driving the disease forward (*page 42*).

Will this ostensible inflection point finally lead to effective treatments? It's too soon to tell, but with guarded optimism we carry on hoping for a breakthrough.

At least with coronavirus, we all have some agency over the blight. Governments are enacting civic restrictions, and people are undertaking "social distancing." I hope these measures will help, but current predictions suggest the pandemic will continue for many months. Whatever the future may hold, stay safe and trust in science, not fear, to guide the way. And remember, subscribers have access to every issue online: visit sciam.com/digital-access for more information. SA

Illustration by Nick Higgins

January 2020

BRAIN EXERCISES

In devising recommendations for exercise regimens to enhance cognition in healthy individuals and those experiencing cognitive decline, as discussed by David A. Raichlen and Gene E. Alexander ["Why Your Brain Needs Exercise"], scientists would do well to talk to experienced older runners, cyclists and dancers. For example, many runners and cyclists participate in group runs and rides, where social interaction might provide enhanced mental stimulation more than exercising solo.

Also, expecting older runners to take up trail running if they do not already do so is unrealistic. For someone like me, who has osteoporosis, trail running has risks. Simply varying one's route while running, particularly in a city, would be a better option.

Roxane Sismanidis *Washington, D.C.*

Raichlen and Alexander conjecture that physical activity outdoors such as running on trails may yield as good or better benefits as indoor treadmill work. This would hardly be surprising because our hominin ancestors exercised outdoors with constant physical and cognitive challenges.

I run on city sidewalks, and I'm constantly challenged by weather, pedestrians, traffic, traffic signals, uneven pavements, dog waste, the gooey residue of gingko fruit and—when I run with a partner—managing a conversation on top of everything else. Researchers might do well to test vulnerable subjects under a version of these conditions, such as jogging in an exercise yard with a simplified obstacle course while following instructions from a coach. A model closer to square dancing might also prove useful to test because group dancing involves cooperative social stimulation in addition to vigorous and changing activity.

Martha Cornog *Philadelphia*

"Our elections must have analog audits, not digital ones."

ALLEGRA DENGLER

CITIZENS FOR VOTING INTEGRITY NEW YORK

LONELY PLANET

"The Galactic Archipelago," by Caleb Scharf, argues that we have likely not found other spacefaring civilizations because our planet is in an out-of-the-way spot during a lull in waves of exploration or settlement.

For me, the critical question is whether H. G. Wells was right, and our native ecosystem would probably destroy invaders, or whether invasive species more often have the advantage. We still don't know whether life on Earth sprang up spontaneously from nonliving matter or whether it evolved once and spread from there. If the latter is the case, then Scharf's model sounds ominous. We may be out on a galactic limb and vulnerable to a huge array of pathogens.

J. Gunn Coolidge *Chevy Chase, Md.*

Sending our massive selves on an interstellar journey requires huge energy at anything near light speed, and at a more modest speed, journey times to even fairly near stars could be hundreds of years. Surely we will instead send out very small spaceships, at a few kilograms of mass, that can report back with pictures after a few years? That's what we should be looking for: small spaceships zipping through our solar system!

Stanley Waterman *Hitchin, England*

Scharf's article presupposes that technological life will be widespread. Such ideas tell us more about ourselves than about the universe: Life arose quickly on Earth, and prokaryotes did their stuff successfully despite the vagaries of the environment, which suggests it may be common. Complex life, on the other hand, to the best of our knowledge, arose only once. The implication is that it's an extremely improbably event.

James Fradgley *Wimborne, England*

SCHARF REPLIES: One of the great challenges of addressing the question "Where is everybody?" is that there are endless caveats and propositions that can seem absolutely necessary. The problem is that we just don't know how to weight their importance. Our own sense of agency and terrestrial bias gets in the way. The model I describe attempts to strip things down to a simple premise that also offers a constraint from Earth's paleontological record. I think it's good that there is incompleteness to this model. It represents a kind of theoretical minimum, a starting point in a vast array of cosmic possibilities. Indeed, it can—and, I hope, will—be developed to quantitatively evaluate the effects of further assumptions.

NO-CONFIDENCE VOTE

"One Phone, One Vote," by Wade Roush, discusses software developed to ensure votes are counted correctly. But technology will never make elections more secure. And praising Senator Mitch McConnell of Kentucky for initially releasing a mere $250 million for election security (since followed by a woefully still inadequate $425 million), without any provisions banning hackable voting machines, is off base.

Our elections are under attack from sophisticated adversaries, foreign and domestic. They must have analog audits, not digital ones. Procedures must be in place for hand counts of hand-marked paper ballots to ensure that any electronic vote count is accurate.

Allegra Dengler

Citizens for Voting Integrity New York

WHO'S A PRETTY BIRD?

In "The Surprising Power of the Avian Mind," Onur Güntürkün writes that his study with Eurasian magpies demonstrated the first observation of a bird exhibiting self-recognition in a mirror test.

This is simply false. Almost four decades ago I and my colleagues, including noted Harvard University psychologist B. F. Skinner, published a paper in *Science* showing the same behavior in pigeons. Birds used a

mirror to locate a spot on their body that they could not see directly. Although this kind of behavior has traditionally been attributed to a self-concept or other cognitive process, our experiment suggested an environmental component.

Further, it's clear there are different degrees of self-awareness/self-recognition. For instance, we didn't report in our paper that the pigeons attacked their own reflection in the mirror. Indeed, we humans are often as oblivious to certain aspects of who we are as those birds were.

Robert Lanza *Wake Forest University*

GÜNTÜRKÜN REPLIES: I do not think that Lanza's study—or a successful replication of it published by Japanese researchers in 2014—shows self-recognition in pigeons.

Using operant conditioning, organisms can be brought to do various behaviors. In both experiments, pigeons were stepwise conditioned to peck a dot on their body that they could see only in a mirror. In Lanza's paper, that result was achieved after first training the birds to peck on visible dots on their body, then conditioning them to peck on dots on the wall and then going through several intermediate steps involving the mirror.

This process is completely different from the procedure used in apes, elephants and magpies. Here the animals are first accustomed to a mirror for some hours. During this time they are not trained to touch their body or to attend to the mark. Then the mark is placed, and the behavior of the animal is observed. In the case of the magpie study, my colleagues and I used various control conditions (no mirror and/or a black mark that wasn't visible to the birds).

Our magpies were never conditioned to, for example, scratch the area under their beak, attend to a mark or look behind the mirror. They acted spontaneously. This is the critical difference between our study and Lanza's, and these papers therefore require different interpretations. To give an extreme example: we could condition monkeys to type "to be or not to be," but we should not subsequently infer that they think about classic literature.

I agree with Lanza that there are possibly different degrees of self-awareness/self-recognition. But I disagree that conditioning the animals can solve this point.

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Get Out of Our Faces

Facial-recognition tech is invasive, inaccurate—and spreading

By the Editors

State and local authorities from New Hampshire to San Francisco have begun banning the use of facial-recognition technology. Their suspicion is well founded: these algorithms make lots of mistakes, particularly when it comes to identifying women and people of color. Even if the tech gets more accurate, facial recognition will unleash an invasion of privacy that could make anonymity impossible. Unfortunately, bans on its use by local governments have done little to curb adoption by businesses from start-ups to large corporations. That expanding reach is why this technology requires federal regulations—and it needs them now.

Automated face-recognition programs do have advantages, such as their ability to turn a person's unique appearance into a biometric ID that can let phone users unlock their devices with a glance and allow airport security to quickly confirm travelers' identities. To train such systems, researchers feed a variety of photographs to a machine-learning algorithm, which learns the features that are most salient to matching an image with an identity. The more data they amass, the more reliable these programs become.

Too often, though, the algorithms are deployed prematurely. In London, for example, police have begun using artificial-intelligence systems to scan surveillance footage in an attempt to pick out wanted criminals as they walk by—despite an independent review that found this system labeled suspects accurately only 19 percent of the time. An inaccurate system could falsely accuse innocent citizens of being miscreants, earmarking law-abiding people for tracking, harassment or arrest. This becomes a civil-rights issue because the algorithms are more likely to misidentify people of color. When the National Institute of Standards and Technology reviewed nearly 200 facial-recognition systems, it found that most of them misidentified images of black and East Asian people 10 to 100 times more often than they did those of white people. When the programs searched for a specific face among multiple photographs, they were much more likely to pick incorrect images when the person being tracked was a black woman.

Some companies are attempting to improve their systems by feeding them more nonwhite and nonmale faces—but they are not always doing it in ethical ways. Google contractors in Atlanta, for example, have been accused of exploiting homeless black people in the company's quest for faces, buying their images for a few dollars, and start-up Clearview AI broke social media networks' protocols to harvest users' images without their consent. Such stories suggest that some companies are tackling this problem as an afterthought instead of addressing it responsibly.

Even if someone releases improved facial-recognition software capable of high accuracy across every demographic, this technology will still be a threat. Because algorithms can scan video footage much more quickly than humans can, facial recognition allows for constant surveillance of a population. This is already happening in China, where the authoritarian government is using the tech to suppress its Uighur ethnic minority and zero in on individuals' movements. These systems can easily be used to treat every citizen like a criminal, which destroys individual privacy, limits free expression and causes psychological damage.

In a democratic country such as the U.S., the government needs to protect all its citizens against these kinds of measures. But existing bans on the technology create an inconsistent patchwork of regulations: some regions have no restrictions on facial recognition, others ban police from applying it, and still others prevent any government agencies or employees from using it.

Federal regulations are clearly needed. They should require the hundreds of existing facial-recognition programs, many created by private companies, to undergo independent review by a government task force. The tech must meet a high standard of accuracy and demonstrate fairness across all demographic groups, and even if it meets those criteria, humans, not algorithms, should check a program's output before taking action on its recommendations. Facial recognition must also be included in broader privacy regulations that limit surveillance of the general population—because other identification tools that flag people based on their gait or even their heartbeat pattern are already in development.

Americans have always been fiercely protective of the right to privacy. Technologies that threaten that must be controlled. SA

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Preserve the Night Sky

Thousands of new satellites could ruin a view that has inspired and connected billions of people throughout history

By Ronald Drimmel

The company SpaceX has already launched hundreds of its Starlink satellites, with plans to put as many as 42,000 of them in Earth orbit. Its goal is to provide high-speed Internet to billions of people. Moving toward that kind of access is laudable and important, but it comes at a cost. Glittering with reflected sunlight, these first orbiters, sent up in the past year, are brighter than 99 percent of the 5,000 or so other satellites now circling Earth, and obviously there are going to be a lot more [see "Satellite Surge," on page 68]. This proliferation is bad for astronomy: the probability of a Starlink satellite crossing a telescope's field of view and ruining an observation will be quite high near sunrise and sunset, when the objects are most brightly illuminated. For that reason, more than 1,800 of my fellow astronomers have signed a petition calling for governments to protect the night sky from this incursion.

This artificial mega constellation, and others being planned, will impact more than astronomy. The current crop of Starlink satellites is also easily visible to the naked eye in a moderately dark sky, and ultimately more than 100 moving points of light could be observable overhead near dawn and dusk from any point on the planet. They would then be about as numerous as the brightest stars that are easily seen above the horizon—the same stars used to trace the constellations.

Humanity is a mix of cultures that originated in diverse places, with diverse histories, but virtually all of them have stirring or cautionary stories inspired by that same star-studded celestial dome. Are we about to lose something that has intangibly bound us together, a common experience that has played its part in making us one human family, in exchange for a modern convenience?

In response to protests, SpaceX has promised to address the visibility problem by, for example, applying experimental coatings—essentially painting the satellites black—but the company's aggressive launch schedule remains unchanged. And the satellites' illuminated surfaces are mostly their solar panels—exactly the part that cannot be painted over.

Unfortunately, at present no regulations govern how bright a single satellite can be, let alone thousands of them together. It has been suggested that the Federal Communications Commission's working assumption that satellites have no significant impact on the environment could be challenged in court, but even then, one nation's laws do not hinder another country's launches. Space literally has no borders, and the sky will need to be protected from orbital illumination at an international level.

UNESCO maintains a registry of World Heritage sites—places of unique and outstanding cultural or natural value to humanity—and is dedicated to their preservation. For some of these locations, such as the Namib Sand Sea and Gran Canaria's Risco Caído, their view of the night sky is a defining characteristic making them worthy of World Heritage status. Unfortunately, under the World Heritage Convention, the UNESCO registry is limited to specific territories, and the sky is attached to no place in particular. So although UNESCO has declared the sky part of humanity's universal heritage, it seems that the unique quality that makes that sky important to all of us excludes it from being protected. Given the planetary consequences, we hope that the United Nations will find a way to think outside of the box to save the sky for everyone.

Until now the dark sky needed no protection. Beyond human reach, it was our unobstructed window on the universe, an expanse unreachable and unchangeable. The transcendent beauty of a star-filled sky reminds us, as it did our ancestors, that we and our problems are small and that part of what makes us human may lie in our ability to recognize and admire the wonder and beauty of a universe larger than us—yet of which we are a part. The use of space as a common resource, by satellite operators in particular, should not destroy our only window on our world.

When I was growing up in Montana, it was a game to be the first to find a moving satellite among the host of stars in the night sky. Soon it could be a game to recognize the constellations behind a swarm of moving points of light. Astronomy will survive; I am much more afraid that we are all about to lose the very thing that inspired me to become an astronomer. SA

Ronald Drimmel is a research astronomer from the U.S. currently living in Italy and working at INAF, the Italian National Institute of Astrophysics.

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Illustration by Martin Gre

Normal Person

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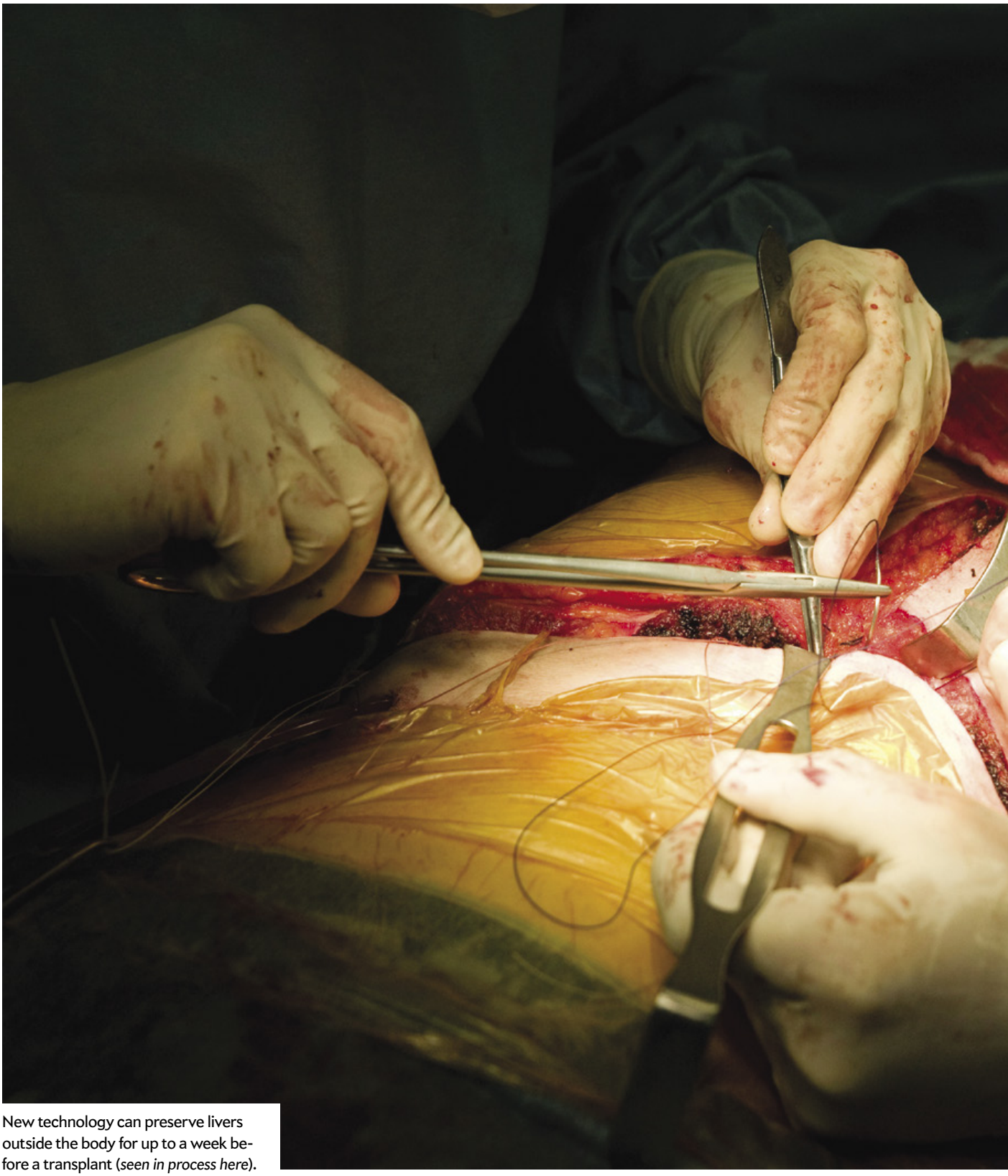
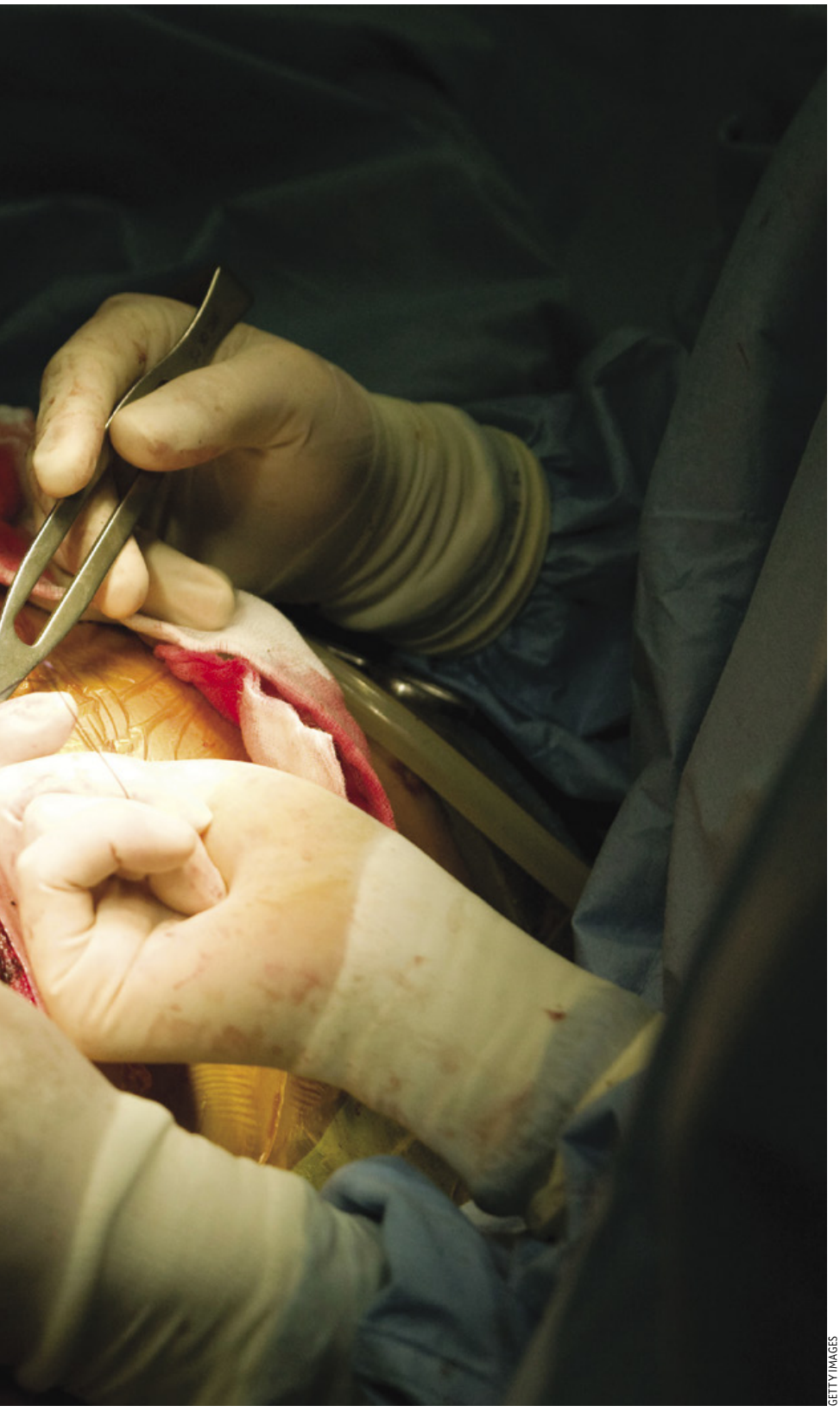


New technology can preserve livers outside the body for up to a week before a transplant (*seen in process here*).



GETTY IMAGES

INSIDE

MEDICAL TECH

Staying Alive

A new machine preserves livers for a week outside the human body

More than 1,000 people in the U.S. died while waiting for a liver transplant in 2018, partly because standard preservation methods can keep a donor liver alive outside the body for only about 24 hours. But now, in a feat of medical engineering, scientists have developed a machine that can keep a liver functional for a week or more. It has not yet been used for human transplants, but the technology represents a leap forward in the field of organ preservation.

Many donor livers do not meet the criteria for transplantation, because they are too old, contain too much fat or have been damaged (by cardiac arrest, for example). Researchers say the new device could keep livers alive long enough to repair themselves—something they can do to some extent in the body—and give doctors time to better assess the organs' condition. "We decided to [study the livers] for one week because this is the amount of time you need for a liver to regenerate" in patients who have had part of the organ removed, says Pierre-Alain Clavien, head of surgery and transplantation at University Hospital Zurich and senior author on a paper describing the research. He says this preservation technique could especially benefit some liver cancer patients, who could have noncancerous portions

of their own livers kept alive for later reimplantation to circumvent problems related to tissue rejection.

The standard method for preserving donor livers is flushing them with a cold solution and putting them on ice, where they can remain viable for 12 to 18 hours. Recently scientists developed a method of cooling livers without freezing them, which can extend that time to 27 hours. But this is still not long enough for an injured liver to repair itself, Clavien says.

> "From a clinical perspective, [keeping livers alive] just a few extra hours will help."
>
> —Korkut Uygun *Harvard Medical School*

The new machine buys crucial time by mimicking key features of the human body. The setup pumps blood through the organ—a process called perfusion—at carefully controlled pressures and oxygen levels. A sugar solution provides energy to red blood cells going through the liver, and the hormones insulin and glucagon are injected to maintain glucose levels. A dialysis unit removes wastes and keeps electrolytes in balance. And an inflatable balloon positioned under the liver replicates the movement of the diaphragm during breathing, which prevents tissue damage from constant pressure on the organ.

The researchers developed and refined their device using pig livers before trying it with human ones. They managed to preserve a total of eight healthy pig livers for one week and successfully transplanted three into live pigs, which survived the surgery. After transplantation the perfused livers showed levels of injury markers comparable to those of five livers that had instead been stored on ice for several hours before transplantation.

The team then tested the machine with 10 human livers that multiple European transplant centers had rejected because of the organs' poor quality. Liver damage can be measured by an increase in proteins called damage-associated molecular patterns (DAMPs); of the 10 livers in the experiment, six showed a decrease in DAMPs and other signs of damage after time in the machine. "We can now consider injured human livers for transplantation without endangering a patient life," Clavien says. He and his colleagues described their work this past January in *Nature Biotechnology*.

"It's a very well-done study," says Korkut Uygun, a surgeon and bioengineer at Harvard Medical School, who was not involved in the new research. "From a clinical perspective, [keeping livers alive] just a few extra hours will help." The study's biggest limitation, Uygun says, is that only 60 percent of the livers remained stable after a week on the machine— if they were healthy livers, "a 40 percent failure rate is not acceptable in the world of transplantation." Uygun is also not convinced the machine can actually enable liver regeneration as opposed to just preserving them. "Regeneration is a tough thing," he says. "The potential is incredible, but we need more time to show this."

The significance of the new findings can be summarized in one word: time, says Stefan Schneeberger, head of transplant and hepatobiliary surgery at Innsbruck Medical University in Austria. "It's the first example of technology allowing for preservation of an organ for a week. That is kind of a milestone," says Schneeberger, who was not involved in the study. He says there is not much evidence that the machine can improve the quality of the livers, and actual "regeneration" is likely further off—but it remains the ultimate goal.

Although the results are promising, the researchers have yet to demonstrate the preserved livers' long-term functionality. The next step is to perform transplant survival experiments in large animals, Schneeberger says. If those experiments are successful, they will make more livers usable for transplant into human patients who have low priority on waiting lists—and Clavien says this could happen as early as this year. In the future, he adds, the new machine could theoretically be used to preserve other organs such as hearts or kidneys.

—*Tanya Lewis*

Rogue waves can pose serious danger.

JOHN LUND *Getty Images*

PHYSICS

Surf's Way Up

A new method can predict the formation of massive rogue waves

When giant waves—sometimes 30 meters tall, many times the height of the surrounding crests—suddenly rear up out of the ocean, they pose severe threats to even the largest craft. Unlike tsunamis, which may follow a large undersea earthquake, these so-called rogue waves have no known definitive origin. Nor can they be predicted. Understanding how they form is key to forecasting where and when they might arise.

A group of mathematicians—Eric Vanden-Eijnden of New York University, Giovanni Dematteis and Miguel Onorato, both at the University of Turin in Italy, and Tobias Grafke of the University of Warwick in England—has now demonstrated a new way to predict rogue waves in experiments using a massive water tank. Their approach draws from the mathematical theory of large deviations, which quantifies how rare events occur. They treated rogue waves as a statistical entity called an instanton, a waveform that also arises from calculations in particle physics, information theory and risk management.

The scientists honed their model, described last December in *Physical Review X,* by mimicking rough sea conditions within a 270-meter-long water tank in Norway. The tank's machinery generated waves with particular characteristics the researchers could

choose; by crashing tailored waveforms into one another, they identified centimeter-scale precursors that resulted in waves up to five times the height of the surrounding ones.

The theory of large deviations also suggested that any combination of waves that leads to a significant height change will create a large wave with one distinctive shape, regardless of initial conditions—mathematically, wave formation should take the most likely route that leads to a rare event. And the tank measurements proved that true. "All rogue waves are alike," Vanden-Eijnden says, "but each ordinary wave is ordinary in its own way."

The team's model "seems to reconcile the two main theories used so far to explain large and rogue wave formation," says Alvise Benetazzo, a researcher at Italy's Institute of Marine Sciences, who was not involved in the study. One theory suggests they come from smaller waves simply combining and piling up, and the other proposes that variations in wave shapes amplify height differences exponentially. Neither model had fully aligned with earlier observations or experiments.

But the new calculations account for both effects, which contribute in different amounts based on water conditions, and they can be used to estimate the likelihood and height of a rogue wave arising from any set of ocean conditions. The team is optimistic that if adapted to real-world oceans with winds, currents and movement in any direction, the model could be integrated into a prediction system on ships, towers and platforms.

"Many experiments still must be performed, especially in the field," Benetazzo says. "That's the real playground where we want to explain rogue wave formation." —*Rachel Berkowitz*

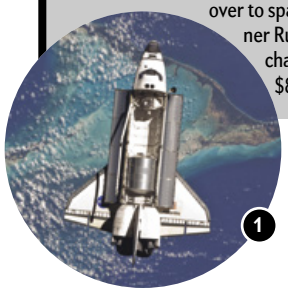
SPACEFLIGHT

Countdown to Commercial Crew

NASA approaches the end of a winding path to commercial astronaut launches

When the space shuttle *Atlantis* landed and rolled to a stop at Florida's Kennedy Space Center in 2011, bringing the 30-year shuttle program to a close, NASA hoped to fly U.S. astronauts onboard privately developed space taxis within four years. But budget shortfalls added two years to development schedules, and then technical problems with parachutes and launch escape systems pushed key flight tests to 2019. Now SpaceX—the company selected along with Boeing in 2014 to fly crews to and from the International Space Station—is finally on the cusp of launching two NASA astronauts on a long-awaited trial run. Boeing plans to follow, possibly this year, although the company ran into software glitches during its uncrewed test flight last December. Here's a look at the ups and downs of NASA's decade-long effort to restore human orbital spaceflight in the U.S. —*Irene Klotz*

JULY 2011 A four-person crew, headed by then NASA astronaut Chris Ferguson, returns from a nearly 13-day cargo run to the space station onboard the shuttle *Atlantis*, capping the 135th and final mission in the three-decade shuttle program. Crew ferry flights are turned over to space station partner Russia, which today charges about $86 million per seat.



1

SEPTEMBER 2014 Boeing and SpaceX win contracts to develop transportation systems and fly NASA astronauts. Boeing receives $4.2 billion for two test flights to the space station—one uncrewed and one crewed—and six operational missions. SpaceX bids and receives up to $2.6 billion for a similar commitment. "Knowing I could have bid more, after the fact, I sure wish I would have bid more," SpaceX president Gwynne Shotwell quipped in 2018. "I hate to talk about profit when we're flying astronauts, but this will [still] not be a losing proposition for SpaceX."

2

MAY 2015 SpaceX demonstrates how its Crew Dragon capsule, also known as Dragon 2, would fly itself to safety if its Falcon 9 rocket failed on the launchpad or shortly after liftoff.

3

JULY 2015 NASA embeds four astronauts—Bob Behnken, Doug Hurley, Sunita Williams and Eric Boe—at SpaceX and Boeing to learn about the new spacecraft and pass along hard-learned lessons from the shuttle program.

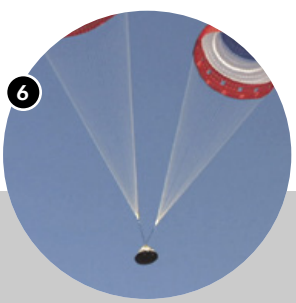
4

JUNE 2018 A propellant leak during an engine test for the Boeing CST-100 Starliner's emergency escape system, which flies a crew to safety in case of an accident during launch, spurs a valve redesign.

SEPTEMBER 2016 A SpaceX Falcon 9 rocket, set to carry an Israeli communications satellite into orbit, explodes on the pad while being fueled for a routine test firing of its engines before launch. The accident prompts a redesign of pressure vessels inside the rocket's fuel tanks and raises questions about the company's plan to fuel rockets with crews onboard.

AUGUST 2018 NASA assigns astronauts to the first four Commercial Crew missions. Behnken and Hurley begin training for a SpaceX Crew Dragon flight test, and Victor Glover and Mike Hopkins begin training for Dragon's first operational mission. Rookie astronaut Nicole Aunapu Mann is assigned along with Boe and Ferguson (who joined Boeing following the shuttle's retirement) for a flight test on Boeing's Starliner; Williams and Josh Cassada are assigned to Starliner's first operational mission. Boe is later pulled from the flight for medical reasons and replaced by Mike Fincke.

5



6

MARCH 2019 A SpaceX Falcon 9 sends an autonomous Crew Dragon capsule with 400 pounds of supplies and equipment into orbit on its first trip to the space station, the Demo-1 mission. The capsule docks at the station for five days before undocking, burning its engines to leave orbit and successfully parachuting into the Atlantic Ocean off Florida.

APRIL 2019 Following Demo-1, SpaceX's Crew Dragon capsule explodes on a test stand during preparations for a static test firing of the capsule's emergency escape system engines.

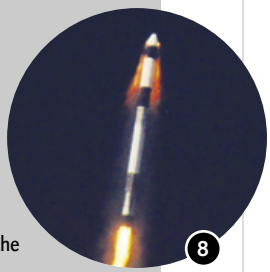
NOVEMBER 2019 Boeing tests Starliner's abort system by firing the capsule off of a test stand in New Mexico. One of Starliner's three parachutes fails to deploy, but the capsule—as designed—safely lands with two chutes.

7

SPRING 2020 Behnken and Hurley are poised to be the first NASA astronauts to fly to the space station onboard a U.S. vehicle since the shuttle program ended. The flight test is the final milestone before certification and the start of routine crew flights by SpaceX.

FEBRUARY 2020 The spacecraft for Dragon's Demo-2 mission, its first crewed flight test, arrives at the Kennedy Space Center.

JANUARY 2020 A Falcon 9 rocket's engines are intentionally shut down 84 seconds after liftoff from Kennedy Space Center to test Crew Dragon's abort system during flight. The capsule separates from the Falcon 9 and fires thrusters to fly away. As expected, the rocket is ripped apart by aerodynamic forces while Dragon deploys four parachutes to successfully splash down in the Atlantic Ocean.



DECEMBER 2019 An Atlas V rocket delivers Boeing's Starliner into orbit for the first time—an autonomous flight—but a software problem sets the craft's clock 11 hours ahead of the actual mission elapsed time, and the capsule runs too low on fuel to reach the station. Starliner spends two days orbiting on its own, testing systems, then successfully leaves orbit and lands by parachute in New Mexico. Boeing and NASA order engineers to completely reverify Starliner's software—roughly one million lines of code.

NASA (1 and 2); SPACE X (3, 8 and 9); AEROJET ROCKETDYNE (4); NASA'S JOHNSON SPACE CENTER (5); NASA'S JOHNSON SPACE CENTER AND BOEING (6); BILL INGALLS AND NASA (7)

ENGINEERING

Strike Back

Charge reduces airplane lightning hits

If you're in an airplane and suddenly hear a loud bang or see a flash outside the window, your plane may have just been hit by lightning. When this happens, pilots are supposed to land as soon as possible so the craft can be inspected for potential damage to its skin, structure or electronics. This protocol is paramount for safety but can create costly flight delays and cancellations. Recent tests show that, perhaps counterintuitively, the best way to reduce the chances of a strike may be to add an electrical charge to the outside of the aircraft.

During flight, positively and negatively charged particles called ions can build up on parts of an aircraft's surface, particularly on pointed features such as the nose, tail fins and wing tips. If a large difference in charge, or polarization, develops on the plane before it flies into a charged region of the atmosphere, ions are more likely to flow along the aircraft and complete an electrical circuit with the clouds, sparking a powerful discharge—a lightning bolt. Computer simulations conducted in 2018 by Carmen Guerra-Garcia, an aerospace engineer at the Massachusetts Institute of Technology, and Colin Pavan, a graduate student in her laboratory, revealed a possible solution to ion buildup: adding negative charge to the plane.

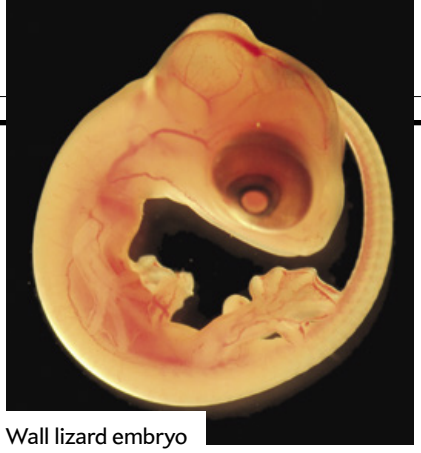
Last year Guerra-Garcia and Pavan tested a model plane with a 10-meter-tall electric field generator and subjected it to various conditions, measuring how charges accumulated and dissipated. The data, published in January in the *Journal of Geophysical Research: Atmospheres,* confirmed that ion flows (or "leaders") along the plane initiated lightning bolts—and that negatively charging the plane helped to prevent such discharges. The team is investigating how devices that pump ions onto the plane's surface could reduce polarization.

"Charging a plane sounds crazy, but adding negative charge to prevent buildup of positive charge could help stop a leader from forming," says Pavlo Kochkin, an aerospace engineer at the University of Bergen in Norway, who was not part of the work. In his own research, he records lightning hits on new aircraft test flights. Inspired by the M.I.T. results, he is creating a thundercloud simulator that can generate different levels of charged air and water vapor. A model plane might test how charge emitters reduce the chances of a strike. —*Mark Fischetti*

PARASITOLOGY

Parasites on the Brain

Lizard embryos host invaders



Wall lizard embryo

NATHALIE FEINER *Lund University*

When Nathalie Feiner spotted a tiny nematode worm wriggling in an embryonic lizard's brain from the French Pyrenees, she thought it was a freak accident. She was dissecting hundreds of common wall lizard embryos for a study and had never encountered this invader before—but soon she started finding them in more of the still unhatched reptiles' brains.

Intrigued, Feiner, then with the University of Oxford, and a colleague examined the embryos' parents. They found nematodes only in the ovaries of mothers that had produced infected embryos, suggesting the parasites were migrating to their offspring in a way researchers had thought impossible.

Parasites such as nematodes, which do not multiply in their hosts, often pass from mother to children through mammals' placentas or milk. But scientists had assumed that in birds and reptiles, the eggshell that forms around the developing animal acts as a barrier to such invasions. Parasite infection through a reptile egg had never been observed before, Feiner says: "It seems like we have hit on an entirely new lifestyle that these nematodes have evolved."

For a paper accepted by the *American Naturalist* last December, Feiner and her colleagues examined 720 eggs laid by 85 female common wall lizards from six locations. The researchers found the nematodes in lizards from only that first Pyrenees population. Infected females transmitted the parasite to between 50 and 76.9 percent of their embryos.

DNA analysis showed these nematodes are similar to, though much smaller than, a species found in the lizards' gut; researchers say they may have evolved from that species.

Feiner says scientists could have missed the possibility of egg transmission because they have mainly looked at parasites in birds and turtles, whose eggshells form shortly after fertilization when the embryo is just a clump of cells—too small to act as a host. But in lizards and snakes, the shells form when the embryo is bigger, making parasite transmission more plausible. James Harris of the Research Center in Biodiversity and Genetic Resources in Portugal, who was not involved with the work, says this form of transmission could be widespread if the team's hypothesis is correct.

Feiner suspects the nematode could change its host's behavior—a technique brain parasites often use to infect an animal's predators. For instance, mice infected with *Toxoplasma* drop their tendency to avoid cat urine. This makes them more easily eaten, transmitting the parasite to the next part of its life cycle. "Identifying the presence of 'our' nematode in a predator of the European wall lizard would make [this strategy] more likely," Feiner says. —*Sandrine Ceurstemont*

BIOLOGY

Ant-agonism

Ants do not attack if they cannot smell enemies' precise scents

Accurately distinguishing friend from foe is a matter of life and death for ants: mistaking an invader for a nest mate—or the reverse—can lead to fatal chaos.

Scientists have long observed ants deftly navigating through crowds, attacking only individuals that might be hostile. New research confirms how smell receptors on the insects' antennae hold the key to this selective violence: without them, ants are socially blind and will not attack.

"The current consensus was aggression between ants follows a simple rule: if [an ant] smells something different from the home colony, attack," says Laurence Zwiebel, a co-author on the new study and a biologist at Vanderbilt University. But the new research shows it is not that simple. Ants hold off on attacking if they cannot smell anything—or even if they do not recognize a scent. "Rather a precise signal present on the non-nest mate must be correctly decoded for aggression to occur," Zwiebel says.

He and his colleagues built on previous studies that identified a mix of odors on ants' exoskeletons, as well as odorant receptors that pick up these scents from others. The new study found that if the receptors were compromised, ants could no longer differentiate nest mates from intruders they would normally fight; instead they became docile. The researchers reported their findings in January in the *Journal of Experimental Biology*.

After designing a miniature dueling arena—a plate with plastic dividers—the scientists chemically manipulated the odorant receptors of Florida carpenter ants from the same and neighboring colonies, either blocking or overexciting the receptors. When the ants were placed into the arena and the dividers lifted, ants with disrupted receptors were meek even when faced with a stranger. "Our study clearly demonstrates that neither the lack of any odor nor the presence of a confusing odor was sufficient to elicit ant aggression," Zwiebel says.

Ants have more than 400 odorant receptors, and Zwiebel says a next step is to determine which of them must function correctly to decode an enemy's smell. (For this study, researchers dampened or excited all of them.)

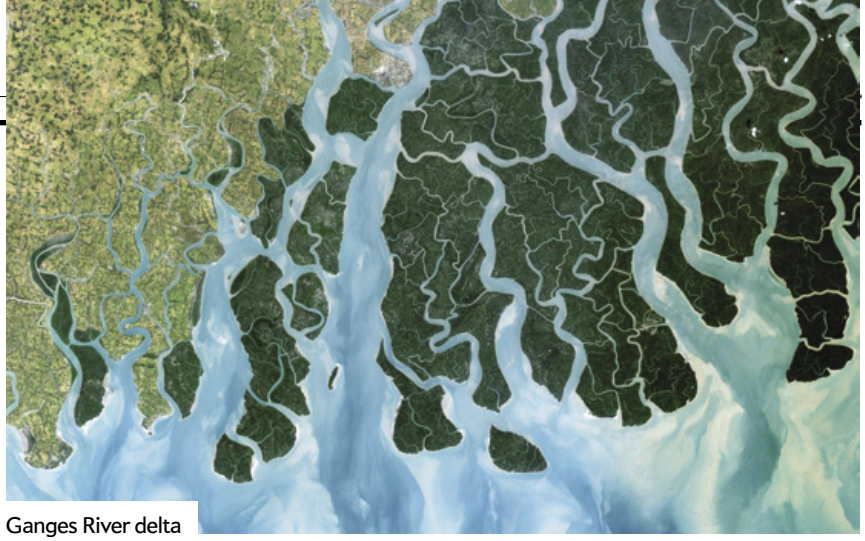
Volker Nehring, a biologist at the University of Freiburg in Germany, who was not involved with the study, says this research could also pave the way for other studies of how animals recognize one another. "We hardly understand how the ants know their own nest odor in the first place," he says, "and temporarily interfering with the receptors might be a good way to address that." —*Jillian Kramer*

Illustration by Thomas Fuchs

ECOLOGY

Deltas Rising

River deltas are gaining ground … for now



Ganges River delta

GETTY IMAGES

Earth's river deltas have long been home to vital ports and wetlands. Despite sea-level rise, these economic and ecological hotspots have expanded on the whole in recent decades, scientists have found—but this trend is unlikely to last. Geoscientist Jaap Nienhuis of Utrecht University in the Netherlands and his colleagues have pinpointed almost 11,000 river deltas in data from satellites and worldwide field studies. Using computer simulations, they estimated how tides, waves and human activity upstream affected each delta's size and shape from 1985 through 2015. In many watersheds along South America's eastern coast, as well as Asia's eastern, southern and southeastern coasts, the researchers found that deforestation increased sediment carried by rivers—and that deltas have grown accordingly. (The Ganges delta, as seen here, is one such example.) In North America, however, dams have trimmed the volume of sediment available to nourish many river deltas.

Although sea levels rose about 10 centimeters during the period studied, river deltas in aggregate gained about 54 square kilometers of new land each year, the researchers reported in January in *Nature*. But they say that growth is most likely only a short-term phenomenon. Molly Keogh, a wetlands ecologist most recently at Tulane University, who was not involved in the study, agrees; she notes that sea levels are projected to increase about 60 centimeters by the end of the 21st century. Also, delta sediments are notorious for compacting under their own weight over time.

This "double whammy," as Keogh describes it, will lead to an overall shrinkage of river deltas across the world in the coming decades. Beyond the loss of low-lying infrastructure and fisheries, consequences could include the inundation of major population centers and agricultural regions. —*Sid Perkins*

TECH

DIY Cell Cracker

For a few dollars, researchers replicated a gene-editing instrument that typically costs thousands

ElectroPen tools

CHRISTOPHER MOORE *Georgia Institute of Technology*

A new DIY machine for opening pores in cells relies on repurposed parts from a common lighter. Called the ElectroPen, it joins a tradition of "frugal science" that aims to equip students and field researchers with low-cost versions of pricey instruments.

"The future is synthetic biology: not just coding in a computer, but really coding living cells such that they help us with grand challenges of disease, of climate change, of environmental pollution," says ElectroPen co-creator Saad Bhamla, a bioengineer at the Georgia Institute of Technology. But editing a cell's genome requires more equipment than modifying computer code does. So Bhamla worked with a local high school science class for about two years to develop cheap versions of several necessary tools—including one called an electroporator.

For tasks such as testing drug reactions or modifying DNA, scientists must first breach protective cell walls. An electroporator forces these membranes open with a brief, high-power burst of electricity. "Electroporation is basically a way to create pores in different cells that allow you to then introduce nucleic acid, for example, [or] protein inside the cells," says Xavier de Mollerat du Jeu, director of product development at biotechnology company Thermo Fisher Scientific, who was not involved in developing the tool. Typical electroporators, which cost thousands of dollars, use electronic circuits to produce tailored shocks. But there is a cheaper method: piezoelectric crystals, which release an electric charge when they undergo mechanical stress. Bhamla's group published an open-source guide to making an electroporator from a piezoelectric butane lighter in January in *PLOS Biology*.

"Creative solutions are almost lurking under our noses," says Manu Prakash, a bioengineer at Stanford University, who once supervised Bhamla but was not involved in the new study. "All of us have used a spark lighter before, and one of the things I find beautiful is it's used [for] a very different purpose."

The ElectroPen produces a five-millisecond burst of 2,000 volts, whereas a commercial machine can be tuned to different durations and voltages for various applications. But the ElectroPen is much more accessible: anyone can build their own for a few dollars to crack at least one cell type. "There is definitely a need for low-cost entry to be able to have everyone do those experiments," du Jeu says. "It's good to democratize it." So far high school students have used an ElectroPen to modify *Escherichia coli* DNA so it produces fluorescent proteins.

Meanwhile Bhamla is already planning his next frugal science project. Making cheap instruments, he says, is "like providing a phone—you leave it to other people to think about what app they want to make on it, what cell they want to modify, what challenge they want to go after."

—Sophie Bushwick

ANIMAL BEHAVIOR

Migration Learning

Cory's shearwaters forge their own paths over the sea

In habitats across the planet, animals periodically drop everything to walk, fly or swim to a new locale—and lightweight tracking technology has given biologists their best-ever understanding of these seasonal treks. Wildlife such as whales and geese learn migration routes by following their parents and other older counterparts. Others, including small songbirds, inherit the distance and direction of their migration deep within their genetic code. And some animals use a combination of genetics and culture to guide their migration.

Another group of migrators does not quite fit either model, and researchers have only recently started to figure out how they find their way. Take the Cory's shearwater, an oceangoing petrel species that migrates over the Atlantic every year. The young do not migrate with their parents, so culture cannot explain their journeys. And the exact routes vary wildly from individual to individual, making genetics equally unlikely.

Cory's shearwaters are long-lived, rarely breeding successfully before age nine. This leaves an opening for learning and practice to develop their migration patterns. Researchers call this the "exploration-refinement" mechanism, and until now it has been largely hypothetical because of difficulties inherent in tracking migratory animals' movements over many seasons.

But a team of researchers has done exactly that by affixing small geolocators to more than 150 of the birds aged four to nine. The group found that younger birds traveled longer distances, for longer periods, and had more diverse routes than older birds. "We actually finally have evidence of [the exploration-refinement] hypothesis for migratory birds," says Letizia Campioni, a biologist at Instituto Universitário in Lisbon, who led the study. This is the first such evidence in a seabird, although earlier research has suggested that other long-lived birds might use the same strategy. The study was published in the January issue of the *Journal of Animal Ecology*.

Younger Cory's shearwaters are capable of flying just as fast as the adults—but they do not, suggesting that juveniles do more exploring, which gradually fades as they mature and settle into a preferred route.

Although it may seem less efficient than other strategies, "exploration refinement could be beneficial to birds and other organisms in a rapidly changing world due to unpredictable anthropogenic changes," says Barbara Frei, director of the McGill Bird Observatory, who was not involved in the study. "It might be safer to repeat a behavior that was recently successful than to rely on cues that were perfected long ago but might no longer be safe."

—Jason G. Goldman

IN THE NEWS

Quick Hits

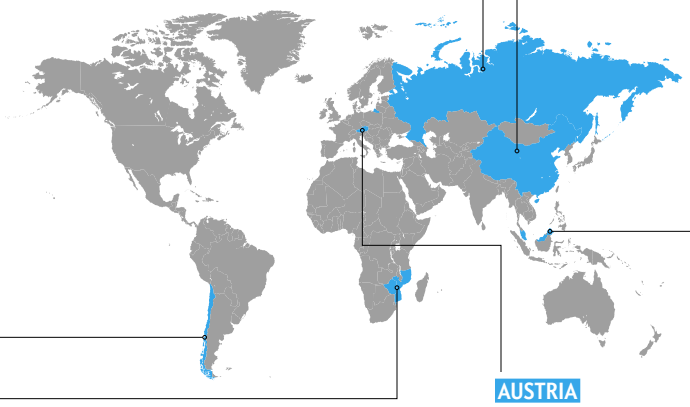
By Sarah Lewin Frasier

RUSSIA

A 46,000-year-old bird recovered from the Siberian permafrost is in such good condition that it looks like it died days ago, researchers say. It is the only nearly intact bird carcass found from the most recent ice age.

CHINA

Researchers in northern China uncovered fossils of the oldest green algae on record, a multicellular two-millimeter organism that lived a billion years ago—the earliest known ancestor of today's photosynthesizing plants.



CHILE

Baffled by unexplained skin lesions on blue whales near Chile, scientists shot darts by crossbow to take samples from the whales' blisters and fat in a bid to identify potential pollutant causes.

MALAYSIA

Scientists say they are scaling up an experimental farm that uses metal-loving plants to draw and harvest nickel from the soil in the Malaysian portion of Borneo. The expanded farm will cover 50 acres.

AUSTRIA

For the first time, engineers executed a new bridge-building technique with two vertical girders, erecting them upward before unfurling the span like an umbrella. Two such structures will form bridges across Austrian rivers. The process saves time and cuts down massively on the scaffolding needed to build horizontally.

ZIMBABWE AND MOZAMBIQUE

New research on African turquoise killifish, which live in ponds that dry up seasonally, reveals that their embryos can suspend development by up to two years, with no impact on their ultimate life span after hatching.

For more details, visit www.ScientificAmerican.com/may2020/advances

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Janet MacFadyen is author of five works of poetry, most recently *Adrift in the House of Rocks*, a collaboration with photographer Stephen Schmidt (New Feral Press, 2019), and *Waiting to Be Born* (Dos Madres Press, 2017). She holds a degree in geology and has written articles on natural history for *Natural New England*.

JOHN LITTLE

The Boulders of Lyell Canyon

I name them Upright, Lengthwise, Split
Down the Middle: these granites strewn
like milky stars. You could orient by them, find
your way through creek, meadow, and wood.
This one is here, and that one is there, its neighbor
next to both, old friends grinding down shards
of philosophy. It could take a million years
to see the argument to conclusion, points
split finer and finer, rubbed to a sheen,
into pebbles, then to sand in an hourglass.
They record the course of floods, huddle
together beneath parent slopes where they
were wrenched and scraped by glaciers, shaped
and molded by teachers of ice, which explains
their patience and hardness, having been milled
so interminably slowly to an exacting rule.
Now they languish, sun seeping into feldspars
and micas, into the quartzes until they quiver
with pure excitation—in heat and cold, wind
and stillness, through minutes and millennia—
and still radiate impassiveness.

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.*

Euthanasia and a Final Gift

Should it be easier for the terminally ill to donate organs?

By Claudia Wallis

The first time Fred Gillis noticed something was wrong he was on the ice, holding his hockey stick but somehow unable to shoot the puck. Was middle age catching up with him, or was it something more serious? Over the following months Gillis's arms continued to weaken. Soon it took two hands to brush his teeth, and he couldn't lift a plate to clear the dinner table. Gillis was 52 in 2015 when he got the diagnosis he dreaded most: amyotrophic lateral sclerosis (ALS), the deadly motor neuron disorder sometimes called Lou Gehrig's disease. "Fred had a co-worker whose husband had ALS," recalls his widow, Lana Gregoire. "He wanted to die from anything but that."

Both Gillis and Gregoire worked in Canadian law enforcement. They were pragmatic, realistic and familiar with death. "We used these three words," she says. "You have to *accept,* then you have to *adapt* and then you have to be at *peace*." A public servant to the core, Gillis found peace by participating in and raising money for ALS research. But a new Canadian law gave him an unexpected opportunity to make his dying days even more meaningful. In June 2016 Canada became the sixth country in the world to permit medical assistance in dying (MAID) to end intolerable suffering for terminally ill patients, and organ donation organizations had begun to develop guidelines that would allow people choosing MAID to also make a plan to donate their organs for transplant.

Gillis had not been a fan of the euthanasia law, but when he learned he could combine MAID with a plan to donate organs, "he was ecstatic," Gregoire says. "His attitude was, 'ALS, you can't take this away. We're going to give life to other people.'"

Combining euthanasia with organ donation may sound logical, but it is ethically fraught and not widely done. In 2017 the Netherlands became the first country to publish clinical guidelines for the practice. It established a key ethical principle: the decision to seek medical assistance in dying must precede and be separate from the organ donation plan, so that patients make their fateful choice without feeling pressure to donate. In Canada, each province has its own organ donation organization, and only some are working with MAID patients. The experience of three such organizations with the first 30 MAID donors was reported in a recent issue of the *New England Journal of Medicine.* In Canada, nearly two thirds of people who qualify for MAID have active cancer and are therefore ineligible to donate organs; others may be too elderly. The report looked at 56 patients who were deemed eligible, 30 of whom went on to donate a total of 74 lifesaving organs.

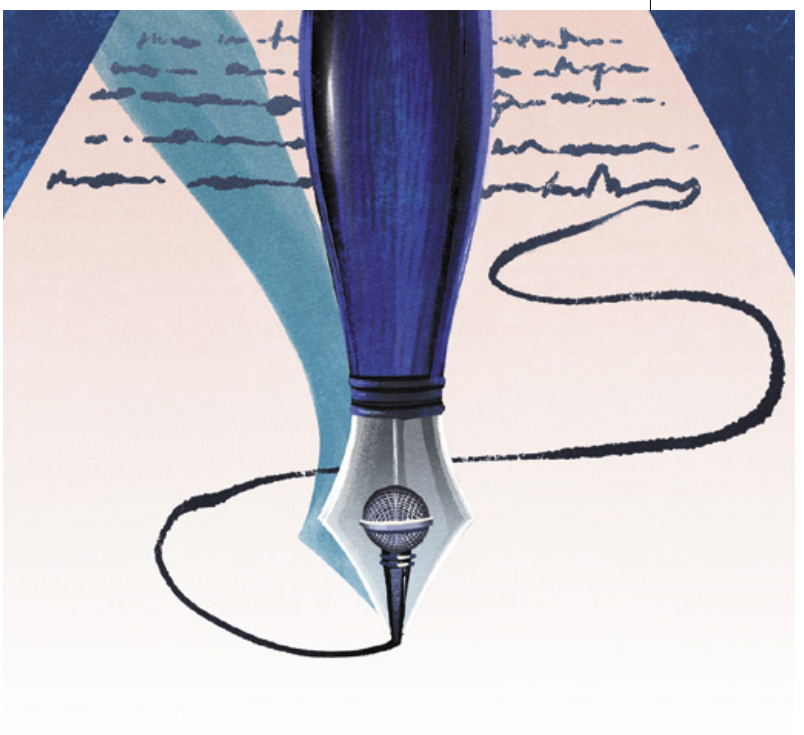
"The feedback we heard from these patients is that they want to hear about the opportunity and make that decision themselves," says Andrew Healey, chief medical officer at the Trillium Gift of Life Network in Ontario and a co-author of the report. "People feel comfortable saying yes, and people feel comfortable saying no." In other countries that permit euthanasia, he says, the patient typically must be the one to broach the idea of donation.

In the U.S., MAID is permitted in nine states and Washington, D.C., but has not been combined with organ donation. Of course, anyone with a terminal disease can designate their organs for donation, but such plans often fail because death comes too slowly, says Joshua Mezrich, a transplant surgeon at the University of Wisconsin School of Medicine and Public Health. Even if the patient is on life support and a decision is made to pull the plug, about 30 percent of the time the organs become nonviable as blood pressure drops and circulation grinds to a halt. Mezrich has written movingly about an ALS patient named Wayne Bender who fervently wished to donate a kidney while he was still alive and hoped to donate more organs after death. In the end, he could do neither. The kidney plan was vetoed by the hospital's legal experts out of concern that Bender might die as a result of donation—an event that would violate the Dead Donor Rule, a cardinal principle of organ transplantation. And Bender died too slowly for his organs to be taken after death.

Some experts have proposed a concept called imminent death donation that would allow the kind of kidney donation Bender had in mind, but its moral and legal status remain murky. Interestingly, donation works well after MAID because patients die quickly from the intravenous euthanasia drugs. Fred Gillis was able to donate two kidneys, his lungs and his liver when he died in April 2018. "He knew he was giving life, and that's all that mattered," Gregoire says. She and their three kids were by his side and toasted him that evening—at a hockey bar. "We knew he would like that." SA

Illustration by Fatinha Ramos

Wade Roush is the host and producer of Soonish, a podcast about technology, culture, curiosity and the future. He is a co-founder of the podcast collective Hub & Spoke and a freelance reporter for print, online and radio outlets, such as *MIT Technology Review*, Xconomy, WBUR and WHYY.



Seeking Software That Hears Better

In the speech-recognition business, 95 percent accuracy might as well be zero

By Wade Roush

Back in 2010 Matt Thompson, then with National Public Radio, forecast in an op-ed that "at some point in the near future, automatic speech transcription will become fast, free, and decent." He called that moment the "Speakularity," in a sly reference to inventor Ray Kurzweil's vision of the "singularity," in which our minds will be uploaded into computers. And Thompson predicted that access to reliable automatic speech-recognition (ASR) software would transform the work of journalists—to say nothing of lawyers, marketers, people with hearing disabilities, and everyone else who deals in both spoken and written language.

Desperate for any technology that would free me from the exhausting process of typing real-time notes during interviews, I was enraptured by Thompson's prediction. But while his brilliant career in radio has continued (he is now editor in chief of the Center for Investigative Reporting's news output, including its show *Reveal*), the Speakularity seems as far away as ever.

There has been important progress, to be sure. Several startups, such as Otter, Sonix, Temi and Trint, offer online services that allow customers to upload digital audio files and, minutes later, receive computer-generated transcripts. In my life as an audio producer, I use these services every day. Their speed keeps increasing, and their cost keeps going down, which is welcome.

But accuracy is another matter. In 2016 a team at Microsoft Research announced that it had trained its machine-learning algorithms to transcribe speech from a standard corpus of recordings with record-high 94 percent accuracy. Professional human transcriptionists performed no better than the program in Microsoft's tests, which led media outlets to celebrate the arrival of "parity" between humans and software in speech recognition.

The thing is, that last 6 percent makes all the difference. I can tell you from bitter experience that cleaning up a transcript that is 94 percent accurate can take almost as long as transcribing the audio manually. And four years after that breakthrough, services such as Temi still claim no better than 95 percent—and then only for recordings of clear, unaccented speech.

Why is accuracy so important? Well, to take one example, more and more audio producers (including myself) are complying with Internet accessibility guidelines by publishing transcripts of their podcasts—and no one wants to share a transcript in which one in every 20 words contains an error. And think how much time people could save if voice assistants such as Alexa, Bixby, Cortana, Google Assistant and Siri understood every question or command the first time.

ASR systems may never reach 100 percent accuracy. After all, humans do not always speak fluently, even in their native languages. And speech is so full of homophones that comprehension always depends on context. (I have seen transcription services render "iOS" as "ayahuasca" and "your podcast" as "your punk ass.")

But all I am asking for is a 1 or 2 percent improvement in accuracy. In machine learning, one of the main ways to reduce an algorithm's error rate is to feed it higher-quality training data. It is going to be crucial, therefore, for transcription services to figure out privacy-friendly ways of gathering more such data. Every time I clean up a Trint or Sonix transcript, for example, I am generating new, validated data that could be matched to the original audio and used to improve the models. I would be happy to let the companies use it if it meant there would be fewer errors over time.

Getting such data is surely one path to the Speakularity. Given the growing number of conversations we have with our machines and the increasing amount of audio created every day, we should not be thinking of decent automatic transcription as a luxury or an aspiration anymore. It is an absolute necessity.

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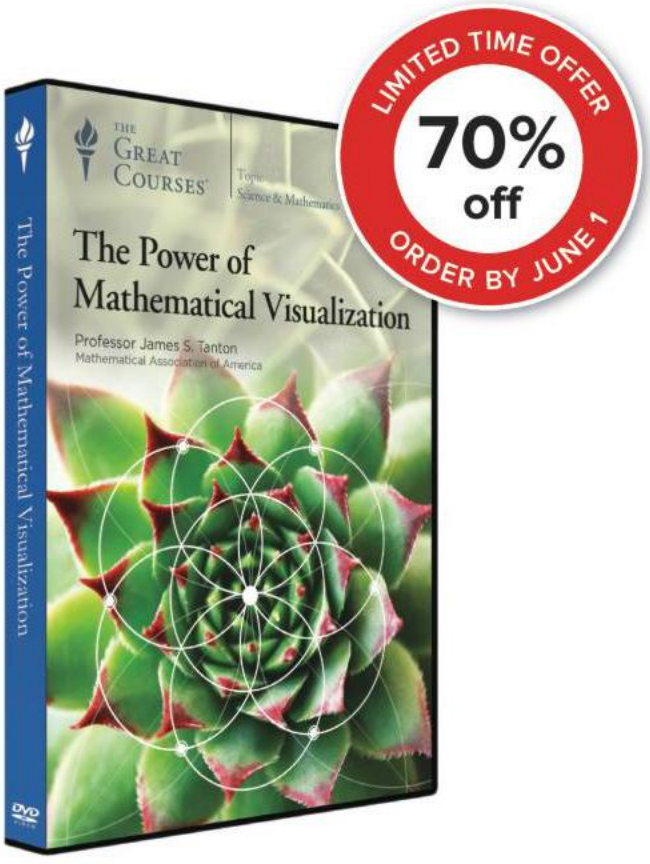

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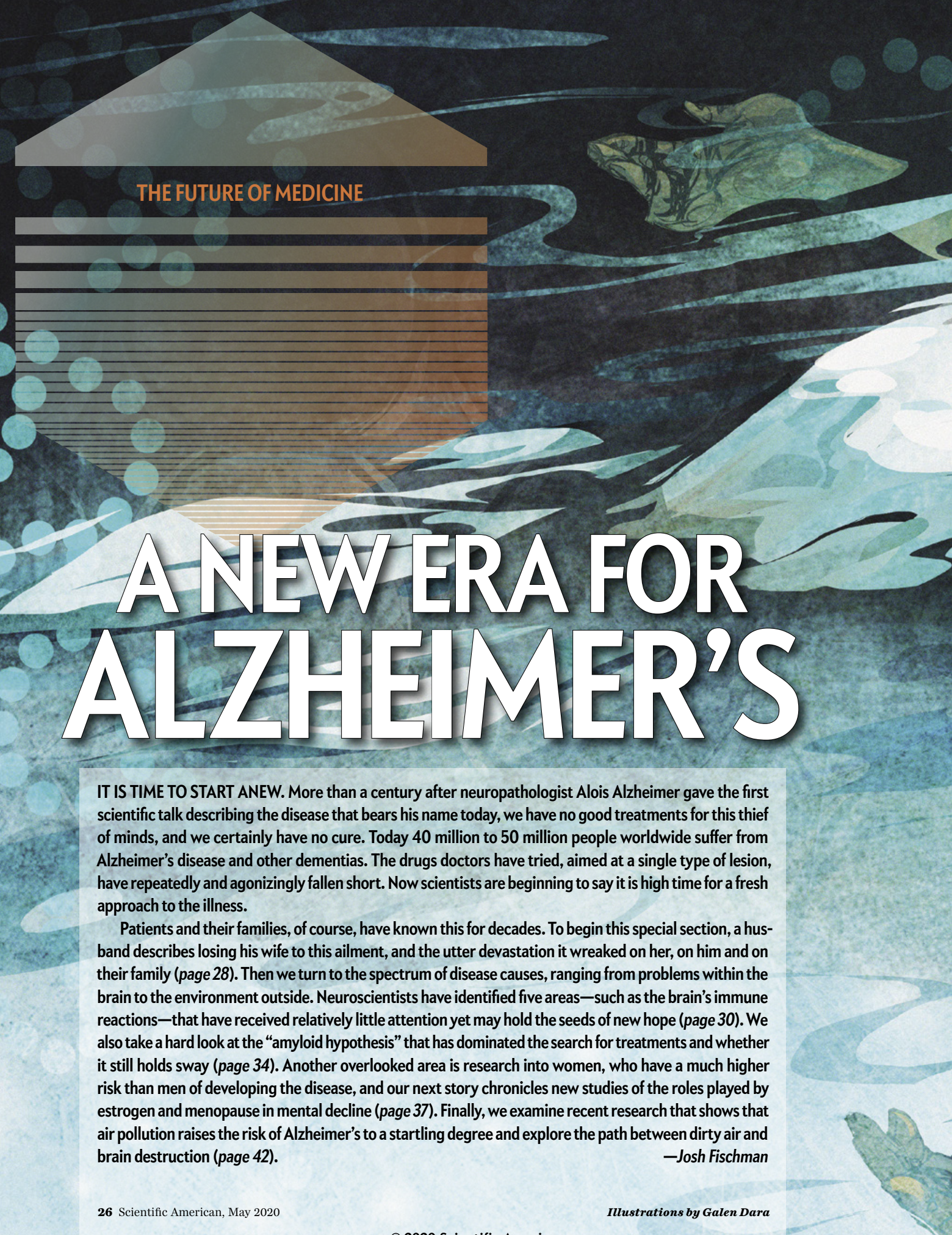


THE FUTURE OF MEDICINE

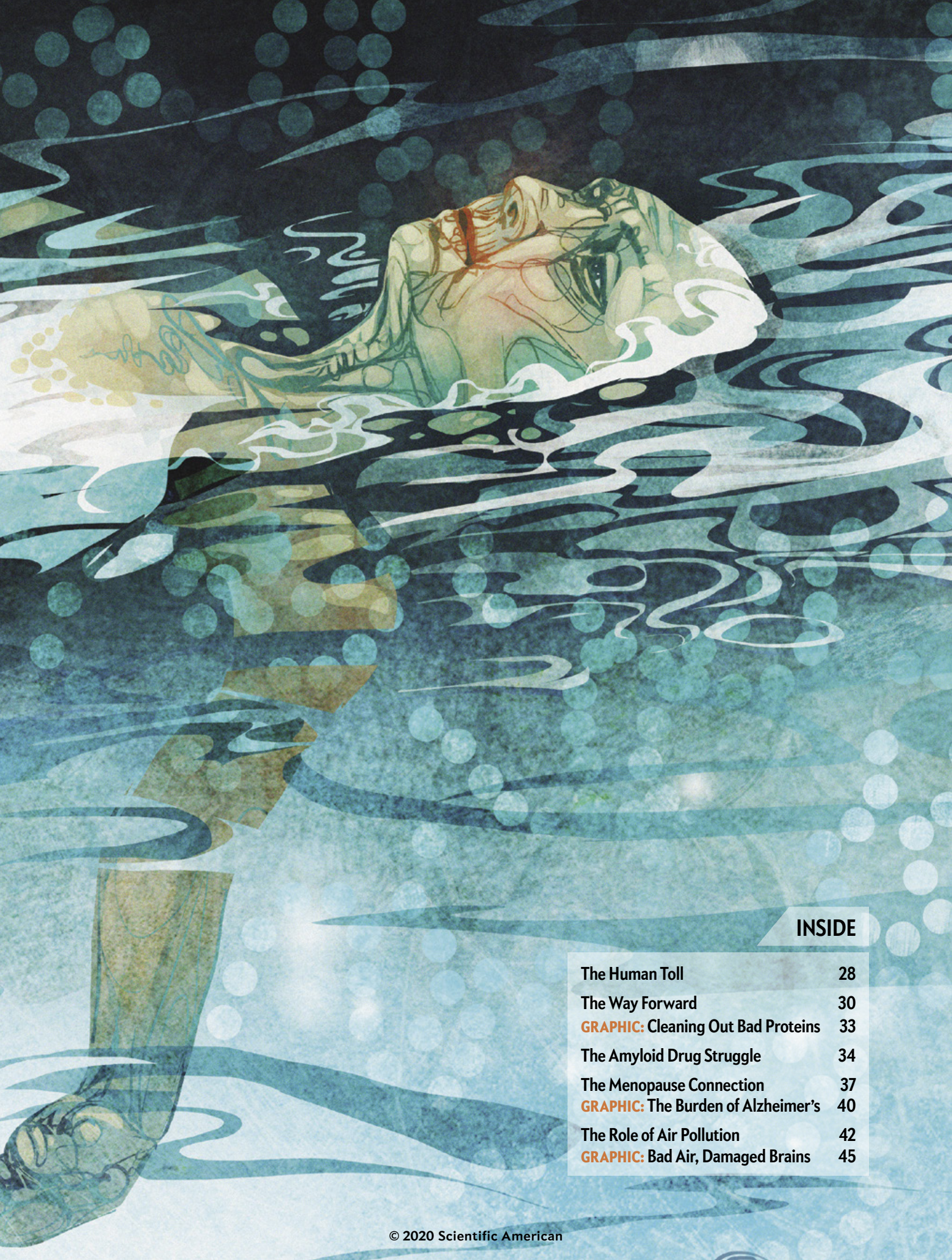
A NEW ERA FOR ALZHEIMER'S

IT IS TIME TO START ANEW. More than a century after neuropathologist Alois Alzheimer gave the first scientific talk describing the disease that bears his name today, we have no good treatments for this thief of minds, and we certainly have no cure. Today 40 million to 50 million people worldwide suffer from Alzheimer's disease and other dementias. The drugs doctors have tried, aimed at a single type of lesion, have repeatedly and agonizingly fallen short. Now scientists are beginning to say it is high time for a fresh approach to the illness.

Patients and their families, of course, have known this for decades. To begin this special section, a husband describes losing his wife to this ailment, and the utter devastation it wreaked on her, on him and on their family (*page 28*). Then we turn to the spectrum of disease causes, ranging from problems within the brain to the environment outside. Neuroscientists have identified five areas—such as the brain's immune reactions—that have received relatively little attention yet may hold the seeds of new hope (*page 30*). We also take a hard look at the "amyloid hypothesis" that has dominated the search for treatments and whether it still holds sway (*page 34*). Another overlooked area is research into women, who have a much higher risk than men of developing the disease, and our next story chronicles new studies of the roles played by estrogen and menopause in mental decline (*page 37*). Finally, we examine recent research that shows that air pollution raises the risk of Alzheimer's to a startling degree and explore the path between dirty air and brain destruction (*page 42*).

—Josh Fischman

Illustrations by Galen Dara



INSIDE

THE FUTURE OF MEDICINE

A NEW ERA FOR ALZHEIMER'S

THE HUM

Alzheimer's took my wife's memory and her life and tortured our family. There was nothing we—or medicine—could do to stop it

By Joel Shurkin

I HAVE LEARNED THAT WHEN SOMEONE YOU LOVE HAS Alzheimer's, he or she is not the only one facing memory issues. Do we remember the bright, sunny person full of life and creativity, or do we remember the person who no longer recognizes us, who lies in a bed in a nursing home, gasping for air? Do we remember the lover with whom we could share our body, our thoughts and our adventures or the person who cannot finish a sentence or find the bathroom? How do we live with the fact that the individual actually died years before his or her body stopped? The ghastliness of Alzheimer's seems to push out everything else. I am finding it hard to remember ordinary life with Carol before Alzheimer's.

My wife, Carol Howard, was diagnosed with early-onset Alzheimer's in her early 60s. I slowly watched her disintegrate, watched her beautiful mind be deconstructed part by part, watched sentience slowly fade until she was, well, not here.

When she learned the diagnosis, she was determined to fight the disease. She enlisted in two clinical trials of potential drugs, both of which failed. When we realized what was inevitable, she told me that she wanted me to scream for her when she was gone. She was angry that several decades' worth of Alzheimer's research had produced no hope. There is no cure; there is no good treatment.

I will tell you who she was and what she became. She was a woman of great beauty, with eyes of summer-sky blue. She was peaceful and brilliant, gentle and kind. I met her when she took a science communication course I taught at the University of California, Santa Cruz. She always put the right word in precisely the right place. Carol studied marine biology and wrote a popular book about her doctoral work with two Atlantic bottlenose dolphins. For 15 idyllic years we lived in the redwood forest of the Santa Cruz Mountains, writing. She eventually moved with me to Baltimore and worked at the Center for Alternatives to Animal Testing at the Johns Hopkins Bloomberg School of Public Health, an excellent job that she loved.

About six years ago odd things began to happen. Carol blacked out occasionally. Her libido disappeared. One night she sat in front of her office computer weeping because she had forgotten how to download a file. She stopped reading books. Soon there was medical testing, and then the dreadful diagnosis.

She still loved walking, but she started getting lost, so I gave her a GPS tracker. When she could not find her way on her own, I would fetch her, or one of our

Joel Shurkin has written nine books on science and the history of science. He has taught science writing at Stanford University, the University of Alaska and the University of California, Santa Cruz.

AN TOLL

neighbors would bring her home. One time she got out of the house (which had not been locked properly) and started shrieking in the street. At a family Thanksgiving gathering she left our bedroom and walked about the house naked. When things got worse, she would sit for hours in a living room chair, staring at nothing, the light in her glorious eyes dead. I would talk to her, tell her about my day, without the slightest reason to think she heard me or would respond. There were two of us in the house, but I was alone.

In January last year I fell, broke my knee and several ribs, and had to be taken to a hospital. Our daughter, Hannah, knowing neither she nor I would be able to take care of her mother, found a good nursing home for Carol that took Medicaid. I recovered and regularly visited her twice a week, monitoring her decline. She once thought I was her father. On two occasions I saw her physically resist help, showing a fierce aggression I never thought possible in her.

The end is an image that will not go away. At noon on October 25, 2019, with Hannah and a friend holding her hands, Carol raised her body slightly, made a gurgling sound and fell back, dead. I closed her eyes. It was a month before her 70th birthday and a month before our 28th anniversary.

One result was financial disaster—the only possible end for many Americans in our dysfunctional health care system. We had to hire lawyers to handle the legal issues ($12,000). I was told that to pay for Carol's nursing home, which cost about $80,000 a year, I had to impoverish myself to qualify for Maryland Medicaid: our attorneys said that I could have no more than $2,500 in the bank. We had to spend Carol's retirement funds, and I had to give up our house and move into an apartment. My life now is upside-down.

So how do I remember her? Her decline and death are more recent, so they are naturally stronger memories. But how do I deal with the horror and indignity of Alzheimer's? The eyes whose light had dimmed? The soiled diapers? The unfinished sentences? The empty bank account? The anger?

I should remember this: Three and a half years ago, before Carol's decline became precipitous, I found out that the Royal Concertgebouw Orchestra, one of the world's best, was playing my favorite piece of music—Gustav Mahler's *Resurrection Symphony*—in Amsterdam. Carol agreed that we had to go.

The concert was stunning. Afterward we walked, holding hands, across a grassy park in a light mist that muted the great city. Carol said not a word. I could tell from her face that she was present and aware and, better yet, that whatever Mahler was saying in his passionate music, she had understood. He had gotten through to her. Scientists say music appreciation is one of the last things to go with Alzheimer's because of where it is processed in the brain.

It was the last time we made love and the last time I had Carol back for any length of time—the living, wise, beautiful Carol. The Carol of the summer-blue eyes. I keep reminding myself. SA

Kenneth S. Kosik is a physician-scientist who has led large research projects about early-onset Alzheimer's disease. His laboratory helped to discover the tangles of tau protein in the brain that are important hallmarks of the illness. He is Harriman Professor of Neuroscience Research and co-director of the Neuroscience Research Institute at the University of California, Santa Barbara.

THE WAY FORWARD

Our inability to come up with a good treatment for Alzheimer's means it is time to reexamine the basic biology of the disease. Progress in five fundamental areas may lead to fresh hope

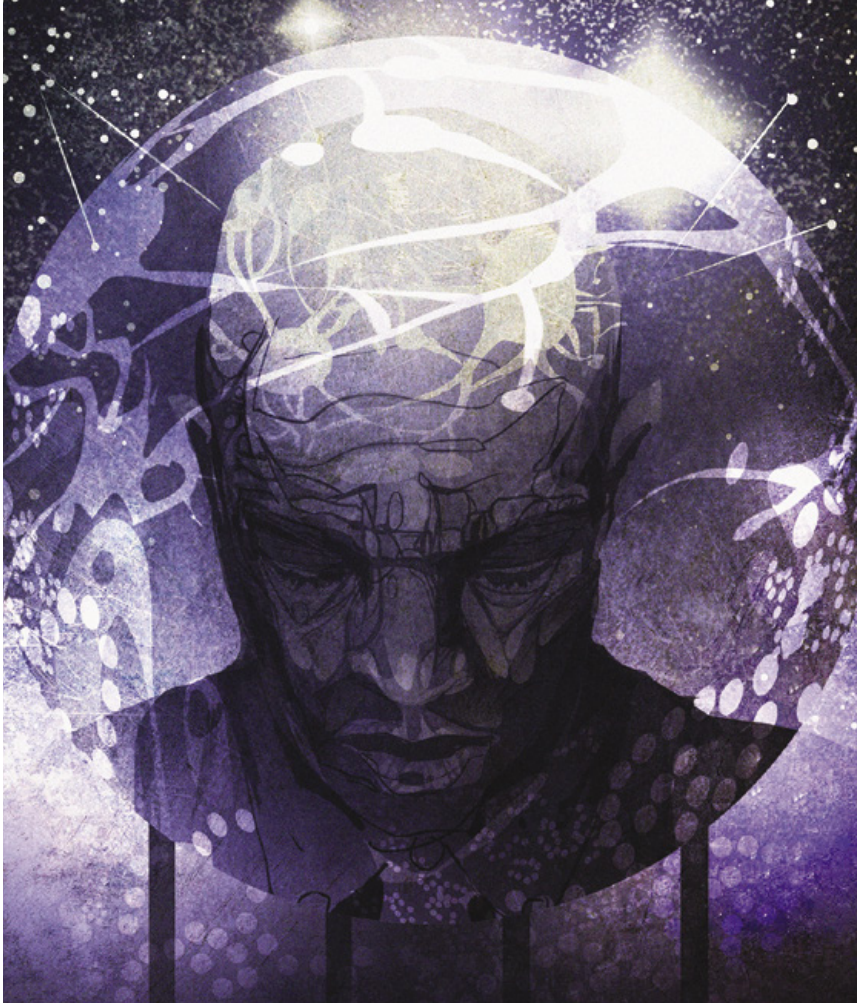
By Kenneth S. Kosik

NO FUNDAMENTAL OBSTACLE PREVENTS US FROM developing an effective treatment for Alzheimer's disease. Other troubles of human nature, such as violence, greed and intolerance, have a bewildering variety of daunting causes and uncertainties. But Alzheimer's, at its core, is a problem of cell biology whose solution should be well within our reach. There is a fairly good chance that the scientific community might already have an unrecognized treatment stored away in a laboratory freezer among numerous vials of chemicals. And major insights may now reside, waiting to be noticed, in big databases or registries of clinical records, neuropsychological profiles, brain-imaging studies, biological markers in blood and spinal fluid, genomes, protein analyses, neuron recordings, or animal and cell culture models.

But we have missed those clues because for decades we have spent too much time chasing every glossy new finding in Alzheimer's research and too little time thinking deeply about the underlying biology of this ailment. Instead our work has been driven by a number of assumptions. Among those assumptions has been the central and dominant role of the protein fragment called beta-amyloid. A large amount of data supports the idea that beta-amyloid plays an important part in the disease. We have developed drugs that can reduce concentrations of the protein fragments in people with Alzheimer's, yet by and large they have not stopped patients' cognitive decline in any meaningful way.

It now seems simplistic to conclude that eliminating or inhibiting beta-amyloid will cure or treat those suffering from the disease, especially without far deeper and more comprehensive knowledge of how it develops and progresses [see "The Amyloid Drug Struggle," on page 34]. We have not been barking up a completely wrong research tree, but our zeal has led us to ignore other trees and even the roots of this particular one.

It is time to go back to basics. I have been a scientist involved in Alzheimer's research for three decades, part of large projects investigating families with a high risk of Alzheimer's, prevention strategies



and the physiology of damage to brain cells that is part of the illness. I and my colleagues, who work across many scientific and medical disciplines, believe that we need to reexamine the fundamental physiology and biology of Alzheimer's, as well as reassess the contents of databases and our lab refrigerators for clues that we may have overlooked. This approach will let us develop theories and models of the way this illness progresses, and we can use those ideas to derive novel strategies to combat the disease.

There are at least five potentially fruitful and timely research directions—areas based on important discoveries made in the past several years—that can extend our knowledge, and I believe that they are quite likely to yield insights needed to find effective treatments. These areas range from malfunctions in the way brain cells get rid of problem proteins, to damage caused by inflammation, to trouble with the ways that cells send electrical signals to one another. These are different domains, but in a person they overlap to create illness in the brain, and individually or in tandem they may lie behind the terrible damage done by Alzheimer's.

PROTEIN-DISPOSAL PROBLEMS

BEGINNING IN THE EARLY 1900S, several neuropathologists—including Alois Alzheimer, the scientist after whom the disease is named—described microscopic lesions in the brains of patients who had died with various forms of dementia. Today we know these are clumps of misshapen proteins. In the case of Alzheimer's, some of the clumps consist of pieces of beta-amyloid protein. They sit between neurons and are called senile plaques. Other clumps reside within neurons, made of a protein known as tau, and are called neurofibrillary tangles.

What we still do not know, more than a century later, is why cells fail to remove these abnormal lumps. Cellular mechanisms for the removal of damaged proteins are as ancient as life itself. What has gone wrong in the case of Alzheimer's? This question is as central to the disease process as a loss of control over cell proliferation is to the progression of cancer. Some recent observations from researchers at the Washington University at St. Louis, among other institutions, indicate that abnormal proteins may find their way out of cells, perhaps evading their natural detection systems for bad molecules. We do not know how they do so, but figuring it out might be a very useful way to start a new search for how and why Alzheimer's progresses.

Cells have two major systems for the removal of abnormal proteins: the ubiquitin-proteasome system (UPS) and autophagy. In the former, proteins are inserted into a barrel-shaped cell structure called the proteasome, where they are chewed up into reusable parts; in the latter, the cell wraps up aberrant proteins and totally destroys them. In neurons, these systems are co-opted to control the composition of cell-signaling connections—formed by anatomical structures known as axons, dendrites and synapses—as they are strengthened or weakened during learning. (Sometimes neurons extrude damaged proteins and turn over their destruction to microglia, brain cells that are part of the immune system.)

The decision about whether to shuttle an abnormal protein toward the UPS or autophagy is mainly based on the protein's size. The proteasome has a narrow, pore-like opening at each end that can accept a small, fine, threadlike protein strand. Inside it are enzymes that break the protein down into its constituent amino acids, which are recycled for use in the synthesis of new proteins. Larger molecules that do not fit into the proteasome, such as protein clumps and old, misshapen proteins with age-related damage, get shuttled toward the autophagy system and its more powerful engine of destruction, the lysosome.

In Alzheimer's, something goes wrong and leaves brain cells with these chunks of tau and amyloid that further damage or choke them. So we could learn an enormous amount about the pathology of Alzheimer's if we understood the details of these systems. We need to examine specific differences in the degradation pathways in different subtypes of neurons, as well as the precise mechanism by which these disposal systems recognize abnormal proteins. Malformations in proteins such as tau do not happen in a single step. Proteins may harbor mutations and accumulate modifications that predispose them to misfolding, which can be followed by aggregation into larger and larger structures in a multistage process. As proteins progress along this pathway, at what point do surveillance systems kick in and recognize them as abnormal? In-depth knowledge about these kinds of processes could lead us to a more strategic approach to treatment and intervention with drugs.

One intriguing finding that plays into

our understanding of such evasion is that tau can travel out of cells and into the spaces between them, and from there it gets taken up by neighboring cells. What purpose this transit system serves is unknown. Is exchange of the protein among cells normal, or do cells disgorge abnormal tau to rid themselves of a toxic substance? We think that in Alzheimer's, at least some of the tau protein outside cells is already misfolded. We believe this because when such tau enters a neighboring cell, it forms a template, an abnormal pattern, that other tau proteins in that cell use to shape themselves in similar odd ways. When it spreads, tau in neighboring cells copies the specific shape of the entering tau protein.

The observations of tau outside cells have prompted some to speculate that the protein could be intercepted and cleared at that point by an antibody delivered to the patient. But that approach is unlikely to work unless we know exactly how tau is misshapen when it does its damage. This precise structure is necessary information for designing a highly specific antibody. Another open question is where tau resides in the complex space between cells. More specifically, does it move across synapses, where two neurons transmit their signals? This synaptic cleft is a narrow gap that is not easily accessible to an antibody. Potentially more promising approaches are to understand exactly how tau is extruded from cells and the receptors that neighboring cells use to pick the protein up; recent experiments in my lab may point to the identity of one such receptor.

IDENTIFYING PROTEIN CHANGES

ONE MAJOR RECENT ADVANCE in Alzheimer's research was the imaging of abnormal tau within a cell, snarled in a neurofibrillary tangle, at a level of detail never before seen. This remarkable image, published in 2017 in *Nature,* showed thousands of tau proteins aligned as pairs tightly locked in a C-shape configuration. It is possible that features seen in this solid inclusion could provide the information necessary to design small molecules that fit within the crevices of the abnormal protein and pull it apart to disrupt the disease process.

But breaking up these structures is a challenging goal for many reasons, not the least of which is how strongly the whole tangle is held together. A more successful direction could be to determine the sequence of microscopic events that takes these tau proteins from their typical liquidlike state to the more rigid and solid state seen in that image and to discover the protein modifications that predispose tau toward this change.

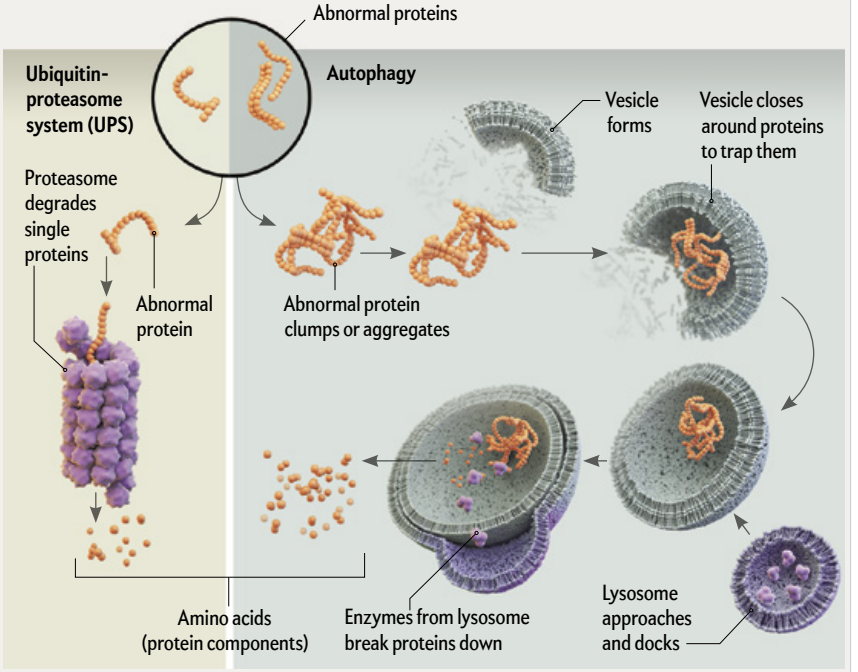
The switch from liquid to solid is called a phase transition. Biologists' interest in such transitions in living cells is now surging because of their possible role in disease. Physical chemists have studied phase separation, such as the condensation of oil drops in water, for many years. Oil and water are both liquids, yet they remain separated because of a balance of attractive and repellent forces. The advantage of phase separation for living cells is that it concentrates a specific set of molecules in one place, which aids certain cellular activities. Multiple proteins near a gene, for instance, can condense to control the expression of that gene, as shown in a 2018 paper in *Science.* Such a condensed set of proteins, though still in a liquid state, do not diffuse away; they are held together as a droplet by weak physical forces. This configuration allows sets of proteins to move and work together without being wrapped together in a membrane, which would require resource-costly maintenance from the cell.

Some proteins, such as tau, are tightly packed when they are located within a droplet, and the high concentrations could make them prone to aggregation into a tangle. Proteins that form droplets in this way share a property known as intrinsic disorder. Like the Greek god Proteus, they can assume numerous shapes, in contrast to more ordered proteins that are limited to a few specific forms. Different shapes require different energy levels. At times, some intrinsically disordered proteins fold into such a low energy state that they cannot shift out of it, which essentially increases their rigidity. And that may exacerbate their tendency to tangle together.

Cells also pack proteins and other mol-

Cleaning Out Bad Proteins

The two classic hallmarks of Alzheimer's are clumps of a protein fragment called beta-amyloid and tangles of a protein called tau. Brain cells' systems for getting rid of abnormal proteins fail in this illness, and scientists would like to understand what goes wrong. Normally cells use two elimination methods. Smaller single proteins are shuttled to the ubiquitin-proteasome system, which involves a barrel-shaped organelle (the proteasome) that chops the proteins into amino acids. Larger clumps, or aggregates, are handled by autophagy, in which clumps are encapsulated so they can be broken down by enzymes from another organelle, the lysosome.



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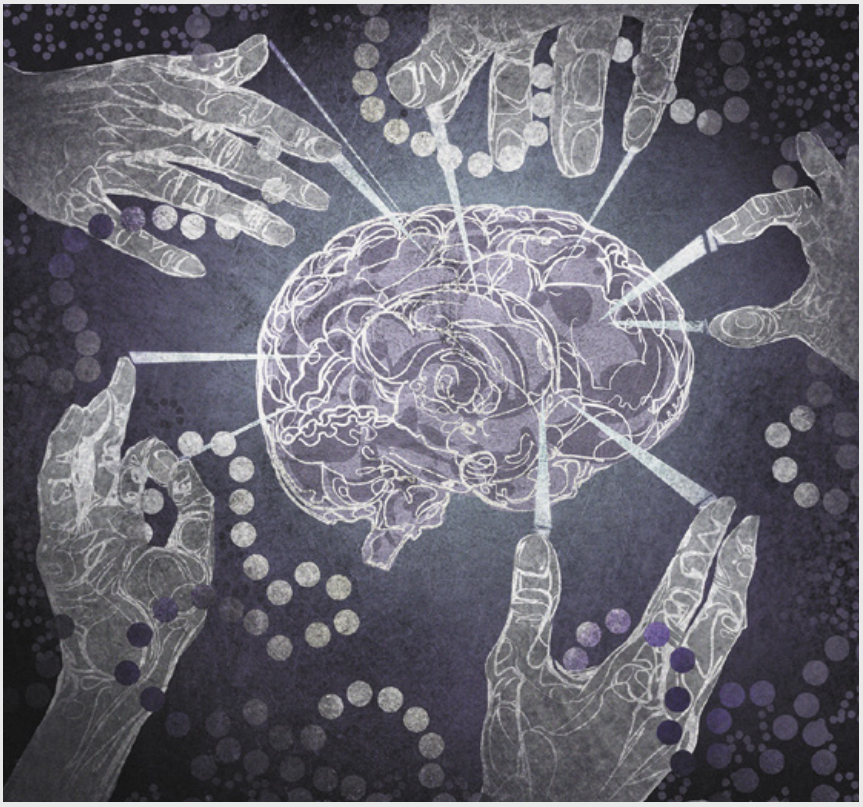

THE AMYLOID DRUG STRUGGLE

A leading idea for Alzheimer's treatment is getting a harder—and sometimes more skeptical—look

By Tanya Lewis

In March 2019 biotechnology giant Biogen stopped two big trials of its experimental Alzheimer's disease drug aducanumab because it did not appear to improve memory in declining patients. Then, in a surprise reversal several months later, the company and its partner, Japanese drugmaker Eisai, said they would ask the U.S. Food and Drug Administration to approve the treatment. A new analysis, Biogen said, showed that a subset of people on the highest doses in one trial did benefit from the compound, which dissolves clumps of a protein called beta-amyloid within the brain.

The back-and-forth decisions, along with the failure of a slew of other amyloid-clearing compounds, have left experts divided about whether treating amyloid buildup—long thought to be the best target for an Alzheimer's therapy—is still a promising approach.

Some of the scientists rethinking the so-called amyloid hypothesis helped to generate it in the first place. "I would say it has legs, but it's limping," says geneticist John Hardy, who co-authored the genetic studies that pioneered the idea more than two decades ago. According to Hardy, who runs a molecular neuroscience program at University College London's Institute of Neurology, "the [concept] we drew in 1998 is cartoonishly oversimplistic. There were lots of question marks. We thought those questions would be filled in within a couple of years. And yet 20 years later they are not filled in." Other experts, though, still contend that the amyloid hypothesis is a strong explanation and that treatments targeting the protein are the right way to go.

Beta-amyloid forms when amyloid precursor protein (APP) is chopped up by the enzymes beta-secretase and gamma-secretase. The beta-amyloid fragments are normally broken down further. But in people with Alzheimer's, beta-amyloid accumulates around neurons. In addition, tangles of another protein, tau, form within neurons. These changes are ultimately followed by cell death and brain degeneration, which prompted suspicions that beta-amyloid was a cause. And people with a particular genetic form of Alzheimer's have mutations in one of three genes that code for APP and two components of gamma-secretase called presenilins. Their brain cells have trouble getting rid of beta-amyloid. Further evidence about amyloid came from individuals with Down syndrome, who have an extra copy of chromosome 21—which carries the gene for APP—and thus make more of the protein. These individuals also have a high risk of developing dementia by age 50. Such discoveries led scientists to infer that a faulty amyloid-clearing mechanism was to blame in the disease.

But the numerous drug failures have led some to reconsider the effectiveness of aiming therapies solely at amyloid. Beta-amyloid often accumulates for years before symptoms start, and not everyone who has this pathology goes on to develop the disease. In February two amyloid-targeting drugs, Eli Lilly's solanezumab and Roche's gantenerumab, failed in a clinical trial for an early-onset, genetic form of the disease thought to be directly tied to amyloid metabolism.

A convergence of research, including work from the Alzheimer's Disease Cooperative Study, supported by the U.S. National Institute on Aging, suggests that amyloid buildup is just one part of a complex cascade of interactions. "Our experiences with a variety of interventions targeting amyloid clearly have brought us to [this] point," says Howard Feldman, director of the cooperative study, which is a consortium of academic and government laboratories that conducts clinical trials of Alzheimer's treatments. "It seems very difficult that a single amyloid intervention is going to stem the tide of the disease." Although the hypothesis may be a good explanation for the early-onset, genetically driven forms of the disease, the late-onset form probably involves multiple problems, so approaches aimed only at amyloid are unlikely to work, says Feldman, who is also a professor and clinical neurologist at the University of California, San Diego.

Some researchers, such as Karen Duff of Columbia University, favor the idea that tau protein tangles play a part that is as big as or bigger than that of beta-amyloid. One reason is that the degree of tau pathology more closely correlates with the seriousness of cognitive symptoms than amyloid pathology does.

Other scientists think inflammation or defects in the blood-brain barrier may play a critical role. But drugs targeting tau and inflammation have so far been ineffective,

Feldman notes. He believes that a combination of interventions might be the best approach: "A single intervention may never be sufficient, outside of genetic [early-onset] forms of disease."

There are other ideas as well. In recent years Hardy and his colleagues have come to view late-onset Alzheimer's and other neurodegenerative diseases as the result of a faulty damage response. They believe that the early accumulation of beta-amyloid might damage neuronal cell membranes, and if immune cells called microglia fail to remove these damaged membrane proteins, it could prevent the cell membranes from adequately clearing more amyloid—spurring a cycle of damage. Recent genome-sequencing studies support this idea, Hardy says: the majority of genes identified as risk factors in late-onset Alzheimer's involve microglial metabolism; others encode proteins that help to build and repair cell membranes.

Some scientists still believe that amyloid has a primary role because of several studies linking its aggregation to the seriousness of symptoms. "In my view, the hypothesis is very much alive and well," says David Holtzman, chair of neurology at the Washington University School of Medicine in St. Louis. "There's no question that science says beta-amyloid is important in the disease. The question is, When can it serve as a treatment?"

Hardy, though more skeptical than he was decades ago, thinks that the hypothesis has strong data behind it, and he believes that amyloid drugs might yield poor results because they are given far too late in the disease's progression. "If I was having a heart attack, a statin might be the right drug, but it's too late," he says. Clinicians may eventually be able to measure genetic, blood or spinal fluid biomarkers to predict who is at risk of developing Alzheimer's, which would make it possible to treat them before they develop symptoms.

Others say amyloid's real importance might be as one of those biomarkers. "I think amyloid is a critically important marker to understand risk and how early we can diagnose disease," says Denise Park, chair in behavioral and brain sciences at the University of Texas at Dallas, who studies brain aging. "I don't think there's anything right now that is better."

Going forward, it seems unlikely that the field will abandon the amyloid hypothesis. But scientists do seem, after a long time, poised to take a broader view of other processes at work in this destroyer of minds and memories.

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ecules prone to phase transitions in membraneless organelles called stress granules and RNA granules. When certain proteins and RNAs coalesce in such granules, they pack tightly together but typically remain in a liquid state. At a certain density, however, they may become predisposed to more clumping and to a phase change to a solid, a change that would increase their ability to cause brain damage and would make them harder for cell-disposal systems to remove. That is why we need to better understand the conditions that trigger this process.

THE INFLUENCE OF GENES

IN MIDDLE-AGED PEOPLE, Alzheimer's can arise from genetic mutations in three genes (*APP, PSEN1* and *PSEN2*) that cause a rare familial form of the disease, a frightful inheritance passed from one generation to the next. But the vast majority of the time, Alzheimer's shows up in individuals older than 65 and does not involve these genes. By combing through tens of thousands of genomes, geneticists have now discovered other DNA changes, about two dozen gene variants, that do increase risk by a small amount. The most influential of these alternative forms is a version of the gene *APOE* known as the e4 variant. A combination of several risk-gene variants adds to one's likelihood of getting the disease. (Because gene variants are frequently associated with ethnicity, we need a much more inclusive data set than the mostly Caucasian-based gene analyses and registries currently available to make a reliable assessment of genetic risk in all populations.)

Each of these variants opens a different door through which we can explore the ways that a small change in our genomes can heighten our likelihood of acquiring Alzheimer's. Some of the more frequently seen variants, and thus the most interesting doors, are genes or other stretches of DNA in the microglia. In a 2019 *Science* paper examining these immune system cells, scientists found one variant associated with Alzheimer's risk in a gene known as *BIN1*. This gene is normally involved in the way microglia engulf potentially harmful outside molecules and move them into the cell, protecting nearby neurons. The variant can affect how efficiently microglia clean up stray proteins.

In microglia and other cells, certain gene variants are also associated with age and sex. Differences exist between men and women, for example, for genes on the 22 pairs of nonsex chromosomes and for genes expressed on the X and Y chromosomes. The effects of these variants may have something to do with the higher rates of Alzheimer's in women, which hold even with correction for women's longer life spans [see "The Menopause Connection," on page 37]. Overall the small effects of any single gene variant associated with Alzheimer's probably contribute, each in its own limited way, to individual differences in the way we handle amyloid and tau accumulations. We need to nail down the how and why of these contributions.

TAMING INFLAMMATION

WHEN THE BRAIN DETECTS a source of damage such as amyloid plaques or tau neurofibrillary tangles, it sounds an alert and releases a barrage of immune system molecules called cytokines, along with a variety of attack cells. This response stems from the microglia, in large part, and it causes an inflammatory reaction intended to destroy any tissue harboring the trouble spots. This brutelike "innate" system operates quite differently from the more refined "adaptive" immune system, which generates immune cells and antibodies that react only to specific invaders, such as bacteria or viruses, and that mount a narrower, more precise defense. The broader innate response dominates in Alzheimer's. As the lesions proliferate beyond the ability of a neuron's internal machinery to get rid of detritus, this general inflammatory response kicks in and, unfortunately, often hits still healthy cells in the brain. Scientists at the University of California, Irvine, recently have found that eliminating the aged microglia in older mice prompted the animals to repopulate their brains with fresh microglia. This rejuvenation improved spatial memory, reversed age-related changes in neuronal gene expression, and increased the birth of new neurons, as well as the density of their dendrites.

This assault triggered by amyloid and tau probably happens on top of a low level of inflammation in the brain that occurs naturally with aging. Many older people have increased concentrations of proinflammatory cytokines such as tumor necrosis factor (TNF), suggesting that a slight inflammatory state exists throughout the body at this point in life. Aging is highly

variable among humans, and the differences mean the progress and the effects of Alzheimer's are quite variable as well. Some of this diversity can probably be attributed to individual variation in human immune systems. Different people inherit distinct configurations of genes involved in immune responses. In addition, during our lives our systems are shaped by nonheritable influences. We get different exposures to symbiotic microbes in places such as our gut and to pathogenic microbes from our surroundings. This all suggests that exposure of the immune system to various pathogens, as well as our genetic differences, may contribute to the way Alzheimer's develops by establishing an individual immune profile, or "immunotype."

The challenge for researchers who want to stop the brain damage caused by widespread inflammation is to distinguish the desirable immune responses the brain uses to combat developing problems and ordinary age-induced degradation from the other, more reckless immune responses to the advancing pathology of Alzheimer's. The research community would like to tame brain inflammation caused by the disease but does not yet know how to deliver an intervention with precision.

ELECTRICAL DISCONNECTIONS

THE BRAIN IS AN ELECTRICAL ORGAN: its most defining feature is its ability to encode and convey information in the form of electrical signals passed between neurons, usually by chemicals called neurotransmitters. How Alzheimer's impairs brain cells' signaling and disrupts the way they assemble into functional memory circuits has been insufficiently studied. But now the ability to detect both structural and functional connections is burgeoning thanks to technical advances that allow us to visualize these links in exquisite detail.

Some of these advances involve optogenetics, a way for scientists to stimulate specific neurons in an animal's brain using light. Researchers can offer the animal a reward or fearful experience, then detect which genes become more active. This approach, in an impressive achievement, is now allowing researchers to observe and manipulate specific neurons that encode a specific memory known as an engram, as noted in a 2020 paper in *Science*. When those cells were stimulated by light alone after the initial experience, the memory of it was recalled. If we can figure out the biology that drives the formation of these electrical memory connections, that information will be crucial in helping us understand how Alzheimer's pathology interrupts this neural circuitry.

Neuroscientists made another advance this year when they discovered that microglia seem to be involved in making the brain forget these engrams by eliminating the synapses that normally connect neurons.

We also know that neurotransmitters are affected in different ways by some of the proteins involved in Alzheimer's pathology. Tau, for instance, accumulates in neurons that use the neurotransmitter glutamate and work to excite signals. But other neurons that inhibit signals—signaling relies on good start-and-stop mechanisms—release a different neurotransmitter, GABA, and are less affected by tau accumulation. The basis for this cellular selectivity and its consequences is unknown, and we need to understand it much better. Scientists have also seen that neuronal activity enhances tau's spread, which could be another important part of the Alzheimer's puzzle.

Not only are signaling cell types affected differently by the disease process, but effects vary in different brain areas, too. For example, areas of the brain related to memory, emotions and sleep are severely damaged, whereas centers related to primary motor and sensory function are relatively spared. One study found that regions of the brain activated when our minds wander, the so-called default or resting state, are the same places where amyloid plaques are first deposited. But we must be cautious in drawing conclusions—a wandering mind does not necessarily cause amyloid deposition.

Sleep is another electrical state of the brain that is increasingly recognized as a factor in the development of Alzheimer's. Levels of both amyloid and tau fluctuate during the normal sleep-wake cycle, and sleep deprivation acutely increases the production of amyloid and decreases its clearance. Deep sleep evokes rhythmic waves of cerebrospinal fluid that may serve to clear toxins, including amyloid, from the brain. Unfortunately, this kind of sleep diminishes with aging. This observation could stimulate work on pharmacological approaches designed to specifically restore deep sleep.

SHARED IDEAS

THESE RESEARCH AREAS are not the be-all and end-all of a rejuvenated Alzheimer's science agenda. There are certainly more. But these five avenues are intertwined and, like biology itself, can be investigated in many cross-fertilizing ways. One hope I have is that as basic science fills in missing information—particularly quantitative information—computational modelers and theoreticians will step in to help predict the impact of Alzheimer's pathology on brain circuitry and cellular pathways. I also would like to see these research directions prompt investigators to think collectively and systematically and to share their ideas in constructive ways. This is how we can come together to push back our ignorance about this terrible disease. SA

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THE MENOPAUSE CONNECTION

Getting older is the biggest risk factor for Alzheimer's. Research indicates that being female is a close second. Why?

By Jena Pincott

THIS IS HOW MEMORY LOSS BEGINS, SOPHIE TELLS ME: YOU SHOW UP AT WORK, FORGETTING THAT YOU ARE supposed to be at a breakfast meeting with a client. You blank on the names of your neighbors. Soon enough you walk into a room without any clue as to why you are there. Sophie, a lawyer in her early 50s, who asked to go by a pseudonym, had been suffering from frequent hot flashes and night sweats, both associated with menopause, but the forgetfulness seemed to be in another league. What was happening to her mind?

Lisa Mosconi, director of the Women's Brain Initiative and associate director of the Alzheimer's Prevention Center at Weill Cornell Medical College in New York City, might know. She has analyzed thousands of positron-emission tomography (PET) scans of patients entering menopause and has seen how their brain metabolism changes over time. "In premenopause, your brain energy is high," Mosconi says, showing me a PET scan of a young woman's brain. It is lit up by many bright red and orange blotches representing high glucose metabolism—a proxy for neuronal activity. In perimenopause, which hits women in their mid- to late 40s, brain glucose metabolism slows by 10 to 15 percent or more, and the scan changes: red and orange spots give way to more yellows and greens, representing less sugar uptake and lower metabolism. "Then, in postmenopause, brain glucose metabolism slows down 20 to 30 percent, sometimes more," Mosconi says, showing me the final scan. Now, clearly, the greens have gained territory.

Estrogen is the master regulator of metabolism in the youthful female brain, orchestrating everything from glucose transport and uptake to its breakdown for energy. Mosconi's scans are rainbow-colored evidence that decreased levels of the hormone during menopause, which often starts when women are between the ages of 45 and 55, lead to a "bioenergetic brain crisis," as she describes it. At some point during this seven-plus-year transition period, up to 60 percent of women experience what is known as menopause-related cognitive impairment: bouts of confusion, distractibility and forgetfulness. These memory problems are normal. The generation of synapses requires energy; as estrogen levels and brain glucose metabolism decline, so does the formation of new connections between neurons.

Fortunately, the impairment is temporary: women rebound, their wits intact, as the brain compensates and taps other sources of energy. A 2009 study found that newly postmenopausal women

score just as well on cognitive tests as they did before the transition. Decades later, however, roughly a fifth of them will be diagnosed with Alzheimer's disease. Mosconi and others believe that for many of the 3.6 million women living with the disease in the U.S. alone, menopause might have been a tipping point for cognitive decline.

Although investigations of Alzheimer's that focus on women have become a top priority, too many questions remain unanswered when it comes to female-specific risk factors, symptoms, prevention and responses to treatments for the disease. Why in the U.S. does a woman have a one-in-five lifetime chance of developing the disease at age 65, compared with one in nine for a man at the same age? American women live an average of five years longer than men, but "longevity does not wholly explain the higher frequency and lifetime risk," noted an expert panel representing the Society for Women's Health Research in a 2018 analysis. Why are females who carry the e4 variant of the gene *APOE* (*APOE4*), which increases the risk of Alzheimer's, likely to acquire the disease at a younger age than male carriers? What is it about women's biology and life experiences that makes them more vulnerable?

The menopause hypothesis—that decline in estrogen levels in this period renders the brain vulnerable to future damage—could offer answers. If Mosconi and other researchers are right, Sophie and the millions of women worldwide who pass through this transition could benefit from lifestyle interventions and, conceivably but controversially, hormone therapy (HT) to prevent the disease.

THINKING WITH LESS ESTROGEN

"IT'S STARVATION MODE," says Roberta Diaz Brinton, director of the Center for Innovation in Brain Science at the University of Arizona, describing what happens when estrogen declines and green patches take over in menopausal women's PET scans. Estrogen plays multiple and wide-ranging roles in brain bioenergetics, she explains. A signaling molecule with receptors throughout the brain, it regulates mitochondria, which generate energy for cells and fuel the formation of neuronal connections. Estrogen also activates the enzymes that enable synapses to function, and it facilitates glucose transport from blood vessels into the brain and from the brain into neurons and glia, the cells that support and protect neurons.

Brinton's research on aging female mice has shown that as estrogen levels fall and glucose metabolism slows down, the brain adapts by using ketone bodies—substances produced from fatty acids, in this case from white matter, including the myelin sheaths that protect neurons—as a supplemental fuel source. This switch—essentially an act of self-cannibalization—also appears to occur to some degree in women, and those whose brains draw more heavily on ketone bodies may suffer greater degeneration of white matter and a higher risk of dementia.

Sometimes a brain energy deficit coincides with the development of hard deposits, or plaques, of beta-amyloid protein. They can show up in some brains that function normally, but every person with Alzheimer's has them. They are thought to interfere with synaptic signaling. In brains of those with the disease, beta-amyloid usually comes along with tau, a tangled protein that wraps around the nucleus inside cells, apparently killing them by blocking nutrient transport. Moreover, low estrogen increases the permeability of the blood-brain barrier, potentially exposing the brain to toxins or infections that can stimulate an aggressive immune response, releasing proteins that seed new plaques and tangles.

In contrast to the brains of women in their 40s and 50s, Mosconi says, brains of males in the same age group are not found to have aged significantly, and fewer have beta-amyloid plaques. One explanation is that testosterone, like estrogen, is neuroprotective—and levels of testosterone never drop as steeply or abruptly in andropause as estrogen's do in menopause. This difference might help explain why fewer men get the disease. Alzheimer's pathology may also develop earlier in women than in men, Mosconi explains, but they compensate so well that they are often not diagnosed until the disease has progressed to a later stage. A 2019 study found that women whose PET scans show biomarkers of Alzheimer's outperform their male counterparts on verbal memory tests. If cutoff scores were sex-specific, the disease could be caught earlier, when intervention is more effective.

To further identify women at risk, researchers have begun to investigate connections between Alzheimer's and lifetime exposure to estrogen. Scientists measure estrogen exposure in terms of the "reproductive period"—the time span between a woman's first menstrual period and her last. A large-scale study of 15,754 members of the health care consortium Kaiser Permanente found that women with a 21- to 34-year reproductive period have a 26 percent higher chance of developing dementia than those with a 39- to 44-year period, suggesting that late onset of menstruation or early menopause poses a higher risk. Yet many factors affect women's lifelong estrogen exposure, and their impact is understudied. For instance, a woman's circulating estrogen is dramatically elevated during pregnancy, but after she gives birth it drops and, for several years, remains at a lower level than that in women who have never been pregnant. But studies that sought to link the number of times a woman has given birth to Alzheimer's risk yielded conflicting results. More than 100 million women worldwide take birth-control pills, which suppress ovarian hormones, yet shockingly little is known about their long-term effects on dementia risk.

THE HORMONE THERAPY DILEMMA

SOPHIE, WHO STARTED TAKING THE PILL when she reached puberty and who has never given birth, says her memory loss peaked in her last year of perimenopause. She often experienced more than three hot flashes an hour—a frequency and severity that correlate with increased dysregulation of glucose metabolism in the brain, greater loss of white matter and a potentially elevated risk of dementia later in life. Sophie's doctor prescribed a new pill: a combination estrogen-progestin tablet (progestin protects the uterus). The effect, Sophie says, was "eerily miraculous": her hot flashes faded, and suddenly she was remembering breakfast meetings again.

It might seem that every menopausal woman should undergo hormone therapy for brain health alone, but the reality is more nuanced. In the early 2000s the National Heart, Lung, and Blood Institute reported results from its massive Women's Health Initiative study and its ancillary memory study showing that HT, usually estrogen plus a progestin, is linked with a heightened risk of breast cancer, stroke, heart disease and blood clots and—in shocking defiance of all expectations—a twofold-higher rate of dementia. Investigators have since identified flaws in the study. Women were prescribed conjugated equine estrogen, a semisynthetic form thought to be less neuroprotective than the 17β-estradiol commonly used today. But a bigger problem was that the women were 65 or older when they started HT.

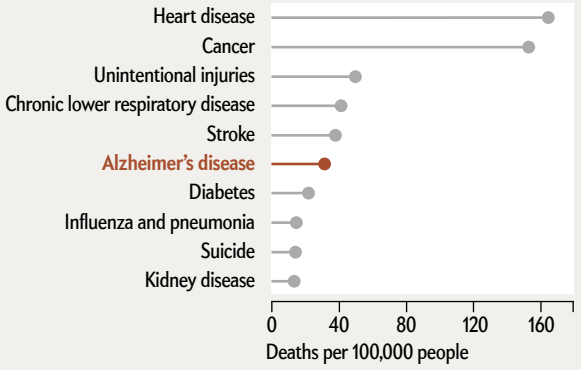
A woman's age when she takes her first HT pill (or applies her first cream, ring or patch) is central to what Brinton calls the

The Burden of Alzheimer's

Deaths

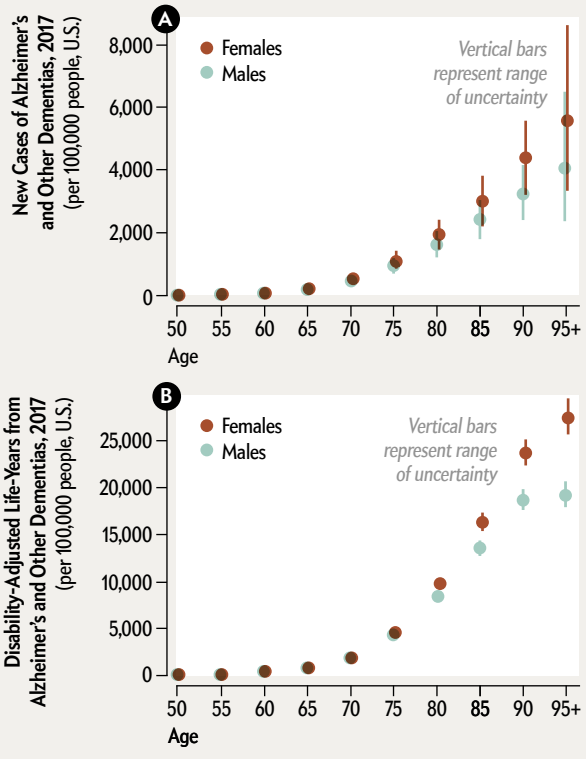
In the U.S., Alzheimer's disease is the sixth leading cause of death, and experts note it may be underreported because death certificates often list the immediate cause, such as pneumonia, and not the underlying dementia.

10 Leading Causes of Death in the U.S., 2017
(age-adjusted death rates)



Gender Differences

Women in the U.S. suffer from Alzheimer's at a higher rate than men do, according to estimates from the Institute for Health Metrics and Evaluation. Beginning at age 50 and continuing through age 95, there are more and more women among newly diagnosed cases (A). A similar growing gap between women and men emerges when the disease is measured by the number of years—based on average life span—lost to disability or early death from the illness (B).



"healthy cell bias of estrogen action." If neurons are healthy, they are responsive to estrogen. If neurons are aged or deprived of estrogen for too long, they become unresponsive to the hormone because signaling pathways deteriorate and receptors become dysfunctional. In this scenario, adding estrogen might even exacerbate neural degeneration. So for HT to do good and not harm, it must be initiated in the so-called critical window, which is usually within five years of the last menstrual period, Brinton says.

Several observational studies attempted to test the critical-window hypothesis in patients who had taken HT for at least 10 years, and their results run the gamut from a 30 percent reduction in Alzheimer's risk in a Utah-based study in which treatment was initiated within five years of menopause onset to a 9 to 17 percent increase in risk in a recent Finnish study in which age at initiation did not appear to affect risk. Which results should we believe? Researchers do not know. Although they consider HT to be safe and effective for many women at the start of menopause, there remains a lack of consensus about dementia protection that is complicated by a variety of factors. "More clinical trials are needed," Mosconi says, "especially on women who start hormone therapy while still in perimenopause." Women with the most severe perimenopausal symptoms, such as Sophie, might be unable to naturally adapt well to the loss of estrogen; in them, HT may prevent neurodegenerative damage during the transition to menopause.

"I don't dare go off it," Sophie says of her HT. She feels that it saved her from a downward spiral of memory loss that would have left her like her grandmother, a loving, strong-willed woman whom Alzheimer's rendered confused and suspicious. Sophie has not been tested for the *APOE4* gene, however, so it is unclear if she would, in fact, have developed the disease—nor have studies confirmed whether HT does help stave it off. Even so, she urges me, a woman in her 40s: "You should start as soon as you need it." But surely there is a better way to prevent Alzheimer's?

A WINDOW OF VULNERABILITY

MENOPAUSE DOES NOT CAUSE ALZHEIMER'S. It is more a window of vulnerability—especially for women with underlying risks, Brinton says. At first glance, its connection with Alzheimer's is not obvious. The average age of women at menopause is 51; the average age for a diagnosis of Alzheimer's is 70 to 75. That is a 20-something-year gap. But the so-called prodromal phase—between initial pathology such as beta-amyloid plaques and full-blown cognitive impairment—is also about 20 years. "Maybe the timing is a coincidence," Brinton observes. "But I don't think so."

Brain scans aside, is it possible to predict a woman's Alzheimer's risk earlier on, when she is still healthy? In a study published in 2016, Brinton and her colleagues sorted 500 healthy postmenopausal women into three groups: metabolically optimal, borderline high blood pressure and borderline metabolic health. Only one group scored significantly lower on verbal memory tests: women with borderline-unhealthy metabolic health.

Technically these subjects' metabolic measures were still in the normal range. Yet there were clues that their health was going in the wrong direction. For one, blood glucose levels in this group were nearing the threshold of prediabetes, a condition that afflicts about 30 percent of women and is itself linked with cognitive impairment. After a meal the hormone insulin helps glucose enter cells for use as energy, but in someone with prediabetes, cells in the body start to resist insulin. When brain cells become resis-

SOURCES: "MORTALITY IN THE UNITED STATES, 2017," BY SHERRY L. MURPHY ET AL. NATIONAL CENTER FOR HEALTH STATISTICS DATA BRIEF, NO. 328, NOVEMBER 2018 (*leading causes of death*); GLOBAL BURDEN OF DISEASE COLLABORATIVE NETWORK—GLOBAL BURDEN OF DISEASE STUDY 2017 (GBD 2017) POPULATION AND FERTILITY 1950–2017. INSTITUTE FOR HEALTH METRICS AND EVALUATION, 2018 (*gender differences*)

Graphic by Jen Christiansen

tant to insulin, they absorb glucose but fail to respond to it—which, compounded by the menopausal slowdown in glucose metabolism, can contribute to neurodegeneration. For many women in this transitional phase, prediabetes is a prelude to type 2 diabetes, which almost doubles Alzheimer's risk. More than 80 percent of Alzheimer's patients are insulin-resistant.

Once we think of menopause—and estrogen depletion—as changing the ecology of the entire body, it is easy to see how a complex array of factors might give rise to Alzheimer's and why managing those factors is key to prevention. Estrogen's healthy effects on the cardiovascular system include cholesterol regulation: it raises levels of "good" HDL (high-density lipoprotein) cholesterol and decreases those of the "bad" LDL (low-density lipoprotein) type that causes the buildup of fatty, waxy deposits in arteries. The *APOE* gene mediates the metabolism of cholesterol and transports it to neurons; carriers of the e4 gene variant have naturally higher levels of LDL cholesterol in the bloodstream and accompanying hardening of the arteries. Loosened by inflammation, these deposits cause "silent strokes" that more than double the risk of Alzheimer's and other forms of dementia.

Sleep also plays a key role in regulating metabolism, including insulin sensitivity, and deficient sleep affects women disproportionately, especially during menopause. During a normal night of rest, glial cells flush out beta-amyloid and tau proteins. Sleep deprivation disrupts this process, causing the proteins to build up and form plaques, which lead to fragmented sleep, which impairs glucose metabolism, which also interferes with sleep, and so on in perilous loops that accelerate neurodegenerative processes. Again, *APOE4* status increases the risk: carriers have a reduced capacity to clear or degrade plaques and tangles.

Stress, too, can move the tipping point during menopause. A 35-year longitudinal study found that the more stressors lasting a month or more women experienced in their 40s and 50s, the likelier they were to have Alzheimer's four decades later. Along with stress, women are more likely than men to report depression, which is associated with a nearly doubled dementia risk. Unsurprisingly, female *APOE4* carriers, who, again, have the strongest genetic risk of Alzheimer's, are four times more susceptible than noncarriers to clinical depression, possibly because of increased numbers of beta-amyloid plaques in brain regions involved in emotion regulation.

A WINDOW OF OPPORTUNITY

IN 2019 BRINTON AND HER COLLEAGUES published a follow-up to their study of metabolic indicators, this time with *APOE* status as a new variable. People with a single copy of the *APOE4* gene, which is present in about 25 percent of the overall U.S. population, are more likely to acquire Alzheimer's than others are and represent about 40 percent of all cases. Women develop the disease much earlier than male carriers, between the ages of 65 and 75, possibly because of the loss of estrogen's neuroprotective effects. Carriers have higher LDL cholesterol, more beta-amyloid plaques and tau tangles, reduced hippocampal volume and greater decreases in brain connectivity compared with noncarriers. During the menopausal drop in brain glucose metabolism, female carriers of the e4 allele may rely more on the brain's ketone bodies as an auxiliary fuel.

As in Brinton's previous study, the group at risk for poor metabolic health had lower scores on some cognitive tests. But this time the analysis revealed that *APOE4* carriers were the main drivers of the group's poor performance. Among carriers, high cholesterol and other effects of poor metabolic health exacerbated the negative effects of *APOE4,* leading to early cognitive decline. When carriers in the poorly performing group underwent HT, however, their metabolic health improved, along with their scores on some cognitive tests.

But Brinton sees *APOE4* status as "a wake-up call, not a death sentence": plenty of women with *APOE4* do not have the disease. In her study, the group with optimal metabolic health, which had the best scores on cognitive tests, included carriers of the Alzheimer's gene. Were those women, along with healthy noncarriers, better at compensating for the "bioenergetic crisis" of menopause? Did their fitness offset other risk factors?

At least one third of Alzheimer's cases are linked with diabetes, obesity, poor diet, and other factors that are preventable and treatable, according to an oft-cited 2017 report in the *Lancet.* "The take-home message is that sustaining metabolic health sustains cognitive health," Brinton concludes. "You can't change your chromosomal sex or age or your gene variant. But you *can* change your metabolic health and thus your level of risk." Mosconi agrees. Everyone, especially women in their 40s and 50s, should "know their numbers," she says, meaning *APOE* status, metabolic profile, blood biochemistry—even brain scans, especially as new sex-specific imaging biomarkers emerge. "I hope scans will become part of the clinical workup for all middle-aged women (and men) for preventive reasons, just as we have our breasts and uterus checked," she says. The mantra is "prevention," a word once seldom paired with Alzheimer's.

Whether HT should be part of a protocol remains controversial. But precision medicine—which uses genetic testing and data analytics—is coming to HT, Brinton says: doctors may soon prescribe precision therapies based on biomarkers of risk such as *APOE* status, reproductive history, menopausal symptoms, and other factors. And new versions of HT are in the works. Karyn Frick, a neuroscientist at the University of Wisconsin–Milwaukee, and her collaborators have developed a "stripped-down" version of 17β-estradiol that is thought to reduce the risk of breast cancer associated with standard HT. The drug, which has yet to undergo clinical trials, showed promise in preliminary studies in mice. "It acted as a memory enhancer," Frick says.

For the Alzheimer's cases that cannot be prevented, Brinton's laboratory is developing a treatment called Allo based on allopregnanolone, a naturally occurring steroid that stimulates the production of new neurons. In a mouse model of Alzheimer's, Allo reversed cognitive deficits and restored learning and memory. In a promising phase 1 clinical trial, patients with mild dementia showed regenerated gray matter volume in their hippocampus and a reduction in brain inflammation. Brinton says a phase 2 clinical trial with *APOE4* carriers, funded by the National Institute on Aging, is scheduled to begin later in 2020.

In 2016 the National Institutes of Health began to require that the research it funds regard sex as a biological variable. The slow course of Alzheimer's means that years will pass before women can benefit from new studies into the menopause transition. Meanwhile prevention remains essential: recommendations include a plant-centered diet that is low in sugar and in trans fats and saturated fats, physical exercise, stress reduction and a nightly seven hours of beta- and tau-clearing sleep, especially for women in midlife. "Women take care of others; we put ourselves last," Brinton says. "But we can't keep putting off health." SA

THE FUTURE OF MEDICINE

A NEW ERA FOR ALZHEIMER'S

Ellen Ruppel Shell is a journalist and professor of journalism focused on science, economics and society. Her most recent book is *The Job: Work and Its Future in a Time of Radical Change* (Crown, 2018). She wrote "Obesity on the Brain" in our October 2019 issue.

THE ROLE OF AIR POLLUTION

Airborne particles spewed by car exhausts and other sources are now strongly linked to Alzheimer's. Recent research shows how they can travel from the lungs and nose to the brain

By Ellen Ruppel Shell

MY FIRST DAY IN MEXICO CITY WAS TOUGH. THE SMOG WAS SO THICK that I gasped for breath while climbing the stairs to my hotel room. I had braced for headaches from the high altitude and thin air, but I was not prepared for how dirty that air was or for the bloodshot eyes and burning lungs.

Declared the world's most polluted metropolis by the United Nations in 1992, greater Mexico City has worked hard to clean up its act. To some degree it has: the city is rightfully proud of its miles of bike paths and lush parks. Yet a casual glance at the smudged horizon shows that those efforts are not enough. Most days the area has levels of airborne sooty particles that greatly exceed standards set by the World Health Organization, as well as elevated amounts of other pollutants. Clogged with more than 9.6 million vehicles and an estimated 50,000 smokestacks, Mexico City stews in a toxic brew known to corrode human lungs and hearts. Now many scientists agree that this pollution also damages the brain.

In 2018 a study found lesions known to be hallmarks of Alzheimer's disease in the brains of Mexico City residents in their 30s and 40s—decades before signs of the disease normally can be detected—and tied this damage to exposure to the city's bad air. The researchers who did that work, who are from institutions in Mexico and the U.S., have also found early forms of this frightening damage in infants and young children. And Mexico City is not the only place where bad air has been linked to Alzheimer's. Just a few years ago a team of Harvard scientists released data from a large study of 10 million Medicare recipients ages 65 and older living in 50 different cities in the northeastern U.S. The researchers reported a strong correlation between exposure to specific air pollutants and a number of neurodegenerative disorders, including Alzheimer's.

Other studies in England, Taiwan and Sweden—among other countries—have turned up similar results. "Air pollution is emerging as one of the hottest areas in Alzheimer's research," says George Perry, a neurobiologist at the University of Texas at San Antonio and editor in chief of the *Journal of Alzheimer's Disease*. In a field where scientists have spent decades focused on genetics and the buildup of damaged protein fragments called beta-amyloid as causes of the disease, Perry says, now many experts agree that air pollution plays a major role. This assessment is echoed by Masashi Kitazawa, a toxicologist at the University of California, Irvine, and an expert on environmental toxins. "Genetics is huge in Alzheimer's research, and for years almost no one wanted to look beyond genes," he says. "But in the past three or four years the number of papers linking air pollution and cognitive decline has exploded." For the most common form of Alzheimer's, known as late-onset disease, researchers now estimate that at least 40 and as much as 65 percent of the risk involves nongenetic influences such as lifestyle and harmful environmental exposure. Air pollution is one of the leading factors.

Much of this concern centers on airborne toxin-packed droplets or solid bits that are about one 30th the diameter of a human hair. Known as fine particulate matter (called PM 2.5 for its specific size), it typically comes from burning oil and gas in cars and trucks and power plants, as well as from burning coal or wood. These particles are inhaled deep into the lungs and can pass quickly into the bloodstream. Scientists have demonstrated that when PM 2.5 enters the body this way, it wreaks havoc on human respiratory and cardiovascular systems, leading to cancer, heart attacks, strokes and early deaths.

Scientists once thought that the brain was protected from similar carnage by the blood-brain barrier, a network of closely packed cells lining blood vessels of the brain that prevents toxic substances from passing from the blood into brain tissue. Unfortunately, there is now compelling evidence that PM 2.5 can and does enter the brain via two pathways. First, the particles can alter the blood-brain barrier itself to make it more permeable to pollutants. Second, the particles can bypass the barrier altogether by slipping from the nose into the olfactory nerves and then traveling to a part of the brain called the

olfactory bulb. The brain, it turns out, is no more protected from the relentless assault of air pollution than is any other organ.

HIGH EXPOSURE

MUCH OF THE RECENT WORK linking poor air quality and brain disease has its roots in the early research of Lilian Calderón-Garcidueñas, a physician and neuropathologist at the University of Montana. Born and raised in a town not far from Mexico City, Calderón-Garcidueñas has studied the health impacts of the region's foul air for decades. In the early 2000s she examined 40 dogs roaming the most polluted parts of Mexico City and found Alzheimer's-like pathology in their brains. This discovery prompted her to look at the brains of humans who had lived in similar neighborhoods. What she saw—Alzheimer's-associated proteins in the brains of children and infants as young as 11 months—alarmed her. "Exposure to air pollution," she wrote in 2008, "should be considered a risk factor" for Alzheimer's, in particular for those who are genetically predisposed to the disease.

Calderón-Garcidueñas's conclusions have been substantiated by other scientists. Jennifer Weuve, associate professor at the Boston University School of Public Health, led one of the first U.S.-wide investigations into the link between air pollution and brain disease and published the results in 2012. "We had two hints on the relationship between the aging brain and air pollution," she says. "The first was the impact of air pollution on the cardiovascular system—heart attacks and strokes. The brain relies on blood circulation, so naturally this raised concern that the brain, too, was being affected. The second hint was subtler. Toxicologists did some well-controlled studies of animals exposed to air with high levels of suspended particles and found that these particles got into the brain. Some of those particles contained known neurotoxins, like manganese. And we knew that couldn't be good."

More epidemiological evidence of an airborne-particle problem has since piled up. In 2018 the *BMJ* published a study of some 131,000 London residents aged 50 to 79 and concluded that those with the most exposure to air pollution were the most likely to be diagnosed with dementia over the eight years they were observed. The link was particularly strong between Alzheimer's and PM 2.5 particles. A study of nearly 100,000 residents of Taiwan found similar results. Researchers in Sweden concluded that air pollution increased dementia incidence even among people with no genetic markers for the disease. And scientists at the University of Toronto looked at 6.6 million people in the Canadian province of Ontario and found that those who lived within 50 meters of a major road, where levels of fine pollutants are very high, were 12 percent more likely to develop dementia than individuals living more than 200 meters from those same roads.

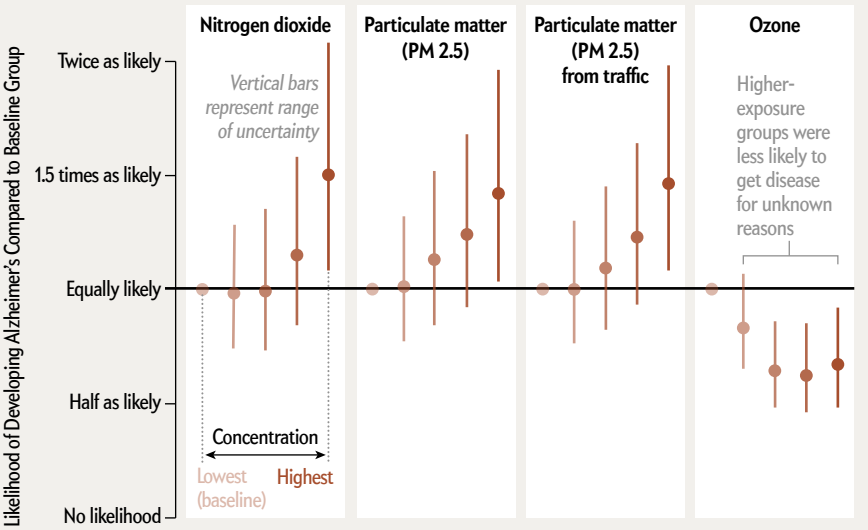
FROM AIR TO BRAIN

OF COURSE, EPIDEMIOLOGICAL STUDIES have limits. It is unethical to ask humans to knowingly expose themselves to polluted air over a period of months or years. This restriction makes it difficult to carry out controlled studies that eliminate many factors other than air pollution that might predispose residents of some regions to Alzheimer's and other forms of dementia.

"In a perfect world, everyone would wear an air-pollution monitor so that we could get real-time data on their exposures," Weuve says. "But this is not a perfect world. So we work with experts to build estimation models. It's not enough. In the case of Alzheimer's, it's chronic, long-term exposure that counts, and we don't even have a worldwide registry of people with Alzheimer's, let alone the resources to follow people for many years prior to their acquiring the disease. So it is quite difficult to nail down causation." Indeed, in some regions of the world, air pollution is so bad that people die of heart dis-

Bad Air, Damaged Brains

From 2005 through 2013 researchers studied some 131,000 people aged 50 to 79 who lived in the greater London area. They had not been previously diagnosed with Alzheimer's. The scientists also mapped concentrations of specific air pollutants where people lived and divided individuals into five groups by their levels of exposure. Compared with the lowest exposure or baseline group, chances of getting Alzheimer's increased in the top two exposure groups for pollutants such as nitrogen dioxide and in the top three groups for toxic exhaust particles known as PM 2.5. The elevated risk remained even when factors such as smoking, age and gender were taken into account.



SOURCE: "ARE NOISE AND AIR POLLUTION RELATED TO THE INCIDENCE OF DEMENTIA?: A COHORT STUDY IN LONDON, ENGLAND," BY IAIN M. CAREY ET AL., IN *BMJ OPEN*; SEPTEMBER 11, 2018

Graphic by Amanda Montañez

ease long before they would ever show symptoms of late-onset Alzheimer's.

To get a better handle on cause and effect, scientists have turned to animal models to search for biological mechanisms that may underlie a link between cognitive decline and various types and amounts of air pollution. In 2015 neurobiologist Colin Combs, chair of the department of biomedical sciences at the University of North Dakota School of Medicine and Health Sciences and an expert on neurodegenerative disease, pumped air containing different levels of particulate pollution into cages with genetically identical mice for different time periods. More exposure, he learned, produced more damage. "What we found supports the theory that long-term exposure to airborne particulate matter has the potential to alter the brain and promote the development of early Alzheimer's-like pathology," he says. In 2018 scientists at Cedars-Sinai Medical Center in Los Angeles and their colleagues reported that heavy metals from polluted air not only found their way into the brains of rats after just a few months but also appeared to activate genes that trigger neurodegenerative disorders and cancer.

A study published last year found clear links among fine-particle pollution, structural changes in the brain and memory loss in older women.

Air pollution might also interact directly with variants of certain genes associated with Alzheimer's, prompting the acceleration of brain aging and neurodegeneration in people who are already genetically susceptible. Not all people with late-onset Alzheimer's have these genetic markers, but many do, and the one-two punch of a gene-environment interaction seems to be particularly potent. Clinical psychologist Margaret Gatz of the University of Southern California explains that damage to the vascular system from pollution and other factors is associated with an increased risk of Alzheimer's and other forms of dementia, especially in people who have a genetic tendency to acquire the disease. "There's a good deal of evidence that vascular risk factors are more dangerous for carriers of the APOE4 variant of the *APOE* gene," she says. "And for this and other reasons, a lot of research has focused on the genetic risk of the disease and all but overlooked the lifestyle and environmental component."

What toxic substances found in air pollutants do when they get to the brain fits well with several ideas about the way Alzheimer's-related damage develops. Neurotoxicologist Deborah Cory-Slechta of the University of Rochester Medical Center says that in both animals and humans, these pollutants prompt the release of cytokines from microglia cells, the resident immune sentinels in the brain. Cytokines are signaling molecules that help to regulate immunity and inflammation. Under normal circumstances, this response can help protect the brain against outside invaders. But chronic exposure to polluted air can result in the overproduction of proinflammatory cytokines and chronic inflammation that leads to nerve cell death. "Ultrafine particles seem to be the most important factor in this process," Cory-Slechta says.

She also notes that it is hard to zero in on specific components of these particles. "For one thing, we have very little historical data on them, so it's hard to judge their relative levels in the environment. For another, they contain lots of different substances that we tend to clump together," making it difficult to know what specifically is causing the negative effect.

Particle pollution from the burning of fossil fuels and other sources contains hundreds of substances, ranging from noxious gases such as sulfur dioxide and nitrogen oxide to the dust emitted from automobile and truck brakes, tires and clutches. Cory-Slechta says that these pollutants tend to accumulate in the brain over many years, which might help explain why Alzheimer's is typically a disease of old age. But, she adds, there are still many unknowns about what exactly gets into the brain from the air—it's not clear that all these substances make it inside—and when those that do cause trouble. "What we do know is that iron, zinc, copper, and other metals are required by the brain, but at a specific level. What happens when that level is exceeded?" she asks. "We know that too much iron can lead to oxidative stress and neurodegeneration. We also know that some pollutants, like aluminum, play no essential role in the brain yet tend to accumulate there and provoke an inflammatory response. Frankly, I think we should be taking a closer look at that. And it's not just metals. Organic contaminants might also be involved in neurodegenerative disease."

One type of such organic pollutants are lipopolysaccharides, large molecules released from bacteria spewed from waste-treatment plants and other sources. Scientists have found these molecules can latch onto particulates and, when inhaled, provoke an inflammatory response in the lungs. In animal studies, lipopolysaccharides and other organic matter have also been shown to provoke inflammation and related cognitive degeneration in the brain.

PARTICLES AND MEMORY LOSS

JIU-CHIUAN CHEN, a physician and epidemiologist at the University of Southern California, specializes in the study of airborne pollutants in the brain and says that although the impact of individual substances is still under debate, the overall effect of the mix is clearly related to brain damage and cognitive problems. Chen was co-author of a study published last year in the journal *Brain* that found clear links among fine-particle pollution, structural changes in the brain and memory loss in older women. Chen and his collaborators used

neuroimaging and cognitive tests to measure brain changes and memory, plus a mathematical model that incorporated two sources of environmental air-quality data.

"What we found was that women with the highest exposure to pollutants showed an early decline in episodic memory," he says. This type of long-term memory involves recalling a previous experience along with the time and place of the event and associated emotions. The decline Chen detected in these women appeared preclinically—before any actual symptoms of Alzheimer's—and was independent of the subjects' cardiovascular status. Alzheimer's research has established that people with a decline in episodic memory have a very high risk of developing the full-blown disease later in life.

"There are more than 10 studies that link late-life exposure to air pollution and dementia," Chen says. "The evidence there is quite compelling. Whether exposure in early life is also a factor, we don't know. But in animal studies, toxicologists start exposure in early life, look at the pathological changes and see problems. It looks like small particles can accelerate the amyloid-deposit process, but we're not yet sure whether this happens in humans. And there might be a genetic component involved—that is, some people might be more susceptible than others to the effect of pollution. There might be a subgroup of individuals who are particularly susceptible and might be at greater risk. We don't yet have enough power in our studies to address this question, but I believe we will."

RISK REDUCTION

WHILE THE DISEASE REMAINS a horror facing millions of people around the globe, there is some encouraging news in these discoveries about air pollution, several scientists say: people can take action to diminish the hazards. Most drugs so far have not helped patients, says George Washington University epidemiologist Melinda Power, who focuses on identifying modifiable risk factors for cognitive decline and dementia. "So at the moment, prevention through the reduction of environmental and lifestyle factors looks like our best bet," she says. "And air-pollution exposure is looking [like it could be] very important."

The evidence about brain damage is a strong argument for stricter air-quality controls, says University of Michigan epidemiologist Kelly Bakulski. "This is a really hopeful area," he says. "Unlike our genes, environmental factors are things we can control—removing these pollutants from our communities will have no ill and many positive impacts."

In addition, Gatz says that simple changes in how we live can help. "Physical exercise is shown to reduce risk," she says, both because it increases blood flow to the brain and because it increases levels of brain-derived neurotrophic factor, a protein that promotes the growth and maintenance of brain cells.

Knowing the havoc that the disease inflicts, it is time to take such changes seriously. "We have the means to do it," Bakulski says, "and given the risk of not doing it, we must." SA

More to Explore on Alzheimer's Disease

Research papers and archival coverage related to the articles in this special report.

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"THE ROLE OF AIR POLLUTION"

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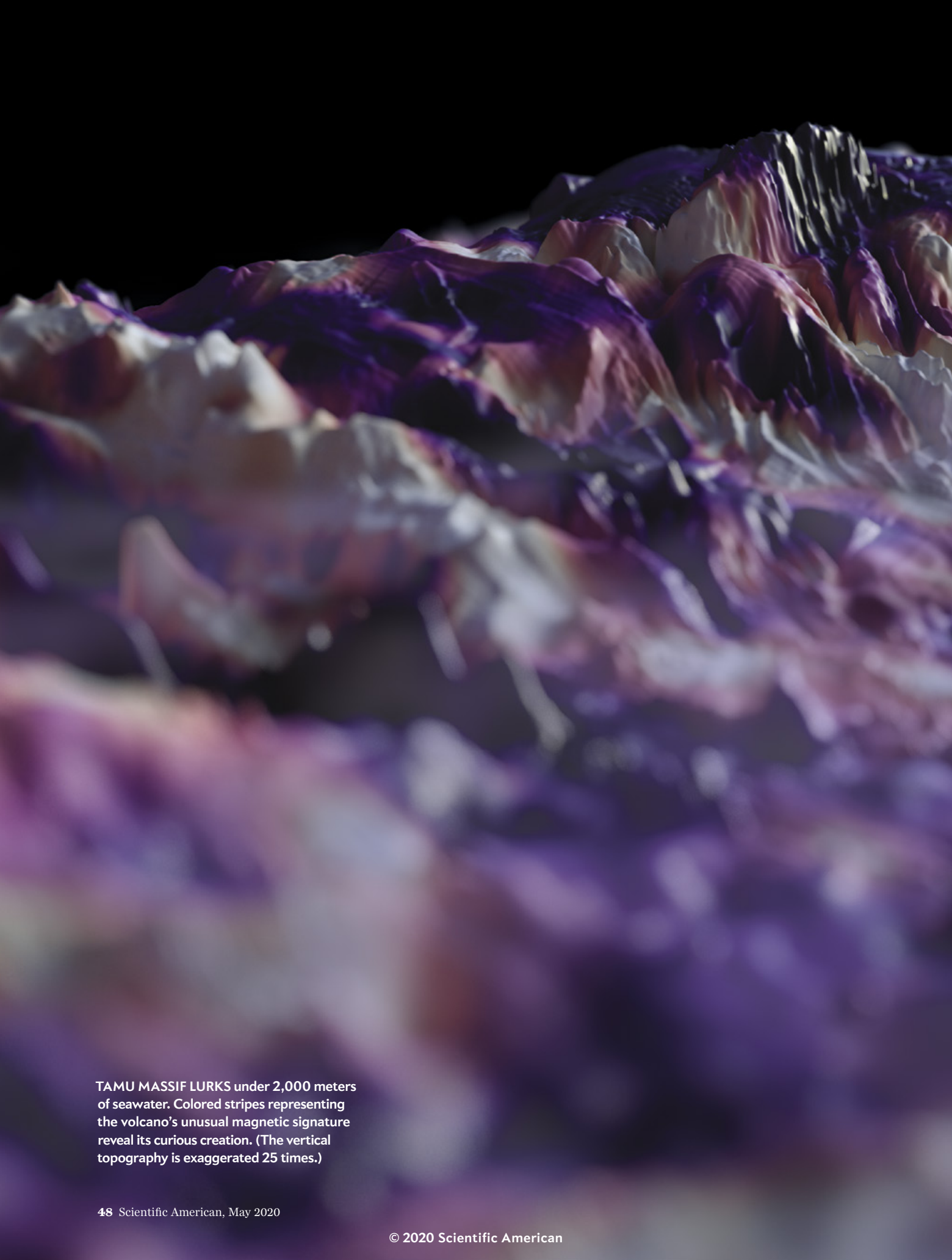
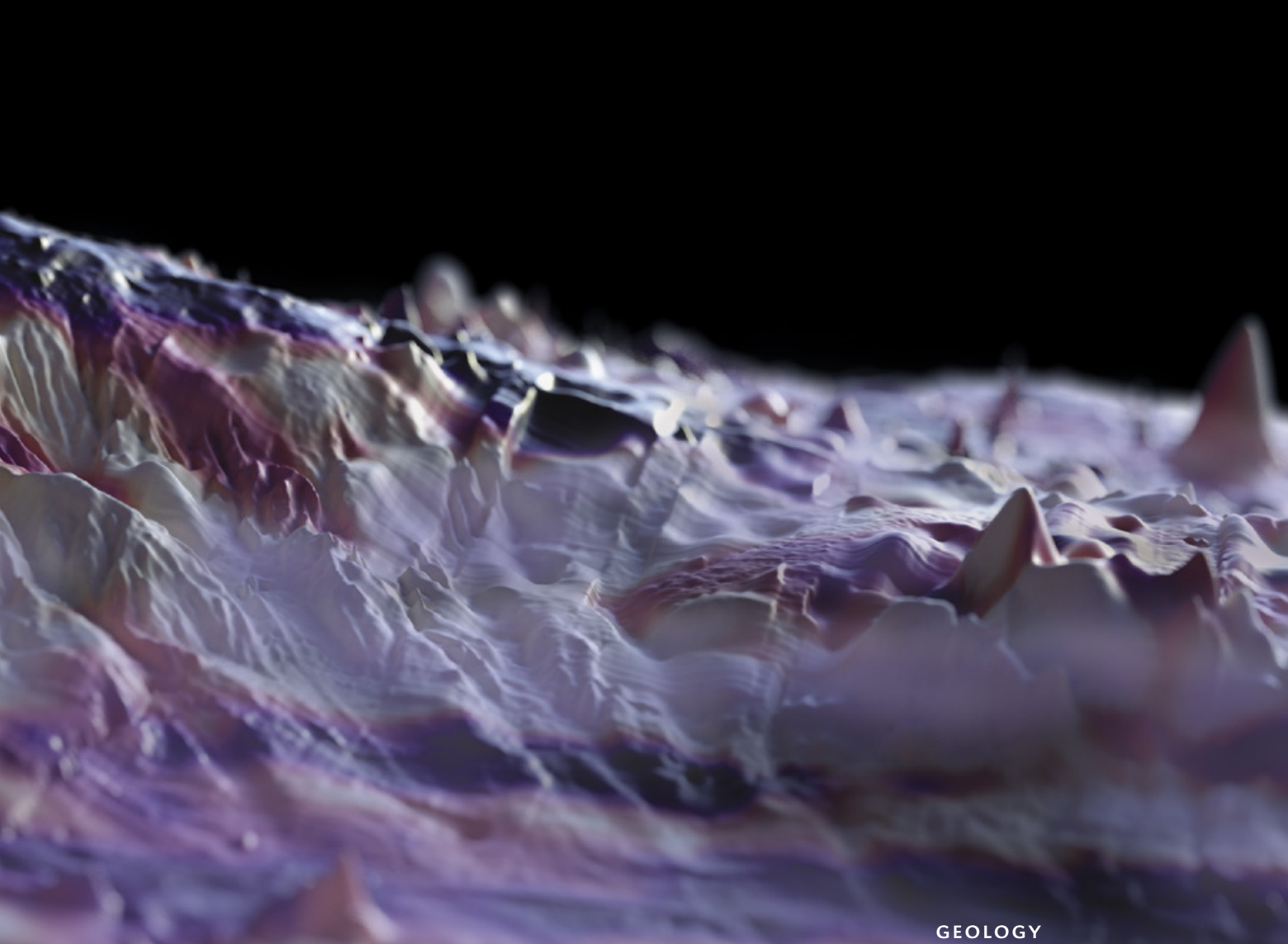


TAMU MASSIF LURKS under 2,000 meters of seawater. Colored stripes representing the volcano's unusual magnetic signature reveal its curious creation. (The vertical topography is exaggerated 25 times.)



GEOLOGY

MASSIF REDO

A new explanation for the giant Tamu Massif volcano rewrites the story of how the seafloor formed

By William W. Sager

Illustration by Craig Taylor, Mapzilla

BIG, DARK OCEAN WAVES WERE ROLLING OUR RESEARCH SHIP FROM SIDE TO side. The *Falkor* is 83 meters long and weighs more than 2,000 metric tons, but a storm from Siberia that had just missed us was still churning the seas. Sitting in the science lab on the main deck, I was trying to keep my coffee from spilling onto my map of the seafloor.

William W. Sager is a professor of geophysics at the University of Houston. He has sailed on 46 oceanographic expeditions and gave the Tamu Massif volcano its name.

IN BRIEF

New magnetic data from the Pacific Ocean seafloor show that the enormous Tamu Massif volcano was not formed the way experts thought. **Rather than erupting** like a volcanic mountain, Tamu Massif was created by lava oozing up between separating tectonic plates. **It appears that** dozens of other seafloor volcanoes formed in this way—a new explanation for how giant Earth features were created.

It was mid-October 2015, and we were in the northwestern Pacific Ocean, about 1,600 kilometers east of Japan. For the umpteenth time I was looking at a map that showed somewhat parallel stripes along the seafloor around Tamu Massif, an enormous, ancient volcano. Each stripe indicated how a band of seafloor was magnetized—positively or negatively—but the pattern did not agree with how I thought Tamu Massif had erupted.

A sudden wave hit the *Falkor* with a loud thud, jarring me, and just then I realized what I had been missing. I had been studying this volcano for more than two decades. I had published the definitive papers giving the volcano its name and explaining its history. So my insight was only partly a "Eureka!" moment; the other part was a Homer Simpson moment: "D'oh!" My old ideas, and everyone else's, about how this volcano formed had been wrong.

Tamu Massif is special. It is roughly 430 kilometers wide and 600 kilometers long, covering an area similar to that of New Mexico. It is more than 50 times bigger than Mauna Loa on the island of Hawaii by volume, yet it is essentially flat. Its broad slopes dip by about one degree from the middle toward the edges, whereas a typical undersea volcano has a decline of five to 10 degrees. Imagine an entire football field covered by a taut gray tarp, with a stick just 60 centimeters high propping it up at midfield.

The volcano is the main mountain in one of the largest oceanic plateaus on the planet: Shatsky Rise. Yet the peak is still about 1,980 meters below the sea's surface. Most oceanic plateaus are made of basalt, implying that great volumes of magma rose from Earth's mantle and moved through the crust, squeezing up through the seafloor and pouring outward. Although Tamu Massif's shape seems to reflect this eruption process, the data I have collected since 2015 show that this is not what happened.

This new insight means scientists have misunderstood how dozens of immense underwater volcanoes have created more than 5 percent of the planet's current seafloor. Indeed, we have stumbled on an entirely new type of volcano.

If Tamu Massif or one of its cousins erupted again, it could make the Pacific Ocean more acidic, killing all kinds of marine life. It could also release large amounts of greenhouse gases into the ocean and the atmosphere. When we look back through history, it appears that eruptions from a similar volcano, the Ontong Java Plateau in the southwestern Pacific Ocean, corresponded with widespread, low-oxygen ocean conditions. Finally, although I am inspired by the thought that we are rewriting our ideas about the seafloor's formation, I also have to accept a hard reality: Tamu Massif, which had been branded "Earth's largest shield volcano," no longer deserves that title.

PIECE OF CAKE

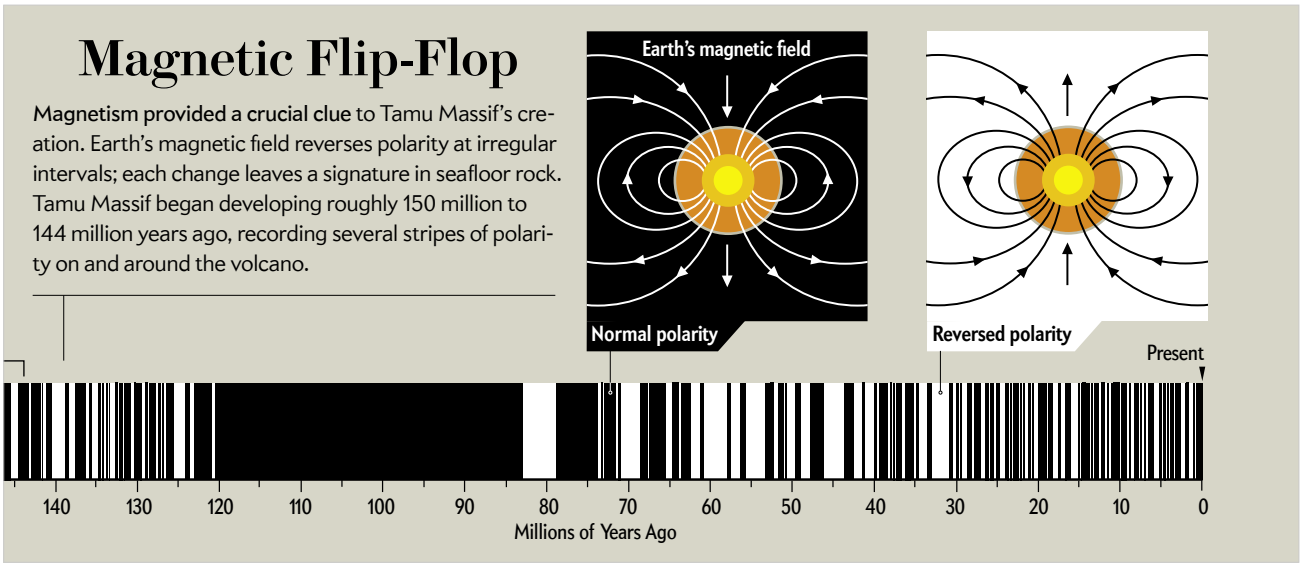
TAMU MASSIF FORMED gradually, over several million years, about 145 million years ago. During that period Earth's magnetic field reversed a couple of times at irregular intervals, leaving telltale magnetic stripes in the oceanic crust.

My first paper about Tamu Massif's magnetic history was published in 1993, when I was at Texas A&M University—the origin of "Tamu" (and *massif* means "massive" in French). In it, I concluded that the volcano must have formed from one eruption event in a short time: a huge blob of magma hundreds of kilometers in diameter rose through the mantle and spread out onto the seafloor. Massive eruptions caused floods of hot basalt to run down the accumulating slopes, building a broad, slightly domed layer of new earth. Subsequent eruptions would have added more layers, creating something like a layer cake, with the oldest basalt layer on the bottom and the youngest basalt layer at the top. On land, this is generally how shield volcanoes form. Other experts had similar thoughts about the world's largest oceanic plateaus: Ontong Java and the Kerguelen Plateau in the southern Indian Ocean.

After more research expeditions to further map Tamu Massif and take samples of its basalts, in 2013 my colleagues and I published a paper in *Nature Geoscience* indicating that Tamu Massif was an enormous shield volcano. Soon enough the media declared that we scientists had discovered "the world's largest shield volcano."

That superlative always made me cringe. I tried to tell journalists that we did not discover Tamu Massif (that happened in the early 20th century) and that there are larger oceanic plateaus. But something else bothered me: the pattern of magnetic stripes was odd for a broad shield that had formed like a layer cake.

If you looked down from space at the floor of the Pacific Ocean with glasses that revealed magnetism, you would see parallel stripes everywhere. But at a volcano, you would expect to see a big splatter mark because lava pouring out from the center would have interrupted that pattern. Not having such glasses, I had been col-



lecting magnetic-field data at sea. My "Eureka!" moment on the *Falkor* happened when it became clear that there was indeed a wide, continuous stripe across Tamu Massif.

Tamu Massif formed at a triple junction—a place where three tectonic plates meet, like three huge wedges converging at a single point. When two of the plates spread apart, a crack opened along their boundary. Magma oozed up to fill the void and solidified as basalt. As the plates moved farther from the center, the new ribbon was torn along its axis and pulled apart, and newer magma filled the newer void.

This process repeated over and over. Tamu Massif was not built like a layer cake at all. Instead imagine a sheet cake being pulled apart horizontally, with new cake filling the crack that formed down the middle. That cake was subsequently pulled apart, newer cake filled the newer crack, and so on. If new ribbons of cake alternated between chocolate and vanilla, over time a pattern of stripes would be created. On Tamu Massif, positive and negative magnetic stripes correspond to this pattern.

There are two physical problems with this explanation, however. The stripes on Tamu Massif's southeastern quadrant turn 90 degrees counterclockwise. In retrospect, the reason for this seems somewhat obvious. As Tamu Massif erupted over time, a piece of the plate to the northeast broke off and moved, causing a segment near the triple junction to rotate 90 degrees. This segment is where Tamu Massif formed. Realizing that the stripe down Tamu Massif's back was a spreading magnetic anomaly was my "D'oh!" moment.

The second problem is that in the sheet-cake model, each newly formed ribbon of cake should have the same height as the existing cake being pulled apart. But Tamu Massif is thickest in the middle. I think this structure developed because the melting at the center increased for some time, forming a higher crust.

TAMU, TAKE TWO

MY COLLEAGUES AND I have collected a lot of seafloor data and core samples drilled from area basalts that are helping us convince other scientists that our interpretation is correct. Our new understanding of Tamu Massif revolutionizes the view of how oceanic plateaus formed. Observations from a few other oceanic plateaus—those for which we have enough magnetic data to map the stripes—imply that many formed in a similar manner. Plateaus that developed where plates were diverging must be a new class of volcano. This means that the widely accepted assumption that oceanic plateaus are large shield volcanoes created by long basaltic lava flows is incorrect.

Why did we get the picture wrong before? And does it matter that Tamu Massif is not a classic shield volcano? We were wrong because submarine volcanoes hide under thousands of meters of water, so we cobbled together a picture from fragmental data. Imagine trying to reconstruct a dinosaur from just a tooth and a toe bone. You would attempt to connect them in a diagram based on what you know about other dinosaurs, but if your assumptions are incorrect, the picture will be incorrect, too. Tamu Massif is no longer the largest shield volcano on Earth, because it is not a shield volcano. We assumed that it formed like other volcanoes, but that was a bad assumption. Instead we found a new family of volcanic mountains—a new explanation for how giant features on Earth were formed. And there are dozens of them under the sea.

Scientists are always trying to understand how things came to be. That is our goal—even if it overrules our own prior findings. Our fresh understanding of Tamu Massif allows me to say, "We finally figured it out." That may not be as headline-worthy as "world's biggest," but I am happier with it. SA

SOURCE: *TIMESCALES OF THE PALEOMAGNETIC FIELD*, BY D. V. KENT AND W. LOWRIE. EDITED BY J. E. T. CHANNELL ET AL. AMERICAN GEOPHYSICAL UNION, 2004 (*time line*)

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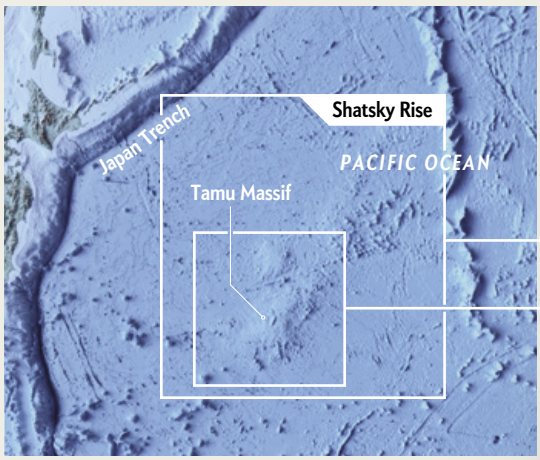
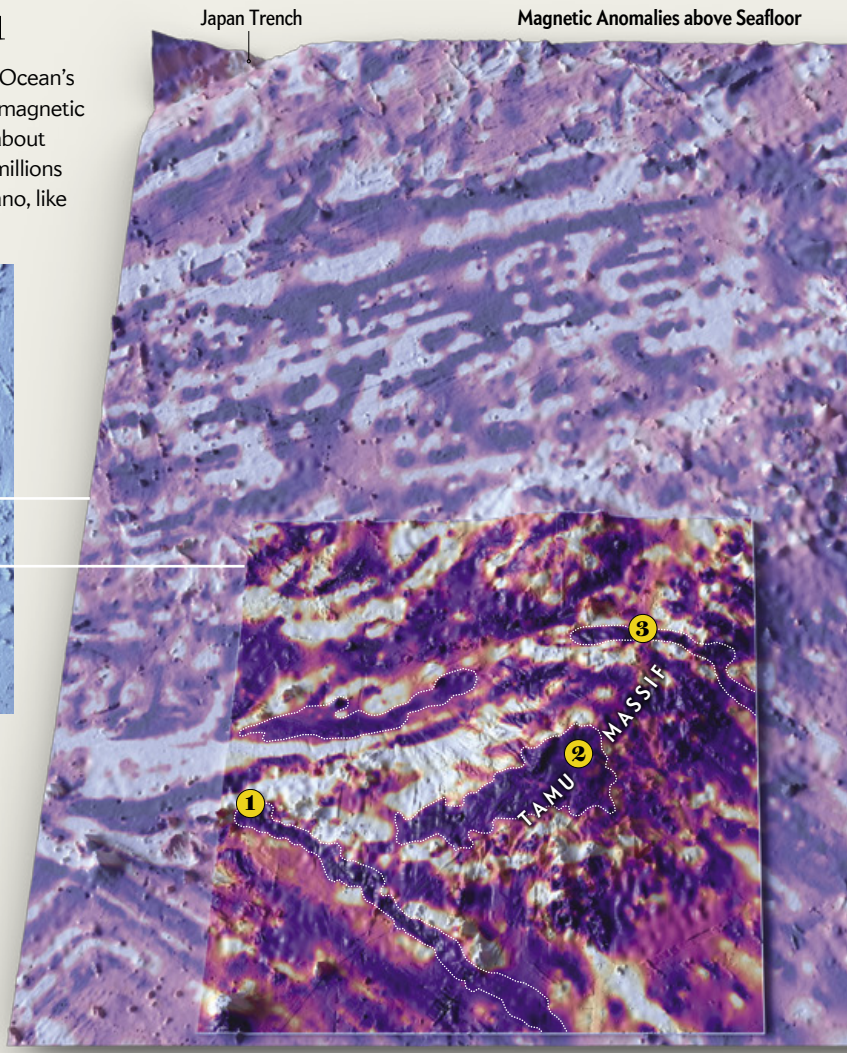
Illustration by Jen Christiansen

New View of Tamu

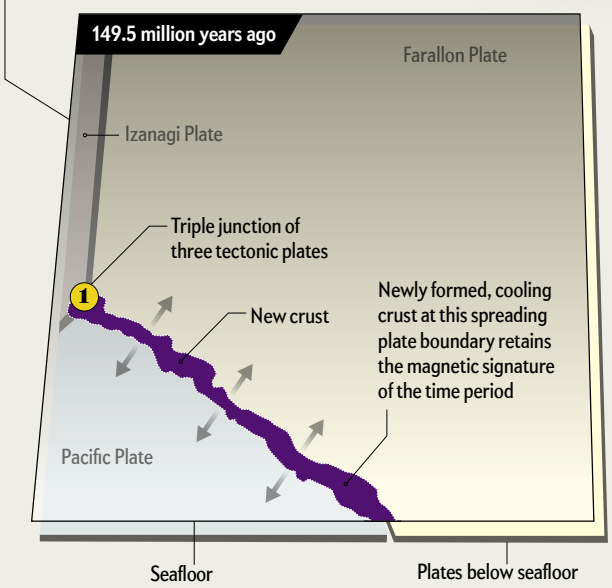
For years scientists thought Tamu Massif, on the Pacific Ocean's seafloor, was a classic shield volcano. But the pattern of magnetic stripes across it does not reflect that view. Recent data about how tectonic plates moved when Tamu Massif formed millions of years ago reveal that magma built a new kind of volcano, like a sheet cake torn in two.

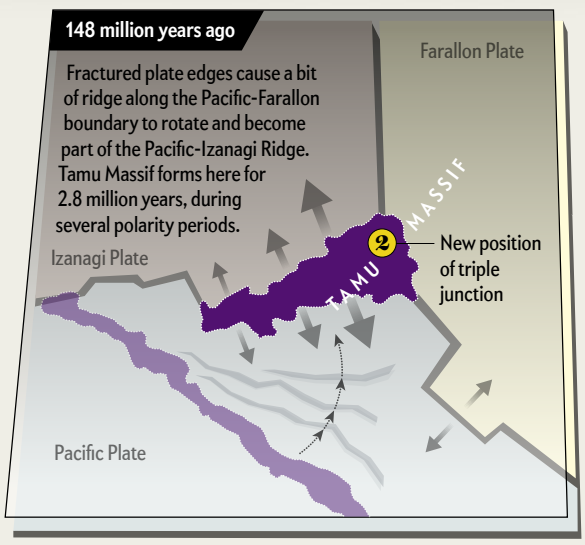


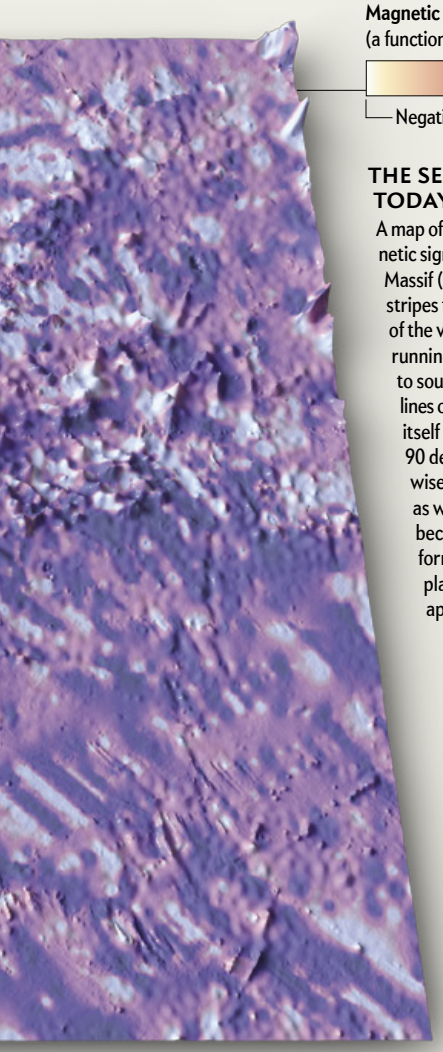


HOW THE VOLCANO GOT ITS STRIPES

About 149 million years ago three tectonic plates under the Pacific Ocean were separating from a triple junction (1), near where Tamu Massif would later arise. A widening crack was filled with new crust. Roughly 148 million years ago, while Tamu Massif was forming, the triple junction jumped northeast, and a bit of ridge from the Pacific-Farallon Plate boundary rotated counterclockwise to become part of the Pacific-Izanagi Ridge (2). This caused the stripes on Tamu Massif to rotate. By 144 million years ago, after the volcano had stopped erupting, the junction had moved again because the Izanagi Plate had migrated farther (3). The wide stripe down the volcano's back indicates that most of the erupting occurred during a single period of reversed polarity.

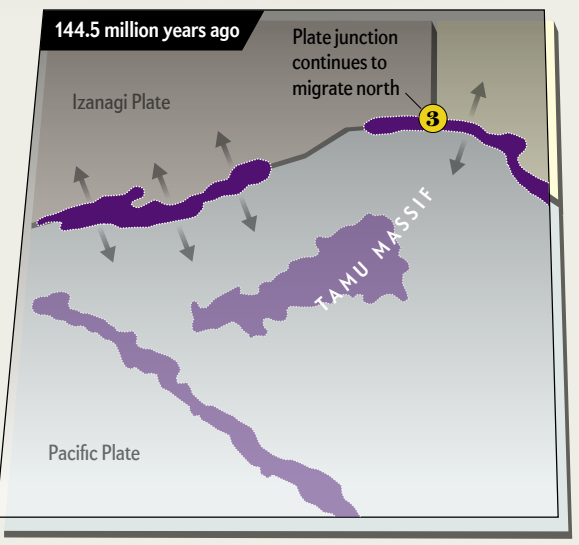






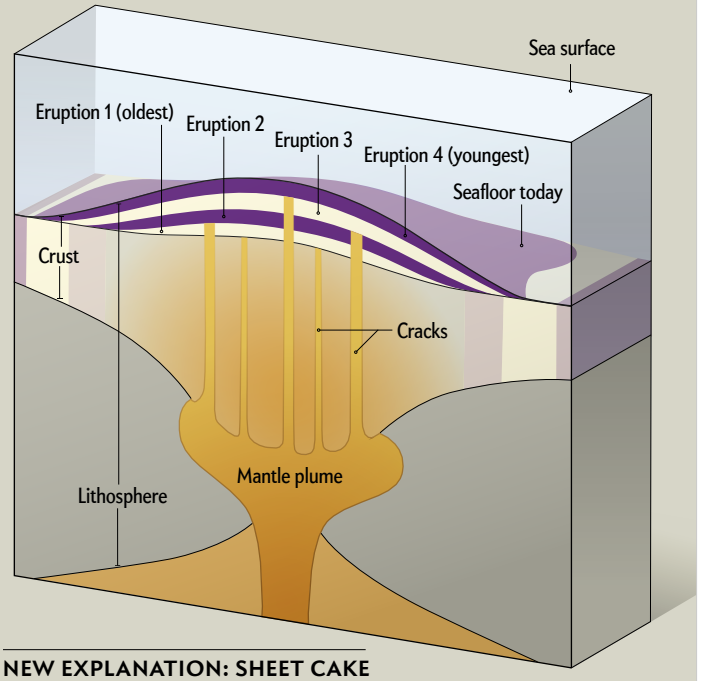
THE SEAFLOOR TODAY

A map of the seafloor's magnetic signature around Tamu Massif (*inset*) shows parallel stripes to the west and east of the volcano's lower half, running from northwest to southeast (1). But the lines on the central volcano itself (2) are turned about 90 degrees counterclockwise and are about twice as wide as the rest because the volcano formed where tectonic plates were rotating apart quickly.



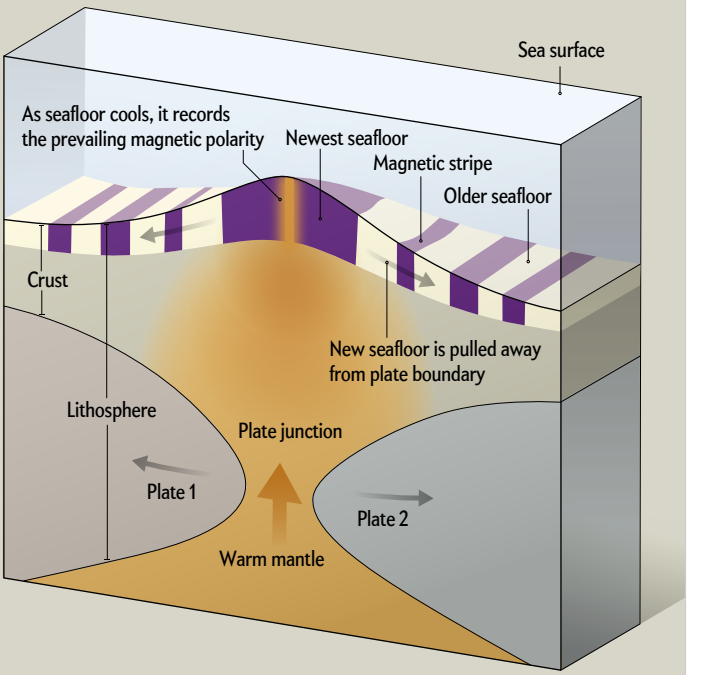
OLD EXPLANATION: LAYER CAKE

A shield volcano—the original description of Tamu Massif—forms like a layer cake. Warm mantle rises and melts underneath the cooler lithosphere. A vertical crack allows hot magma from the plume to move up through the ocean crust and erupt, flooding out across the seafloor and cooling as a low dome. Over time subsequent eruptions add newer layers, building up the dome like a layer cake.



NEW EXPLANATION: SHEET CAKE

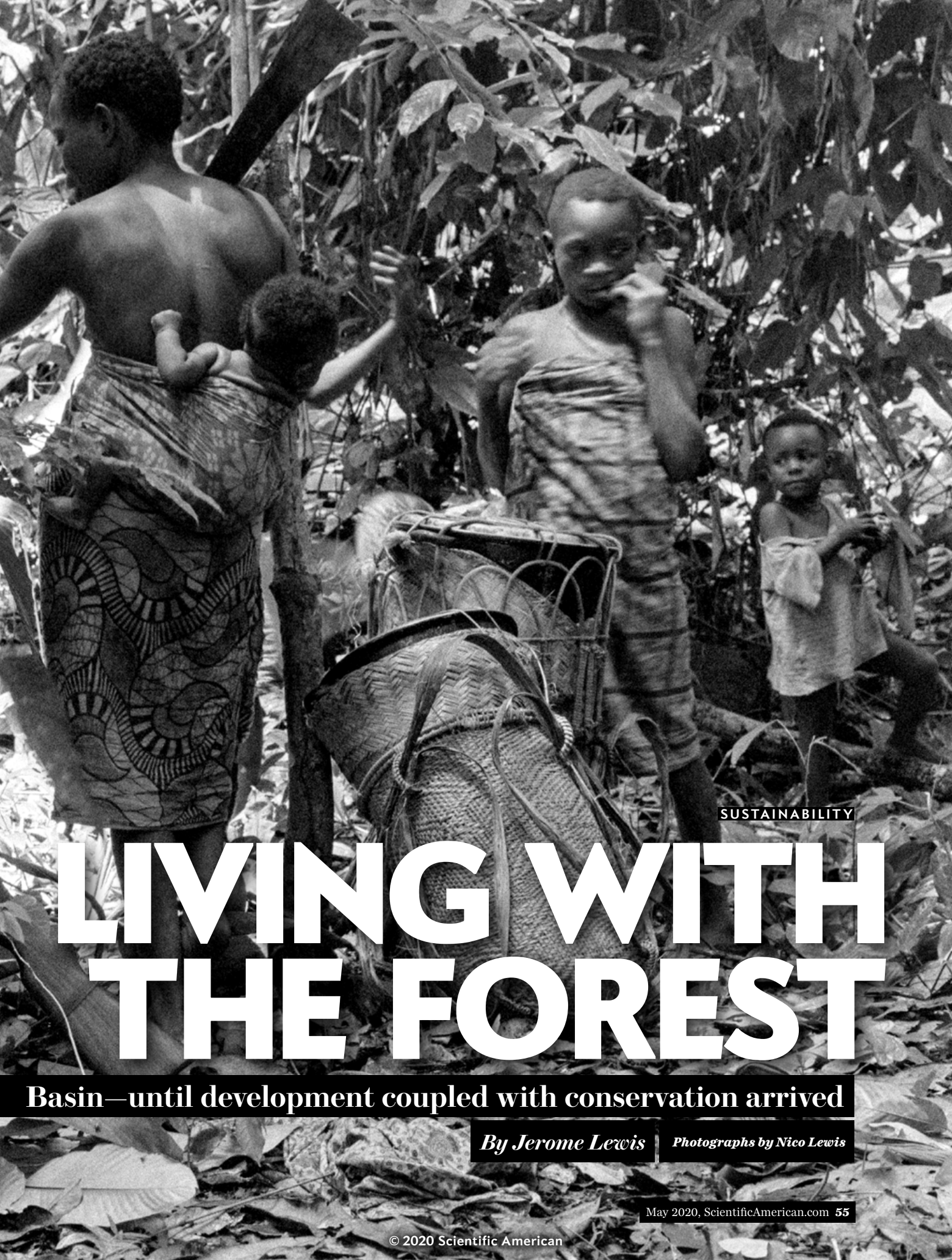
As tectonic plates separate, they pull the lithosphere and crust apart, opening a crack along the boundary—as if a sheet cake were cut down the center and separated horizontally. Hot magma oozes up to fill the void and solidifies as seafloor. As the plates continue to diverge, they pull apart the newer seafloor, creating another crack that fills with fresher magma. This process repeats; each time new rock cools, it takes on the prevailing magnetic signature, creating magnetic stripes over time.



Maps by Craig Taylor, Mapzilla, Illustrations by Jen Christiansen

GWANJENJE, a BaYaka Pygmy, chooses a spot for her hut at a new campsite in northern Congo in 1997. The hunter-gatherers move seasonally through the forest, each woman carrying her entire household in one basket.

Pygmies thrived in the Congo



SUSTAINABILITY

LIVING WITH THE FOREST

Basin—until development coupled with conservation arrived

By Jerome Lewis | *Photographs by Nico Lewis*

Jerome Lewis is an associate professor of anthropology, director of the Center for the Anthropology of Sustainability and co-director of the Extreme Citizen Science group at University College London. In 2019 he founded Flourishing Diversity, an initiative to raise awareness of indigenous ways of protecting biodiversity.

IN THE PITCH-BLACK DARKNESS, sitting on the forest floor with our bodies so close that we touch, we sing, each voice producing a different yodeled melody to create a densely overlapping harmony. As the hours pass, individual melodies melt into one another, and we begin to lose ourselves in the human and acoustic tapestry we have created. The intensity of the singing builds, its coordination increasingly perfected until the music is so beautiful that the self melts away. Such splendor attracts forest spirits into the camp to join us, the BaYaka believe. As tiny dots of luminescence, they float around us, coming close and then retreating toward the forest, their subtle voices whistling sweet tunes that occasionally slip through the polyphony. Overwhelmed by the beauty we have created together, some call out "*Njoor!*" ("My word!"), "*Bisengo*" ("What joy!") or "*To bona!*" ("Just like that!").

PYGMY BANDS across the Congo Basin share similar solutions to living in the forest, including their characteristic "spirit plays" and their leaf-and-liana shelters. At a new campsite in 1997, Ingoyo tiles the roof of her hut with leaves.

In such moments, you feel that you are the forest, your awareness expanding to encompass the trees, the animals and the people around you. Experiencing such expansiveness, as I did during my doctoral research among the BaYaka Pygmies of the Republic of the Congo in the 1990s, is deeply moving and establishes a loving and joyful connection to everything and everyone in the vicinity. During such "spirit play," an intensely immersive form of theater, the BaYaka feel themselves communing directly with the forest, communicating their care and attention to it and reaffirming a profound relationship of mutual support and love. As my friend Emeka said, "A BaYaka loves the forest as he loves his own body."

The BaYaka follow strict rules in their hunting and gathering. They harvest wild yams in such a way that they regenerate and multiply, they try to avoid killing pregnant animals, and they consume everything that they take from their environs. Over millennia their actions and those of other Pygmy tribes in the Congo Basin have enhanced the forest's productivity not just for humans but for all creatures. The BaYaka do not have a word for famine. When I tried one evening to explain to Emeka and others assembled around a fire that there are places where people starve to death, I was met with skepticism and disbelief.

Also in the 1990s, however, international institutions such as the World Bank, working in partnership with national governments and conservation agencies, began to implement sustainable-development models in the Congo Basin. They zoned the rain forest into expansive sections for logging and other activities while setting aside "protected areas" as safe havens for wildlife. In accordance with the belief that nature thrives if left untouched by

IN BRIEF

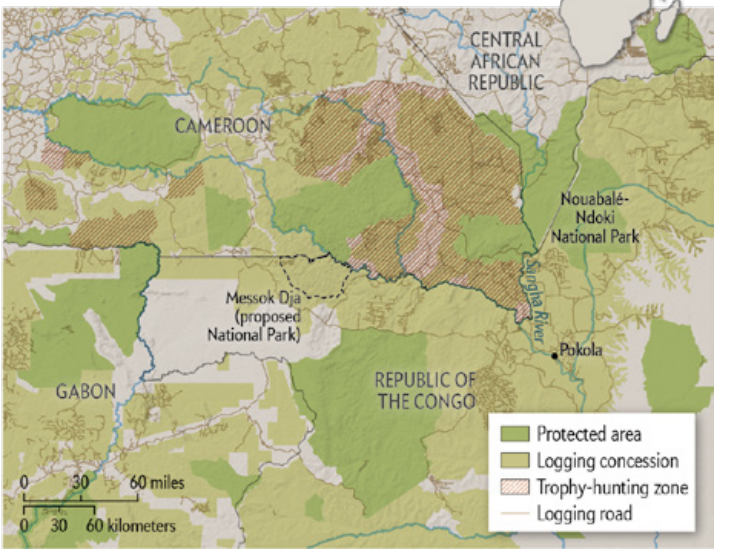
Pygmy bands roamed the Congo Basin for more than 55,000 years, evolving elaborate ecological and cultural strategies for thriving in the forest.

Sustainable development, in the form of extractive industries alongside conservation areas, generated a network of roads, enabling commercial poaching.

As wildlife declined, conservationists used "eco-guards" to curb poaching. But some began persecuting Pygmies, forcing many into hunger and depression.

Development in the Congo

Since the 1990s international institutions, conservation agencies and local governments have zoned the Congo Basin into areas for logging or other activities, along with protected areas for wildlife. Pygmies are allowed to hunt for subsistence in some areas, but in practice many are too afraid of attacks by eco-guards to venture into the forest. Unable to pursue their original way of life, many hang out near logging towns such as Pokola in the hope of odd jobs.



SOURCES: GLOBAL FOREST WATCH (*protected areas, logging concessions, logging roads*); SURVIVAL INTERNATIONAL (*trophy hunting areas*); WORLD WILDLIFE FUND (*Messok Dja*)

humans, which originates in 19th-century U.S. policy, regional governments banned Pygmy groups from the wildlife reserves.

Since then, I have watched an abundant forest teeming with elephants, gorillas, chimpanzees, wild boars, monkeys and antelope become a degraded woodland as national and international markets suck out forest produce. Central African elephant populations fell by more than 60 percent between 2002 and 2011, and the decline continues. The formerly active, well-fed and lively BaYaka are now often malnourished, depressed and alcoholic casual laborers dwelling on the edges of their former territories, terrorized by so-called eco-guards and subjected to commercial and sexual exploitation by outsiders. They thrived in the Congo Basin for tens of millennia only to succumb within a few decades to industrial civilization's appetite for natural resources and a colonial approach to securing them—by expelling the natives from their homelands.

In opposition to such "top-down" conservation, which is often paired with extractive industries and which regularly fails to meet its stated objectives, a "bottom-up" approach to defending forests and wildlife is steadily gaining ground. A 2019 report by the United Nations' Intergovernmental Science-Policy Platform on Biodiversity and Ecosystem Services found that indigenous peoples are better at maintaining biodiversity on their land than practically everyone else. Moreover, 80 percent of the planet's remaining terrestrial biodiversity coincides with the 65 percent of Earth's surface that is under some form of indigenous or local community management. Recognizing this reality, this new conservation paradigm seeks to empower local communities to resist the commercial forces invading their territories.

The BaYaka themselves helped me in one such endeavor. Called the Extreme Citizen Science (ExCiteS) program, it enables local peoples to map their resources and the dangers threatening them and to share their ecological knowledge with outsiders. The tools and methodologies we designed in the Congo Basin are proving useful in diverse parts of the world. The community network in the Prey Lang forest in Cambodia has been so successful in using the latest version of our mapping tool, the Sapelli app, to protect the forest that it won the U.N.'s prestigious Equator Prize in 2015, the Yale International Society for Tropical Foresters Innovation Prize in 2017 and the Energy Globe Award 2019.

AN IDEAL BAYAKA MAN

WHEN MY WIFE, INGRID, our three-year-old son, Nando, and I apprehensively climbed off the dugout onto the sandy bank of the Sangha River in northwestern Congo in 1994, it was Emeka who greeted us with a warm smile. A charismatic man in his 30s, he was one of a group of about 40 Pygmies camped there. Living throughout the Congo Basin—from Uganda, Rwanda and Burundi in the east to the Atlantic Ocean in the west—Pygmy hunter-gatherer bands speak a range of different languages and are believed to number anywhere between 300,000 and a million. All regard themselves as the orig-

Map by Mapping Specialists

BAYAKA CHILDREN enjoy a swing crafted out of lianas in 1997. The forest provides all their playthings.

inal inhabitants of the forest; DNA studies indicate that their ancestors have been living in the region for at least 55,000 years.

Despite their superficial differences, those Pygmy groups still living in intact forests share similar approaches for living well in this environment—their igloo-shaped leaf-and-liana huts, the tools they use for hunting or honey collecting, their distinctive singing style for communing with forest spirits. Over the next three years, as Ingrid, Nando and I covered many thousands of kilometers traveling through the forest with Emeka, his wife, Mambula, and many other members of his extended family, we were immersed in their vibrant and egalitarian way of life. Our companions taught us how to live successfully as hunter-gatherers: how to walk and wade across huge marshes; navigate using elephant trails; hunt wild animals; collect fruit, wild tubers, edible leaves and seasonal insects; dam forest streams to trap fish; and play with forest spirits.

Emeka was our guide. He proved to be a strong and courageous hunter; a caring, indulgent and diligent father and husband; an even-tempered mediator and wise counselor; a skilled orator, singer, storyteller and director of impromptu theatrical productions in the camp; and generous to a fault. The BaYaka's economy is based on the principle that if you see someone with something you want, you simply ask for it. Living in such a demand-sharing

economy (as anthropologists call it) is like living in a place where goods are free. Even if you rarely contribute—say, because you are a child or an old person or are mentally or physically challenged—no one ever questions your right to demand a share of whatever is brought into camp. Emeka invariably gave away everything he had.

The BaYaka vociferously reject the idea that the natural world can be owned. "Komba [the creator] made the forest for all creatures to share," Emeka told me. Once, on an overnight hunting trip, he and I made camp near a group of gorillas. The silverback smelled the smoke from our fire and began roaring and retching to intimidate us. Emeka was furious. Shouting and swearing, he berated the silverback for thinking that the forest belonged to him: it is there to satisfy all creatures' needs. Another time my friend Tuba pointed to his young son: "Look, he eats the forest foods, and it grows his body strong." In effect, the BaYaka see themselves as forest transformed into persons—so much a part of it that they can no more imagine selling a portion of it than I can sell my thumb or my foot.

In the same spirit, the BaYaka hold that the forest is abundant so long as everyone respects certain principles. Scarcity or want derives from people not sharing properly and from the social disharmony that follows—not from inadequacies in nature's ability to provide. A set of rules called *ekila* ensures plenitude. If a patch of forest becomes unproductive, for example, the BaYaka seal it off so that no one hunts or gathers there; the ban is lifted when the area recovers. Everyone in the camp must get a portion of meat from a hunt and treat the animal's carcass with respect. The forest cares about its inhabitants and desires to hear delightful sounds emanating from them; sharing song and laughter with it will induce it to be munificent. Thus, the key social institutions of the BaYaka not only ensure abundance but also celebrate and generate joy.

Our time roaming the forest during the 1990s was idyllic. We ate wild foods and moved freely and without fear. We danced and performed spirit plays for days, sometimes weeks. "They were a people who had found in the forest something that made their life more than just worth living, something that made it, with all its hardships and problems and tragedies, a wonderful thing full of happiness and free of care," anthropologist Colin Turnbull had written of the BaMbuti Pygmies of northeastern Congo, almost 1,000 kilometers away, three decades earlier. I feel much the same about the BaYaka.

But trouble was brewing. In 1993 the Wildlife Conservation Society (WCS) had worked with the World Bank to establish the Nouabalé-Ndoki National Park in the Republic of the Congo. Covering 4,000 square kilometers on the country's border with the Central African Republic, it was intended to protect elephants, bongo antelopes, chimpanzees and gorillas. Because Pygmies left hardly a trace of their presence, the authorities and scientists from the WCS claimed that the area was uninhabited. When forest patrols came across hunter-gatherers in the reserve, they evicted them. In consequence, BaYaka clans of the Congo became separated from their kin in the Central African Republic and lost access to large areas of forest that they had known intimately for generations.

The park's borders lay some 150 kilometers north of where I was roaming with Emeka's band, so we did not directly feel its impact. But we were in the broad "buffer zone," which included extensive logging concessions around the protected area. So began the end of an abundant and thriving space in which diverse species flourished.

THE SAPELE TREE

I REMEMBER THE FIRST TIME we came across a logging road, in 1994. My BaYaka companions complained about how hard the surface was underfoot, how hot it was without the shade of the trees and how many flies bothered us. Emeka and I laughed as women scattered deep into the forest as if a buffalo were chasing them when the first logging truck rumbled by. Over time roads came to criss-cross the forest, facilitating the extraction of bushmeat, edible plants and other forest goods to supply urban markets.

Of particular interest to logging companies was the magnificent sapele (*Entandrophragma cylindricum*). Waterproof, incredibly strong, resistant to pests and possessing a beautiful, iridescent grain, this hardwood is in great demand on international markets. But the sapele was crucial to the Pygmy way of life. Once, after a 60-kilometer trek, I was moaning about my sore feet. Emeka cut a diamond-shaped slab of bark from a nearby sapele—a layer of its skin just below the bark is a strong analgesic and antibacterial agent. Emeka placed it upside-down on the campfire to heat the oils in the medicinal layer. Then he put it on the ground and told me to rest my feet on it. Relief was immediate and blissful. I often saw BaYaka children with malaria inhaling steam from hot water infused with sapele bark to reduce their fever.

Most crucially, the tallest sapele trees emerge high above the canopy. Just before the rainy season, they attract hordes of butterflies (*Imbrasia oyemensis*) that lay eggs on the leaves. On hatching, the larvae grow quickly into large, utterly delicious and highly nutritious caterpillars so abundant that they thickly carpet the ground under these trees. Pygmies prize the caterpillars not just for their flavor but also for their timing: the rains disperse animals from water holes, making hunting unpredictable. "Komba sends the caterpillars to feed people when hunting is hard," Emeka told me as we sat roasting them on skewers over hot embers and savoring their clean, meaty taste.

Although the BaYaka were deeply upset when loggers cut down "caterpillar" trees that they had exploited for generations, their strong sharing ethos made them feel that they could not resist or refuse. "There are plenty of trees in the forest for everyone; we can share some of them," several said in the early days.

My family and I left the Congo in 1997 at the onset of a civil war, but I continued to visit the region regularly for research purposes. After the conflict ended, in 2000, a cash-strapped new government opened all remaining forest to loggers. They constructed numerous roads, deepening their reach into ever more remote areas. By 2003 annual log production had more than doubled compared with rates in the 1990s, to more than 1.3 million cubic meters, and it was continuing to rise.

Noticing this trend, environmentalists put pressure on logging companies operating in the Congo Basin to follow Forest Stewardship Council (FSC) guidelines, which oblige companies to obey national laws, to minimize environmental impacts, to stay away from areas with high conservation value (such as patches with a greater density of chimpanzees), and to respect the rights of workers and forest peoples. The multinational company Congolaise Industrielle des Bois (CIB), which was operating in 1.3 million hectares of BaYaka forest out of its base at Pokola, a logging town on the Sangha River, decided to try for FSC certification.

In my estimation, the company was likely to continue felling trees with or without the FSC label—which offered a rare and valuable opportunity to protect the rights and resources of the

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Pygmies. Having previously researched how to implement the principles of "free, prior and informed consent" when vulnerable peoples face the prospect of development projects in their territories, I became a paid consultant with the Tropical Forest Trust (currently called Earthworm), a nongovernmental organization that CIB had hired to help it address the social issues involved in FSC certification. The trust charged me with setting up a system by which the Pygmies inhabiting CIB's concessions could determine whether to permit logging in their territories.

When I discussed the social and economic significance of the sapele with CIB's managers, they worried about coming into conflict with the 10,000 or so BaYaka inhabiting their concessions, which would rule out an FSC certificate. Tense meetings between the BaYaka and logging staff followed, with me serving as mediator, but the cultural divide proved to be insurmountable. The hunter-gatherers were extremely uncomfortable in office buildings: seemingly simple tasks such as opening doors proved daunting to them, let alone more specialized ones such as comprehending agendas and forms. In their camps, however, Emeka and others explained that only the emergent sapele trees (those whose crown emerged above the canopy) reliably hosted the caterpillars. The BaYaka asked that the loggers protect those trees, as well as natural springs, the tombs of their ancestors, sacred groves, medicinal trees and a few other significant resources.

2

I proposed to CIB's managers that they support the BaYaka in mapping these sites, and to my relief, they agreed. Ingrid, who worked in public health, had designed a set of icons to help BaYaka healers read medicine labels for use in a mobile pharmacy she had set up with them to treat worms, malaria and other ailments. That gave me an idea. Working with the BaYaka and a private software company called Helveta, which was developing tools for tracing supply chains of scarce materials (in this case, hardwoods), we designed a pictorial interface for the touch screen of a GPS-equipped handheld computer. One of the BaYaka would go to the resource the tribe wanted to save—say, an emergent sapele—and simply touch the "caterpillar" symbol to mark its location.

The tagging helped to cut through the language and culture barriers. When they layered the maps the BaYaka had made over those of sapeles they had marked for felling, the loggers realized that they could still cut down enough trees to turn a profit. Together with the hunter-gatherers and company managers, I developed a set of procedures (such as taking entire families along on mapping trips because BaYaka men and women value different resources) to determine the terms on which the different BaYaka groups would allow loggers into their forest. In 2006 CIB became the first major logging company to achieve an enduring FSC certificate in the Congo Basin, and other companies in this vast region also later used this model as the basis for their efforts to protect Pygmy rights to secure FSC certification.

LOGGERS, POACHERS, CONSERVATIONISTS

AS YEARS PASSED, I watched these efforts unravel. Overworked company staff began a slow but inexorable process of eroding procedures—bypassing burdensome obligations (taking only a BaYaka man along on a mapping trip, for example) or ignoring technical problems with the equipment. Still, the resources the Pygmies marked were largely protected. Had the hunter-gatherers—or I, as their mediator with the outside world—foreseen a key collateral

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BAYAKA ELDERS Ngeshe and Ngwenye wear white clay on their foreheads (*1*) in December 2019 to mourn a recently deceased sister. Unable to pursue their original forest-based way of life, they live mostly near Indongo, a former logging camp. Keyo (*right*) and her friend sit close by, on abandoned forestry machinery (*2*). At a sacred glade in the vicinity, Emeka, now around 60, explains how the BaYaka care for the forest (*3*).

impact of logging, however, they might have withheld consent.

Previously, if anyone wanted to enter the forest, they had to have Pygmy guides, and if the hunter-gatherers did not approve of them, they would not take them. But the network of logging roads gave commercial poachers—who hunted not for their own consumption but for insatiable domestic and international markets—access to pristine areas without the Pygmies being able to control them. They used the new roads to intensively raid the forest for meat to feed urban consumers. So lucrative was the bushmeat trade that it spawned well-organized poaching networks, often promoted by elite sponsors such as military or police officials. In addition, as logging camps sprang up deep inside the forest, they attracted Bantu villagers from its periphery, who arrived to provide food and other services to the workers. The resulting shantytowns grew to each contain hundreds of settlers, many of whom also began to hunt for bushmeat.

Frustrated conservationists from the WCS, the World Wildlife Fund (WWF) and other organizations responded by employing squads of eco-guards to police wildlife crime, inadvertently creating militias they could not control. Many of the guards began to extract wealth from the forest, sometimes cooperating with the poaching networks, and they beat and tortured the Pygmies if they found them with wild meat, even if it had been legally hunted. After human-rights organizations publicized these abuses in the 2000s, conservation organizations formally distanced themselves from the eco-guards by encouraging local governments to integrate them into their respective forestry ministries. They continued to support the forces financially and logistically, but they could no longer discipline or fire them, reducing accountability.

Around 2010, conservation agencies began to collaborate with logging companies to police poaching in the concessions that bordered protected areas. The loggers audited the eco-guards for numbers of arrests and seizures of contraband (such as bushmeat). Unable to act against the powerful perpetrators of the illegal wildlife trade, eco-guards began to attack softer targets: the hunter-gatherers and villagers. Although local people were legally allowed to hunt cert ain species for subsistence using traditional methods, in practice the eco-guards took possession of any meat as evidence of poaching to justify intimidation, torture and beatings.

Worsening the problem, from 2007 onward China had been building roads and other infrastructure in the Congo in lieu of mining and other rights. Hundreds of Chinese workers arrived for road construction—an influx that coincided with a major increase in elephant poaching. The roads constructed by loggers connected with the national roads built by Chinese contractors to establish an efficient transportation network for ivory and bushmeat.

Wildlife protectors reacted to the accelerated poaching by doubling down on "fortress conservation," as Victoria Tauli-Corpuz, the U.N.'s special rapporteur on the rights of indigenous peoples, and others describe it. The WCS, the WWF and others expanded the existing national parks by connecting them into cross-border "conservation landscapes" such as the 750,000-hectare Sangha Trinational, which includes the Nouabalé-Ndoki National Park. Often working with extractive industries, development agencies and conservation organizations continued to conceive of new protected areas in the Congo Basin without the consent of local people. This past March investigators from the U.N. Development Program reported that Baka Pygmies of northwestern Congo were alleging "indiscriminate violence, humiliation and intimidation" by WWF-supervised eco-guards, who were evicting them from within the boundaries of the proposed Messok Dja National Park. "As a result,

the Baka's traditional hunting activities are being criminalized," the researchers charged.

FEAR, HUNGER AND ALCOHOL

WITH ALMOST ALL of the forest divided into conservation parks and logging concessions, where Pygmies are persecuted for hunting and gathering, the BaYaka can no longer thrive or maintain their forest-based identity. "Oh, it was good, so good! Honey for everyone! Wild yams … more than you can carry!" said Emeka's disabled older brother, Mongemba, in 2013. "Now it's all finished, all finished! Now there is just sadness! We have such hunger. Fear, such fear! The boys are frightened to go in the forest." Maindja, a 45-year-old grandmother, explained: "If we walk in the forest, we are taken by eco-guards. That is why we don't put our bodies in the forest anymore. Now we just stay in the villages, not the forest camps. And so the wisdom of the ancestors' ways goes away."

Afraid to camp in the forest as they used to and compelled by economic necessity, many BaYaka hang around logging camps or farming villages, seeking work as farm hands, odd-jobbers and home help. Most men feel too frightened to go hunting anymore. Because the men's cultural and social value has historically depended on their bringing meat to feed their families—which they can no longer accomplish—their self-esteem has crashed. Working instead as marginal laborers and often paid only in illegally distilled alcohol, many men have become alcoholics, with all the psychological, social and economic problems the addiction brings. Many BaYaka women suffer from domestic abuse, and those living around logging encampments are often sexually exploited by outsiders.

From the Pygmies' perspective, their forest has been converted into a collection of floral and faunal assets seized by outsiders to profit in mysterious ways. The logic of sustainable development—meeting the global demand for resources by opening up the forest to extractive industries while offsetting the damage with militarized protected areas—completely escapes them. Loggers justify their continued felling as a form of development, yet its benefits rarely reach forest people. Conservationists point to the harm done to endangered species by logging, roads and market pressures to justify the draconian hunting restrictions imposed on the hunter-gatherers and the abuses by eco-guards. But in the experience of Pygmies, elephants, leopards, gorillas and chimpanzees were common in their forest—and their present-day scarcity stems directly from outsiders' presence.

They have a point. Fiona Maisels of the University of Stirling in Scotland and her co-workers estimated in 2013 that elephant populations in the Congo Basin have declined to a little more than a third of what they were at the turn of the millennium. The numbers of western lowland gorillas have also decreased sharply. The U.S. Fish and Wildlife Service reports that roughly five million metric tons of wild animals are being extracted annually from these forests, causing local extinctions. And according to the U.N. Environment Program, 80 percent of the large mammals in many national parks of the Democratic Republic of the Congo (which neighbors the Republic of the Congo) had disappeared by 2010.

The disconnect between hunter-gatherers and conservationists ultimately arises from their conflicting philosophies. For the BaYaka, abundance is the natural state of things, and it is ensured by fair sharing among all present. The forest is a sentient being with whom they maintain social relationships of mutual care and support through taboo, ritual, song and dance. The plethora of animals encountered in this region until very recently is testament to the long-term success of this approach to forest management. In contrast, conservationists and development experts represent a global economic system that objectifies nature, encourages its conversion into commodities and allows elites to dominate decisions over resource distribution, resulting in species becoming scarce.

A NEW PARADIGM

AROUND THE WORLD, however, a novel conservation paradigm is taking root. Researchers, activists and others from mainstream society are recognizing that local communities are the primary protectors of nature and are seeking to help them. Although the mapping concept that Emeka and others helped me design ultimately could not save the Pygmy way of life, it is proving more successful in less institutionally and technologically challenging places—those with less corruption, more democracy and stronger governance, for example, or with better access to mobile phone networks.

1

My experiences in the Congo Basin eventually led to the ExCiteS research group at University College London. We have since developed Sapelli, a modifiable smartphone app for collecting information on vital resources, the activities of poachers, and other variables; Geokey, a data-storage system; Community Maps, used to view the data with an appropriate background; and a methodology for co-designing projects with indigenous and other communities based on the concerns and needs that they identify.

2

SAWN TIMBER and logs stacked (*1*) for floating down the Sangha River near Pokola, a logging town, in 2019. Elsewhere, a timber-laden truck (*2*) awaits a ferry to cross the Sangha. The Congo forests export hardwoods around the world.

These tools help local peoples manage resources by collecting data, monitoring changes and challenges, determining how to respond to them and partnering with outsiders to achieve their goals.

Using these devices, the Ju/'hoan San in Namibia are documenting illegal cattle drives by their non-San neighbors to water holes in their conservancy, which are used by the wild animals they hunt, while also keeping tabs on their populations. In Kenya, the Maasai in the Maasai Mara worry about the increasing scarcity of the wild medicinal plants they use. In an effort to understand what was damaging them, they documented 123 species of medicinal plants, 52 percent of which were healthy and unharmed. It turned out that burgeoning numbers of tourist camps were responsible for much of the damage to the rest. The Maasai are now expanding the project to the Mau Forest Complex. Best of all, a group from the University of Copenhagen worked with the Prey Lang community in Cambodia to stop illegal logging. Communicating via mobile phones, volunteers track illegal loggers, descending on them en masse, photographing and geotagging their activities with Sapelli and confiscating their chain saws. With support from local administrators, they were able to stop all unauthorized logging.

These efforts rest on the reality that many parts of the world are rich in biodiversity because of the communities that have been living in them for hundreds or thousands of years, not in spite of them. Local peoples are also the most ardent defenders of the environment—because they have the most to lose when it is degraded.

When I last visited the Congo, in December 2019, Emeka gave me a message to convey to *Scientific American*'s readers: "We are the forest's guardians. We have always been here, taking care of the forest. Since time began we have killed animals, and they have always been there for us. We kill animals to feed our children. We don't farm! We don't fish! But now the eco-guards stop us; they have forbidden us our forest …. We want our children not to have to go far to find animals—just close to where we stay, as it was before, when we cared for the forest. But our world has been spoiled. It's a big problem. We want to be well. Sort this out, people, so that we can know joy again!" SA

MORE TO EXPLORE

Managing Abundance, Not Chasing Scarcity: The Real Challenge for the 21st Century. Jerome Lewis in *Radical Anthropology,* Vol. 6, No. 2, pages 11–19; 2008.

The Anthropology of Sustainability: Beyond Development and Progress. Edited by Marc Brightman and Jerome Lewis. Palgrave, 2017.

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Cornered by PAs: Adopting Rights-Based Approaches to Enable Cost-Effective Conservation and Climate Action. Vicky Tauli-Corpuz et al. in *World Development,* Vol. 130, Article No. 104923; June 2020.

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scientificamerican.com/magazine/sa

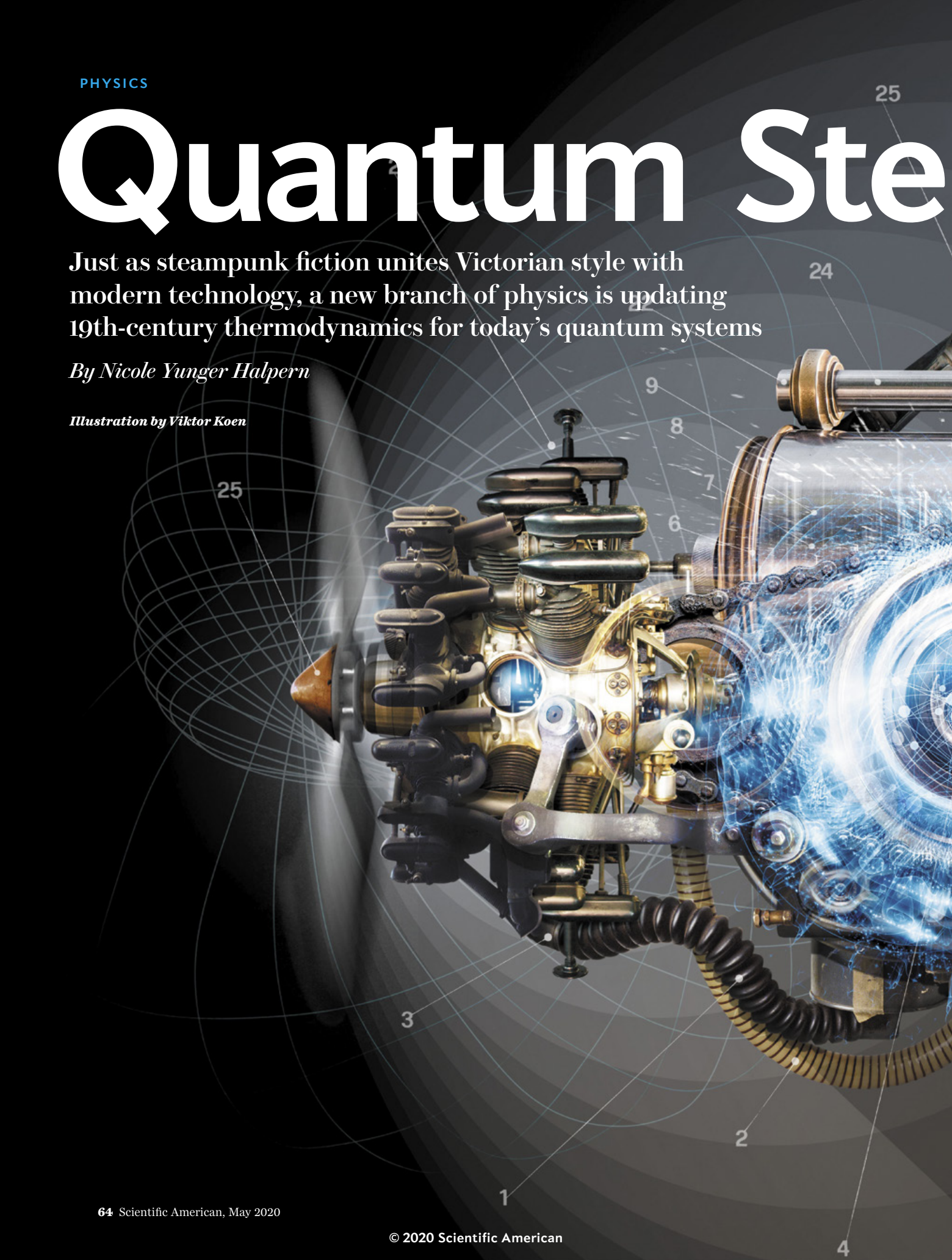
PHYSICS

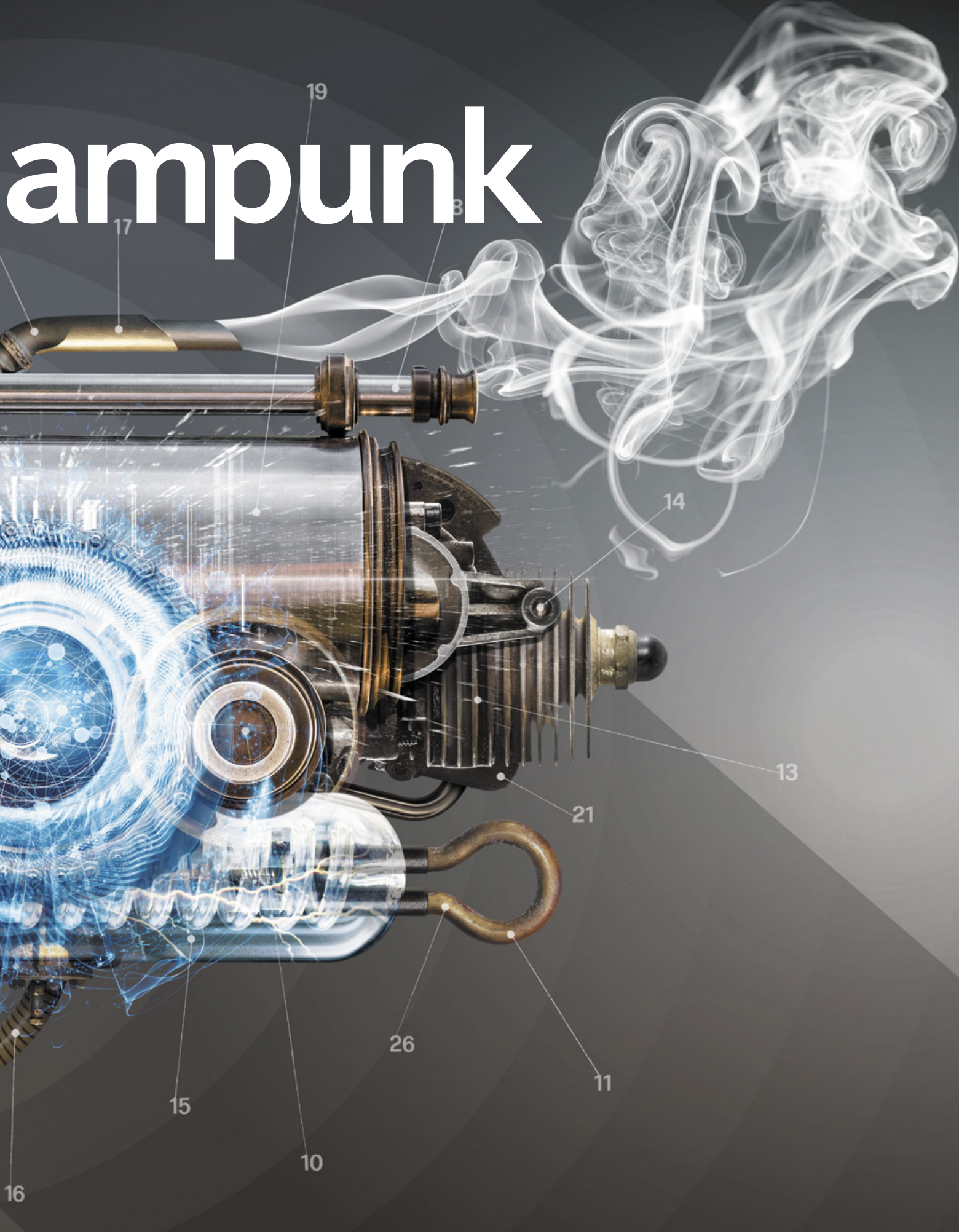
Quantum Ste

Just as steampunk fiction unites Victorian style with modern technology, a new branch of physics is updating 19th-century thermodynamics for today's quantum systems

By Nicole Yunger Halpern

Illustration by Viktor Koen





Nicole Yunger Halpern is a theoretical physicist and an ITAMP Postdoctoral Fellow at Harvard University. She writes monthly stories for Quantum Frontiers, the blog of the California Institute of Technology's Institute for Quantum Information and Matter. Follow her on Twitter at @nicoleyh11

LONDON, AT AN HOUR THAT MADE ROSALIND GLAD SHE'D NICKED HER BROTHER'S black cloak instead of wearing her scarlet one. The factory alongside her had quit belching smoke for the night, but it would start again soon. A noise caused her to draw back against the brick wall. Glancing up, she gasped. An oblong hulk was drifting across the sky. The darkness obscured the details, but she didn't need to see; a brass-colored lock would be painted across the side. Mellator had launched his dirigible.

Welcome to steampunk. This genre has expanded across literature, art and film over the past several decades. Its stories tend to take place near nascent factories and in grimy cities, in Industrial Age England and the Wild West—in real-life settings where technologies were burgeoning. Yet steampunk characters extend these inventions into futuristic technologies, including automata and time machines. The juxtaposition of old and new creates an atmosphere of romanticism and adventure. Little wonder that steampunk fans buy top hats and petticoats, adorn themselves in brass and glass, and flock to steampunk conventions.

These fans dream the adventure. But physicists today who work at the intersection of three fields—quantum physics, information theory and thermodynamics—live it. Just as steampunk blends science-fiction technology with Victorian style, a modern field of physics that I call "quantum steampunk" unites 21st-century technology with 19th-century scientific principles.

Our goal is to update the laws of thermodynamics—the study of work, heat and efficiency—to meet the demands of cutting-edge experiments, technologies and theory. Thermodynamics was born when steam engines drove the Industrial Revolution. But as technology shrinks, thermodynamics and information couple in smaller and smaller systems. The spotlight has swept from trains to nanoscale engines, living cells' molecular motors and the smallest possible refrigerators. We must now investigate how to apply traditional thermodynamic concepts such as heat, work and equilibration to modern quantum systems.

VICTORIAN PHYSICS MEETS MILLENNIAL SCIENCE

BY 1800 THOMAS SAVERY and Thomas Newcomen had invented, and James Watt and Matthew Boulton had refined, the steam engine. Thinkers then wondered how efficiently such engines could pump water out of mines. Their studies grew from practicalities to questions of fundamental physics, such as why time flows only in one direction. The field of thermodynamics is grounded in this work.

IN BRIEF

The field of thermodynamics—which deals with the physics of heat and efficiency—arose during the Industrial Revolution. Scientists today are working to update these laws to address modern technology, particularly quantum computers, quantum communication and quantum information.

This melding of 19th-century science and futuristic technology resembles the combination of Victorian style and sci-fi invention in the genre of fiction called steampunk, earning the field the moniker "quantum steampunk."

One recent quantum steampunk success is an engine that scientists have proposed using quantum and thermodynamic principles.

This branch of physics describes many-particle systems, such as steam, in terms of large-scale properties, such as temperature, pressure, volume and energy. Energy in transit falls into two classes, work and heat. Work is well-organized energy usable for a purpose, like turning a mill wheel. Heat is the energy of random motion—of particles jiggling.

Thermodynamicists quantify randomness with a number called entropy. Every particle in a canister of steam has a position and a momentum (the particle's mass times its velocity). The set of all the particles' positions and momenta we call the steam's microstate. We cannot know the microstate, because the canister contains about 10^{24} (1 followed by 24 zeroes) particles. Imagine trying to locate them all! Instead we track the probability that the steam occupies this or that microstate. Entropy quantifies our uncertainty. According to the second law of thermodynamics, the entropy of a closed, isolated system cannot shrink. This fact underlies the reality that time flows in a single direction.

But the steam engines central to traditional thermodynamics resemble today's technologies about as much as top hats resemble virtual-reality headsets. Many modern inventions and experiments involve small, complex quantum systems. Quantum theory is the physics of atoms, electrons and other constituents of matter. They can behave in ways impossible for larger, classical systems, such as steam canisters, factories and people. For instance, quantum particles can share entanglement, a type of ultrastrong correlation. If you entangle two atoms and measure one, the other atom changes instantaneously, even if it is across a continent. Physicists can use entanglement to process information in ways impossible with classical systems. The study of how we can solve computational problems, communicate, secure information and enhance measurements with quantum systems is called quantum information theory. This theory is a useful mathematical tool kit for implementing our update to thermodynamics. How do the two fields connect? To reason about information, we have to confront ignorance. Information theorists quantify ignorance with entropy, just as thermodynamicists do.

Quantum computers, for instance, are systems where both quantum information theory and thermodynamics are key. Google, IBM and other institutions are hard at work building such machines, which aim to break certain encryption schemes and to model certain materials far more quickly than any classical computer. Most quantum-computing systems need to be cooled to a temperature near absolute zero. Cooling amounts to dissipating heat, a thermodynamic quantity. Yet quantum computers look nothing like the engines for which thermodynamics was developed.

Efforts to apply thermodynamic concepts to quantum settings date to the mid-20th century, when Joseph Geusic, E. O. Schulz-DuBois and H. E. Derrick Scovil proposed the first quantum engine. It was made from a maser, which operates like a laser but releases microwave light. Later, Ronnie Kosloff of Hebrew University of Jerusalem and his colleagues helped to turn quantum engines into their own subfield. Another pioneer is Marlan Scully, sometimes called the "quantum cowboy," who works on quantum optics at Princeton University and Texas A&M University and also raises cattle. Meanwhile theorists Gian Paolo Beretta, the late Elias Gyftopoulos and the late George Hatsopoulos studied the arrow of time from a quantum perspective. And a seminal publication was Seth Lloyd's 1988 Ph.D. thesis at the Rockefeller University, "Black Holes, Demons, and the Loss of Coherence: How Complex Systems Get Information, and What They Do with It," which established many important ideas for the field of quantum thermodynamics.

QUANTUM STEAMPUNK TOOLS

AS WE HAVE SEEN, entropy plays an important role in thermodynamics, information theory and quantum theory. Entropy is often thought of as a single entity, but in fact, many breeds of entropy exist in the form of different mathematical functions that describe different situations. The best-known breeds were introduced into thermodynamics by Ludwig Boltzmann and Josiah Willard Gibbs during the 1800s, into information theory by Bell Telephone Labs employee Claude Shannon in 1948, and into quantum information theory by theoretical physicist John von Neumann in 1932. These entropies quantify not only uncertainty but also the efficiency with which we can perform information-processing tasks, like data compression, and thermodynamic tasks, like the powering of a car.

Identifying new entropy functions for modern, small-scale quantum systems is one of the key tasks of quantum steampunk theorists. Suppose we are trying to use entanglement to share information in a certain channel. We might ask, Is there a theoretical limit to how efficiently we can perform this task? The answer will likely depend on an entropy.

Another quantum steampunk goal is building what physicists call resource theories. These theories highlight the constraints under which we operate. For instance, the first law of thermodynamics constrains us to conserve energy: We cannot create or destroy energy; we can only shunt it from one form and one system to another. Physicists might find a situation in which there is a constraint, such as an environment with a fixed temperature, and then try to model the situation mathematically with a resource theory. Using the resource theory, we can calculate the optimal efficiency with which a task can be performed. Typically the efficiency equals a function of an entropy.

A third area of focus in our quest to update thermodynamics is to derive equations called fluctuation relations. These equations are extensions of the second law of thermodynamics, which dictates that the entropy in a closed, isolated system cannot decrease. Fluctuation relations govern small systems subjected to strong forces and tell us about the work those forces perform.

In 1996 Christopher Jarzynski, now at the University of Maryland, proved one of the best-known fluctuation relations. Thermodynamicists call it Jarzynski's equality, although Jarzynski is so modest, he never does. Experimentalists use this equality to measure a certain thermodynamic property of small systems. As an example, imagine a DNA strand floating in water, with the same temperature as its surroundings. The strand has some amount of free energy, which is basically the energy that a system can draw on to perform work. Using lasers, scientists can trap one end of the strand and pull the other end. After they hold the strand taut for a while, the DNA will return to the solution's temperature, at which point the strand will have a different amount of free energy. The difference in free energies has applications in chemistry, pharmacology and biology. We can estimate the free-energy difference by stretching the strand in many trials, measuring the work required in each trial, plugging our data into Jarzynski's equality and solving the equation.

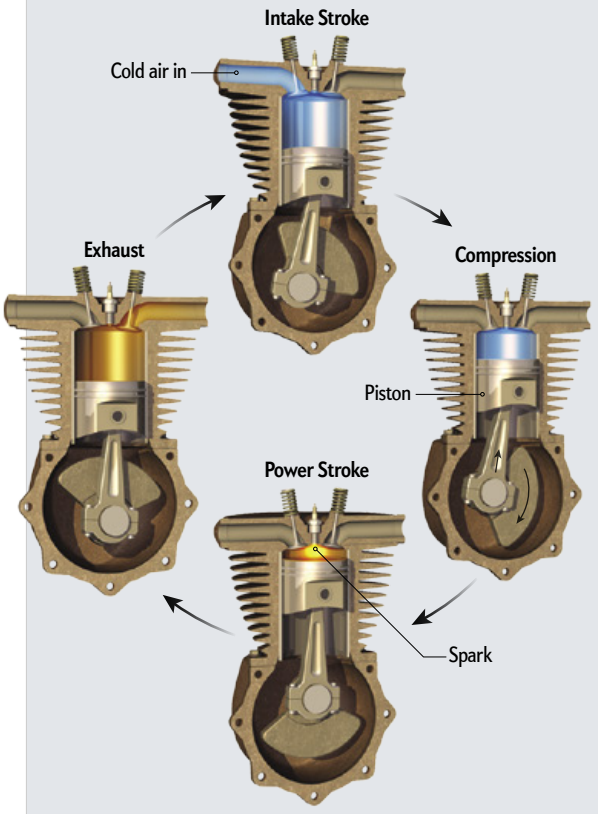
How many trials must we perform, Jarzynski and I asked, to estimate the free-energy difference with a certain precision? We calculated the minimum number of trials that one would likely

Envisioning a Quantum Engine

The field of thermodynamics arose in the era of steam engines. "Quantum steampunk" physicists work to update this area of physics for quantum technologies, as in quantum engines. One such engine, the many-body-localization (MBL)-mobile shown here, exists as a thought experiment now, but it could be built in the near future. Just as a car engine goes through four steps in a cyclic process that pushes a car forward, the MBL-mobile goes through a four-step quantum process to produce work.

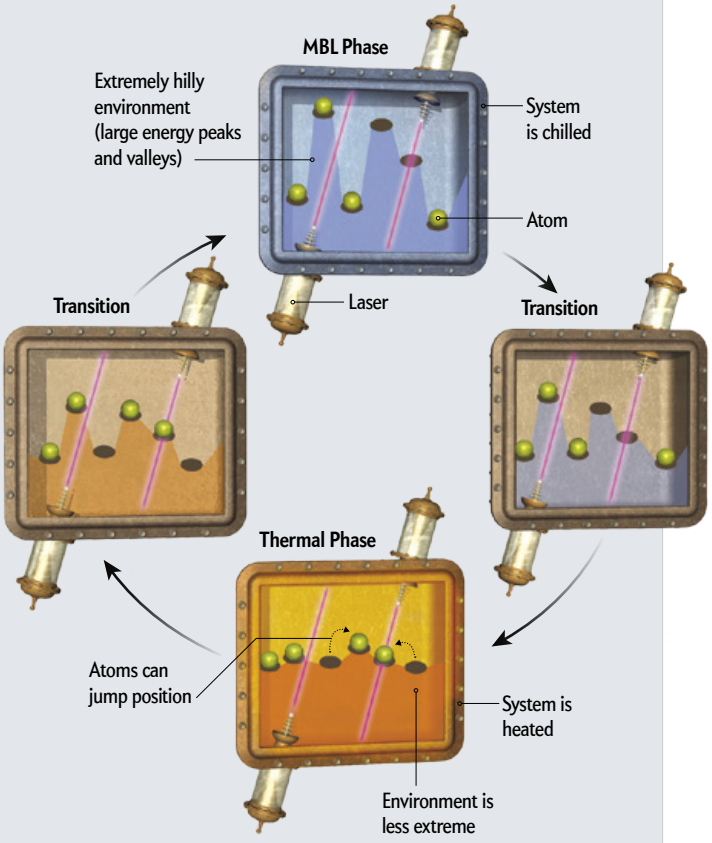
Car Engine

A car engine pulls in cold air and lets out hot air in a four-step cycle that pushes a car forward. During the intake stroke, the engine draws in cool air; gasoline is injected. During compression, a piston moves upward inside a cylinder to compress this mixture. Then during the power stroke, spark plugs ignite the air and gasoline. The combustion pushes the piston down and turns the car's wheels. Finally, during exhaust, the hot combustion gases are expelled.



Many-Body-Localization-Mobile

The MBL-mobile goes through a four-step process that begins with atoms in a phase of matter called many-body localization. The atoms are chilled while in an environment with tall energy hills and low valleys, which keep the atoms from moving around much. Next, we change the lasers' settings to flatten the hills and valleys in the atoms' landscape. The engine enters a thermal phase where its atoms can move around, and the engine absorbs heat. Finally, we transition back.



have to perform and proposed a scheme for quantifying the precision, using small-scale information theory. In other recent work, my collaborators and I showed that fluctuation relations and newfangled entropy functions are two consistent approaches to small-scale thermodynamics, and we used each approach to elucidate the other. Quantum thermodynamicists in London, Cologne, and elsewhere have extended and sharpened this research.

A NEW QUANTUM ENGINE

JUST AS TRADITIONAL THERMODYNAMICS helped to describe the physics of steam engines, our efforts in quantum thermodynamics can help us invent quantum engines. Experimentalists have now created quantum engines with photons (particles of light), electronic systems and superconducting qubits (quantum circuits in which current can flow forever without dissipating).

Recently I designed a new quantum engine with Christopher D. White, now at the University of Maryland, Sarang Gopalakrishnan, now at the City University of New York, and Gil Refael of the California Institute of Technology. Being theorists, we initially devised the engine as a thought experiment that existed in our minds. But we are also envisioning how scientists could build a real version of the engine using the quantum tools found in laboratories today. For instance, by cooling atoms, then trapping and manipulating them with lasers, one could bring our design to life.

Illustration by George Retseck

Our engine involves a phase of matter called many-body localization (MBL)—a variation on the more familiar phases liquid, solid and gas. Quantum particles can be in this phase if they repel one another and can hop slowly around a rough, steep, random landscape. A key element of an MBL system is its "athermality": It is not in thermal equilibrium. Particles in thermal equilibrium explore the available space quickly and randomly. If you let steam explore for a long time, large-scale properties such as the temperature and volume will settle down and quit changing much.

But MBL particles stay in one area rather than moving around, in contrast with steam particles. A lack of thermal equilibrium serves as a resource in thermodynamic tasks. Car engines, for instance, rely on having a hot fluid near a cold fluid. The pair of fluids is not at thermal equilibrium, because the hot particles are localized in one region and the cold particles in another—no particle explores the whole space. As a car engine takes advantage of the fluids' athermality, my collaborators and I took advantage of MBL particles' athermality. We call our construction the MBL-mobile.

A car engine undergoes four steps that form a cycle, or a closed loop. By the end of the loop, the engine returns to its initial state, having propelled the car some distance by transferring heat from the hot fluid to the cold. The MBL-mobile, too, undergoes a four-step cycle. In our engine cycle, we ratchet, or transition, the atoms from a thermal phase, in which particles can spread throughout the space, to MBL and back. To ratchet the engine, we change the landscape the particles inhabit from fairly flat to rough by manipulating the lasers' settings. Before each ratcheting, the engine exchanges heat with an external environment. The engine interacts with a hot environment when in its thermal phase and with a cold environment when in its MBL phase. In summary, the four steps are: (1) exchange heat with a hot environment in the thermal phase, (2) ratchet from the thermal phase to MBL, (3) exchange heat with a cold bath and (4) ratchet from MBL to the thermal phase.

We assessed how well an MBL-mobile could work by calculating its power and efficiency and comparing them with those of other engines. For instance, some bacteria have flagella, or long, whippy tails rotated by motors. How do these small engines compare with ours? Our engine, we estimated, can output about 10 times a flagellum's power. On the other hand, how does our quantum engine compare with a car's engine? We estimated the two engines' power densities, or the power output per unit volume: a car engine uses space more effectively, though only about 10 times more.

The MBL phase gives our engine four advantages. First, the engine can have any size, from 10 particles to infinitely many. To build a large engine, you start with a mini engine of 10 particles. You build many copies of the mini engine and then operate them side by side. If the mini engines behaved thermally, they would interfere with one another because one mini engine's particles would stray into another mini engine. MBL ensures that what happens in one mini engine stays there. Thus, you can cram many mini engines close together, giving the entire engine a high power density: the MBL-mobile's second advantage.

The third advantage surfaces if you run the engine in many trials. In some trials, the engine will perform work. In a few trials, though, the engine will absorb work, doing the opposite of what it should. Fewer of these worst-case trials occur if you ratchet the engine between MBL and thermal phases than if you ratchet the engine around within the MBL phase. Moreover, the amount of work varies less from successful trial to successful trial if you take advantage of MBL; MBL enhances the engine's reliability.

Our success with the MBL-mobile, at least in thought experiments, suggests that MBL may have more applications in other thermodynamic tasks that need undertaking. For example, imagine reversing our cycle. The engine should refrigerate, transferring heat from the cold environment to the hot. Quantum systems require refrigeration for properties such as entanglement to manifest. An MBL refrigerator could serve to cool many-particle quantum systems. Alternatively, scientists also wrote a proposal to use MBL to store energy. And recently, along with my collaborators, I have begun trying to create a real-life version of the engine using another set of tools: superconducting quantum bits set in a magnetic field. Opportunities abound when we apply quantum steampunk thinking to materials science.

GAZING THROUGH A QUANTUM MONOCLE

A STEAMPUNKER GAZES into the future through a monocle. What does she see? A mathematical and physical tool kit is solidifying at the intersection of quantum theory, information theory and thermodynamics. We are also working to apply that tool kit to other spheres of science: materials science, as in the MBL-mobile; chemistry; high-energy physics, such as black holes and the fabric of spacetime; and atomic, molecular and optical physics.

Technologies cry out for applications. Most quantum steampunk work is theoretical, although real-world experiments have begun and are multiplying. But just as the development of thermodynamics helped to drive the Industrial Revolution, new inventions should follow from quantum, small-scale and information thermodynamics. MBL engines will not power our cars this decade. But molecular switches, solar-fuel harvesters and heat-dissipating transistors are small-scale technologies tied to thermodynamics. They should guide theory.

Another challenge is to unify the different efforts within quantum steampunk—newfangled entropies, resource theories, fluctuation relations, quantum-thermal machines, and more. These are just some of the many different kinds of work going on around the world and new tools being developed. Reconciling these realms' different definitions and results will solidify a theory for quantum thermodynamics.

Thermodynamics carries the whiff of engine grease and grit, of steaming across the countryside in the first trains and conquering the waves in the first ocean liners, of marveling at the landscape from a hot-air balloon. Quantum information science is transforming how we understand computation, communication, cryptography and measurement. You are reading about this confluence of old and new in *Scientific American,* but you might as well be holding a novel by H. G. Wells or Jules Verne. SA

MORE TO EXPLORE

Quantum Steampunk: Quantum Information, Thermodynamics, Their Intersection, and Applications Thereof across Physics. Nicole Yunger Halpern. Ph.D. dissertation, California Institute of Technology, 2018.

Quantum Engine Based on Many-Body Localization. Nicole Yunger Halpern et al. in *Physical Review B,* Vol. 99, No. 2, Article No. 024203; January 2019. https://journals.aps.org/prb/pdf/10.1103/PhysRevB.99.024203

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The Long Arm of the Second Law. J. Miguel Rubí; ScientificAmerican.com, November 1, 2008.

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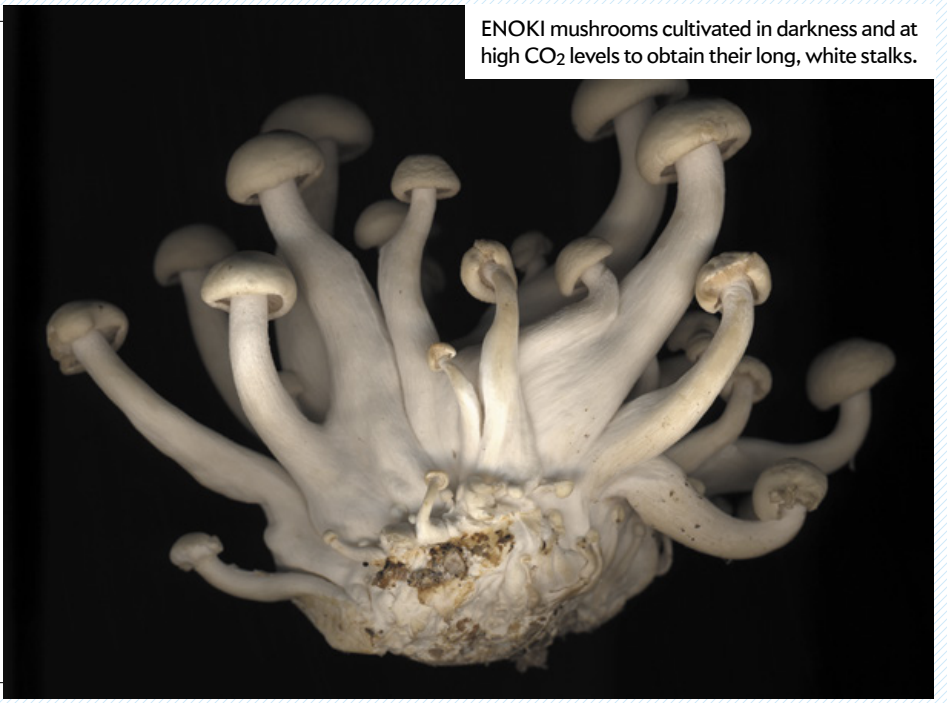
RECOMMENDED

By Andrea Gawrylewski

Entangled Life:
How Fungi Make Our Worlds, Change Our Minds & Shape Our Futures

by Merlin Sheldrake. Random House, 2020 ($28)



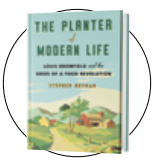
ENOKI mushrooms cultivated in darkness and at high CO_2 levels to obtain their long, white stalks.

Fungi make up an understudied kingdom of life-forms, often ignored unless they manifest as mushrooms, ferment a drink or rot a wood structure. But behind the scenes—and often belowground—fungi are the heavy lifters in complex nutrient exchanges and critical chemical reactions that sustain our more familiar world of plants and animals. In winding prose, biologist Sheldrake explores every aspect of what we know about these unusual beings. He documents impressive fungal feats, exploring how the organisms process toxic waste, synthesize medicines, build materials that act like leather, foam or concrete, and more—looking to a future where humans can harness fungi's ability to make new things and break down old things that nothing else can.

—Sarah Lewin Frasier

The Planter of Modern Life:
Louis Bromfield and the Seeds of a Food Revolution

by Stephen Heyman. W. W. Norton, 2020 ($26.95)

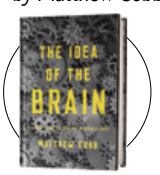


As a Pulitzer Prize–winning author living in post–World War I France, Louis Bromfield cultivated friendships with luminaries such as Edith Wharton and Gertrude Stein—often by helping them cultivate their gardens. By the 1930s Bromfield's writing and movie career had made him rich enough to establish Malabar, a cooperative farm where he advocated for pesticide-free practices and soil conservation. Writer Heyman brings this champion of the organic food movement to life—for example, he vividly describes Bromfield's Indian tour, which included a visit to a soil institute and an all-night poker game with a maharani. With keen attention to detail, Heyman dusts off this forgotten figure who divided his time between filmic flashiness and farming.

—Sophie Bushwick

The Idea of the Brain:
The Past and Future of Neuroscience

by Matthew Cobb. Basic Books, 2020 ($32)

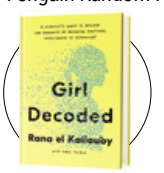


If you know nothing about neuroscience and need to get up to speed fast, don't go out and buy an "Idiot's Guide." Instead try this brilliant offering, in which zoologist and science historian Cobb dives into the fundamentals—and the frontiers—of our understanding of the brain. For centuries scientists have compared the three-pound organ to a machine but have struggled to make the metaphor fit reality. "Even the simplest animal brain is not a computer like anything we have built, nor one we can yet envisage," the author writes. Despite much progress in the field, he notes, we still lack a solid idea of how billions of neurons synchronize their signals to produce a myriad of brain activities. It may be centuries, Cobb posits, before we achieve a fundamental understanding of consciousness and other related mind mysteries.

—Gary Stix

Girl Decoded: A Scientist's Quest to Reclaim Our Humanity by Bringing Emotional Intelligence to Technology

by Rana el Kaliouby. Penguin Random House, 2020 ($28)



Is the Internet making us meaner? We have gotten used to hateful rhetoric and cruelty on the Web, but it can bleed into our real lives, too. Computer scientist el Kaliouby argues that society is facing an "empathy crisis," a widespread inability to feel compassion. This engaging memoir traces her formative experiences as a Muslim woman in the Middle East and as a lead researcher at Cambridge. She co-founded a tech start-up with the mission to alter how people interact in the digital world. A pioneer in the field of artificial emotional intelligence, el Kalioby focuses on teaching computers how to respond to the gamut of facial expressions, with the aim of devising tools that will humanize technology before it dehumanizes us.

—Sunya Bhutta

ROY HSU Getty Images

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).

Keep American Science Great

Funding cuts haven't crippled research yet, but things are heading that way

By Naomi Oreskes

One of the benefits of modern technology is the ability it gives us to catch up on films and television that we missed the first time around. Recently I watched the *Up* series, a remarkable documentary project by filmmaker Michael Apted that has tracked the lives of 14 British people since 1964, when they were children, revisiting them every seven years as their lives have unfolded. (The "children" turned 63 last year.)

The original premise was that the British class system would largely determine the course of these kids' lives, irrespective of how bright or charming or kind they were to begin with. Thus, the athletic and irrepressible Tony, from London's East End, seems destined for a working-class life, whereas the posh prep-school boys John, Andrew and Charles will presumably continue to enjoy lives of privilege. And in fact, Tony drives a London cab as an adult, and John, Andrew and Charles become a barrister, a solicitor and a television producer, respectively.

But Nick (William Nicholas Hitchon) defies those expectations. At age seven he was living on a family farm, walking four miles to a one-room schoolhouse where he wanted to learn about "the moon and all that." By his late 20s he had earned a Ph.D. in physics and a faculty position at the University of Wisconsin–Madison, where he has since published more than 100 journal articles and three books, including a highly cited guide to plasma theory. All the participants express satisfaction with their lives as they reach middle age. But to me, the star of the show is Nick—the only one whose life refutes the class-deterministic hypothesis of the series.

Nick grew up in modest circumstances, but his aptitude was recognized and rewarded with a university scholarship. When he graduated from the University of Oxford, however, the only job he could find in the U.K. was "in a lab that seemed to be in the process of shutting down." Class prejudice may have played a role, but the bigger problem was more likely the fact that at the time basic research was not as well supported in the U.K. as it was in the U.S.

The scientific enterprise that Nick joined in the 1980s rested on the premise that America needed science. This was the vision of Vannevar Bush, dean of engineering at the Massachusetts Institute of Technology from 1932 to 1938 and head of the World War II Office of Scientific Research and Development, who stressed the importance of choosing future scientists on the basis of talent, not social class or family background.

But all is not well in American science today. Compared with that of many other countries, our research funding is still robust, but it is not what it was when Nick came over. According to the Brookings Institution, federal monies for scientific research and development peaked in 1987, and by 2001 they had fallen from that high by 18 percent. (The Brookings folks argue that increases in private R&D largely made up for the decline in federal support, but such subsidies rarely support basic research.) Since the early 2000s there has been robust funding of health-related research, but budgets for nearly everything else have remained pretty much flat.

We can't expect anything to grow infinitely, but this weakened support for basic science has been matched or exceeded by cuts to science in federal agencies. President Donald Trump's proposed catastrophic cuts to the U.S. Geological Survey and other science agencies were rejected by Congress, but many agencies have seen significant budget cuts and attrition of scientists over the past decade. State research support has declined even more: at many state universities, public monies now account for less than 30 percent of operating budgets, with the shortfall compensated for by tuition increases and private donations. The decrease in public support for research universities is particularly troubling in terms of scientific talent because when the going gets tough, people often close ranks and are less open to newcomers who might not "fit in."

In the 20th century America outcompeted Europe in science largely because many of the world's best scientists came to us. To keep American science great, we need to keep it open to talented people, wherever they come from and with whatever accent they speak, so that future Nick Hitchons can pursue their dreams—and make all of us better for it. SA

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Illustration by Shaw Nielsen

Steve Mirsky has been writing the Anti Gravity column since a typical tectonic plate was about 36 inches from its current location. He also hosts the *Scientific American* podcast Science Talk.

Flat Wrong

If there's a bad idea, they'll get around to it

By Steve Mirsky

On February 22 "Mad" Mike Hughes died when his self-built steam rocket crashed shortly after takeoff. Hughes was a famous flat-earther, one of a growing group who do not accept that Earth is an oblate spheroid (which it is). His fatal launch was apparently general daredevilry and not an attempt to gather data for flat-earthism. Although coverage by our friends at Space.com quoted him as saying in a 2017 documentary, "I'm going to build my own rocket right here, and I'm going to see it with my own eyes what shape this world we live on."

Either way, Hughes's demise put flat-earth belief in the news briefly, which got me to dig out an interview I did last year with Michael Marshall, project director of the Good Thinking Society. The U.K. society has taken on the Sisyphean task of "encouraging curious minds and promoting rational inquiry." And Marshall has become well versed in why on Earth people would believe it's flat.

"Some do believe it's a disk," Marshall said. "But there's more than one way to think it's flat ... some people believe that Earth is actually an infinite plane in all directions ... and so when I first came across the flat-earth movement in 2013, this was quite a vociferous debate."

While those factions fought at conferences, other attendees were actually round-earth accepters who thought it would be fun to mix it up with the flat-earthers. Turned out it wasn't.

"And so they were stomping into these arguments, saying, well, what about photos of Earth from space and what about ships going over the horizon," Marshall said, "not realizing that those were the first things [flat-earthers] thought about." And they had convincing, if incorrect, responses. "And so [the flat-earthers] were winning those arguments … and in winning those arguments, they were converting even more people."

Then, in 2016, some YouTube videos threw gasoline on the two-dimensional fire. Marshall said the video content was straightforward: "Proof number one: the horizon looks flat. Proof number two: even if you go up a mountain, the horizon looks flat. Proof number three: water can't stick to a curved surface. It always goes level, so there's no way it could stick to a ball. They're all very simplistic arguments."

YouTube's recommendation algorithm appears to have then amplified the signal by bringing flat-earth info to the attention of fans of other questionable notions. "So you'd be watching a video about moon-landing denial," Marshall explained, "and YouTube would say, 'I think someone who's a bit into moon-landing denial might also be into the flat-earth theory.' And it would float it there as a suggestion. And if people clicked it, that solidified that link." Flat-earth belief, quirky and perhaps humorous on its own, thus became part of what Marshall called "an ecosystem of conspiracy theory."

"One thing that really surprised me at a convention I went to," Marshall said, "was how little material was about the flat earth." For example, he saw a presentation by a conspiracy theorist about the New World Order and the Illuminati. "But he was also pointing out how dinosaurs were faked." The presenter tapped into the mother lode of conspiracy thinking by recommending a virulently anti-Semitic book that allegedly reveals what's really going on behind the scenes. Which reminds me, I have to wrap this column up so I can get to the Secret Jewish Cabal That Runs the Global Media meeting. (George Soros is serving hamantaschen!)

Not surprisingly, antivaccine material and other terrible health information are also passed around in conjunction with flat-earth ideas. Marshall recalled a convention speaker telling the assembled that "you can cure all manner of diseases, including HIV and AIDS, by drinking or injecting your own urine." I would have thought that even someone who didn't know that Greek mathematician Eratosthenes nicely estimated Earth's circumference more than 2,000 years ago—proving that the planet was round—would consider urine injection to be a piss-poor idea. SA

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Illustration by Matt Collins

50, 100 & 150 YEARS AGO

INNOVATION AND DISCOVERY AS CHRONICLED IN *SCIENTIFIC AMERICAN*

Compiled by Daniel C. Schlenoff

MAY

1970 Monkey War Resumes

"The classic controversy about evolution has resumed once again in California. The State Board of Education inserted into new guidelines, which had been prepared by a committee of science teachers, a statement that 'scientific evidence concerning the origin of life implies at least a dualism or the necessity to use several theories.' This will presumably require that such competing theories as the story given in Genesis and Aristotle's theory of spontaneous generation be taught along with Darwinism. The decision could affect the teaching of biology throughout the country, since California accounts for some 10 percent of all textbook sales and publishers are not likely to give up the California market or to publish special versions tailored to one state's requirements."

1970

1920

1870

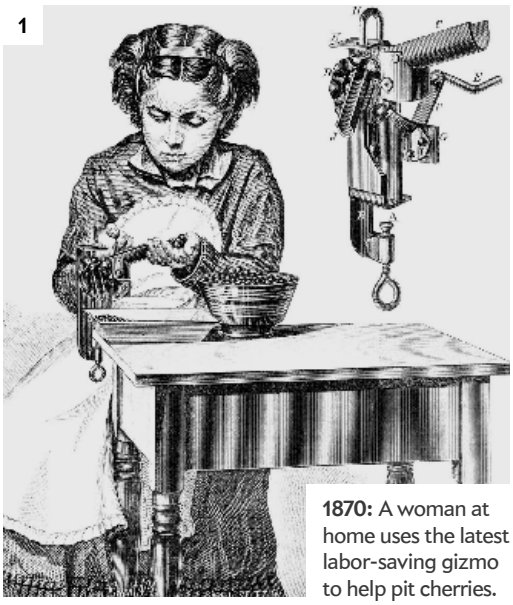
1920 Airborne Horse

"From Santa Barbara, California, comes word that a horse entered in an exposition held in that city arrived by airplane from Los Angeles. The trip was delayed a day until officers of the Humane Society were fully convinced that no cruelty was involved in the trip."

Vehicle Link

"Strikes of one sort or another have emphasized New York City's physical isolation and made it imperative that the Island of Manhattan have transportation links that will permit a continual interchange of vehicular traffic between the New Jersey and the New York side of the Hudson River. It should be no wonder to the technical world that Chief Engineer Clifford M. Holland, and his associate experts, should have decided in favor of twin cast-iron tubes and the adoption of the shield method of tunneling. This procedure has heretofore been followed in the driving of twenty-two railroad tubes under the Hudson and the East Rivers."

The Holland Tunnel opened in 1927.



1 **1870:** A woman at home uses the latest labor-saving gizmo to help pit cherries.

1870 Live Animal Trade

"An English magazine says, 'the trade in wild beasts is a system as regular as the trade in tea, coffee, or cotton. Some creatures, of which parrots are the most numerous, are brought over by sailors, who intend them, perhaps, as presents for their sweethearts, but they sell them for grog or tobacco as soon as they land. If any gentlemen or lady would like an elephant for private riding, a tiger as an ornament to the garden, a crocodile or hippopotamus for the lake, or an ostrich or emeu for the lawn, the wish can be gratified by merely addressing a letter to the London dealer.'"

Food Prep at Home

"We publish an engraving of a neat and ingenious device for removing the pits from cherries, plums, and the like, and also the seeds from raisins, cranberries, etc. The improved form of the machine was patented by George Geer, of Galesburg, Ill."

2

EPIC TALES

CELEBRATING 175 YEARS

The Evolution and Technology of How We Eat

The way humans prepare food is intertwined with our evolution and our technology. The first use of fire to cook food unlocked nutrition not available in raw foods. Our cover from August 1994 ("The Eloquent Bones of Abu Hureyra") shows the toll on Neolithic skeletons of the effort spent grinding grains after the rise of agriculture 12,000 years ago. In the mid-19th century most food (for instance, the cherries shown above) was generally grown close to home and processed and eaten there. A continual stream of innovations in transport, refrigeration, shipping, mass processing and agriculture (Mike Bloomberg, please take note) has brought us our modern system of food, with all its benefits and the complex side effects that bedevil us.

Neolithic bones from a woman who lived in northern Syria 10,000 years ago bear distinctive marks of the hard labor of grinding grains.

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SCIENTIFIC AMERICAN, VOL. 271, NO. 2, AUGUST 1994 (2)

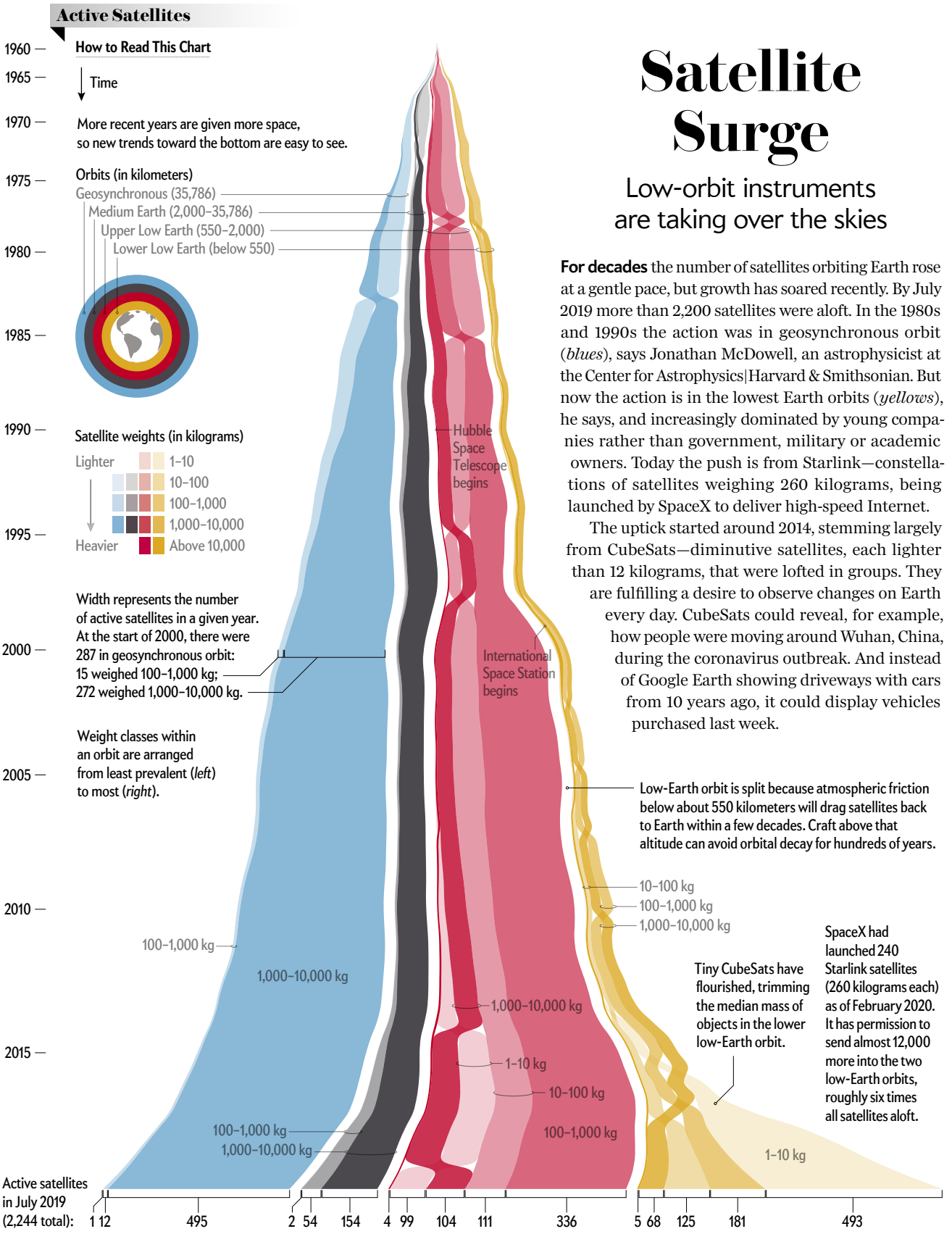
Text by Mark Fischetti | Graphic by Nadieh Bremer

Satellite Surge

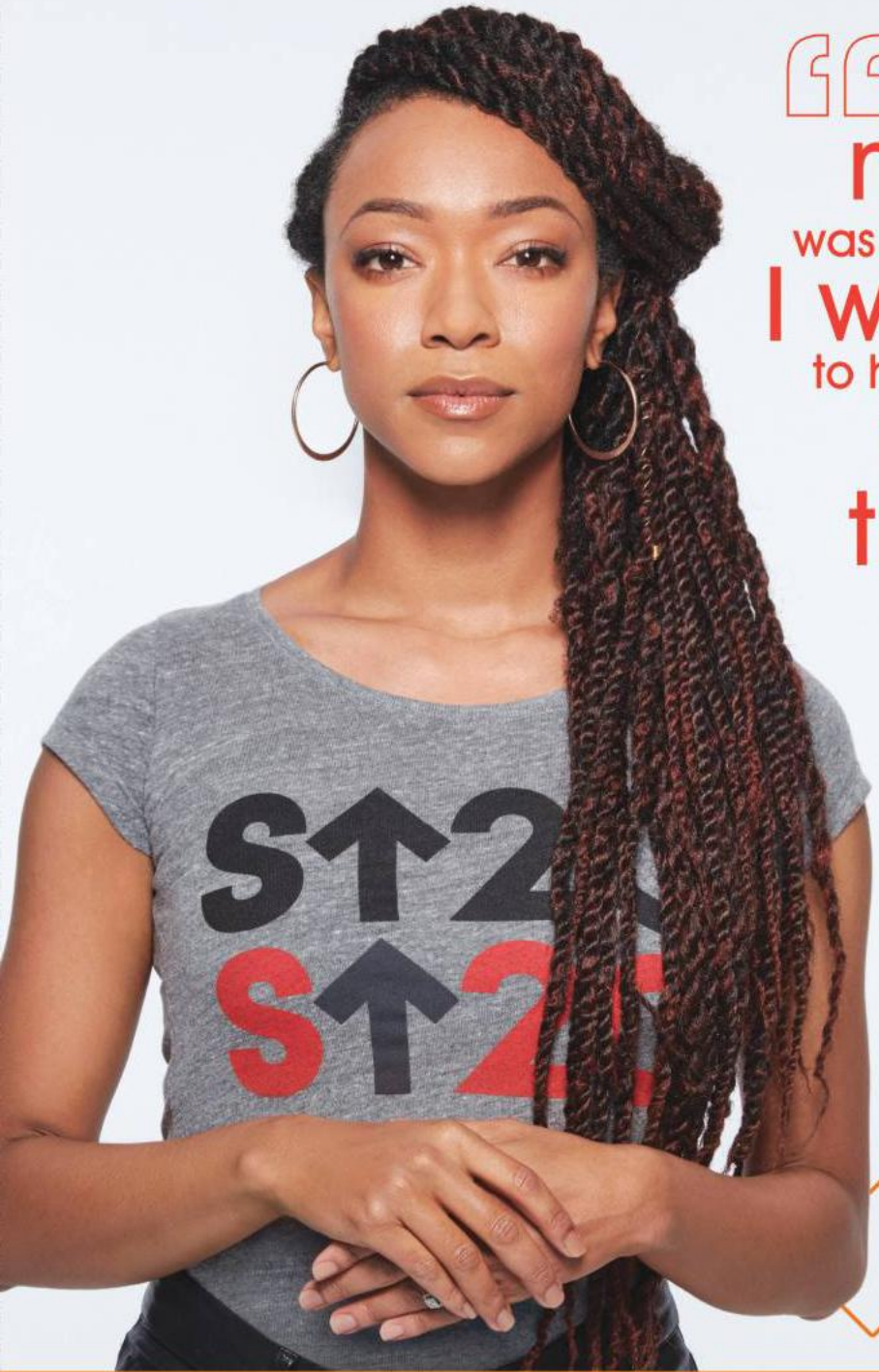
Low-orbit instruments are taking over the skies

For decades the number of satellites orbiting Earth rose at a gentle pace, but growth has soared recently. By July 2019 more than 2,200 satellites were aloft. In the 1980s and 1990s the action was in geosynchronous orbit (*blues*), says Jonathan McDowell, an astrophysicist at the Center for Astrophysics|Harvard & Smithsonian. But now the action is in the lowest Earth orbits (*yellows*), he says, and increasingly dominated by young companies rather than government, military or academic owners. Today the push is from Starlink—constellations of satellites weighing 260 kilograms, being launched by SpaceX to deliver high-speed Internet.

The uptick started around 2014, stemming largely from CubeSats—diminutive satellites, each lighter than 12 kilograms, that were lofted in groups. They are fulfilling a desire to observe changes on Earth every day. CubeSats could reveal, for example, how people were moving around Wuhan, China, during the coronavirus outbreak. And instead of Google Earth showing driveways with cars from 10 years ago, it could display vehicles purchased last week.



SOURCE: JONATHAN MCDOWELL'S SPACE REPORT, 2019 (HTTPS://PLANET4589.ORG)



"When my mom was diagnosed with cancer, I wanted her to have access to the best treatments available."

SONEQUA MARTIN-GREEN
Stand Up To Cancer Ambassador

Photo By
MATT SAYLES

THAT'S WHY I'M SO PASSIONATE ABOUT EXPANDING AWARENESS OF CLINICAL TRIALS

You want the best treatments for your loved ones. My mom's cancer was treated using a therapy made possible by clinical trials. I want all people diagnosed with cancer to have access to the treatments that will make them long-term survivors, like my mom.

Cancer clinical trials may be the right option for you or a loved one. The more information you have about clinical trials, the more empowered you will be to seek out your best treatments.

Learn more at **StandUpToCancer.org/ClinicalTrials**

STAND UP TO CANCER®