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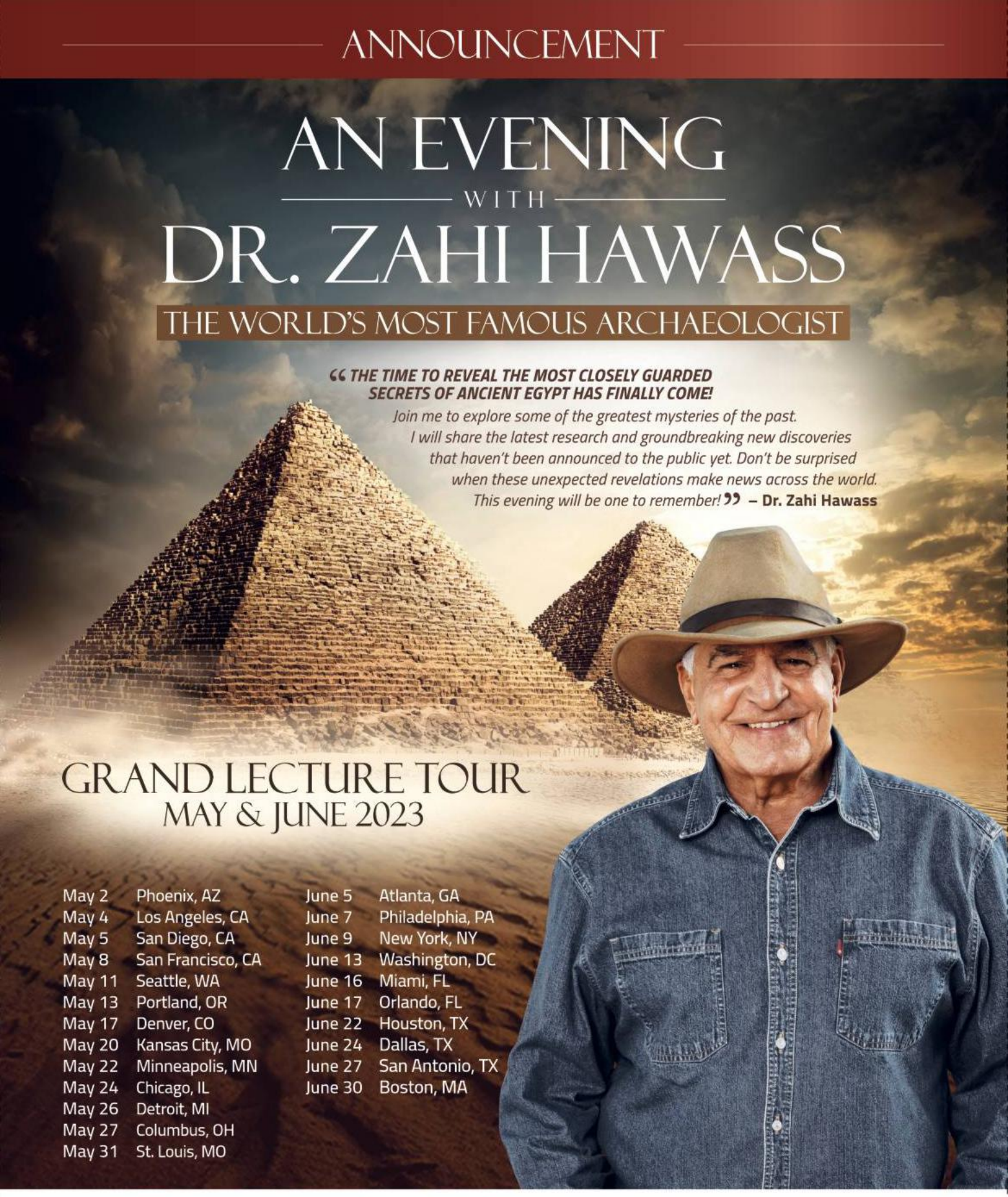

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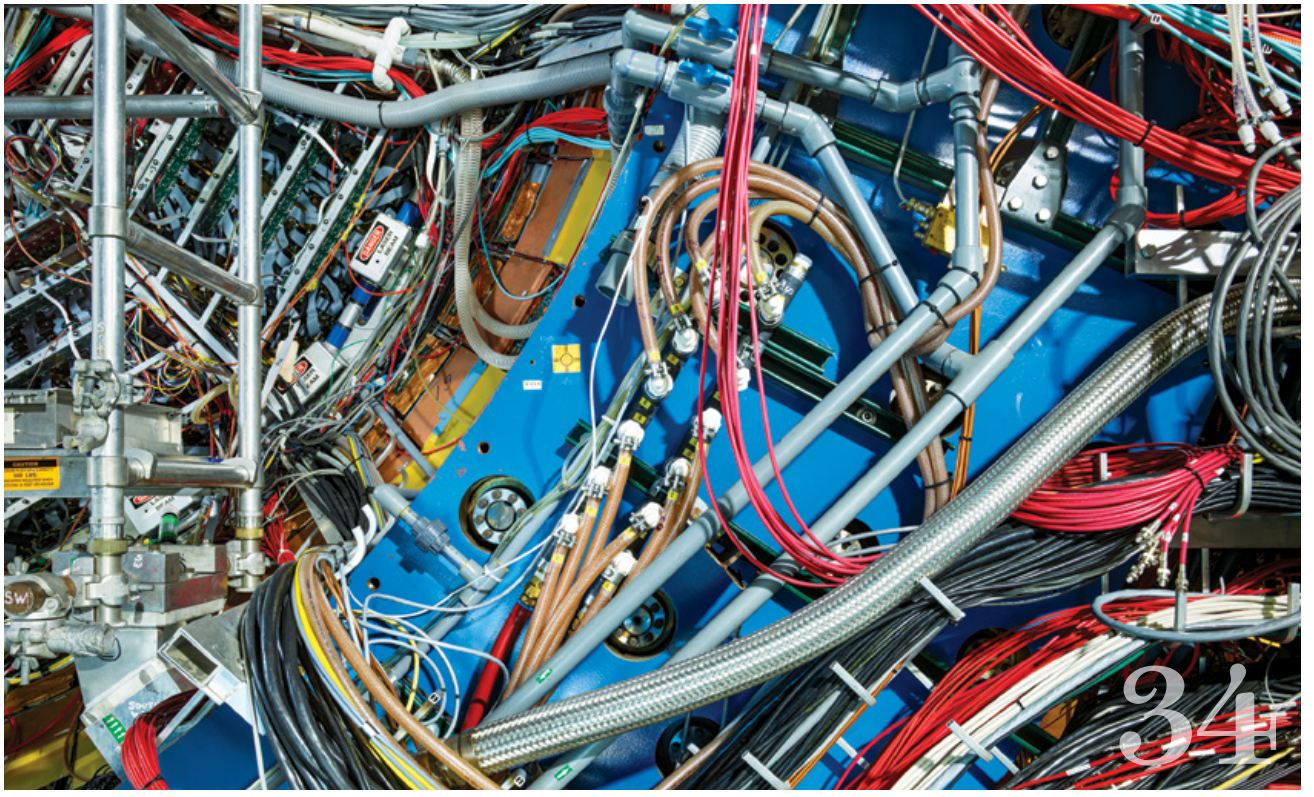

ON THE COVER

For months and years after virus infection, people with long COVID suffer from devastating pain, extreme fatigue, and a "brain fog" that can make it nearly impossible to think, work, and perform daily activities. New discoveries show many symptoms have roots in the brain and the nervous system. This realization points to novel treatments for the estimated tens of millions of people in the U.S. with the syndrome. **Illustration by Stephanie Shafer.**

Photograph by Christopher Payne

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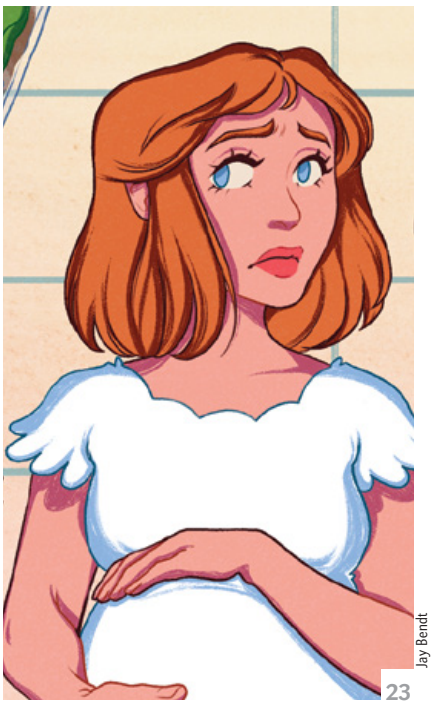
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Laura Helmuth is editor in chief of *Scientific American*.
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Quark Soup

In the first fraction of a second after the big bang, the universe was a hot, dense ocean of perfectly free-flowing particles called a quark-gluon plasma. It didn't last long—all the gluons and various flavors of quarks and antiquarks were almost immediately sucked into protons and neutrons and held in place by the powerful fundamental force called the strong force. And that's where they all remained for 13.7 billion years, until scientists figured out how to re-create a quark-gluon plasma in a particle accelerator. By studying this fleeting primordial ooze, they hope to better understand the beginnings of the universe, as well as what's really happening inside a proton, which, as *Scientific American* senior space and physics editor Clara Moskowitz explains on page 34, is basically chaos.

Do you ever have the sense that you can perceive numbers? One of the oldest debates in philosophy is whether people have an innate ability to process numbers or must be taught. Philosophers Jacob Beck and Sam Clarke on page 42 say they can finally answer the question. According to recent research in infants, young children, adults and animals, it's clear to the authors that humans do have some natural perception of quantities that is inborn and unconscious. It's fun to explore how we think about numbers and how our numeracy may have evolved.

The world population recently surpassed eight billion people, up from seven billion in 2011, six billion in 1999 and five billion in 1987, and doubling the planet's 1975 population of four billion. Such growth presents challenges for us and other species on Earth, as historian of science and *Scientific American* columnist Naomi Oreskes observes on page 76. Graphic journalist and *Scientific American* contributor Katie Peek on page 68 shows how birth rates are beginning to decline, especially in poorer countries. The best way to make the world population healthy and sustainable, experts agree, is to educate and empower girls and women.

Researchers are coming to a consensus that long COVID is in many cases a neurological disease. The virus that causes COVID, SARS-CoV-2, can persist in the nervous system for months, and it may bring on ministrokes, inflammation, or immune system disruptions that affect the nervous system. Neuroscientist and science journalist Stephani Sutherland discusses on page 26 the various ways COVID can produce lasting symptoms and how understanding these mechanisms suggests more ways to treat the syndrome.

Our universe may be a hologram. As author Anil Ananthaswamy describes on page 58, physicists made a conceptual breakthrough 25 years ago: the four-dimensional world we inhabit could emerge out of a reality that has a different number of dimensions, just as a hologram, which looks three-dimensional, emerges from two dimensions arrayed just right.

New approaches to treating schizophrenia are helping people manage some of the social and emotional aspects of the disorder. Matthew M. Kurtz, a professor of psychology and neuroscience, writes on page 62 that people with schizophrenia can learn to improve personal problem-solving and control distressing beliefs—things today's antipsychotic medications aren't always useful for.

Barbara Natterson-Horowitz, a cardiologist and evolutionary biologist, started understanding her human patients better once she began treating zoo animals (*page 50*). Giraffes, zebras, cheetahs and hyenas have gestational adaptations that could help pregnant people, and studying heart disease and breast cancer across species could identify novel treatments. She refers to the similarities among female animals as "the sisterhood of species." Isn't it nice when you learn something that makes you look at the world in a different way? SA

Illustration by Nick Higgins

Hey. Maybe we could start fresh?

—Earth

Our world is trying to tell us something. For humans to thrive, we must rethink our values and systems to craft a framework for a healthy future relationship with our planet that isn't at odds with prosperity. Better is possible. Join us!

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Reshaping our relationship with our world

November 2022

COOL METAMATERIALS

I was fascinated by "Tricking Light," Andrea Alù's report on the metamaterials that can now be made that can modify light waves. What particularly interested me was the claim that materials could be constructed that could absorb more radiation than they emitted in an equilibrium state, or vice versa. Does this mean that a cladding could be made that would warm or cool the building it covered? Enormous amounts of energy are used to keep us warm or cool, and this sort of development could help save the planet.

Robert East *London*

ALÙ REPLIES: Indeed, metamaterials have been opening exciting opportunities in the context of green energy applications. Metasurfaces engineered at the nanoscale are being explored to enhance the efficiency of photovoltaics and energy harvesting, as well as for passive daytime radiative cooling, which cools a surface through thermal emission without requiring any external energy source.

I want to emphasize that these surfaces still operate in equilibrium. As I mentioned in the article, by breaking time-reversal symmetry, it is also possible to realize more sophisticated thermal emission responses, such as surfaces that thermally emit in one direction but absorb from a different one.

"Talking about peer exclusion based on race, ethnicity and gender helps students to understand what makes it wrong and how it feels."

MELANIE KILLEN *UNIVERSITY OF MARYLAND*

REDUCING RACISM IN THE CLASSROOM

I enjoyed reading "In Schools, Talk about Racism Can Reduce Bias," by Camilla Mutoni Griffiths and Nicky Sullivan [Mind Matters]. Not only does talking about general racism in society reduce bias, as the article describes, but recent evidence reveals that providing children an opportunity to reflect on and discuss peer exchanges involving social exclusion based on gender, race and ethnicity does so as well. Additionally, it promotes positive academic and social expectations about others in children and increases their desire to play with peers from different backgrounds.

My team and I at the University of Maryland recently completed testing the effectiveness of our Developing Inclusive Youth intervention program in third, fourth and fifth grade students in public schools. The program involves watching a web-based curriculum tool that portrays everyday peer-exclusion scenarios, followed by a teacher-led classroom discussion. We used a randomized control trial in 48 classrooms, and the results are very promising.

In contrast to the control group, children in the program were more likely to view interracial peer exclusion as wrong, to assign more positive traits such as "friendly" and "hardworking" to diverse peers, and to have more positive math and science competency beliefs about those with different racial and gender backgrounds. Our results were published in the May/June 2022 issue of the journal *Child Development*.

Talking about peer exclusion based on race, ethnicity and gender helps students to understand what makes it wrong and how it feels and to recognize that many peers experience these forms of exclusion. Changing group norms in the classroom is the first step toward rejecting individual explanations for group differences and learning about structural explanations that reflect prejudice and bias. Creating a safe space to talk about these issues in the classroom is necessary for promoting positive learning environments for all students.

Melanie Killen
University of Maryland

The article notes that a law in Iowa effectively prohibits teaching about race, partly on the basis that "teachers must ensure that no student feels 'discomfort, guilt, anguish or any other form of psychological distress on account of that individual's race or sex.'" I was immediately struck by the dangerous possible generalization of this rationale to all educational subjects. What child struggling to learn to read or to do mathematics does not experience psychological distress?

The real issue is not the distress but how it is managed. Teachers can help students to do that, to try harder rather than give up, to understand and to grow as humans. Truly, this is a fundamental life lesson. Otherwise we have the perverse outcome described in the article.

Bill Jones *Toronto*

BE AWARE

In "Hidden Consciousness," Jan Claassen and Brian L. Edlow discuss how some patients who appear to be in a coma may be aware of their surroundings. Almost immediately after I began to read the article, my recollections of Dalton Trumbo's 1939 novel *Johnny Got His Gun* and his 1971 film adaptation came to mind.

In the story, intended as an antiwar cautionary tale, a young World War I veteran awakens in a hospital bed with massive injuries—amputations in both legs and both arms and the complete erasure of his face. He has total consciousness but is trapped in a body that is incapable of communicating with the world. Unable to commit suicide, he eventually gets through to his day nurse by banging his head repeatedly on his pillow in Morse code.

Whether by Trumbo's book or the movie or this article, one's empathy is aroused for folks trapped in their own body. All

must hope that the reported techniques for opening communication with patients with "covert consciousness" make dramatic improvements. Finally, we have to wonder how many sentient beings in the past who were in that state had their life support withdrawn and knew what was about to happen.

JOHN KOPP *Eastvale, Calif.*

RELIGION AND MORAL INJURY

I was very happy to read "An Invisible Epidemic," by Elizabeth Svoboda [December 2022]. Her description of "moral injury" rang true to the experience of many people I have dealt with in my priesthood, ranging from women facing clearly their decision of years earlier to seek an abortion to those who, out of fear or material self-interest, did not report financial or sexual misconduct of their religious superiors.

Svoboda is right to portray this problem as a moral one rather than another instance of post-traumatic stress disorder or depression. It is a conflict within oneself over deeply held moral principles succumbing to outside pressure or inner weakness. One must be honest about one's past actions, regret one's failure to live by one's principles, even if nothing better could have been done at the time, and then trust that peace may be achieved by a clearer understanding of one's situation and a renewed commitment to those moral values.

It was encouraging to see Svoboda's recognition of the role that religious leaders—priests, rabbis, ministers, imams—may have in dealing with moral injury. They often have experience in counseling in such situations.

MARK E. BRENNAN
Bishop of Wheeling-Charleston, Wheeling, W.V.

ERRATA

"Hidden Consciousness," by Jan Claassen and Brian L. Edlow, should have said Maria Mazurkevich is now working as a pharmacy technician, not a pharmacist.

"Dialogues with the Dead," by Piers Vitebsky [January 2023], should have described mourners stitching leaves from a sacred Sal tree into bowls before a ritual involving a trance state, not after. And it should have described Sora men drinking palm wine outdoors, not in the jungle.

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Stop Giving Healthy Animals Antimicrobials

Governments must regulate drug misuse in food animals that is contributing to antimicrobial resistance

By the Editors

The COVID pandemic has taught us that we shouldn't ignore warnings about dire health threats. And scientists have been warning about the dangers of antimicrobial resistance, or AMR, for decades. In 2019 the World Health Organization declared AMR one of the top 10 global public health threats to humanity, and the United Nations estimated it could kill as many as 10 million people a year by 2050. We are already seeing high numbers of such deaths: drug-resistant infections killed nearly five million people in 2019.

AMR means the treatments we use to fight bacteria, viruses, fungi and other pathogens no longer work. Resistance evolves naturally over time, but the overuse and misuse of antimicrobial drugs in medicine and agriculture are speeding it up.

Fixing this problem will require a focus on human, animal and environmental health. The food animal industry is one of the chief users of antibiotics and one of the largest contributors to antimicrobial resistance. Governments need to better regulate livestock farmers' use of these drugs, and restaurants, supermarkets and consumers must demand antibiotic-free meats wherever they buy them.

About 70 percent of medically important antibiotics sold in the U.S. are for animals. Sometimes they are needed to treat illness, but for many years livestock and poultry farmers also gave healthy animals antibiotics to promote their growth. Although it is no longer legal to administer antibiotics for that purpose, farmers still give them to "prevent" infections, despite little evidence that this works.

Modern factory farms are the ideal breeding grounds for antibiotic-resistant infections: many animals are raised in crowded, unsanitary conditions. Add to that the fact that the antibiotics are given at low doses that can kill off weak pathogens while inadvertently selecting out the strongest ones, and you've got the "perfect storm" to create bacterial resistance, says Gail Hansen, a consultant on public health policy and antibiotic resistance.

The chicken industry has made some progress in reducing antibiotic use over the past 10 to 15 years—mainly thanks to consumer pressure, according to Hansen. Farmers stopped injecting chicken eggs with antibiotics to prevent new chicks from catching an infection from microbes on the egg. Instead they now wash eggs.

These changes are an improvement, but chickens receive only a small fraction of the total amount of antibiotics used in food animals. Cattle and pig farming collectively account for about 80 percent. Reducing their antibiotic use will require more significant changes to their diets and living conditions. But given the importance of these drugs, we need to pressure livestock farmers to make those changes.

Farmers are not the only ones who should be taking responsibility. Food retailers have a lot of power, too. In 2018 McDonald's pledged to set reduction targets for the amount of medically important antibiotics in its beef by the end of 2020, but it did not do so until late 2022. A recent investigation by the Bureau of Investigative Journalism and the *Guardian* found that companies supplying beef to McDonald's, Taco Bell and Walmart are still getting meat from farms using antibiotics classified by the WHO as "highest priority critically important" to human health.

Medical settings such as hospitals have created stewardship committees that evaluate whether a given use of antimicrobials is appropriate. The U.S. should create similar programs in the food animal industry. Ideally it would also set target limits for antimicrobial use, as European countries have done. The Netherlands, for example, set a policy that decreased the use of antibiotics in animals by 50 percent within three years. The U.S. government should do something similar but can't: no federal agency—not the FDA, not the U.S. Department of Agriculture—has the power to set limits on the amount of antibiotics used or offer incentives to reduce their use. Any efforts by Congress to give an agency these powers are likely to be fiercely fought by agricultural lobbyists, but it's worth trying.

Antibiotic use in agriculture is just one factor contributing to the rise of antimicrobial resistance. The human health-care system, including doctors and pharmacies that distribute the drugs, can also follow best practices to help antibiotics stay useful longer. If we can't stop resistance from occurring, we can at least slow it down until researchers and pharmaceutical companies can develop new infection-targeting drugs. After all, our lives depend on it. SA

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Illustration by Martin Gee


George Maliha is a third-year internal medicine resident at the University of Pennsylvania Health System. **Ravi B. Parikh** is an oncologist and policy researcher at the University of Pennsylvania who develops ways to integrate AI into clinical care.

Who Is Liable When AI Kills?

We need to protect people from faulty AI without curbing innovation

By George Maliha and Ravi B. Parikh

Who is responsible when artificial intelligence harms someone? A California jury may soon have to decide. In December 2019 a person driving a Tesla with an AI navigation system killed two people in an accident. The driver faces up to 12 years in prison. Several federal agencies are investigating Tesla crashes, and the U.S. Department of Justice has opened a criminal probe into how Tesla markets its self-driving system. And California's Motor Vehicles Department is examining its use of AI-guided driving features.

Our current liability system—used to determine responsibility and payment for injuries—is unprepared for AI. Liability rules were designed for a time when humans caused most injuries. But with AI, errors may occur without any direct human input. The liability system needs to adjust accordingly. Bad liability policy won't just stifle AI innovation. It will also harm patients and consumers.

Sergii Iaremenko/Science Photo Library/Getty Images

The time to think about liability is now—as AI becomes ubiquitous but remains underregulated. AI-based systems have already contributed to injuries. In 2019 an AI algorithm misidentified a suspect in an aggravated assault, leading to a mistaken arrest. In 2020, during the height of the COVID pandemic, an AI-based mental health chatbot encouraged a simulated suicidal patient to take her own life.

Getting the liability landscape right is essential to unlocking AI's potential. Uncertain rules and the prospect of costly litigation will discourage the investment, development and adoption of AI in industries ranging from health care to autonomous vehicles.

Currently liability inquiries usually start—and stop—with the person who uses the algorithm. Granted, if someone misuses an AI system or ignores its warnings, that person should be liable. But AI errors are often not the fault of the user. Who can fault an emergency room physician for an AI algorithm that misses papilledema—swelling of a part of the retina? An AI's failure to detect the condition could delay care and possibly cause a patient to lose their sight. Yet papilledema is challenging to diagnose without an ophthalmologist's examination.

AI is constantly self-learning, meaning it takes information and looks for patterns in it. It is a "black box," which makes it challenging to know what variables contribute to its output. This further complicates the liability question. How much can you blame a physician for an error caused by an unexplainable AI? Shifting the blame solely to AI engineers does not solve the issue. Of course, the engineers created the algorithm in question. But could every Tesla Autopilot accident be prevented by more testing before product launch?

The key is to ensure that all stakeholders—users, developers and everyone else along the chain—bear enough liability to ensure AI safety and effectiveness, though not so much they give up on AI. To protect people from faulty AI while still promoting innovation, we propose three ways to revamp traditional liability frameworks.

First, insurers must protect policyholders from the costs of being sued over an AI injury by testing and validating new AI algorithms prior to use. Car insurers have similarly been comparing and testing automobiles for years. An independent safety system can provide AI stakeholders with a predictable liability system that adjusts to new technologies and methods.

Second, some AI errors should be litigated in courts with expertise in these cases. These tribunals could specialize in particular technologies or issues, such as dealing with the interaction of two AI systems (say, two autonomous vehicles that crash into each other). Such courts are not new: in the U.S., these courts have adjudicated vaccine injury claims for decades.

Third, regulatory standards from federal authorities such as the U.S. Food and Drug Administration or the National Highway Traffic Safety Administration could offset excess liability for developers and users. For example, federal regulations and legislation have replaced certain forms of liability for medical devices. Regulators ought to proactively focus on standard processes for AI development. In doing so, they could deem some AIs too risky to introduce to the market without testing, retesting or validation. This would allow agencies to remain nimble and prevent AI-related injuries, without AI developers incurring excess liability.

Industries ranging from finance to cybersecurity are on the cusp of AI revolutions that could benefit billions worldwide. But these benefits shouldn't be undercut by poorly developed algorithms: 21st-century AI demands a 21st-century liability system. SA

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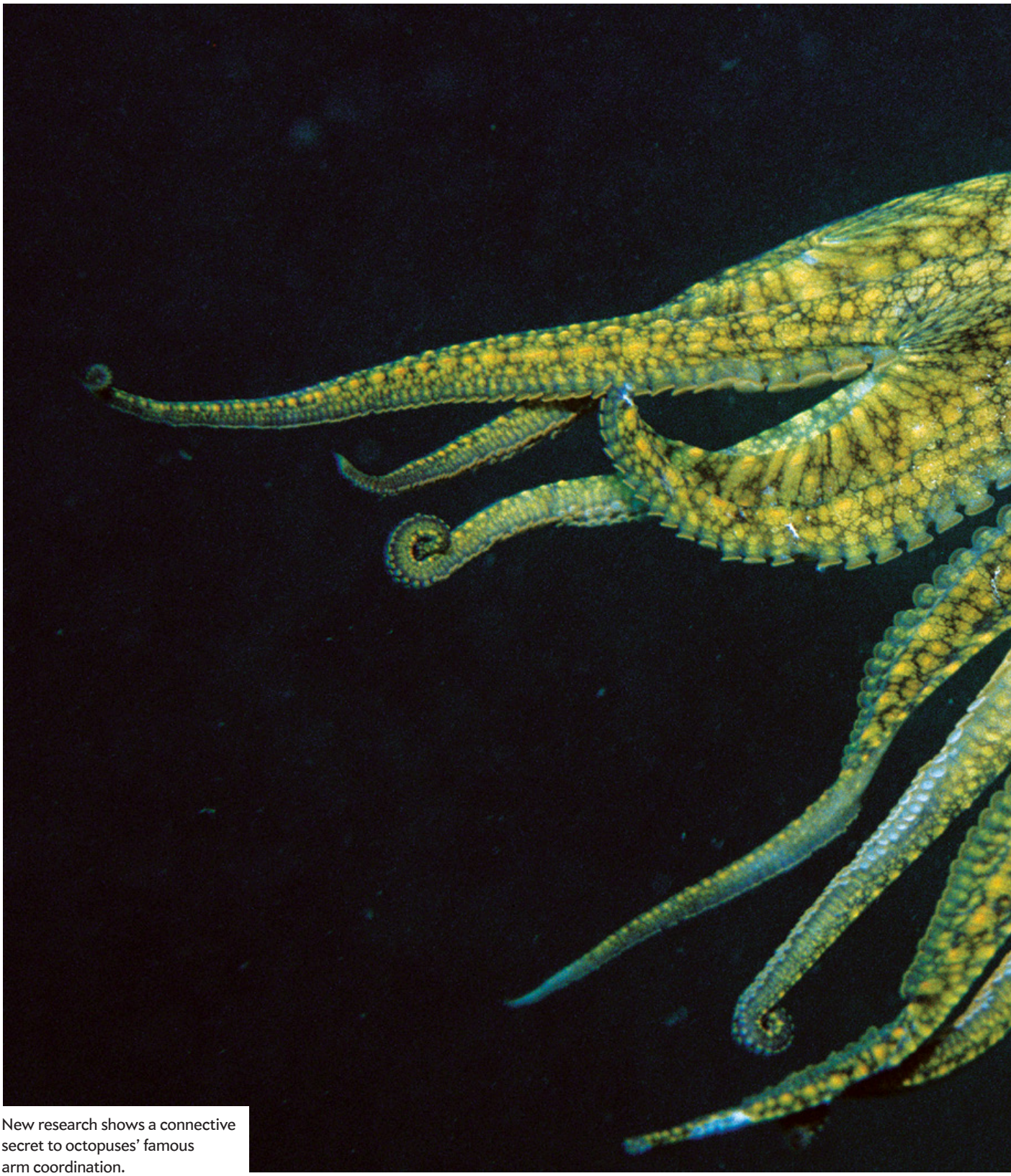
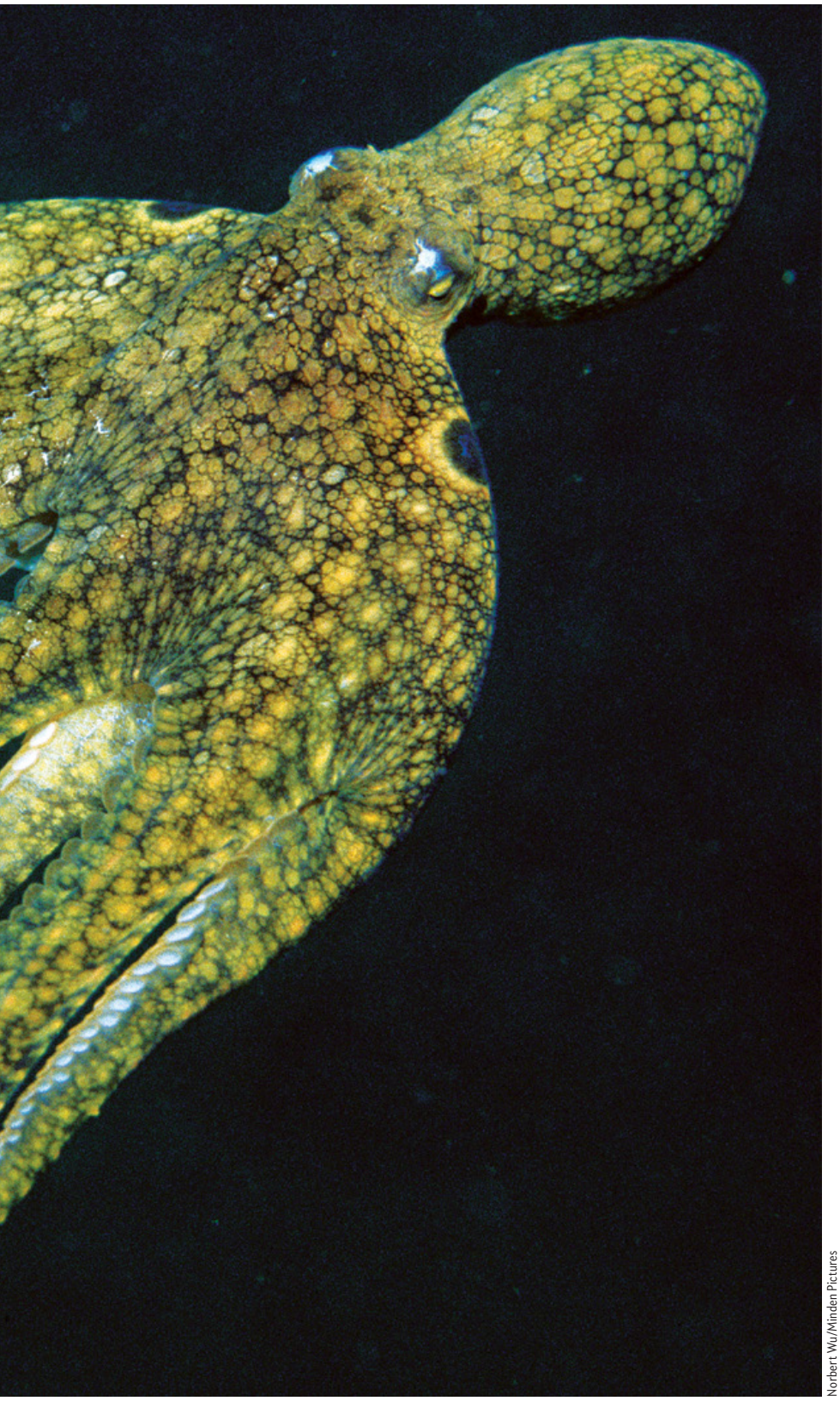


New research shows a connective secret to octopuses' famous arm coordination.

INSIDE



Norbert Wu/Minden Pictures

BIOLOGY

Octopus Nerves

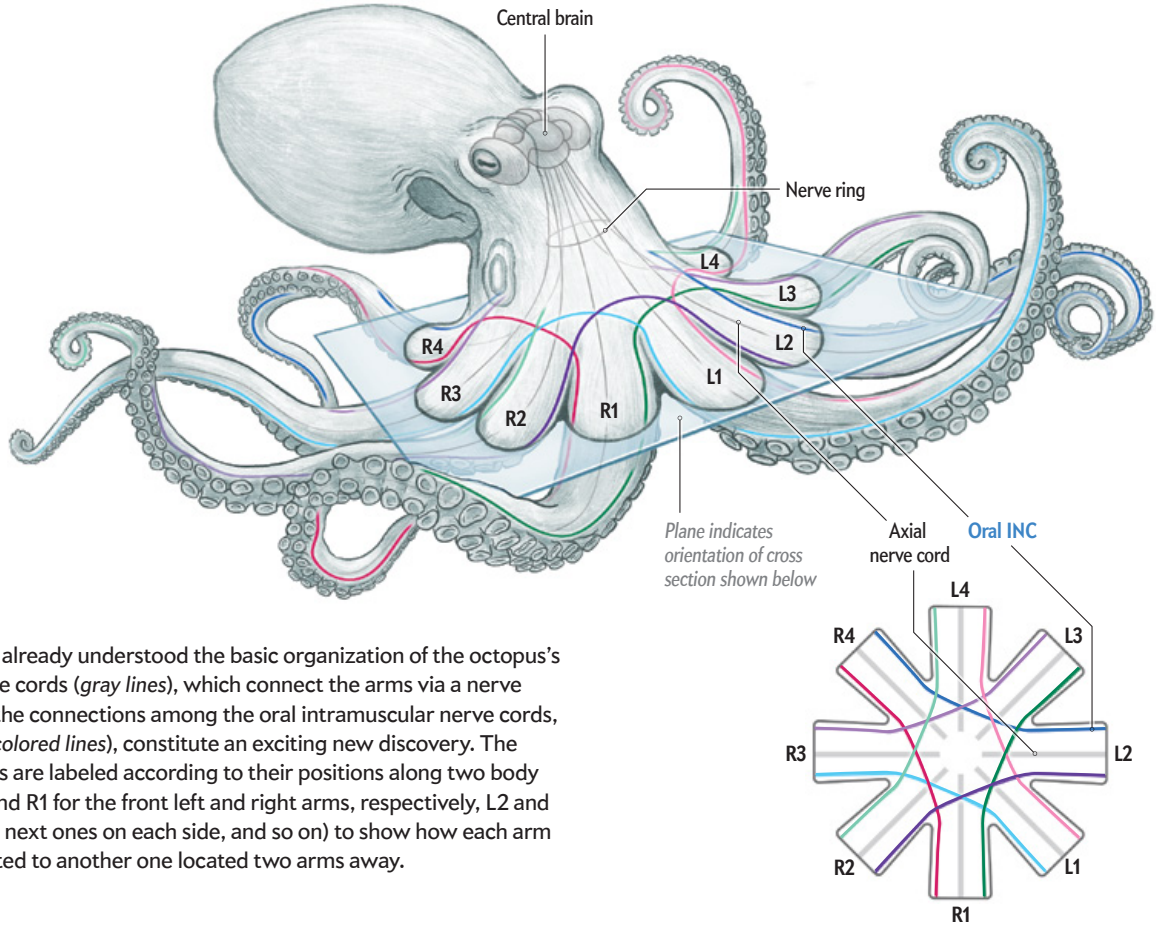
A hidden pattern connects eight cooperating limbs

Octopuses' sucker-covered arms can act as if they contain partly independent mini brains. Each arm gathers sensory information to drive its own movements—and even those of other arms—without consulting major brain regions.

"Their arms are so mobile; they're soft, and they can bend and twist and do all sorts of things," says Melina Hale, a biologist at the University of Chicago. In a study in *Current Biology*, she and her colleagues reveal the strange connections that may facilitate these supple limbs' decentralized coordination.

The researchers investigated the anatomy of young *Octopus bimaculoides,* which are the size of "a big Tic Tac," says study lead author Adam Kuuspalu, also at Chicago. They examined the octopuses' intramuscular nerve cords: key pieces of invertebrate anatomy that contain multiple types of neurons and contribute to whole-arm movement. In most past research, "other parts of the arm nervous system were really well described, but those are just left a mystery," Hale says.

The researchers traced the nerve cords with a powerful microscope and found that one type—the cords closest to the suckers—not only ran the length of an arm but also extended down another arm two arms away. All eight arms show this pattern. The



Scientists already understood the basic organization of the octopus's axial nerve cords (*gray lines*), which connect the arms via a nerve ring. But the connections among the oral intramuscular nerve cords, or INCs (*colored lines*), constitute an exciting new discovery. The eight arms are labeled according to their positions along two body axes (L1 and R1 for the front left and right arms, respectively, L2 and R2 for the next ones on each side, and so on) to show how each arm is connected to another one located two arms away.

layout was "totally different from anything that we'd ever seen before," says Hale, who had expected the cords to create a structure similar to the central ring formed by larger peripheral nerves.

"I think it's as simple as saying that it's mathematically efficient," Kuuspalu says of the newly discovered pattern. If these connections carried sensory and motor signals, they would allow for rapid communication between relatively distant arms.

San Francisco State University biologist Robyn Crook, who was not involved in the new study, says it is interesting and relevant to her work on sensorimotor integration in octopuses, squid and cuttlefish. "It's not clear yet how the [intramuscular nerve cords] communicate or even if they do send signals across the body over long distances," she adds. The study authors plan to delve into these questions next.

"We can now approach our anatomical and behavioral studies a bit differently, with more focus on what any one arm is doing in concert with more distant arms in the ring," says Roger Hanlon, a researcher at the Marine Biological Laboratory and frequent collaborator with Hale's group. "We are in that intriguing 'mild state of confusion' that is simultaneously perplexing and exhilarating when unexpected discoveries are revealed."

—Nora Bradford

Source: "Multiple Nerve Cords Connect the Arms of Octopuses, Providing Alternative Paths for Inter-Arm Signaling," by Adam Kuuspalu et al., in *Current Biology*, Vol. 32; December 19, 2022 (*reference*)

ROBOTICS

Soft Power

Squishy robots get ready to set out on their own

Constructed from delicate, flexible and lifelike materials, soft robots have the potential to improve on their clunky, metal-bodied predecessors. Such machines could more nimbly explore other planets, gently collect organisms from the ocean depths and even lend surgeons a hand. But stubborn design challenges have long held them back from making it out of the lab and into our lives. Now a new generation of soft robots is navigating, growing and self-repairing its way to meeting researchers' lofty expectations.

Squishy materials let robots deform to adapt to changing environments, such as constricting tunnels. Soft robots can also handle fragile materials, such as human organs or brittle rocks, without crushing them. Even some mostly rigid-bodied robots, including the famously agile walkers made by Boston Dynamics, incorporate soft parts for better movement. Many developments in soft robotics are inspired by traits of living organisms, such as octopuses' flexibility or the high water content of jellyfish. And new designs seek something less tangible: animal-like independence.

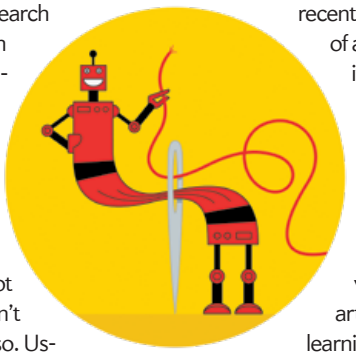
"The robotics community has been continuously focusing on the science and engineering of autonomy," says Massachusetts Institute of Technology roboticist and computer scientist Daniela Rus. "We have made advancements on the soft body components

Graphic by Mesa Schumacher

and also on the algorithmic control … and we are now using these advancements to make increasingly more capable and self-contained autonomous soft robots."

When independently exploring treacherous territory, soft robots are more prone to cuts and punctures than rigid machines are. One group of researchers, inspired by the self-healing properties of human skin, recently created an experimental robot that can bounce back from small injuries. The team described its study findings in *Science Advances*.

"If we have our druthers and achieve robots that operate for years at a time while performing dexterous tasks, then many opportunities open up for us," says study co-author Robert Shepherd, an engineer at Cornell University. "One clear example is space exploration—perhaps building research habitats on the moon or even surveying the oceans of Europa. In these remote operating environments, robots will accumulate damage and may not have anyone around to repair them."



Shepherd and his team designed a soft robot that not only heals damage but doesn't need to be told when to do so. Using fiber-optic sensors, the robot can detect when its material has been punctured. Then it uses a hyperelastic material, called polyurethane urea elastomer, to quickly heal the wound. The robot is also programmed to move in a new direction after damage—ideally escaping whatever caused it. Later work could expand these repairs to bigger missing chunks and holes.

Another team created a soft robot that "grows" like a plant or fungus for a study published last year in the *Proceedings of the National Academy of Sciences USA*. Growing robots could burrow underground or lay new infrastructure on other planets. But to grow, soft robots typically have to drag material behind them and use it to 3-D-print new structures. This can hinder a robot's work like lugging around a garden hose would for a person, says study co-author Chris Ellison, a University of Minnesota engineer and materials scientist. "If you drag your garden hose, and you turn a corner around a tree, the force on the hose goes up," he says. And it continues to increase exponentially with each bend.

The researchers turned to plants for a solution. "They don't extend their roots by dragging more roots behind them," Ellison says. "They transport liquids, and then they transform those liquids to solids, and that ultimately is what builds a structure." His team's new robot uses light to solidify a liquid while spitting it out of a small hole to form a tube, which extends from its launching point to wherever it needs to go. The robot can control the tube's shape as it grows, allowing for navigation of complicated paths without running into the garden hose problem. Robots might one day use this technology to smoothly inspect pipes underground or to pass through the human body for medical applications, Ellison adds.

Engineers have also made major progress in improving soft robots' sensing and motion abilities, which will aid deployment in remote environments. For example, Rus's group recently built a robot with networks of air-filled channels throughout its body. It can measure pressure changes within these channels to determine where its body parts are in space, similar to human proprioception. Other groups have experimented with various types of sensors, artificial muscles and machine learning to create smoother movement and precise perception.

Building soft robots that can work, heal and grow independently could change many areas of human life. "Soft robot hands are enabling a new age for manufacturing," Rus says. Dexterous robots could fit into factory settings more easily if they had humanlike hands that could use the same tools we do, notes ETH Zürich roboticist Robert Katzschmann, who was not involved in the above studies.

Soft robots could also find a place in hospitals. Working alongside nurses and doctors, a robot could help softly and safely hold organs in place during surgery. "Helping hands could make medicine a bit less costly," Katzschmann says, "so you don't need 10 people in an OR. You could do with just one or two." Ellison's team says its robot could someday grow through tissue and search for cancerous tumors, potentially replacing a dangerous surgery altogether.

"I think soft robots are an avenue to endurance and agility not seen before in artificial machines," Shepherd says. With heightened sensing and motion skills, robust compositions, and newfound independence, these squishy machines' future looks solid. —*Nora Bradford*

NEWS AROUND THE WORLD

Quick Hits

By Daniel Leonard

CZECH REPUBLIC

Centuries-old tree rings in today's Czech Republic and southeastern Bavaria suggest drought may have driven Attila the Hun's invasion of the Roman Empire. The rings helped researchers to reconstruct the fifth-century climate, identifying dry spells that may have forced the Huns to move on.

GREENLAND

Scientists have identified two-million-year-old DNA, the oldest ever recovered, from Arctic permafrost. The DNA fragments come from more than 100 species, revealing that Greenland's environment was once much more diverse than today.

INDIA

A Ph.D. student solved a 2,500-year-old linguistic puzzle, decoding a perplexing "metarule"—what option to choose when multiple Sanskrit grammar rules are in conflict—written by an ancient Indian scholar. This gives linguists a better understanding of Sanskrit, including how to teach its grammar to computers.

PAPUA NEW GUINEA

Recent work shows that Indigenous New Guineans' immune systems were shaped by the DNA of Denisovans, an extinct human species. Denisovans mated with *Homo sapiens*, and their DNA may have conferred resistance to certain diseases—a legacy that persists in today's descendants.

TANZANIA

Biologists typically posit that human ancestors learned to walk on two legs on the savanna's flat expanses. But new research shows that wild chimpanzees walk upright in trees far more often than on the ground, suggesting bipedalism could have first evolved up high.

SOUTH AFRICA AND AUSTRALIA

Construction has begun on the Square Kilometer Array, which, when finished, will be the world's largest radio telescope. Half is in South Africa's Northern Cape and half in Western Australia; the first phase of construction is set to conclude in 2028.

For more details, visit www.ScientificAmerican.com/mar2023/advances

Illustrations by Thomas Fuchs

GENETICS

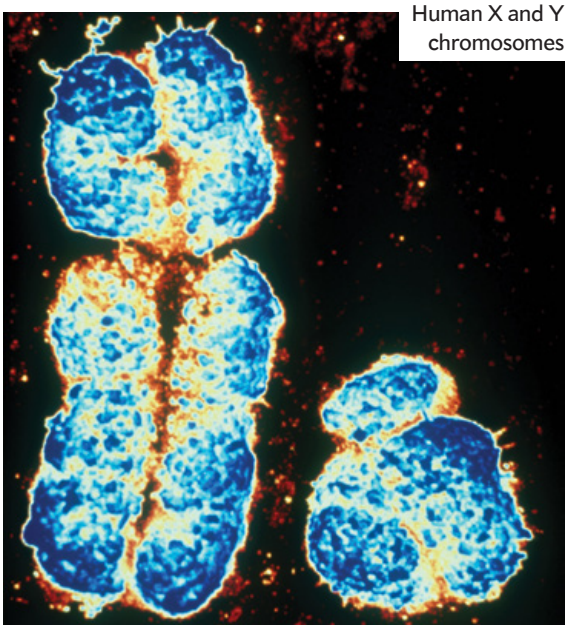
Chromosome Crossing

Researchers generated male and female cells from the same person

For the first time scientists have created two lines of human cells that are identical aside from their sex chromosomes: one has XX chromosomes, and one has XY. This unique set of cells could help researchers answer long-standing questions about how sex chromosomes affect disease and the roles they play in early development.

Most people have two sex chromosomes, either two X's or an X and a Y, which give rise to a spectrum of female or male biological attributes. Studies suggest these chromosomes contribute to processes including immune system function, brain development, disease susceptibility and reactions to drugs. But scrutinizing the specific role of X and Y chromosomes is challenging. With current tools, it is difficult to disentangle the effects of chromosomes versus hormones, for example. These cells could offer a new way to do so.

"This is a really cool set of cell lines," says Northwestern University pharmacologist Barbara Stranger, who was not involved in the new project. "We've had cell lines from males and females before, but the fact that they're coming from the same person with just [a] sex chromosome difference—it's a big step."



Human X and Y chromosomes

Biophoto Associates/Science Source

Benjamin Reubinoff, a developmental biologist at the Hadassah Medical Center in Israel, and his team hope their project will lead to better investigations of human sex differences. Currently two major barriers exist, according to Reubinoff: the difficulty of separating chromosomal and hormonal effects and the inability to pinpoint the effects of X and Y chromosomes while ruling out contributions from the rest of a person's genetic makeup. "There have been animal models, but a model in humans was not available," Reubinoff says.

To create such a model, Reubinoff, his former M.D. and Ph.D. student Ithai Waldhorn, and their colleagues first obtained white blood cells previously collected from a person with Klinefelter syndrome. This condition describes male individuals born with an extra X chromosome, meaning their cells hold two X chromosomes and one Y. The white blood cells came from the repositories of the Coriell Institute for Medical Research, where people donate samples for use in biomedical research projects. The donor had a rare "mosaic" form of the condition, in which some of their cells had three sex chromosomes (XXY), some had two X chromosomes, and some had one X and one Y. The researchers reprogrammed all three cell types into induced pluripotent stem cells, which are in an embryonic state and can develop into neurons, muscle or other cell types.

Ultimately the team generated XX and XY cells that—apart from their sex chromosomes—were genetically identical. The

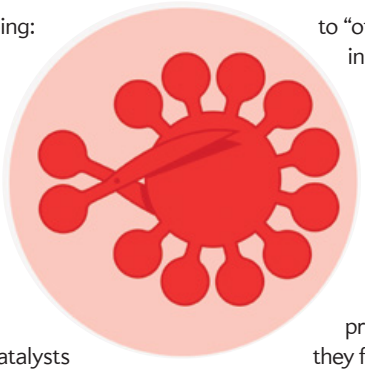
MEDICINE

Cutting Out COVID

Tackling COVID (and more) with synthetic biology

Artificial enzymes can fight the COVID-causing virus by selectively snipping apart its RNA genome, a new study suggests. Researchers say the technique may overcome key problems with previous technologies and could help create rapid antiviral treatments as threats emerge.

When the COVID pandemic struck, University of Cambridge chemical biologist Alexander Taylor scrambled to repurpose a gene-cutting technology he and his colleagues had been developing: synthetic enzymes called XNAzymes (xeno nucleic acids) formed from artificial RNA. Working single-handedly during lockdown, Taylor generated five XNAzymes targeting sequences in SARS-CoV-2's genome in a matter of days.



Enzymes are natural catalysts that facilitate chemical transformations—in this case, by chopping other molecules apart. But previous DNA- and RNA-based enzymes have struggled to cut long, highly structured molecules such as virus genomes. Instead they destroy targets by recruiting existing enzymes inside cells—a less precise process that can lead to "off-target" cuts and increased side effects.

Taylor and his colleagues showed last year that XNAzymes can recognize and not cut sequences differing by a single "letter" of genetic code. And they perform better than previous efforts because they form tighter chemical bonds, the researchers say, maintaining their structure and function in conditions where DNA and RNA enzymes unfurl.

Popular CRISPR gene-editing tools can also target RNA, but the human immune system sometimes reacts poorly to the bacterial enzymes used. XNAzymes are not found in nature, making them less

researchers then conducted a series of experiments replicating findings from prior studies. For example, they confirmed previously reported differences in genes that were turned on in XX or XY cells. And when they coaxed the induced pluripotent stem cells to develop into immature versions of neurons, they found evidence of previously documented sex differences in early neural development. "It was reassuring to see that the model really shows differences between the sexes that were reported from other systems," Reubinoff says. The findings were published in *Stem Cell Reports*.

"This is a very well-designed study that validates the notion that sex differences start early in development—and that they depend on the sex chromosomes, because that's the only thing that can account for those differences," says Nora Engel, a cell biologist and cancer researcher at Temple University, who was not involved in the new study.

In the past, researchers have probed the effects of sex chromosomes in animals using the "four core genotypes" mouse model, which includes manipulating a gene usually found within the Y chromosome called *Sry*. This gene contains instructions for developing testes, and the process creates animals with XX chromosomes and testes or XY chromosomes and ovaries. Animals with the same sex organs but different chromosomes let scientists distinguish the chromosomes' effects from those of sex hormones, which are secreted by the reproductive organs. The mouse model was transformative for the field of sex difference research, Stranger says, and being able to move this research into humans "is really neat."

"I think this is going to open up avenues for new research," says Jessica Abbott, an evolutionary geneticist at Lund University in Sweden, who was not involved in the research. Abbott notes that it will be important to derive XX and XY stem cells from another person to see how much variation there is between individuals—which will help determine whether the findings from these cells can be generalized to the broader population.

Cells, of course, cannot model the entire human body or interactions between organs—at least not yet. But Reubinoff notes that with the development of new techniques, such as microfluidic "body on a chip" systems that replicate the connections between cells from different organs, scientists may soon be able to address a broader array of research questions. For now Reubinoff is excited about the experiments that will be possible with stem cells alone. "You have a tool that you can, at least theoretically, use [indefinitely to] generate any cell type and develop models for various types of diseases," he says. "The model we developed opens wide horizons." —*Diana Kwon*

likely to trigger an immune system attack. They also don't rely on co-opting extra components from within the cell; this might reduce side effects. "All contemporary RNA treatments make use of cellular machinery," says biomedical engineer Roy van der Meel of Eindhoven University of Technology in the Netherlands, who was not involved in the new research. "This is a pair of stand-alone scissors."

In the new study, published in *Nature Communications*, XNAzymes reduced replication of the SARS-CoV-2 virus in infected cells by up to 75 percent. "We're pretty comparable to other approaches with years more development behind them," Taylor says, although he notes direct comparisons have yet to be done.

The scientists used XNAzymes to target three parts of the virus's genome, making it harder for mutations to dodge the attack. The approach can be quickly adapted to other viruses because the core system remains the same; only the part that binds the target is reprogrammed. "XNAzymes have great potential for precision medicine," says study co-author Maria Donde, also at Cambridge. The group's previous research suggests that XNAzymes might be effective against numerous diseases—potentially even targeting mutated cancer genes.

The researchers note that they haven't yet designed a way to get these XNAzymes into human cells, but van der Meel says methods used for other RNA therapeutics could work. The team is currently working on XNAzymes' stability and precision and testing additional target sequences. —*Simon Makin*

EVOLUTION

Deadly Roots

Trees' evolution may have wiped out other species

More than 360 million years ago, during the Devonian period, life was flourishing in spectacular fashion. As fish and invertebrates populated the seas, the first trees emerged on land. But by the end of the Devonian, more than half of all Earth's species had disappeared in a series of mass extinctions. New research shows how tree evolution could have contributed to these extinction events.

As land plants diversified, "they started to grow more complex root systems that were able to reach farther [down] to grab water," says U.S. Naval Academy oceanographer Matthew Smart, lead author of the new study in the *Geological Society of America Bulletin*. One type of tree, a proto-evergreen called *Archaeopteris,* even clustered into primitive forests. Deep tree roots drew crucial minerals such as phosphorus out of the bedrock and then eventually decayed, forming mineral-laden soil. Periodically, large quantities of this soil washed into the seas and lakes—where the sudden phosphorus influx triggered harmful algal blooms that pulled oxygen from the waters below.

The researchers tracked this deadly pattern in five prehistoric lake beds in Scotland and Greenland. They measured a gradual phosphorus decrease in sediment layers from the middle to late Devonian, punctuated by sudden spikes of the mineral with evidence of corresponding oxygen depletion.

Fossilized *Archaeopteris* leaf

"We've been working on the Devonian for a long time, and we have been thinking that these cycles have occurred, but we couldn't really explain it," says Anne-Christine Da Silva, a sedimentologist at the University of Liège in Belgium, who was not involved in the new research. "This paper could bring an explanation."

University of New Mexico planetary scientist Maya Elrick, who was also not involved in the study, says that while the oxygen depletion incidents coincided with extinctions, it is unclear how much of a role tree roots played. Phosphorus levels did gradually decrease overall as trees evolved, but she says this reduction may have already been occurring: "If it's a trend that was happening prior, you can't blame it on the plants."

Other hypotheses link the Devonian extinctions to massive volcanic eruptions, meteor impacts or disrupted ocean currents. Next, Smart's team plans to test its results using computer models to see whether terrestrial plants could have caused ocean-wide oxygen depletion and corresponding extinction—analysis that could also help predict modern algal blooms' impact.

Harmful blooms are on the rise in places such as the Gulf of Mexico, where agricultural fertilizers run off into the water. This leads to "dead zones" devoid of dissolved oxygen. "Those who don't learn from history are doomed to repeat it," Smart says. "In this case, we're studying history that's 400 million years old, but it can still teach us the same lessons."

—Joanna Thompson

Richard Jones/Science Source (*top*); John Cancalosi/Minden Pictures (*bottom*)

A male mason wasp's spiky pseudo stinger

ANIMAL BEHAVIOR

Wasp Defense

Male wasps wield an unusual protective strategy

Males of one wasp species use their genitals as an antipredator defense, mimicking females and jabbing potential attackers with spines mounted on their reproductive organs, a new study has found.

One day while studying the life cycle of mason wasps (*Anterhynchium gibbifrons*), researcher Misaki Tsujii of Kobe University in Japan felt a "pricking pain" as she handled one of the male insects. At first she thought she'd been stung—a surprise because most males of the insect order Hymenoptera, to which wasps belong, do not have stingers. But further examination showed that the jab likely came from two sharp protrusions, one on each side of the male wasp's genitalia. Rather than aiding in mating, these spines seem to serve the purpose of poking predators—and a new study by Tsujii and Kobe University insect ecologist Shinji Sugiura explores how.

"This study highlights the significance of male genitalia as an antipredator defense and opens a new perspective for understanding the ecological role of male genitalia in animals," says Sugiura, lead author of the paper published in *Current Biology*.

To confirm that pseudo stinging is used as a defense, the researchers placed wasp females, intact wasp males and wasp males whose genitalia had been removed in tanks with species of known wasp-eating tree frogs and pond frogs. The frogs devoured all 17 male wasps without genitalia. Pond frogs ate every wasp they encountered, but 35 percent of the intact male wasps were able to fight off tree frog predation with pseudo stings, causing the frogs to spit them out. Eighty-seven percent of the female wasps escaped the tree frogs as well.

Justin Schmidt, a stinging insect expert at University of Arizona and author of the book *The Sting of the Wild,* says that the males' pseudo stinging probably contributed to the experimental results. The frogs' somewhat small size, relative to the wasps, and the size difference between male wasps and naturally larger females were also likely factors. Schmidt, who was not involved in the new study, adds that it's not surprising that wasps with their whole genitals removed were less effective at fighting the frogs—and that he'd like to see the experiment replicated with wasps that had only the spines removed. Removing the entire apparatus, he notes, might be "awfully traumatic" for the wasps.

The male wasps may gain an evolutionary advantage by acting like females, whose stings inject venom and cause serious harm. To scare a predator into spitting it out, a male wasp "doesn't actually have to do the damage," Schmidt says. "It has to trick us into thinking that it's doing the damage."

Few other animal species have been shown to use their genitals as a defense mechanism, the authors write in their study—although hawk moths occasionally use special scales on their genitals to produce ultrasonic noises that are hypothesized to confuse predatory bats.

—Grace van Deelen

Shinji Sugiura

ASTRONOMY

Star Child

"Baby" galaxy could provide a glimpse into the early universe

A galaxy that is just emerging from hiding may be one of the youngest ever discovered, offering a potential portal to the secrets of the early universe. Aptly named "Peekaboo," the galaxy moved from behind a bright star (from our perspective) only within the past 50 to 100 years. But it's not just the galaxy's relatively recent appearance that has astronomers excited. In results published in *Monthly Notices of the Royal Astronomical Society*, scientists report that Peekaboo appears to have a significant lack of old stars. The new measurements suggest the dwarf galaxy may have formed billions of years after the big bang—much later than other galaxies close to ours.

"Pretty much every galaxy in the nearby universe has very, very old stars dating back to shortly after the big bang," says Gagandeep Anand, an astronomer at the Space Telescope Science Institute and co-author of the new study. As stars age, they create heavier elements, including metals. Peekaboo is one of just three comparatively nearby galaxies that astronomers have found to be extremely metal-poor—and at 22 million light-years away, it's by far the closest, making it favorable for further study.

Peekaboo galaxy shimmers to the right of a foreground star.

NASA, ESA and Igor Karachentsev/ SAO RAS; Image processing: Alyssa Pagan/ STScI

Astronomers first spotted a hint of the Peekaboo galaxy in 2001 during an all-sky survey, but the glare of a closer star largely obscured it from additional scrutiny. High-quality images taken by the Hubble Space Telescope in 2020 confirmed the partially hidden object to be a dwarf galaxy, and later optical observations revealed a lack of elements heavier than hydrogen and helium—suggesting that Peekaboo's conditions could mimic those of galaxies in the early universe.

Researchers don't yet know whether Peekaboo's metal-poor state definitively

HEALTH

Preeclampsia Prediction

New test assesses risk of life-threatening pregnancy disease

Even after thousands of studies, questions still linger about one of the most common diseases unique to pregnancy: preeclampsia. This disorder leads to dangerously high blood pressure in about 5 percent of U.S. pregnancies, with significantly higher rates in Black women. And it is becoming more common.

The only known cure is delivery, which creates a serious dilemma: the longer that people with preeclampsia remain pregnant, the sicker they get—but the longer a fetus gestates, the healthier it will be at birth. It is challenging for doctors to predict how intense a case will be in order to make individual treatment decisions.

A study in *NEJM Evidence* offers a way to predict whether pregnancy-related high blood pressure will deteriorate into severe preeclampsia, which can cause organ failure, vision loss and stroke. The new research focused on the balance between two pregnancy proteins, says lead author Sarah Kilpatrick, chair of obstetrics and gynecology at Cedars-Sinai Medical Center in Los Angeles. A high level of the protein PIGF (placental growth factor), which stimulates placental growth, is good. A high level of the protein sFlt-1 (soluble fms-like tyrosine kinase) is bad—and is known to rise well before a patient shows signs of preeclampsia. But high sFlt-1 numbers alone don't predict progression to a serious case.

To determine how the proteins' levels align with sickness, Kilpatrick's team studied 1,014 racially and geographically diverse high-risk patients between 23 and 35 weeks of gestation. All had already been admitted with high blood pressure to one of 18 urban or suburban hospitals.

lostinbids/Getty Images

The team found that when the ratio of the "bad" to the "good" protein was 40 or more, patients had a high chance of developing severe preeclampsia within two weeks. When the ratio was under 40, that chance was less than 5 percent. Kilpatrick suggests doctors could monitor a high-risk patient at home if the ratio is, say, 10, whereas someone with a ratio of 100 could be transferred

indicates its age. "There are other possibilities to consider as well," says Rutgers University astrophysicist Kristen McQuinn, who was not involved in the new study. One alternative possibility she suggests is that Peekaboo, as a dwarf galaxy, has a relatively weak gravitational pull that allowed its heavy metals to be expelled by galactic winds.

Current measurements don't suggest that the galaxy has any stars older than two billion or three billion years, but Anand notes that follow-up observations, perhaps with the ultrapowerful James Webb Space Telescope, would allow the researchers to search for fainter stars as old as 13 billion years. If found, such stars would call Peekaboo's youth into question.

But if the Peekaboo galaxy is as young as the researchers think it could be, it would be one of the best laboratories available to study the way the universe was closer to the big bang. Researchers could come away with a better understanding of the physics of gas cooling and star formation in an environment like the early universe, McQuinn says.

—Allison Gasparini

to a hospital that can manage preeclampsia complications as well as a preterm baby. "For an incredibly complicated disease, that's really the clinical benefit of knowing this risk," Kilpatrick says. "To me, that's probably the most important thing."

Right now there is no fast, decisive preeclampsia test, says William Grobman, a specialist in maternal-fetal medicine at the Ohio State University who was not involved in the research. Although this study doesn't remove all uncertainty, he says, it offers clinicians "a better understanding of who is going to deteriorate with that condition in a given period of time." Grobman looks forward to seeing if the results can be replicated. Kilpatrick, meanwhile, views this study as a key step toward FDA approval for such a test.

—Cari Shane

PALEONTOLOGY

Pockets of Survival

Key air sacs evolved more than once in dinosaurs' bones

Some of the largest and most ferocious dinosaurs of all time had an anatomical secret to their success. Like many modern birds, *Tyrannosaurus, Apatosaurus* and other giants had complex networks of air sacs that grew out of their throats and lungs and into their bones. The resulting porousness made them lighter, saving energy while maintaining bone strength. The sacs also let the dinosaurs breathe more efficiently and may even have aided cooling. But researchers have been unsure of when and how this valuable adaptation first emerged in the animal kingdom.

Paleontologists have found these air sacs in flying reptiles called pterosaurs, in theropod dinosaurs such as *Allosaurus,* and in long-necked dinosaurs, including *Diplodocus.* The sacs' presence can be detected from indentations and cavities in fossilized bones, even when the soft tissues are long gone. A new study in *Scientific Reports* suggests that rather than evolving air sac systems more than 235 million years ago, in the last common ancestor of dinosaurs and pterosaurs, the different lineages each developed these systems independently.

"Animals with air sacs have a tremendous advantage compared to us mammals," says paleontologist Tito Aureliano of the University of Campinas in Brazil, lead author of the new study. Many of dinosaurs' unique features, he notes, were made possible by these systems.

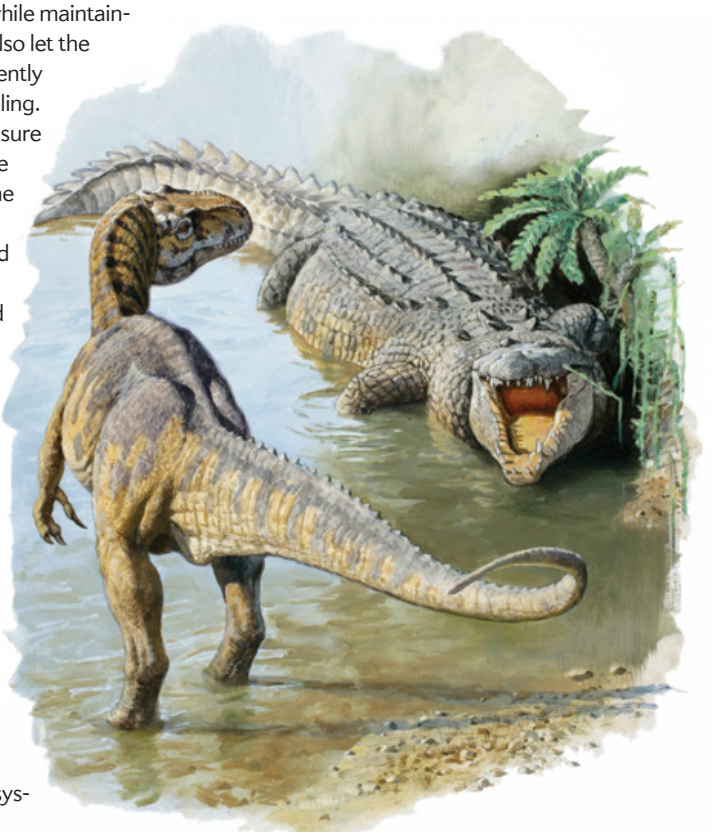
To explore the sacs' origins, the researchers turned to bones from three ancestral dinosaur species. Using CT scans and examining the bones' exteriors, they looked for openings or pockets that could house air sacs. They then compared the bones with those of other animals such as modern alligators and deer, which are known to lack these structures.

The researchers were surprised to find that the early dinosaur bones were more similar to those of alligators and deer than to those of the dinosaurs' later descendants. "Prior to this study, it looked unlikely to me that invasive air sacs would have evolved three times independently" in separate dinosaur lineages, Aureliano says—but the new results suggest that scenario.

This work confirms that the early dinosaurs did not have these extensive air sac systems, says Ohio University paleontologist Patrick O'Connor, who was not involved in the new study. That doesn't mean that they had no air sacs at all, he adds, noting that some modern birds, such as ducks, have more minimal arrangements. Instead the study most likely indicates that air sacs invaded the bone multiple times independently, as the reptiles became larger and more diverse.

"New fossils are showing more and more cases of convergent evolution," Aureliano says, suggesting that part of what made dinosaurs so successful was this repeated development of key traits.

—Riley Black



James Gurney

TECH

Taste Changers

High-tech cutlery tweaks the flavor of food

Foods high in sugar and salt can be unhealthy, but these additives are too delicious for many to give up. What if people could somehow enjoy these compounds' tastes without actually eating them? A student team has now designed a spoon with a structure that stimulates taste buds to produce a sensation of sweetness—without adding calories or chemicals. The project follows previous work involving flavor-enhancing cutlery, such as chopsticks that amplify saltiness with a mild electric current.

The five undergraduate and graduate research students wanted to develop their new spoon for people with disorders such as diabetes, which affects 11.3 percent of the U.S. population. Many with this condition have to limit their sugar intake.

The spoon, called Sugarware, would have several bumps on its underside, creating a greater surface area to press against the tongue, and its surface would be coated with a permanent layer of molecules called ligands. These ligands bind with cell-surface receptor proteins that typically react to sugar molecules or artificial sweeteners, triggering a cascade of nerve signals that cause the brain to register a sensation of sweetness. A diner could thus "stimulate sweetness receptors … without actual injection of sugar or artificial sweeteners," the team explained during the 2022 Biodesign Sprint, an online educational competition. Sugarware won its designers the runner-up spot in the student category.

The researchers cite two influences for Sugarware. "We got our design inspirations from a Korean designer, Jinhyun Jeon," says Shiyu Xu, who was a graduate researcher in animal science at Cornell University when the project was developed. Jeon's work on synesthesia has explored how the senses can affect one another while eating. In one project, "she was using a similar kind of knobby spoon to experiment [with] how the eating experience can change and can get affected by those spoons," says team member Weiran Tao, a graduate telecommunications researcher at New York University.

Xu says the Sugarware team also looked at a Japanese study, by Homei Miyashita of Meiji University and his colleagues, that found ways to stimulate salt receptors in the tongue. With the company Kirin Holdings, Miyashita's group developed specialized chopsticks: a weak electric current runs through this novel cutlery, shifting the sodium ions in a mouthful of food to excite the tongue's salt receptors. The researchers reported that their chopsticks could increase diners' perception of salt by up to one and half times. A U.S. company, Taste Boosters, took a similar microcurrent-based approach with a utensil called SpoonTEK.

These ideas are similar to Sugarware in that they all use utensils to enhance taste without a user having to actually consume any salt or sugar. "But the mechanism for stimulating the taste buds is completely different in Sugarware," Xu says: it uses texture and taste-bud-stimulating molecules rather than electricity.

The Sugarware researchers are also interested in reducing the need for artificial sweeteners. These compounds are integrated into many foods and "consumed by hundreds of millions worldwide with the notion that they generate the sweetest sensation without having the caloric price," says Eran Elinav, a microbiome researcher at Israel's Weizmann Institute of Science, who is not involved with the student project. But these chemicals do have an effect on the body. In 2014 Elinav's team gave mice the artificial sweetener saccharin and found that the rodents' gut microbiome interacted with the sweetener, affecting the animals' regulation of glucose levels. Other research has demonstrated that humans who consume some sugar substitutes also experience changes in the gut microbiome, as well as spikes in blood glucose. "Artificial sweeteners are clearly not inert in the human body," Elinav says. Because Sugarware would stimulate a sweetness reaction without requiring users to consume anything, it might be able to sidestep this type of interaction.

The idea is "very creative," says one of the Biodesign Sprint judges, Paola de Almeida, who is global director of corporate innovation at candymaker Mars. But the product's commercial success would require a significant behavioral shift among consumers: instead of adding the usual sugar or artificial sweeteners, "now we're saying, 'Use this utensil,'" de Almeida says.

It remains to be seen whether flavor-enhancing utensils will catch on. The Japanese team does not plan to commercialize its electric chopsticks until later this year, and the Sugarware researchers are still working on a prototype. Part of their contest prize includes a mentorship from Mars staff.

But if you want to play around with cutlery and flavor right now, you don't need specially designed forks or knives. Previous research shows that the weight, color and shape of normal utensils can change how people perceive food's taste. So grab a variety of cutlery and hold an independent taste test. You may find some spoons are sweeter than others, even if they're bump-free.

—Saugat Bolakhe

kzenon/Getty Images

Ceres Accelerator

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How companies are— and are not— leading on U.S. climate policy

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Photo Credit: Adobe Stock

Kate Gleason is author of two science poetry collections, *Laika in Space* (Main Street Rag Press, 2020) and *Measuring the Dark* (Zone 3 Press, 2009). Her work has also appeared in *Best American Poetry, Los Angeles Times Book Review, Southern Review, Rattle, Green Mountains Review, Alaska Quarterly Review, Crab Orchard Review, Notre Dame Review,* and others. Gleason has led writing workshops for 30 years.

Jupiter's Moon Europa

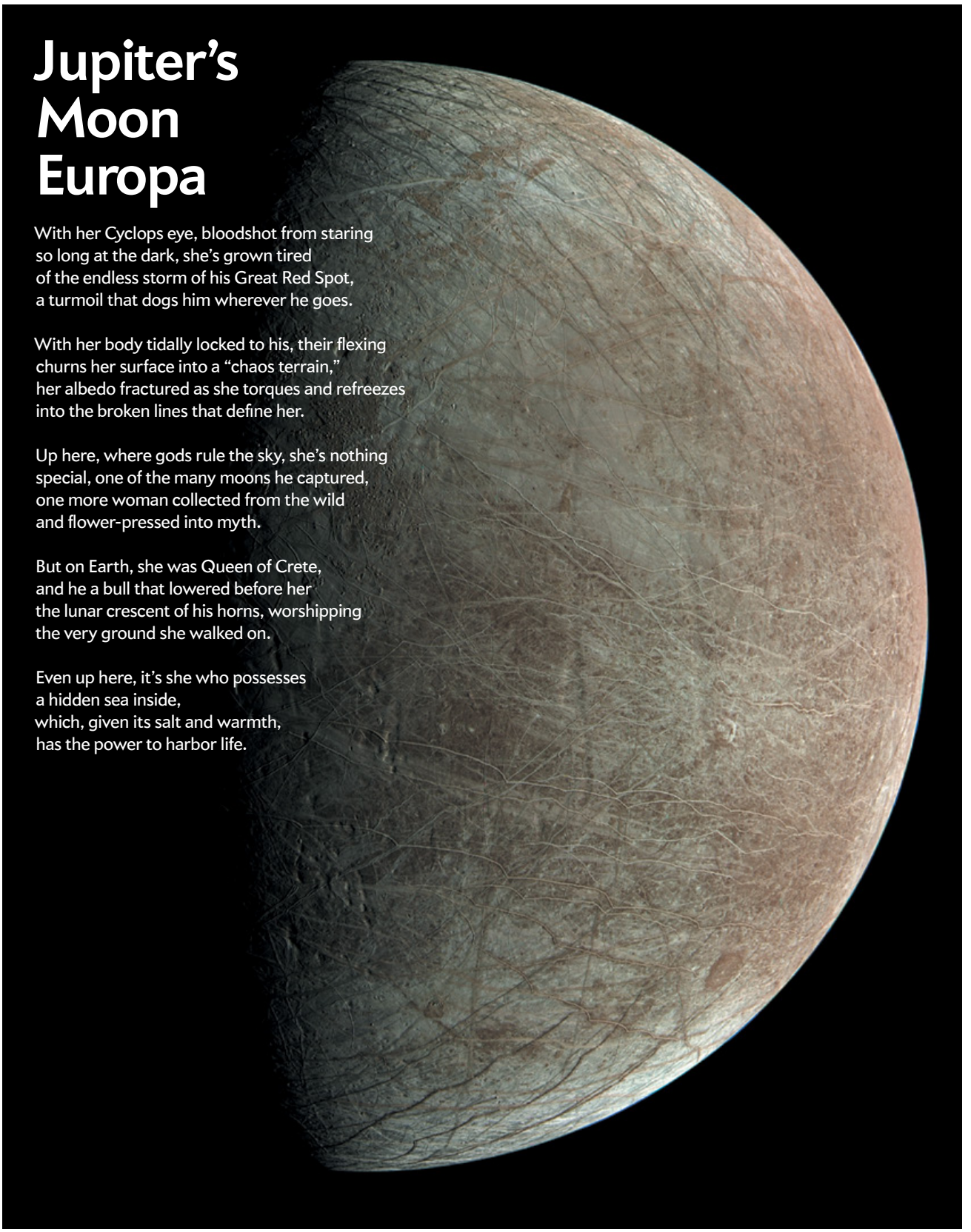
With her Cyclops eye, bloodshot from staring
so long at the dark, she's grown tired
of the endless storm of his Great Red Spot,
a turmoil that dogs him wherever he goes.

With her body tidally locked to his, their flexing
churns her surface into a "chaos terrain,"
her albedo fractured as she torques and refreezes
into the broken lines that define her.

Up here, where gods rule the sky, she's nothing
special, one of the many moons he captured,
one more woman collected from the wild
and flower-pressed into myth.

But on Earth, she was Queen of Crete,
and he a bull that lowered before her
the lunar crescent of his horns, worshipping
the very ground she walked on.

Even up here, it's she who possesses
a hidden sea inside,
which, given its salt and warmth,
has the power to harbor life.



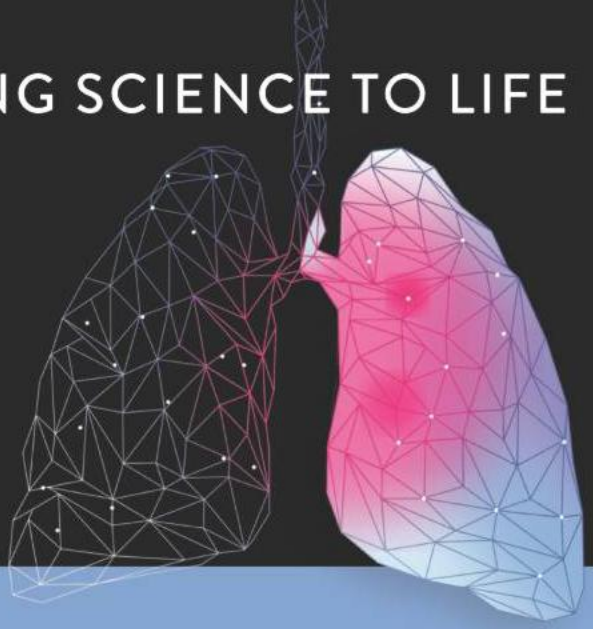
NASA/JPL-Caltech/SwRI/MSSS

AGENDA SETTERS: BRINGING SCIENCE TO LIFE

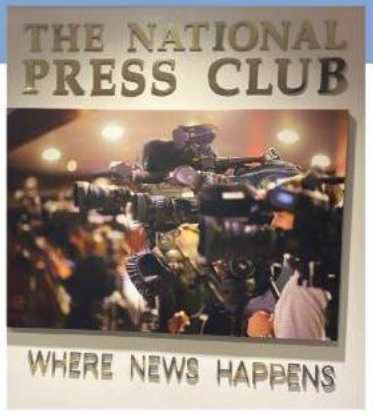
THE HUNT FOR A VERSATILE RESPIRATORY VIRUS KILLER

THE NATIONAL PRESS CLUB

WASHINGTON, DC | DECEMBER 6, 2022



SCIENTIFIC AMERICAN'S Custom Media division hosted an engaging event in collaboration with Synairgen on Tuesday, December 6th in Washington, DC at the National Press Club. The forum, *The Hunt for A Versatile Respiratory Virus Killer* attracted a rich panel of opinion leaders in the academic and industry space.



The event opened with remarks by the moderator, Jeremy Abbate, VP and Publisher, Scientific American, followed by an inspiring and thought-provoking discussion exploring respiratory viral infections such as influenza, RSV and coronaviruses, which have plagued humanity for a millennium. The panel discussed new approaches to antivirals that could strengthen the human immune response and offer protection against a wide range of viral pathogens and highlighted the barriers that need to be broken down in order to achieve success. The panel included **Charles Dela Cruz**, MD, PhD, ATSF, Yale School of Medicine, and American Thoracic Society Representative, **Rick Bright, PhD**, International Expert on Preparedness and Response and **Phillip Monk, PhD**, Chief Scientific Officer, Synairgen.

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*.

Reproduction Disrupters

Ubiquitous chemicals called phthalates may harm sperm and pregnancies

By Claudia Wallis

Epidemiologist Carmen Messerlian does her best to avoid potentially harmful chemicals. As she glanced around her home a few days before the new year began, she took inventory of her seasonal exposure to substances called phthalates, which are widely used to make plastic more flexible and durable. They also bind fragrances to products ranging from candles to laundry detergent and cosmetics. "I'm anticandle," she said, but she had three or four scenting her home. It was, after all, the season. Then there were the soft plastic earbuds she had picked up at an airport and the shiny enamel sparkling on her fingernails. "You break all your rules over the holidays because you want to look good and you want your house to look and smell nice." But she certainly knows better.

At Harvard University's T. H. Chan School of Public Health, Messerlian has conducted more than a dozen studies indicating that certain phthalates impair reproductive health. Her work, and that of many others, has demonstrated that men with higher concentrations of phthalates in their urine (a measure of exposure) have lower sperm counts and poorer sperm motility than men with less of these substances. Women with high levels of exposure are more likely to have fertility problems, miscarriages, preterm labor and low-birth-weight babies. Recent research also implicates the chemicals in the growth of uterine fibroids—noncancerous tumors that can cause pain, bleeding, diminished fertility and pregnancy complications. In 2017 the U.S. government banned the use of certain phthalates in toys because they were linked to changes in male genital tract development, but regulatory agencies have been slow to limit their use in other products. As evidence of harm continues to build, many researchers see a need for greater regulation and more public awareness.

The case against phthalates is complicated because researchers cannot ethically expose people to the chemicals in order to study the effects. The evidence is therefore based on animal research and observational data among humans, including decades of studies comparing health outcomes among people with higher versus lower levels of exposure. Adding to the complexity are the large variety of phthalates, the difficulty in separating their effects from those of other environmental chemicals that similarly disrupt human hormones and reproductive tissues, and the advent of phthalate substitutes that are not necessarily safer than the originals.

There are certain windows of time when phthalate exposure is particularly concerning, research suggests. These include the preconception period when eggs and sperm mature, pregnancy and gestation, and early childhood. Last year a large study led by Kelly Ferguson of the National Institute of Environmental Health Sciences found that high exposure to each of four types of phthalates during pregnancy was associated with a 12 to 16 percent increase in the probability of giving birth three or more weeks early—which can put newborns at risk. The study, which pooled data from more than 6,000 pregnancies, was the largest ever to examine the issue, Ferguson says. It is also one of the first "to address this question in a diverse population," she says, an important consideration because lower-income and marginalized minorities appear to have greater exposure to the chemicals. She and her colleagues estimate that cutting the study group's exposure to phthalates in half would have reduced the incidence of preterm births from 90 per 1,000 live births to 79 per 1,000.

To achieve a reduction in phthalates, "we need a multipronged approach," says Russ Hauser, an expert on phthalates and reproductive health at Harvard. "That includes federal regulations to reduce and ban their use, increased public knowledge so people can make informed decisions, and more transparent labeling of consumer products." The Food and Drug Administration is currently reviewing the safety of phthalates in plastics used to process and wrap food. The Environmental Protection Agency is still determining how best to evaluate the risks posed by phthalates. But the regulatory process moves at a sluggish pace.

Messerlian suggests that people can lower their exposure by making small changes in their homes and habits, such as replacing scented detergents and skin creams with fragrance-free varieties and buying cold cuts wrapped in paper at a deli counter rather than items prepackaged in plastic. Such actions also can pressure industry to make safer products. Messerlian's website, seed-program.org, offers other tips for reducing exposure. "Even if you swap out one or two things," she says, "that's a win." SA

Illustration by Jay Bendt

Why 2 Is the Best Number

Mathematician Melanie Matchett Wood seeks creative ways of solving open math problems

By Rachel Crowell

"Many people don't realize that there are math questions that we don't know how to answer," says mathematician Melanie Matchett Wood of Harvard University and the Radcliffe Institute for Advanced Study at Harvard. She recently won a MacArthur Fellowship (or "genius grant") for her work seeking solutions to some of those open problems. The award honors "extraordinarily talented and creative individuals" with an $800,000 "no strings attached" prize.

Wood was recognized for her research "addressing foundational questions in number theory," which focuses on whole numbers—1, 2, 3, and so on, rather than 1.5 or $^{3}/_{8}$, for instance. Prime numbers—whole numbers that are greater than 1 and divisible only by 1 and themselves (such as 2 and 7)—also fascinate her. Much of her work uses arithmetic statistics, a field that focuses on discovering patterns in the behavior of primes and other types of numbers. She has tackled questions about the nature of primes in systems of numbers that include the integers (these are 0, the whole numbers and negative multiples of the whole numbers) as well as some other numbers. For example, the system $a + b\sqrt{2}$ (where a and b are integers) is such an extension. She also uses a smorgasbord of tools from other areas of math to help solve challenging questions.

"The nature of the work is 'Here's a question that we have no method to solve. So come up with a method,'" Wood says. "That's very different from most people's experience of mathematics in school. It's like the difference between reading a book and writing a book."

Illustration by Aya Eltilbani

Rachel Crowell is a Midwest-based writer covering science and mathematics.

Wood spoke to Scientific American about her recent win, her favorite mathematical tools and her methods for tackling "high-risk, high-reward" problems.

[*An edited transcript of the interview follows.*]

What makes a mathematical question intriguing?

I'm drawn in by questions about foundational structures, such as the whole numbers, that we don't really have any tools to answer. These structures of numbers underpin everything in mathematics. Those are hard questions, but that is certainly exciting to me.

If you were to build an imaginary tool belt with some of the mathematical instruments and ideas you find most useful in research, what would you put in it?

Some of the key tools are being willing to look at a lot of concrete examples and try to see what phenomena are emerging—bringing in other areas of math. Even though, maybe, I work on a question in number theory about something like prime numbers, I use tools from across mathematics, from probability, from geometry. Another is the ability to try things that don't work but learn from those failures.

What's your favorite prime number?

My favorite number is 2, so it's definitely my favorite prime number.

It seems so simple. Yet such rich mathematics can come out of just the number 2. For example, 2 is kind of responsible for the concept of whether things are even or odd. There is a tremendous richness that can come from just considering things in complicated situations, about whether numbers are even or odd. I like it because even though it's small, it's very powerful.

Here's a fun story: I was an undergraduate at Duke University, and I was on our team for the William Lowell Putnam Mathematical Competition. For the math team, we have shirts with numbers on the back. Many people have numbers like pi or $\sqrt{5}$—fun irrational numbers. But mine was 2. When I graduated from Duke, they retired my math jersey with the number 2 on it.

Have you always approached your number theory research from the perspective of arithmetic statistics?

Starting with my training in graduate school, I have always come from this arithmetic statistics perspective, in terms of wanting to understand the statistical patterns of numbers, including primes and the ways they behave in larger number systems.

A big shift for me, especially lately, has been bringing more probability theory into the methods for working on these questions. Probability theory, classically, is about distributions of numbers. You could measure the length of fish in the ocean or performance of students on a standardized test. You get a distribution of numbers and try to understand how those numbers are spread out.

For the kind of work that I'm doing, we need something that is more like a probability theory, where you're not just measuring a number for each data point. You have some more complex structure—for example, maybe it's a shape. From a shape, you might get numbers, such as "How many sides does it have?" But a shape is not just a number or a couple of numbers; it has more information than that.

What does winning this MacArthur prize mean to you?

It's a tremendous honor. It is, in particular, exciting to me because the MacArthur Fellowship really celebrates creativity, and most people associate that more with the arts. But to make progress on math questions that no one knows how to answer also requires a lot of creativity. It makes me happy to see that recognized in mathematics.

Harvard mathematician Michael Hopkins described your work on three-dimensional manifolds as "a dazzling combination of geometry and algebra." What is a three-dimensional manifold?

It's a three-dimensional space that, if you just look around in a small area, looks like the kind of three-dimensional space that we're used to. But if you go on a long walk in that space, it might have surprising connections. For instance, you walk in one direction and end up back where you started.

That might sound kind of wild. But think about two different two-dimensional spaces. There's a flat plane, where you can walk straight in every direction, and you'll never come back to where you start. Then there's the surface of a sphere: if you walk in some direction, you'll eventually come back around. We can picture those two different kinds of two-dimensional spaces because we live in three-dimensional space. Well, there are in fact three-dimensional spaces that have these funny properties that are different from the three-dimensional space that we're used to interacting with.

What is the essence of the work you're doing on these spaces?

We find that certain kinds of three-dimensional spaces exist with certain properties having to do with how you can walk around and come back to where you started in them. We don't exhibit, construct or describe those spaces. We show that they exist using the probabilistic method.

We show that if you take a random space in a certain way, there is some positive probability that you'll get a certain kind of space. This is a beautiful way that mathematicians know something exists without finding it. If you prove that you can do something randomly, and there's some positive chance, no matter how small, that you can get it from some random construction, then it must exist.

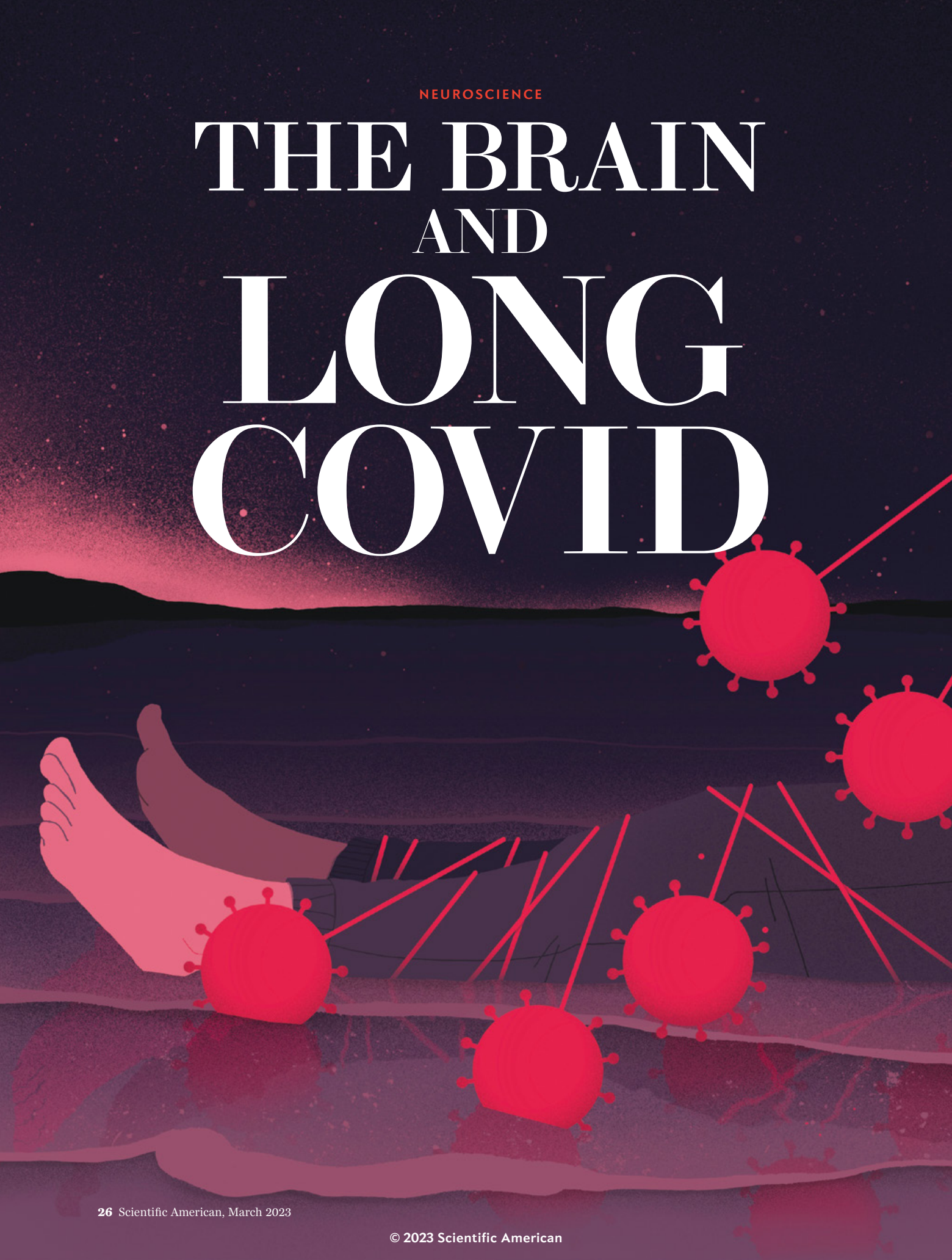
We use these tools to show that there exist three-dimensional spaces that have certain kinds of properties. Even though we don't know of any examples, we prove they exist.

In 2021 you won a $1-million Alan T. Waterman Award from the U.S. National Science Foundation. The *Harvard Gazette* noted that you planned to use that funding to tackle "high-risk, high-reward projects." What are some examples?

This direction of developing probability theory for more complicated structures than numbers is an example. It's high risk because it's not clear that it's going to work, or maybe it won't turn out to be as useful as I hope. There's no clear blueprint for where it will go. But if it does work out, it could be very powerful. SA

NEUROSCIENCE

THE BRAIN AND LONG COVID



Millions of people are still suffering long after infection. Now researchers are finding neurological causes for their symptoms

By Stephani Sutherland

Illustration by Stephanie Shafer

Stephani Sutherland is a neuroscientist and science journalist based in southern California. She wrote about the causes of autoimmune diseases in our September 2021 issue. Follow her on Twitter @SutherlandPhD

TARA GHORMLEY HAS ALWAYS BEEN AN OVERACHIEVER. SHE FINISHED AT THE TOP of her class in high school, graduated summa cum laude from college and earned top honors in veterinary school. She went on to complete a rigorous training program and build a successful career as a veterinary internal medicine specialist. But in March 2020 she got infected with the SARS-CoV-2 virus—just the 24th case in the small, coastal central California town she lived in at the time, near the site of an early outbreak in the COVID pandemic. "I could have done without being first at this," she says.

Almost three years after apparently clearing the virus from her body, Ghormley is still suffering. She gets exhausted quickly, her heartbeat suddenly races, and she goes through periods where she can't concentrate or think clearly. Ghormley and her husband, who have relocated to a Los Angeles suburb, once spent their free time visiting their "happiest place on Earth"—Disneyland—but her health prevented that for more than a year. She still spends most of her days off resting in the dark or going to her many doctors' appointments. Her early infection and ongoing symptoms make her one of the first people in the country with "long COVID," a condition where symptoms persist for at least three months after the infection and can last for years. The syndrome is known by medical professionals as postacute sequelae of COVID-19, or PASC.

People with long COVID have symptoms such as pain, extreme fatigue and "brain fog," or difficulty concentrating or remembering things. As of February 2022, the syndrome was estimated to affect about 16 million adults in the U.S. and had forced between two million and four million Americans out of the workforce, many of whom have yet to return. Long COVID often arises in otherwise healthy young people, and it can follow even a mild initial infection. The risk appears at least slightly higher in people who were hospitalized for COVID and in older adults (who end up in the hospital more often). Women and those at socioeconomic disadvantage also face higher risk, as do people who smoke, are obese, or have any of an array of health conditions, particularly autoimmune disease. Vaccination appears to reduce the danger but does not entirely prevent long COVID.

The most common, persistent and disabling symptoms of long COVID are neurological. Some are easily recognized as brain- or nerve-related: many people experience cognitive dysfunction in the form of difficulty with memory, attention, sleep and mood. Others may seem rooted more in the body than the brain, such as pain and postexertional malaise (PEM), a kind of "energy crash" that people experience after even mild exercise. But those, too, result from nerve dysfunction, often in the autonomic nervous system, which directs our bodies to breathe and digest food and generally runs our organs on autopilot. This so-called dysautonomia can lead to dizziness, a racing heart, high or low blood pressure, and gut disturbances, sometimes leaving people unable to work or even function independently.

The SARS-CoV-2 virus is new, but postviral syndromes are not. Research on other viruses, and on neurological damage from the human immunodeficiency virus (HIV) in particular, is guiding work on long COVID. And the recognition that the syndrome may cause its many effects through the brain and the nervous system is beginning to shape approaches to medical treatment. "I now think of COVID as a neurological disease as much as I think of it as a pulmonary disease, and that's definitely true in long COVID," says William Pittman, a physician at UCLA Health in Los Angeles, who treats Ghormley and many similar patients.

Although 16 million U.S. sufferers is a reasonable estimate of the condition's toll, there are other, more dire assessments. A meta-analysis of 41 studies conducted in 2021 concluded that worldwide, 43 percent of people infected with SARS-CoV-2 may develop long COVID, with about 30 percent—translating to approximately 30 million people—affected in the U.S. Some studies have offered more conservative numbers. A June 2022 survey reported by the U.S. National Center for Health Statistics found that among adults who had had COVID, one in five was experiencing long COVID three months later; the U.K. Office for National Statistics put the estimate at one in 10. Even if only a small share of infections result in long COVID, experts say, they will add up to millions more people affected—and potentially disabled.

Most of the first recognized cases of long COVID were in patients who needed extended respiratory therapy or who had obvious organ damage that caused lasting symptoms. People reporting neurological symptoms were often overlooked or dismissed as traumatized by their initial illness and hospitalization. But as

"EVERYTHING FELL APART FOR ME," says Tara Ghormley, who has been struggling with long COVID since 2020.

2020 came to an end, says Helen Lavretsky, a psychiatrist at the University of California, Los Angeles, "we started getting to a place of sorting through what was really going on … and it became very evident at that time that neuropsychiatric symptoms were quite prevalent," most commonly fatigue, malaise, brain fog, smell loss and post-traumatic stress disorder, as well as cognitive problems and even psychosis.

Ghormley was in her late 30s and relatively healthy when she caught the virus, but she had underlying conditions—including rheumatoid arthritis and asthma—that put her at risk for severe COVID. She spent several days at home, struggling to breathe, and then she went to the hospital, where her blood pressure soared and her blood glucose dropped precipitously. She mostly recovered from this acute phase within a few weeks, but, she says, "I never really got better."

Soon after coming home from the hospital, Ghormley developed what her husband called "goldfish brain." "I'd put something down and have no idea where I put it," she recalls. "It kept happening over and over. I was thinking, 'This is getting weird.' My husband said I was not remembering anything. I'd try to talk, and I knew what I wanted to say, but I couldn't think of the word."

She also experienced tremors, dramatic mood swings and painful hypersensitivity to sounds. "My husband opening a paper bag felt like knives stabbing me in the ear," she recounts. Any exertion—physical or mental—left her exhausted and in pain. The changes were jarring to Ghormley, who prided herself on her sharp mind. "The thing that bothered me the most was that I was really having trouble thinking, speaking, remembering—trying to complete a task and having no idea what it was. Suddenly I had quite profound neurological deficits. Everything fell apart for me at that time. That was horribly traumatic … it kind of broke me. I didn't feel like me."

ROOTS OF DYSFUNCTION

AS A VETERINARY INTERNIST, Ghormley says, it's her job to problem solve when mysterious symptoms arise, including her own. "I was actively trying to find reasons and find what I could do." She theorized that some of her neurological symptoms might be the result of thrombotic events, blood clots that can cause mini-strokes. Several early studies showed that COVID attacks endothelial cells, which line blood vessels. That can lead to clotting and oxygen deprivation in multiple organs, including the brain. Even subtle disruption of endothelial cells in the brain could contribute to cognitive dysfunction.

One study found that in people with neurological COVID symptoms, the immune system seems to be activated specifically in the central nervous system, creating inflammation. But brain inflammation is probably not caused by the virus infecting that organ directly. Avindra Nath, who has long studied postviral neurological syndromes at the National Institutes of Health, found something similar in an autopsy study of people who died of COVID. "When you look at the COVID brain, you don't actually find [huge amounts of virus, but] we found a lot of immune activation," he says, particularly around blood vessels. The examinations suggested that immune cells called macrophages had been stirred up. "Macrophages are not that precise in their attack," Nath says. "They come and start chewing things up; they produce all kinds of free radi-

Photograph by Ewan Burns

cals, cytokines. It's almost like blanket bombing—it ends up causing a lot of damage. And they're very hard to shut down, so they persist for a long time. These are the unwelcome guests" that may be causing persistent inflammation in the brain.

Determining which patients have ongoing inflammation could help inform treatments. Early research identified markers that often are elevated in people with the condition, says Troy Torgerson, an immunologist at the Allen Institute in Seattle. Three cell-signaling molecules—tumor necrosis factor alpha, interleukin 6 and interferon beta—stood out in long COVID patients. But this pattern wasn't found in absolutely everyone. "We're trying to sort through long COVID patients and say, 'This would be a good group to take to trials of an anti-inflammatory drug, whereas this group may need to focus more on rehabilitation,'" Torgerson says. He led a study (currently released as a preprint, without formal scientific review by a journal) in which his team measured proteins from the blood of 55 patients. The researchers found that a subset had persistent inflammation. Among those people, they saw a distinct immune pathway linked to a lasting response to infection. "One subset of patients does appear to have an ongoing response to some virus," Torgerson says.

Isolated pockets of SARS-CoV-2 or even pieces of viral proteins may remain in the body well after the initial infection and continue to elicit an immune attack. The first solid evidence for "viral persistence" outside the lungs came in 2021 from researchers in Singapore who found viral proteins throughout the gut in five patients who had recovered from COVID as much as six months earlier. A study conducted at the University of California, San Francisco, found evidence for viral particles in the brains of people with long COVID. Scientists collected exosomes, or tiny packets of cellular material, released specifically from cells of the central nervous system. The exosomes contained pieces of viral proteins as well as mitochondrial proteins, which may indicate an immune attack on those vital cellular organelles. Amounts of such suspicious proteins were higher in patients with neuropsychiatric symptoms than in those without them.

The virus could linger in the brain for months, according to research conducted at the NIH and reported in *Nature* in December 2022. The autopsy study of 44 people who died of COVID found rampant inflammation mainly in the respiratory tract, but viral RNA was detected throughout the body, even in the brain, as long as 230 days after infection. Two other studies, both published last year in the *Proceedings of the National Academy of Sciences USA,* showed evidence that SARS-CoV-2 may infect astrocytes, a type of neural support cell, gaining entrance via neurons in the skin lining the nose.

Researchers are examining inflammatory signals in patients with long COVID in increasingly fine detail. A small study led by Joanna Hellmuth, a neurologist at U.C.S.F., found that patients with cognitive symptoms had immune-related abnormalities in their cerebrospinal fluid, whereas none of the patients without cognitive symptoms did. At the 2022 meeting of the Society for Neuroscience, Hellmuth reported that she had looked at more specific immune markers in people with cognitive symptoms and found that some patients had an elevated level of VEGF-C, a marker of endothelial dysfunction. Higher VEGF-C concentrations are associated with higher levels of immune cells getting into the brain, she says, and "they're not doing their normal function of maintaining the blood-brain barrier; they're distracted and perhaps activated." Although the studies are small, Hellmuth adds, they reveal "real biological distinctions and inflammation in the brain. This is not a psychological or psychosomatic disorder; this is a neuroimmune disorder."

What keeps the immune system in attack mode? According to Torgerson, "one option is that you've developed autoimmunity," in which antibodies produced by the immune system to fight the virus also mark a person's own cells for immune attack. The response to the virus "turns the autoimmunity on, and that doesn't get better even when the virus goes away," he says. Several studies have found evidence of autoimmune components called autoantibodies that interact with nerve cells in people with long COVID.

Clues about the inflammatory processes at work could point toward treatments for neurological symptoms. "If it's a macrophage-mediated inflammatory process … intravenous immunoglobulin could make a difference [to] dampen the macrophages," Nath says. The treatment, referred to as IVIg, contains a cocktail of proteins and antibodies that can mitigate an overactive immune response.

IVIg can also be used to block autoantibodies. And a therapy called rituximab that targets antibody-producing B cells provides "a time-tested therapy for a lot of autoantibody-mediated syndromes," Nath says. Another strategy is to use corticosteroids to dampen immune activity altogether, although those drugs can be used for only a limited time. "That's a sledgehammer approach, and you can see if it makes a difference. At least it gives you an idea that, yes, it's an immune-mediated phenomenon, and now we need to find a better way to target it," Nath says.

If the virus does hang around in some form, antiviral medications could potentially clear it, which might help resolve neurological symptoms. That's the hope of scientists running a clinical trial of Paxlovid, Pfizer's antiviral drug for acute COVID.

A CHRONIC FATIGUE CONNECTION?

POSTVIRAL SYNDROMES have been documented for more than a century, arising after infection with viruses from HIV to the flu. Epstein-Barr virus, which causes mononucleosis, is one of several viruses linked to a condition called myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), which is estimated to affect at least one and a half million people in the U.S. ME/CFS bears striking resemblances to long COVID, with symptoms such as immune system dysregulation, fatigue and cognitive dysfunction. "One of the patterns we see is patients who definitely meet the criteria for ME/CFS. This is something we are seeing and treating all the time" in long COVID patients, Pittman says. ME/CFS can be severe, with some people losing mobility and becoming bedbound.

Nath, who also studies ME/CFS, says that "we think mechanistically they are going to be related." Researchers suspect that ME/CFS, like some cases of long COVID, could be autoimmune in nature, with autoantibodies keeping the immune system activated. ME/CFS has been difficult to study because it often arises long after a mild infection, making it hard to identify a viral trigger. But with long COVID, Nath says, "the advantage is that we know exactly what started the process, and you can catch cases early in the [development of] ME/CFS-like symptoms." In people who have had ME/CFS for years, "it's done damage, and it's hard to reverse that." Nath speculates that for long COVID, if doctors could study people early in the illness, they would have a better chance of reversing the process.

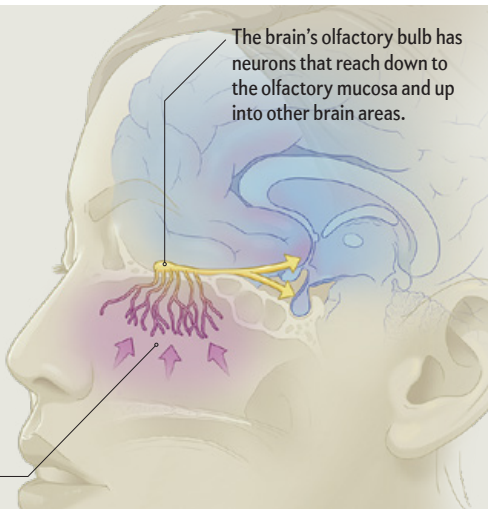
Torgerson hopes that researchers will ultimately come to bet-

How SARS-CoV-2 Can Harm the Brain and Nerves

Researchers have found evidence that the COVID-causing virus, SARS-CoV-2, can reach the brain and other parts of the central nervous system. This contact may lead to persistent and devastating symptoms of long COVID, which—more and more scientists say—appears to be a neurological disease. Cognitive symptoms include difficulty thinking and remembering things. And physical ailments, such as pain, extreme fatigue and a racing heartbeat, are tied to problems with the autonomic nervous system, which ordinarily runs our bodies on autopilot.

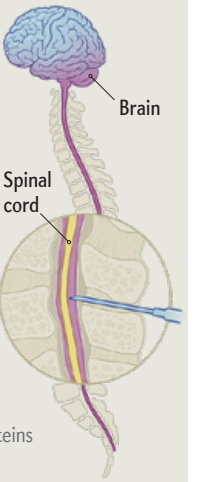
Into the Brain

Genetic material from the virus, and viral proteins, has been found in cells that line passages deep within the nose. Neurons project into this lining, and the virus can travel through them into brain areas that control breathing and the heart. It can also infect astrocytes, a crucial neural support cell.



Immune System Abnormalities

Studies of long COVID patients with cognitive problems found signs that immune system cells from blood vessel walls had moved into the brain. These cells are not supposed to be in that organ and can cause damaging inflammation there. Patients without cognitive difficulties had lower levels of this unusual immune activity.



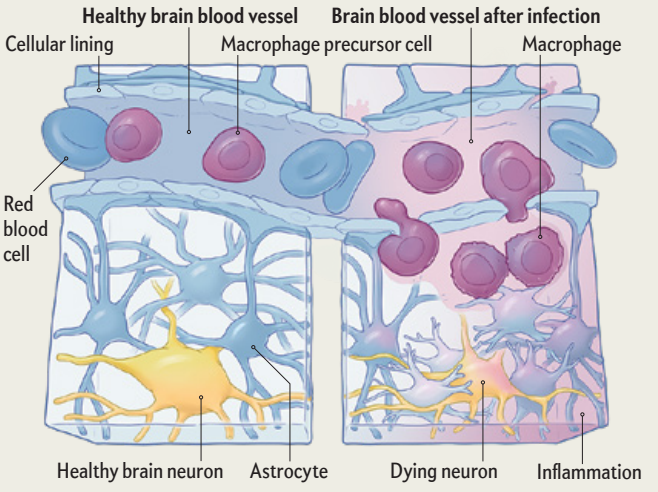
Cerebrospinal fluid collected from patients' spinal cords via a lumbar puncture (spinal tap) included proteins associated with inflammation.

Lingering Virus

In COVID patients with neuropsychiatric symptoms, proteins specific to SARS-CoV-2 appeared in small packets of cellular material that came from their neurons and astrocytes as long as three months after initial infection. This indicates the virus persists in the central nervous system for a long time. Another study found genetic material from the virus in a patient's brain almost eight months after symptoms began.

Macrophage Attack

Brains of people who have died from COVID show signs of an assault from macrophages, a type of immune system cell that reacts to invaders such as viruses. The cells surround and destroy the interlopers. But macrophages also damage nearby tissue, especially around brain blood vessels, says Avindra Nath, a neurologist at the National Institutes of Health.



Sources: "Neurovascular Injury with Complement Activation and Inflammation in COVID-19," by Myoung-Hwa Lee et al., in *Brain*, Vol. 145; July 2022 (*blood vessel reference*); "Olfactory Transmucosal SARS-CoV-2 Invasion as a Port of Central Nervous System Entry in Individuals with COVID-19," by Jenny Meinhardt et al., in *Nature Neuroscience*, Vol. 24; February 2021 (*nasal passage reference*)

ter understand ME/CFS because of COVID. "COVID has been more carefully studied with better technology in the time we've had it than any other infectious disease ever. I think we'll learn things that will be applicable to other inflammatory diseases driven by infection followed by an autoimmune process."

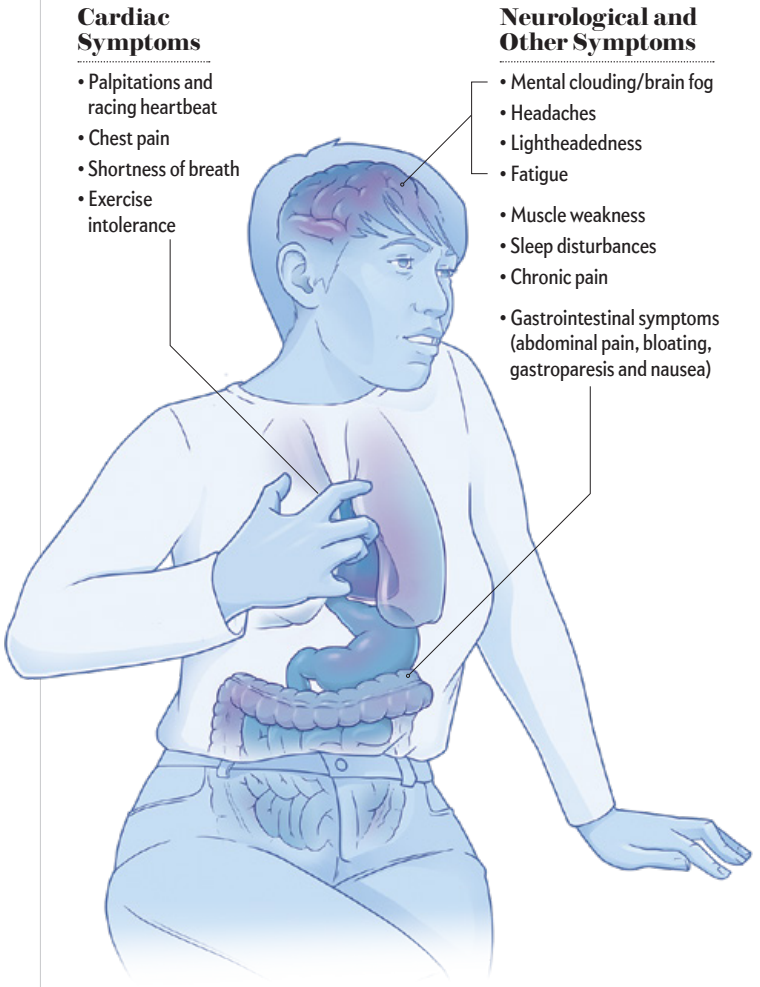
TEAM TREATMENT

GHORMLEY, AFTER MONTHS of illness, sought care at UCLA Health's long COVID clinic, among the country's few comprehensive, multidisciplinary programs for people with this syndrome. Even though her symptoms are rooted in nervous system dysfunction, she needed an array of medical specialists to treat them. The clinic grew out of a program aimed at coordinating care for medically complex COVID patients, says its director Nisha Viswanathan, an internist and primary care physician. In following up with COVID patients after several months, she realized that "we had a group of patients who still had symptoms. There was no understanding around the condition; we were just trying to see what we could offer them." Viswanathan and others convened a biweekly meeting of UCLA Health doctors in pulmonology, cardiology, neurology, psychiatry and other specialties to discuss individual cases and overall trends.

Graphic by Now Medical Studios

COVID from the Brain to the Heart

One common affliction of people with long COVID is a heart condition called postural orthostatic tachycardia syndrome, or POTS. When a person stands up or even sits up after lying down, their heart starts racing. It accelerates by 30 beats per minute or more. This makes it hard to breathe or think ("brain fog"), and it leads to exhaustion, headaches and other symptoms. What's happening is that the brain and nervous system are losing control of the heart, something that is ordinarily managed unconsciously and automatically.



Long COVID Connections

Medical scientists have several theories about the ways that the COVID-causing virus can lead to POTS. One idea is that when a person is infected, fever, sweating and spending a long time in bed can reduce blood volume. The heart can also lose strength. To compensate and get more blood around the body, the brain gets the heart to beat faster. A second notion is that the virus could directly infect and damage nerves that set heart rhythm and send signals for blood vessel contraction. A third theory is that infection triggers an overreaction by the immune system, whose cells harm nerves in their zeal to attack the virus; some of those nerves affect heartbeat control. It is possible that some or all of these mechanisms may overlap.

At UCLA Health, Pittman coordinates Ghormley's treatment. He says the interdisciplinary team is crucial to getting patients the best possible care. "Oftentimes there are so many symptoms," and some patients have seen multiple specialists before arriving, but not necessarily the right ones. As long COVID primary care providers, he says, "we do the initial testing and get them to the right person." For Ghormley, that list of providers includes Pittman, along with a neurologist, a pulmonologist, a cardiologist, a psychiatrist, a trauma counselor, a rheumatologist and a gynecologist.

The team approach has also been critical for doctors trying to understand a brand-new disease, Pittman says. "It's been a very interesting journey from knowing almost nothing to knowing a little bit now, and we're learning more every day, every week, every month," he says. The term "long COVID" "is an umbrella, and I think there are multiple diseases under that umbrella." Although each long COVID patient is unique, Pittman says, "we start to see patterns developing. And with Ghormley, we saw a pattern of dysautonomia, which we see frequently."

Dysautonomia impairs the autonomic nervous system, a network of nerves that branch out from the brain or spinal cord and extend through the body, controlling unconscious functions such as heartbeat, breathing, sweating and blood vessel dilation. For Ghormley, like many people with long COVID, dysautonomia takes the form of postural orthostatic tachycardia syndrome, or POTS. The syndrome encompasses a collection of symptoms that include a racing heart rate—particularly on standing—and fatigue, and it can cause bowel and bladder irregularities. POTS can also be a component of the exhaustion that comes with PEM. Although the symptoms may seem to affect the body, they stem from nervous system dysfunction.

Ghormley's dysautonomia led her to see cardiologist Megha Agarwal at a UCLA clinic near her home. Many physicians are not familiar with POTS, but Agarwal is particularly attuned to it, having seen it in some of her patients before COVID hit. "There's dysregulation of the nervous system, and so many things can cause it: some cancer therapies, viruses, autoimmune conditions." Agarwal recognized POTS in Ghormley in the fall of 2020, when very little was known about long COVID. Now she believes "POTS is really what long-haul COVID is causing" in many patients. Luckily, Agarwal says, there are medical interventions that can help.

Tachycardia—the T in POTS—causes the heartbeat to speed up, contributing to exhaustion and fatigue in addition to stressing the heart itself. Drugs called beta-blockers (for the beta-adrenergic receptors they shut off in the heart) can lower the heart rate and improve symptoms. "When heart rate is controlled, not only does the pump improve," Agarwal says, "[but people's] energy improves, their fatigue is gone, and sometimes there's better mental clarity." For some patients like Ghormley, beta-blockers are not enough, so Agarwal adds a medication called ivabradine. "It's a bit off-label,

Sources: "Postural Orthostatic Tachycardia Syndrome as a Sequela of COVID-19," by Cameron K. Ormiston et al., in *Heart Rhythm*, Vol. 19; November 2022; "Long COVID-19 and Postural Orthostatic Tachycardia Syndrome—Is Dysautonomia to Be Blamed?" by Karan R. Chadda et al., in *Frontiers in Cardiovascular Medicine*; March 2022 (*references*)

Graphic by Now Medical Studioes

but it's currently being aggressively studied" for POTS. For Ghormley, the combination led to real improvements, "so now she doesn't feel like she ran the Boston Marathon when all she did was sit down and stand up at work or take a shower," Agarwal says.

Among Ghormley's toughest symptoms is her brain fog, a catchall term for a slew of cognitive problems that make it hard for her to function. For days when Ghormley works, her psychiatrist prescribes Adderall, a stimulant used to treat attention deficit hyperactivity disorder that helps her concentrate and stay focused. That has "helped immensely," Ghormley says.

Ghormley credits her doctors and Agarwal in particular with doing the detective work to dig into her symptoms. "Nobody knew anything about it, but everyone listened to me," Ghormley says. Perhaps because she was a professional from a medical field, no one "brushed me aside."

That's unusual for people with long COVID, many of them women, who are often dismissed by physicians who doubt their complaints are real. "Patients just don't feel heard," Viswanathan says. "I had a patient who told me everything, and after, I just said, 'This must be so hard for you. I want you to know that everything you're feeling is real, and I've seen so many patients like you.' And she started crying. She said, 'No one has told me that. I can't tell you the number of times I was told it was in my head.'"

In addition to drugs, other types of therapies, including physical therapy, can help improve some symptoms. But people who experience PEM face a particular challenge when using movement therapies. Pittman says the exertion can make these patients feel worse. "We don't want patients to go to not moving at all, but sometimes the type of movement they're doing may be flaring their symptoms." He notes that often PEM strikes young, previously healthy people who will say, "'I need to push myself,' and then they go way too far and get worse. Our job is to try to find that middle ground and then make that consistent over time, so they're not getting further deconditioned but they don't have the PEM, which has been shown to set them back."

THE LONG HAUL

SOME PATIENTS, Pittman says, "have the expectation that they're going to come in, and within a month they're going to be back to normal. And resetting those expectations can be really challenging. You have to be really empathetic because people's lives have completely changed." But sometimes patients' quality of life can improve noticeably when they are able to adjust to a new normal. Still, he says, "patients have so many questions, and I can't lead them down a physiological pathway. I can tell them there's neuroinflammation, maybe there's autoimmunity, but we still don't have the answers. Sometimes it's really tough for us to accept and for the patient to accept that we just have to try our best."

A number of people, Viswanathan says, benefit from reducing various treatments they have accumulated. Some people become so desperate that they will try anything from supplements to off-label medications to untested potions from the Internet. Stopping those sometimes leads to improved symptoms, she says.

Psychological care and support groups can help. Lavretsky adds that "lifestyle choices can play a huge role in improvement," particularly better sleep habits and the use of breathing exercises to control anxiety. She tells people their bodies can heal themselves if the patients and clinicians find the right tools.

Whether that's true for everyone remains to be seen, Viswanathan says. "We see many patients who have gotten better with time. I have patients whose symptoms have disappeared in the course of a year, or they disappear and occasionally flare up again." But for some, she says, "it could last many years."

"We're going to be addressing this for probably decades," Viswanathan says. "COVID is not going to go away so much as we're just going to get used to living with it, but part of [that] means that people will continue to develop long COVID."

Vaccination appears to reduce the risk of long COVID. But a study published in May 2022 in *Nature Medicine* suggests the protection, though real, is not as good as one might hope. The survey of electronic health records from the U.S. Department of Veterans Affairs looked at the relatively small portion of vaccinated people who subsequently became infected. They developed long COVID only 15 percent less often than unvaccinated people.

An interdisciplinary medical team is crucial to getting patients the best care because often there are so many symptoms.

"These patients can have symptoms for one to two years or longer, and so every month you're racking up more patients. Even if it's 15 percent less, the total population of patients is still growing and exploding," Pittman says. The best way to avoid getting long COVID, experts all agree, is to avoid getting COVID at all.

The syndrome is still mired in a lot of medical uncertainty. Patients might have one or a combination of the problems investigated so far: Long COVID might be caused by viral particles that persist in the brain or other parts of the nervous system. Or it might be an autoimmune disorder that lasts long after the virus has disappeared. Maybe overactive immune cells continue to perturb the nervous system and nearby blood vessels. Fortunately, the increasing ability to recognize specific problems is helping clinicians hone treatments that give patients the best chance of recovery.

Although Ghormley says her care has dramatically improved her symptoms and allowed her to "do some normal things again," she continues to experience flare-ups that make it impossible for her to work for weeks at a time. One day last year she skipped a dose of her heart medication and made a Target run in the southern California heat. "I got home and basically collapsed in the hallway. Since then, everything has been out of whack. If I try to move around, my legs give out." Most frustrating—and scary—to Ghormley is the unpredictability of her symptoms. "They have changed so much; some are manageable, some debilitating. One thing will get better, and another thing comes back. I'm always hopeful that it's going to get better, but I just don't know." SA

FROM OUR ARCHIVES

Long Haulers Called Attention to Chronic Illnesses. Meghan O'Rourke; March 2022.

scientificamerican.com/magazine/sa

NUCLEAR PHYSICS

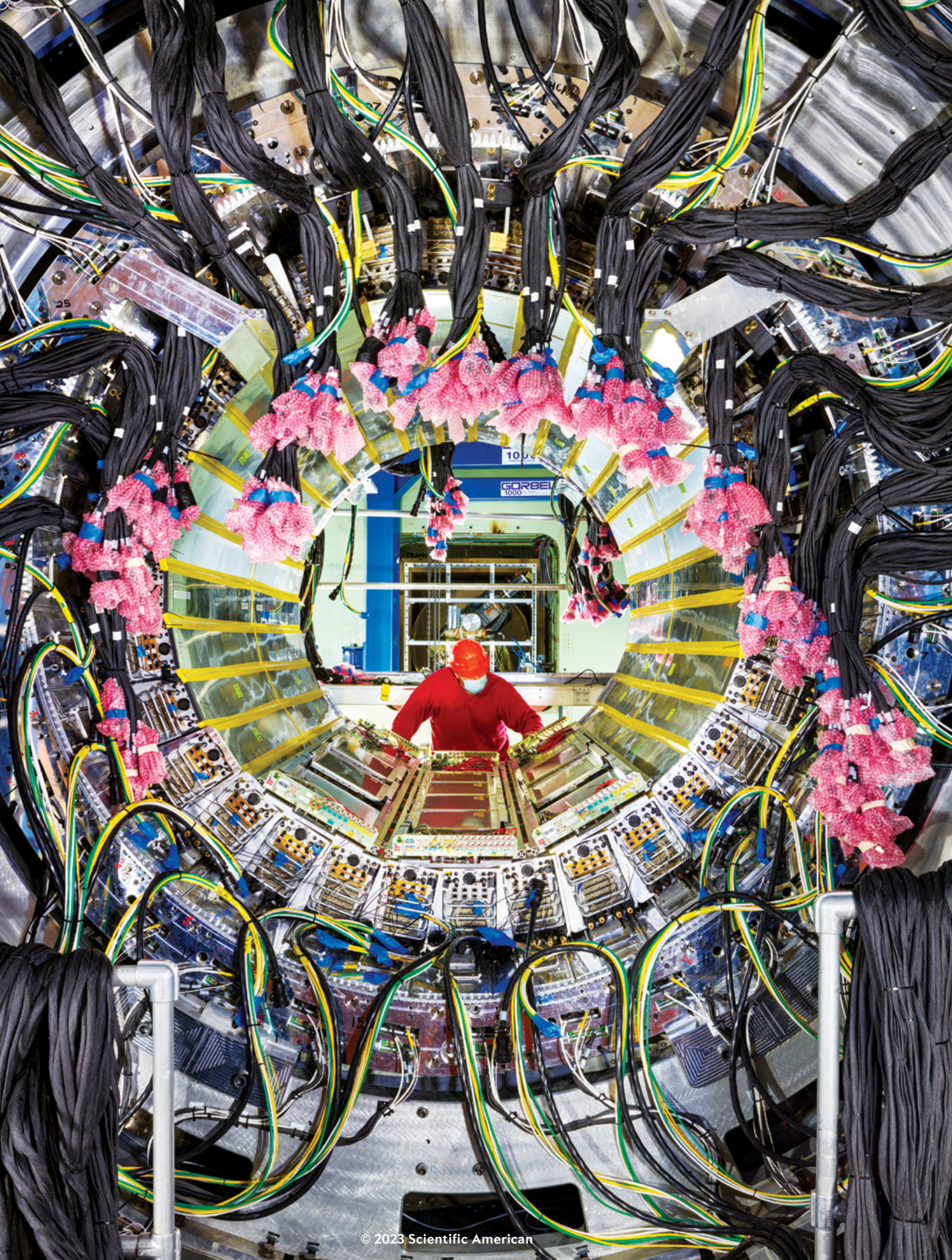
PRIMORDIAL SOUP

New experiments can re-create the early universe, when it was a mash of fundamental particles, more precisely than ever before

By Clara Moskowitz

Photographs by Christopher Payne

A TECHNICIAN installs cables on the new sPHENIX detector at the Relativistic Heavy Ion Collider (RHIC) at Long Island's Brookhaven National Laboratory. Inside sPHENIX's cylindrical interior, atomic nuclei will collide to make droplets of a plasma that existed at the beginning of the cosmos.



Clara Moskowitz is a senior editor at *Scientific American*, where she covers space and physics. She has a bachelor's degree in astronomy and physics from Wesleyan University and a graduate degree in science journalism from the University of California, Santa Cruz.

IMAGINE YOU HAVE A MICROSCOPE THAT WOULD LET YOU SEE A SINGLE ATOM UP CLOSE. LET'S SAY IT'S a hydrogen atom, the smallest kind. Zoom in past the single electron orbiting at the outskirts, and you'll find the nucleus—in this case a lone proton. High school physics would have you believe that inside this proton you'll find a simple triad of three fundamental particles called quarks—two up quarks and one down quark. But the reality inside a proton is so much more complex that physicists are still trying to figure out its inner structure and how its constituents combine to produce its mass, spin and other properties.

The three quarks in the basic picture of the interior of a proton are merely the "valence quarks"—buoys bobbing on top of a roiling sea of quarks and antiquarks (their antimatter counterparts), as well as the sticky "gluon" particles that hold them together. The total number of quarks and gluons inside a proton is always changing. Quark-antiquark pairs are constantly popping in and out of existence, and gluons tend to split and multiply, especially when a proton gains speed. It's basically pure chaos. The strong force—the most powerful of the four fundamental forces of nature—keeps this mess confined to the insides of protons and neutrons. Except when it doesn't.

In the first tiny fractions of a second after the big bang, the universe was too hot and dense for the strong force to bind quarks and gluons together. Instead they became an ocean—a perfect liquid of particles flowing with almost no resistance, called a quark-gluon plasma. This stage of the universe's history ended quickly. Within 10^{-6} second, quarks and gluons were caged inside protons and neutrons. But then, 13.7 billion years later, physicists learned how to re-create the quark-gluon plasma inside particle accelerators. When two large atomic nuclei (such as gold) smash together at nearly the speed of light, the collision produces the temperatures and pressures needed for droplets of quark-gluon plasma to form, briefly, before disintegrating.

The machines that capture these collisions are towering constructions, stacks of detectors and instruments arranged in concentric rings, all of it connected with thousands of wires. When I visited two of them last year at the Brookhaven National Laboratory's Long Island campus, I marveled at the painstaking work of large teams of technicians climbing multiple levels of scaffolding to access the devices. Standing underneath such a colossus feels like witnessing the pinnacle of what humans can achieve—these are some of the largest and most intricate machines ever built, all to study a drop of primordial ooze even smaller than an atom. Investigating droplets of quark-gluon plasma gives scientists a chance to learn how matter got its start. "This is what filled the entire universe about 10 microseconds after the big bang," says Bjoern Schenke, a Brookhaven theoretical physicist. "Studying it allows us to go back in time as much as we possibly can."

The research is also a window into the strong force, the least understood of all nature's forces. This force is described by a theory called quantum chromodynamics (QCD), which is so complicated that scientists can almost never use it to calculate anything directly. The best they can do is to use supercomputers running simulations to get approximate answers. "As human beings, we want to understand nature, and part of understanding nature is to understand quantum chromodynamics and the strong force," says physicist Haiyan Gao, associate laboratory director for nuclear and particle physics at Brookhaven. "We need to do experiments on quark-gluon plasma to understand how this theory works."

In April 2023 Brookhaven scientists will turn on the latest experiment designed to study quark-gluon plasma. The device, called sPHENIX, is one of two detectors at the lab's Relativistic Heavy Ion Collider (RHIC), one of the largest particle accelerators in the world. The other detector there, the Solenoidal Tracker at RHIC (STAR), is also reopening after major upgrades. Across the Atlantic at the European CERN physics lab near Geneva, the globe's biggest accelerator, the Large Hadron Collider (LHC), recently began a new run with upgraded detectors and an ability to smash many more atoms at once. Together these tools should reveal the most detailed picture yet of this primordial fluid, bringing us closer to unraveling the secrets of the tiniest constituents of matter.

PARTICLES CIRCULATE along RHIC's 2.4-mile ring at close to the speed of light before colliding inside detectors such as sPHENIX.

A SURPRISING DISCOVERY

SCIENTISTS PREDICTED quark-gluon plasma long before they discovered it—although they expected it to take a very different form. The predictions came about in the 1970s and 1980s, following the discovery of quarks in the late 1960s and of gluons in 1979. Physicists expected that quarks and gluons, when freed from nuclei, would take the form of a uniformly expanding gaseous substance. "Usually fluids turn to gas as they get hotter," says Berndt Mueller, a physicist at Duke University, who started working on theoretical models for quark-gluon plasma in the 1980s. It was a reasonable assumption: quarks and gluons aren't released from nuclei until they reach temperatures of trillions of degrees.

Mueller was attracted to the field because the theoretical possibilities were wide open, and experimental data were set to start arriving soon. "At that time I was about 30 years old, and you look around for new things you could work on where you have lots of interesting stuff to discover." During this era physicists were developing technologies to smash together heavy ions—nuclei with dozens of protons and neutrons inside them—and they expected these collisions to generate temperatures and densities that would break subatomic particles apart. The earliest heavy ion collisions, which took place in the 1970s at Lawrence Berkeley National Laboratory, weren't powerful enough to create quark-gluon plasma, but in 1986 the Super Proton Synchrotron (SPS) accelerator at CERN began its own heavy ion collisions, and those produced the first evidence for the new state of matter.

It took a while. The CERN team eventually announced their findings in 2000, but even then researchers were divided over whether the data were strong enough to claim a discovery. That same year Brookhaven's RHIC opened and started crashing heavy ions at higher energies than at the SPS. Within five years this accelerator had amassed enough data that physicists declared quark-gluon plasma officially found.

It wasn't what they had imagined. Instead of an expanding gas, the quark-gluon plasma looked like a liquid—a nearly perfect one, with almost no viscosity. In a gas, particles act individually; in a liquid, particles move cohesively. The stronger the interactions among particles—the more they can pull one another along—the "better" the liquid is at being a liquid. The RHIC observations showed that quark-gluon plasma exhibited less resistance to flow than any substance ever known. This, Mueller says, "was very much unexpected."

In 2010 RHIC researchers announced the first measurement of the quark-gluon plasma's temperature. It was a scorching four trillion degrees Celsius, far hotter than any other matter ever created by humans, and about 250,000 times hotter than the middle of the sun. "Usually the hotter something becomes,

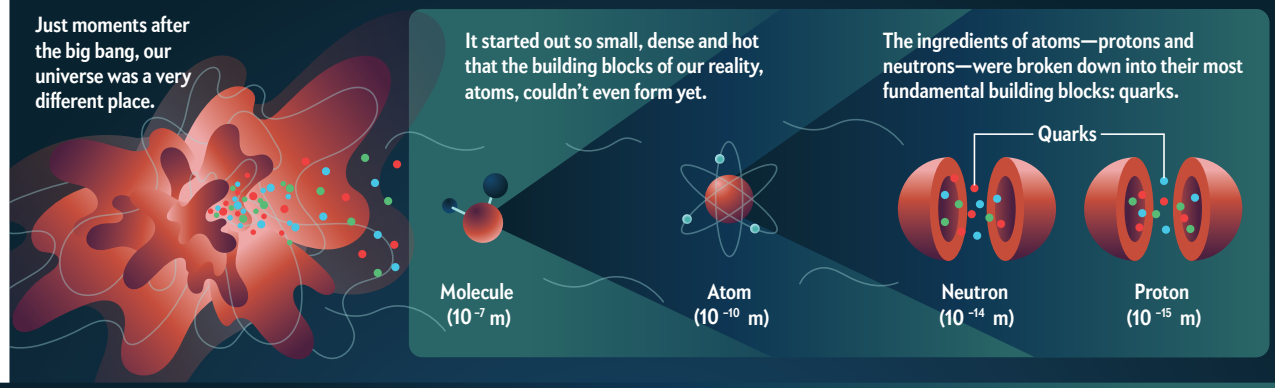
Quark Soup

Particle accelerators give scientists a glimpse of the beginning of time by re-creating the "soup" of our newborn universe, called quark-gluon plasma.

Just moments after the big bang, our universe was a very different place.

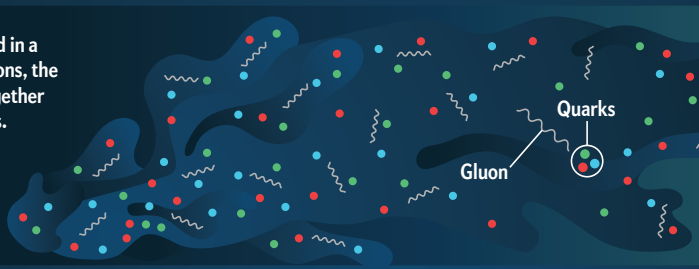
It started out so small, dense and hot that the building blocks of our reality, atoms, couldn't even form yet.

The ingredients of atoms—protons and neutrons—were broken down into their most fundamental building blocks: quarks.



These quarks floated around in a perfect fluid along with gluons, the particles that bind them together inside protons and neutrons.

Scientists call this universe-creating fluid "quark-gluon plasma."

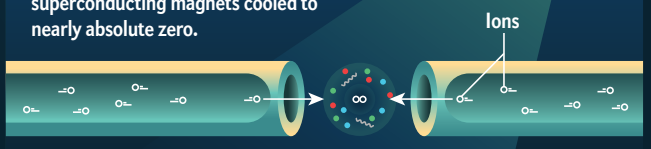


The soup hasn't been found in nature since the beginning of time. But scientists can re-create it inside particle accelerators.

It was officially observed first at the Brookhaven National Laboratory in Long Island, where researchers use the Relativistic Heavy Ion Collider (RHIC) to smash atoms together.

RHIC's 2.4-mile-long ring speeds atomic nuclei around its massive circle 80,000 times a second, at 99.995 percent the speed of light.

They are steered in this ring by massive, superconducting magnets cooled to nearly absolute zero.

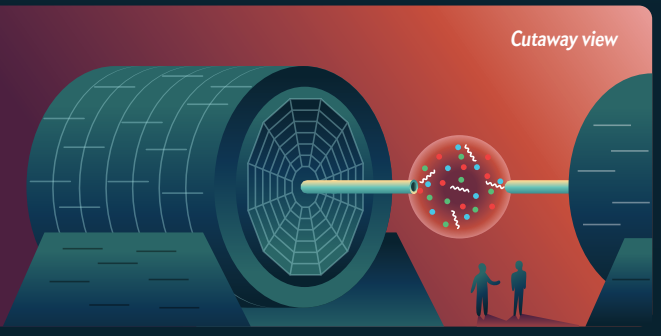


At several points along the path, the two opposing beams of nuclei intersect and collide. The crashes give rise to explosions of particles, as well as to tiny droplets of quark-gluon plasma.

At Brookhaven, there are two collision points where detectors can watch the action: sPHENIX and STAR.

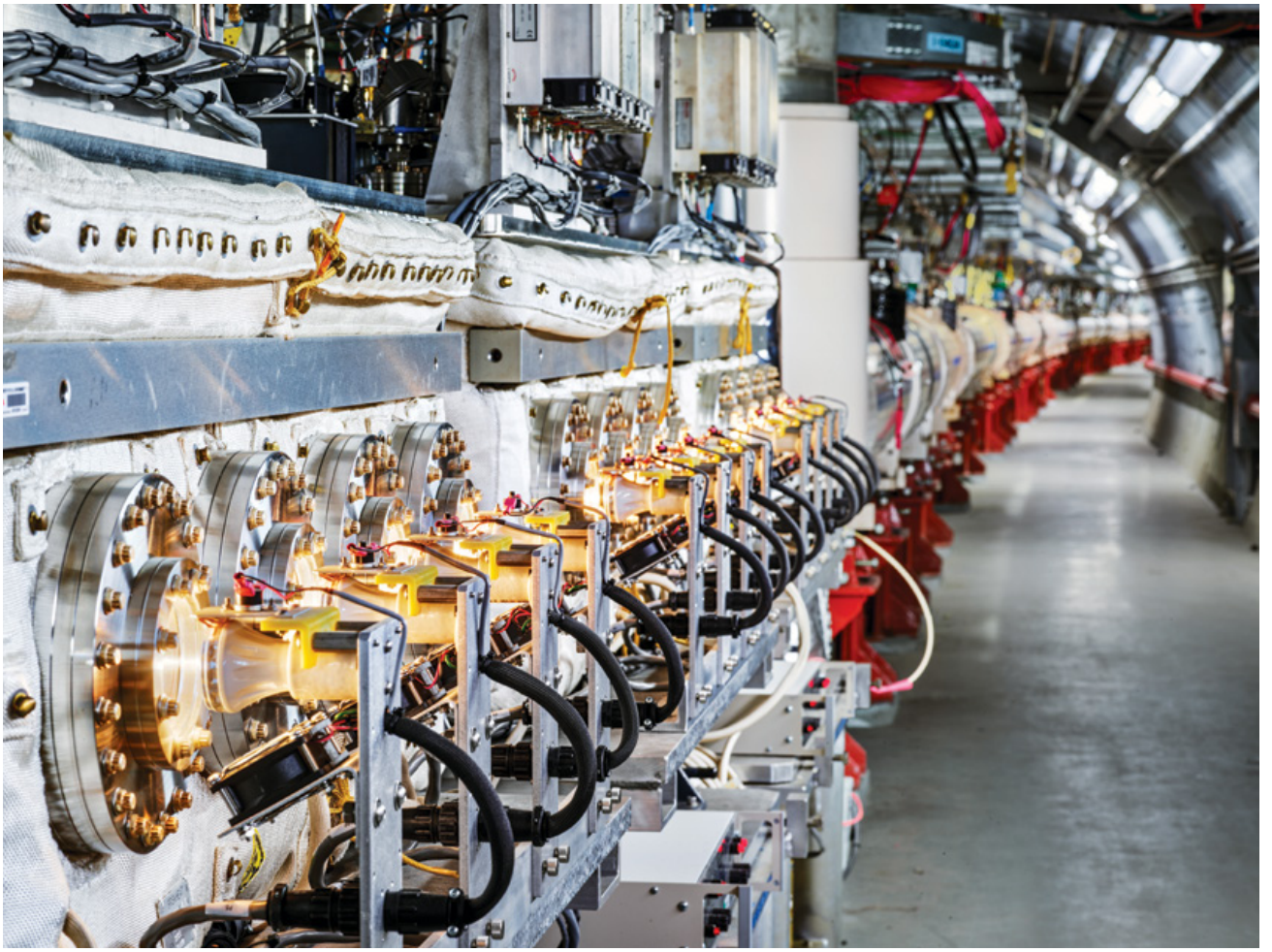
Each detector is like an onion, with layer on layer of nested detectors, wires, cooling tubes and electronics, pulling massive amounts of data, tracking and detecting particles' energies and motions.

At the core of each device is a powerful superconducting magnet that can bend the paths of charged particles and identify particles of different masses.



These measurements can reveal secrets about the quark-gluon plasma, giving us a deeper understanding of how the tiniest bits of matter behave and how the universe got its start.

Graphic by Jason Drakeford



INSIDE RHIC'S TUNNELS "stochastic cooling kickers" push the particles within the rings closer together to correct for their tendency to spread out as they travel. This ensures that as many particles as possible will collide inside the detectors.

the less of a perfect fluid it becomes," Mueller says. "But in this case, it's the opposite—when you reach the critical temperature, it turns into a liquid." Scientists suspect the strong force is behind this odd behavior. When the particles become hot enough to escape from protons and neutrons, the strong force acts over the entire plasma, causing the collective mass of particles to interact strongly with one another.

THE MYSTERY OF THE STRONG FORCE

ONE OF THE BIGGEST open questions about quark-gluon plasma is when, exactly, the quarks and gluons break out of their confinement. "Where is the boundary between casual matter and quark-gluon plasma?" Gao asks. "Where is the so-called critical point where the nuclear matter and the quark-gluon plasma coexist?" Understanding where that transition happens, and how many particles it takes to initiate the collective behavior, will be among the main goals of the new and upgraded experiments.

Another question is whether quark-gluon plasma is a fractal—that is, whether its structure has a complex, repeating pattern that appears the same at every scale, whether you zoom out or in. Some researchers have been arguing that quark-gluon plasma has these two properties and that fractal theory could offer insights into how the plasma behaves. "There is evidence that we have fractal structure in quark-gluon plasma," says Airton Deppman, a physicist at the University of São Paulo's Institute of Physics. "We are also investigating if the fractal structure survives the phase transition" from plasma to proton.

Answering these questions could help with a larger goal: understanding the strong force, the most confusing of nature's fundamental forces. Quantum chromodynamics describes the interactions between quarks and gluons by ascribing them a property called color charge. This color charge is akin to electrical charge in the theory of electromagnetism, and it also explains why quantum chromodynamics so quickly gets out of hand. Whereas electromagnetism has only two charges—positive or negative—QCD has three—red, green or blue. And antimatter particles can carry antired, antigreen or antiblue charge.

In electromagnetism, the particle that carries the electromagnetic force, the photon, is itself electrically neutral, which keeps things somewhat simple. In QCD, though, the force carrier, the gluon, also carries a color charge and can interact through the strong force with itself *and* with quarks. These self-interactions and extra charges have made QCD prohibitively complicated. "You can write down the theory essentially in two lines, but actually solving it has not been really achieved," Schenke says.

"The process of confinement—how gluons and quarks are being trapped in the proton, for example—has not been solved."

Scientists hope that studying quark-gluon plasma—the only situation in which scientists have ever detected free quarks—could reveal more about how confinement works. "One way to get at that is to free them and see how they then recombine again to protons, neutrons and other particles that we can observe from the detector," Schenke adds. Thus, experimental data from heavy-ion collisions can be used to better understand the mechanisms within QCD that lead to confinement.

NEW AND IMPROVED

WITH THE RHIC'S new experiment, sPHENIX, and the upgraded STAR detector, scientists should be able to take the most precise measurements of the plasma yet. For instance, sPHENIX has a superconducting magnet that is roughly three times stronger than STAR's. "That's important for many of the things we want to measure," says David Morrison, a Brookhaven physicist working on the new machine. "If you have a collision, particles come out every which way, and then the magnetic fields bend their paths. We can look at that to start unraveling what kind of particle was it and how much energy and momentum did it have?" The team is hoping to spot composite particles called upsilons, for example. Upsilons, which contain a bottom quark and an anti-bottom quark, can form in collisions and then fly through the quark-gluon plasma, acting as test probes to reveal how the plasma changes them. "We can really unravel the physics that underlies a lot of the weird properties of the quark-gluon plasma," he adds.

The experiment will also benefit from being able to record much more data—meaning many more collisions and the particles they result in—than was possible before. STAR captures around 10 petabytes of data a year; sPHENIX will take around 150 petabytes annually. That increase will bring previously unanswerable questions within reach.

STAR also has novel capabilities, such as new calorimeters for measuring the energies of particles and tracking detectors for identifying particles with different electrical charges. Among the most significant additions, says Brookhaven's Lijuan Ruan, one of STAR's spokespeople, are "forward" detectors that can record particles flying out of collisions at wider angles than before, including particles moving in the same direction as the beams that fed into the crash. "Now that's basically it—we're not going to upgrade anymore," says Ruan, who has been working on STAR for many years and helped to build some of its early components around 20 years ago as a graduate student. "It's a different feeling when you just use a detector, compared to when you actually build it and the entire collaboration can use it," she says. "I feel proud." STAR, which was among the original RHIC experiments that helped to discover quark-gluon plasma, will operate for another three years before shutting down.

In Europe, the LHC recently began its third run, which started in July 2022 and will continue until 2025. After the latest upgrades, LHC scientists can analyze about 100 times more lead-lead collisions than they could during the first two runs. The extra collisions will also increase the precision of measurements. "One of the important goals for run three is to understand the onset of the quark-gluon plasma and how it gradually emerges," says Luciano Musa, a member of the ALICE experiment at the LHC.

Compared with the RHIC experiments, the LHC collisions occur at higher energies and produce a hotter, denser and longer-lived quark-gluon plasma. These energetic smashups also create a larger variety of particles that scientists can use to probe the plasma's properties. "The studies at RHIC and LHC really go hand in hand," Musa says. "Whenever there is a finding at the LHC, at RHIC they try to understand if the same phenomena are also observed at low energy."

PHYSICIST LIJUAN RUAN peers inside the heart of the STAR detector at RHIC. At STAR's core, heavy ions collide inside a cylindrical solenoid electromagnet. The energy created in the crashes can generate thousands of new particles.

The different energy ranges reveal different aspects of the plasma. Raghav Kunnawalkam Elayavalli, a physicist at Vanderbilt University, did their Ph.D. work at the LHC, but recently became a member of the STAR and sPHENIX collaborations to focus on the particles coming out of lower-energy collisions. "They are closer to the scale of the plasma; they talk to it a lot more," Kunnawalkam Elayavalli says. "Think of it like a party: there's a lot of people, and you're making a beeline to the exit. But if you're kind of slow and you don't want to leave that fast, you get a chance to talk to people on your way out." Because particles flying through the quark-gluon plasma at RHIC take longer to move through it, they can extract more information from it. "The things we're trying to measure are the transport properties—the average distance you can go without interacting with another particle," they add. "It tells us about the fundamental scale of the plasma."

BACK TO THE BEGINNING

THE NEW ERA of quark-gluon plasma experiments should move the field beyond the basics and toward concrete answers to long-standing questions. "There was a period of physics at RHIC that was basically, 'Wow, this happening—this is new physics,'" Kunnawalkam Elayavalli says. "And now we are in the precision era. We can ask, 'Why is this happening?'"

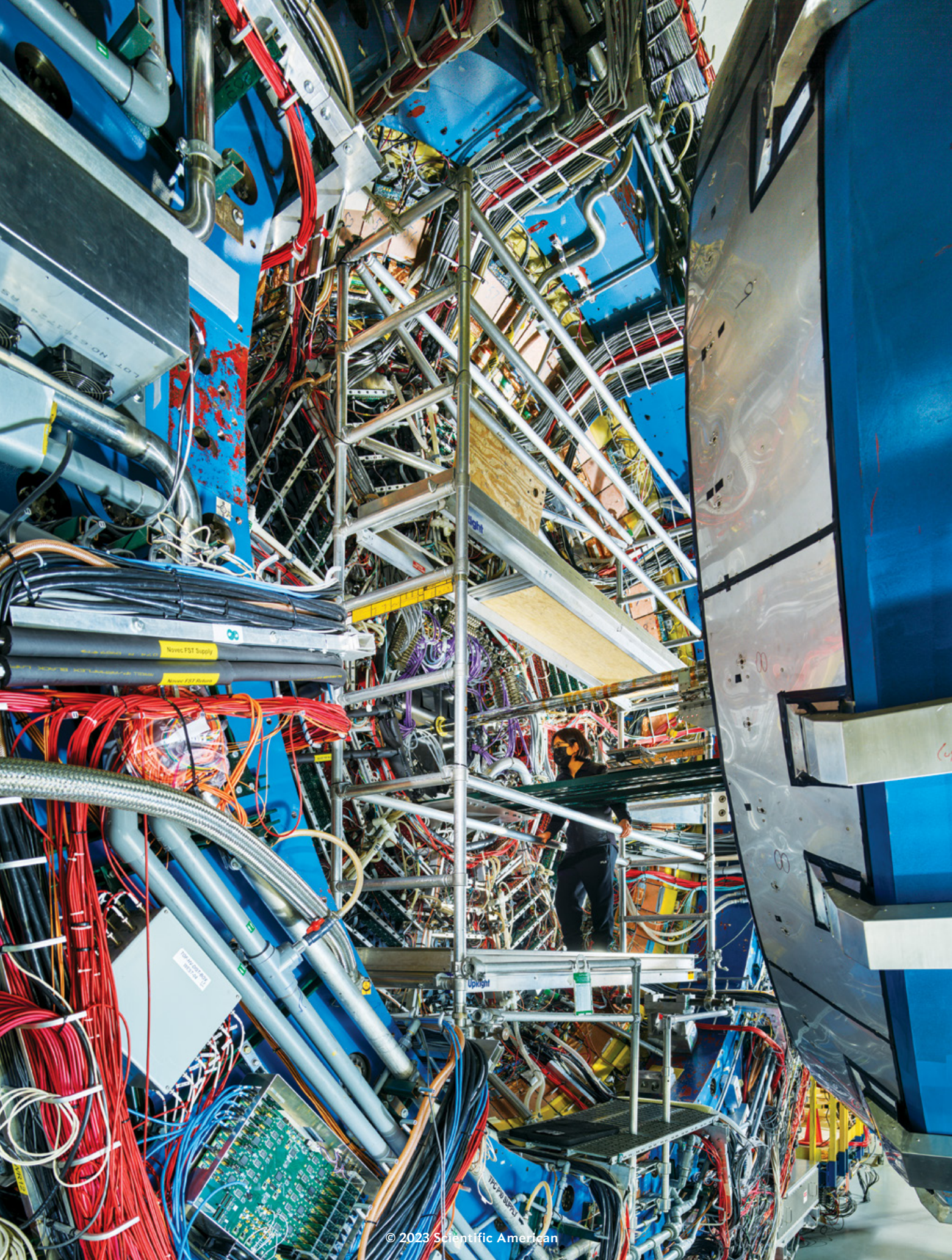
RHIC and the LHC are leading the effort to understand this special state of matter, but upcoming experiments elsewhere will also add insights. At CERN, alongside the LHC, the SPS accelerator is still running. A planned experiment there called NA61/SHINE will collide moving ions into a stationary target to measure the critical point when protons and neutrons turn into quark-gluon plasma. A second fixed-target experiment, the Facility for Antiproton and Ion Research (FAIR) at GSI Darmstadt in Germany, is due to open in 2028. And at the Joint Institute for Nuclear Research in Dubna near Moscow, a collider called the Nuclotron-based Ion Collider fAcility (NICA) will also probe the critical point.

"It's an exciting time," Mueller says. "We know the quark-gluon plasma existed in the early universe, but we have no way of probing that. This is our way of probing a physics situation that otherwise we don't have any hope to reach." SA

FROM OUR ARCHIVES

The Glue That Binds Us. Rolf Ent, Thomas Ullrich and Raju Venugopalan; May 2015.

scientificamerican.com/magazine/sa



COGNITIVE SCIENCE

BORN TO COUNT

As Plato anticipated, babies do math

By Jacob Beck and Sam Clarke

Photograph by Jamie Chung

HOW MANY GUMBALLS are in the jar? This popular guessing game involves our innate number sense. (Find the answer in the fold on page 49.)

Jacob Beck is York Research Chair in the Philosophy of Visual Perception and an associate professor in the department of philosophy at York University in Toronto.

Sam Clarke is a MindCORE research fellow at the University of Pennsylvania, where he divides his time between philosophy and psychology. Beginning in summer 2023, he will be an assistant professor of philosophy at the University of Southern California.

IMAGINE HOSTING A PARTY. YOU ARRANGE SNACKS, CURATE A PLAYLIST AND PLACE A VARIETY OF BEERS in the refrigerator. Your first guest shows up, adding a six-pack before taking one bottle for himself. You watch your next guest arrive and contribute a few more beers, minus one for herself. Ready for a drink, you open the fridge and are surprised to find only eight beers remaining. You haven't been consciously counting the beers, but you know there should be more, so you start poking around. Sure enough, in the crisper drawer, behind a rotting head of romaine, are several bottles.

How did you know to look for the missing beer? It's not like you were standing guard at the refrigerator, tallying how many bottles went in and out. Rather you were using what cognitive scientists call your number sense, a part of the mind that unconsciously solves simple math problems. While you were immersed in conversation with guests, your number sense was keeping tabs on how many beers were in the fridge.

For a long time scientists, mathematicians and philosophers have debated whether this number sense comes preinstalled or is learned over time. Plato was among the first in the Western tradition to propose that humans have innate mathematical abilities. In Plato's dialogue *Meno,* Socrates coaxes the Pythagorean theorem out of an uneducated boy by asking him a series of simple questions. Socrates's takeaway is that the boy had innate knowledge of the Pythagorean theorem all along; the questioning just helped him express it.

In the 17th century John Locke rejected this idea, insisting that the human mind begins as a tabula rasa, or blank slate, with almost all knowledge acquired through experience. This view, known as empiricism, in contrast to Plato's nativism, was later further developed by John Stuart Mill, who argued that we learn two plus three is five by seeing many examples where it holds true: two apples and three apples make five apples, two beers and three beers make five beers, and so on.

In short, empiricism dominated philosophy and psychology until the second half of the 20th century, when nativist-friendly thinkers such as Noam Chomsky swung the pendulum back toward Plato. Chomsky focused on language, proposing that children are born with an innate language instinct that enables them to quickly acquire their first language with little in the way of explicit instruction.

Others then extended Chomsky's hypothesis to mathematics. In the late 1970s cognitive scientists C. R. Gallistel and Rochel Gelman argued that children learn to count by mapping the number words in their language onto an innate system of preverbal counting that humans share with many other animals. In his landmark book *The Number Sense,* first published in 1997, French neuroscientist Stanislas Dehaene drew attention to the converging evidence for this preverbal system, helping researchers from diverse disciplines—animal cognition, developmental psychology, cognitive psychology, neuroscience, education—realize they were all studying the same thing.

In our 2021 paper in the journal *Behavioral and Brain Sciences,* we argued that there is no longer a serious alternative to the view that humans and many nonhuman animals have evolved a capacity to pro-

cess numbers. Whereas Plato proposed that we have innate mathematical knowledge, or a capacity to think about numbers, we argue that we have innate mathematical perception—an ability to see or sense numbers. When you opened the fridge, it's not that you saw the beer bottles and made an inference about their number in the way that you saw Heineken labels and inferred that someone brought a pale lager from the Netherlands. Rather you saw their number much the way you perceived their shape and color.

But not everyone agrees with this emerging consensus, and a new wave of empiricism has emerged over the past decade. Critics who reject the existence of an ability to innately sense numbers highlight a broader and important scientific challenge: How could we ever know the contents of an infant's or a nonhuman animal's mind? As philosophers of cognitive science, we supplement thousands of years of philosophical thinking about this issue by drawing on a mountain of experimental evidence that simply was not available to past thinkers.

EMERGING EVIDENCE

IMAGINE YOU SEE TWO collections of dots flash on a computer screen in quick succession. There's no time to count them, but if you're like the thousands of people who have done this exercise in studies, you'll be able to tell which grouping had more dots if the two are sufficiently different. Although you might struggle to distinguish 50 from 51 dots, you'll be pretty good at recognizing that 40 dots are less numerous than 50. Is this ability innate or the product of years of mathematical education?

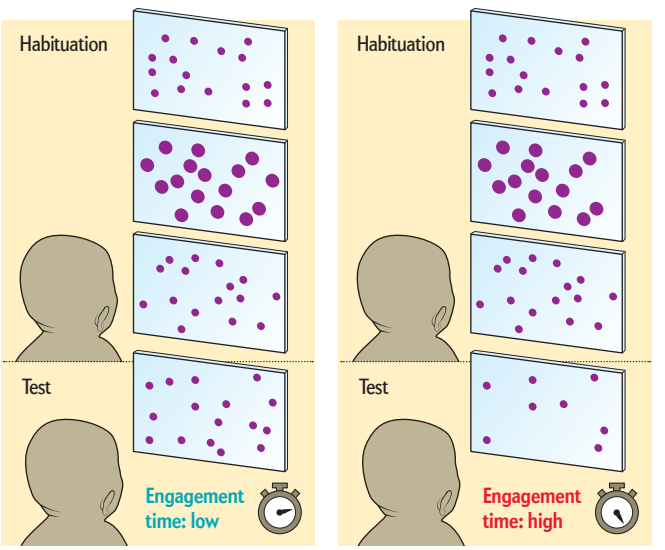
In 2004 a team of French researchers, led by Dehaene and Pierre Pica, took that question deep into the Brazilian Amazon. With a solar-powered laptop, Pica performed the same dot-flashing experiment with people from isolated Indigenous villages. People from this Indigenous group had the same ability to distinguish between sufficiently different numbers of dots, even though they had limited or no formal mathematical training and spoke a language in which precise number words went no higher than five.

Around the same time, a different group of researchers, including developmental psychologists Elizabeth S. Spelke and Hilary Barth, then both at Harvard University, used a modified dot-flash experiment to show that five-year-olds in Massachusetts also had this ability. One possible explanation is that the children weren't really tracking the number of dots but rather were focusing on some other aspect, such as the total area the dots covered on the screen or the total perimeter of the cluster. When one collection of dots was replaced with a rapid sequence of audible tones, however, the children determined which quantity was greater—that is, whether they had heard more tones or seen more dots—equally as well as in the dots-only experiment. The children couldn't have used surface area or perimeter for that comparison, because the tones didn't have those features. Nor do dots have loudness or pitch. The children weren't using sound duration, either: the tones were presented sequentially over variable durations, whereas the dots were presented all at once for a fixed duration. It seems that the five-year-olds really did have a sense for the number of dots and tones.

Barth and her colleagues proceeded to show that these numerical abilities support basic forms of arithmetic. In another experiment, the five-year-olds saw two collections of blue dots move behind an opaque block, one after the other. From that point on, none of the blue dots were visible. Then some red dots appeared beside the block. The children were asked whether there were more blue dots or red dots in total. They answered correctly, indicating that they could add the two groups of blue dots together even though they couldn't see them anymore and then compare their total to that of the red dots. In 2021 Chuyan Qu and her colleagues in Elizabeth Brannon's

Number Sense in Infants

Fei Xu and Elizabeth Spelke repeatedly presented six-month-old infants with different displays containing either 8 or 16 dots. They then presented the infants with a new display. When the new display contained a new number of dots (8 when they had initially seen 16 or 16 when they had initially seen 8), the infants looked longer, an indication that they noticed something different. But when the new display contained the same number of dots, they did not. Six-month-olds showed the same behavior for other dots in a 2:1 ratio, such as 4 vs. 8 and 16 vs. 32. By nine months they also showed sensitivity to dots in a 3:2 ratio, such as 8 vs. 12, 4 vs. 6, and 16 vs. 24. Because the displays controlled for confounding variables such as brightness, density and area, these results suggest that infants have an innate number sense that, like visual-spatial acuity, becomes more precise with age.



Source: "Large Number Discrimination in 6-Month-Old Infants," by Fei Xua and Elizabeth S. Spelke, in *Cognition*, Vol. 74; January 2000 (*reference*)

Graphics by Jen Christiansen

laboratory at the University of Pennsylvania took this further, showing that children as young as five can perform approximate multiplication—an operation that isn't taught until third grade in the U.S.

It's easy to wonder whether these five-year-olds had learned something about numbers from their adult caretakers who had learned math in school. But similar results have been found in a wide range of animal species. Wolves consider the size of their pack before deciding to hunt, preferring a group of two to six to attack an elk but a group of at least nine to take on a bison. Rats learn to press a lever a certain number of times in exchange for food. Ducks take account of how many morsels of food each of two people is throwing into a pond before deciding whom to approach. This behavior suggests that the number sense is evolutionarily ancient, similar to the ability to see colors or to feel warmth or cold.

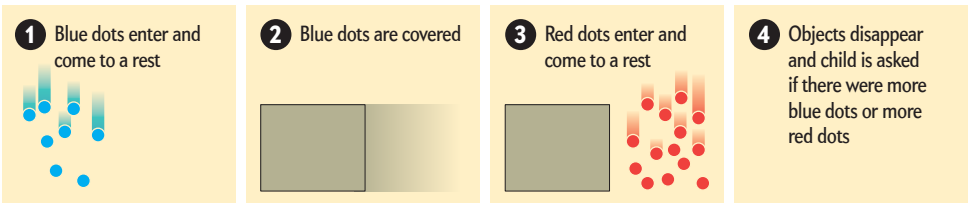
These examples don't quite get at the question of whether the number sense is innate, though. Perhaps all they suggest is that formal schooling isn't necessary for humans or animals to learn to count. The ideal subjects for testing an innate number sense are newborn infants because they haven't had time to learn much of anything. Of course, they can't talk, so we can't ask them which of two collections contains more. They don't even crawl or reach. They are, however, capable of a simpler action: *looking*. By measuring where infants look and how much time they spend gazing there, scientists have discovered a window into their minds.

In a 2009 collaboration between Spelke and a team of researchers in France led by Véronique Izard and Arlette Streri, newborns at a hospital in Paris—all younger than five days old—listened for two minutes to auditory sequences containing either four sounds ("tuuu tuuu tuuu tuuu") or 12 sounds. The researchers then presented the infants with a visual display containing four or 12 objects. Infants are known to like looking at familiar things, such as their mother's face. Izard and her colleagues reasoned that if the infants extracted numbers from the auditory stimuli, they would prefer to look at a display containing a matching number of items—four objects right after they had heard sequences containing four sounds or 12 objects right after hearing sequences containing 12 sounds. Thus, they should look longer at the display when it numerically matches the sounds than when it does not.

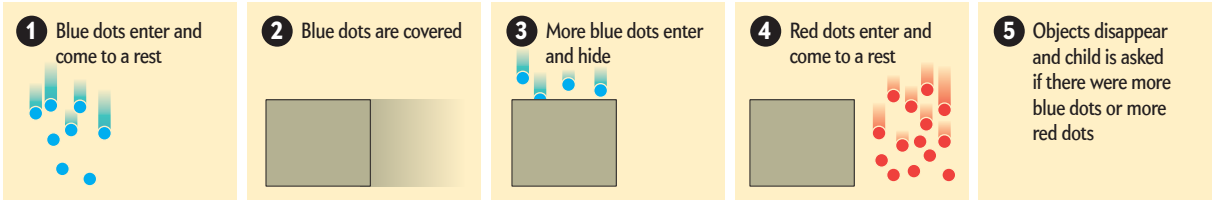
And that's exactly what Izard and her colleagues found. (Just as a smile doesn't always mean the same thing, nor does longer looking: Here newborns looked longer at a match in number, indicating coincidence, whereas the six-month-olds in the box on page 45 looked longer at a change in number, reflecting surprise at the unexpected. In either case, reliable differences in looking behavior show that infants are sensitive to number.)

Preschool Mathematicians

Hilary Barth and her colleagues presented preschoolers with a collection of blue dots moving onto a screen and then being covered up by an opaque block. A collection of red dots then appeared, and the children were asked if there were more blue dots behind the barrier or red dots on the screen. They answered correctly even though they had not yet studied math.



They also succeeded when they had to add two collections of blue dots and compare them with a third collection of red dots.

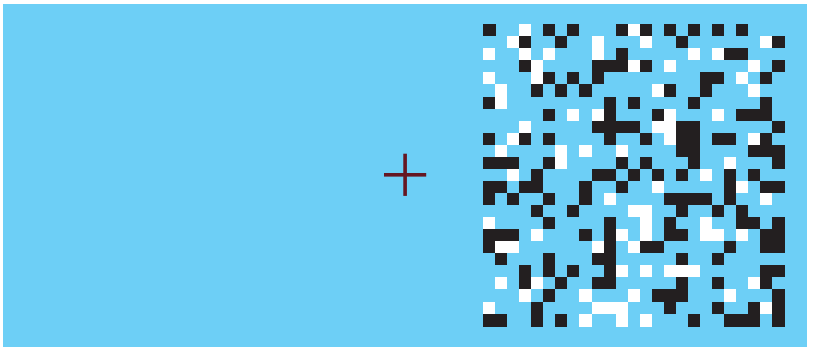


Interestingly, follow-up experiments found that their performance was just as good when the collection of red dots was indicated by a sequence of beeps. This is striking because it suggests that the preschoolers were really tracking number. For example, they couldn't have simply compared the total surface area of the collections, because the beeps didn't have a surface area. Conversely, they couldn't have simply compared the loudness of the collections, because the blue dots didn't make a noise.

Source: "Abstract Number and Arithmetic in Preschool Children," by Hilary Barth et al., in *PNAS*, Vol. 102, September 19, 2005 *(reference)*

Seeing Numbers, Part 1

Stare at the red cross for 30 seconds and then quickly turn the page. Does the collection of dots on the left now appear more or less numerous than the one on the right?



Critics such as Tali Leibovich of Haifa University and Avishai Henik of Ben-Gurion University of the Negev in Israel raised concerns about overinterpreting these results, given that newborns have poor eyesight. But the fact that this result held for 15 of the 16 infants tested who didn't succumb to sleep or fussiness is certainly suggestive.

NUMBERS VS. NUMERALS

RECALL OUR SUGGESTION that when you opened your fridge at the party, you saw how many beers were present in much the way you saw their shape and color. This wasn't thoughtlessly worded: You didn't see the beer bottles and then judge their number. Rather the number sense enabled you to see the number like you see colors and shapes.

To clarify this idea, it's first important to distinguish numbers from numerals. Numerals are symbols used to refer to numbers. The numerals "7" and "VII" are distinct, but both refer to the same number. The claim that you see numbers should not be confused with a claim that you see numerals. Just as seeing the word "red" is distinct from seeing the color red, seeing the numeral "7" is not the same as seeing the number seven.

Moreover, just as seeing the size of a beer bottle does not involve a symbol like "12 oz" popping up in your visual field, seeing the number of beers in the fridge does not involve seeing a numeral such as "7." When you see the size of a beer bottle, it looks a certain way—a way that would change if the bottle got bigger or smaller. You can tell by looking that one bottle is bigger than another. Correspondingly, when you see how many beers there are, the beers look a certain way—a way that would change if there were more or fewer of them. Thus, you can tell, just by looking, whether there are more beers over here or over there.

Of course, even once numbers are distinguished from numerals, the concept of seeing numbers may still seem puzzling. After all, numbers are abstract. You can't point at them, because they aren't located in space, and your eyes certainly can't detect any light being reflected off them.

But the idea that you see numbers is not so different from the idea that you see shapes. Although you can see the sail of a boat as triangular, you cannot see a pure triangle on its own, independent of any physical objects. Likewise, although you can see some beers as being about seven in number, you cannot see the number seven all by itself. You can see shapes and numbers but only as attributes of an object or collection of objects that reflects light into your eyes.

So how can we tell when something is seen? If two lines appear on your COVID test, you might say that you can "see" that you have COVID. But that's loose talk. You certainly see the lines, but you merely judge that you have COVID. How can we draw this distinction scientifically?

Whereas Plato proposed that we have a capacity to think about numbers, we argue that we have an ability to see or sense numbers.

There are many answers to this question, but one of the most helpful appeals to what is called perceptual adaptation. An example is the way a person's eyes eventually get used to the sun when they go picnicking on a sunny day. When that person later heads indoors, the bathroom appears dimly lit even when all the lights are on. After someone's eyes adapt to bright light, a normally lit room looks dark.

Adaptation is a hallmark of perception. If you can perceive something, you can probably adapt to it—including its brightness, color, orientation, shape and motion. Thus, if numbers are perceived, people should adapt to numbers, too. This is precisely what vision researchers David Burr of the University of Florence and John Ross of the University of Western Australia reported in a paper published in 2008.

Burr and Ross showed that if a person stares at an array of lots of dots, a later array containing a mid-

Source: "A Visual Sense of Number," by David Burr and John Ross, in *Current Biology*, Vol. 18; 2008 *(reference)*

dling number of dots will appear less numerous than it would have otherwise. For instance, they found that after someone stared at 400 dots for 30 seconds, they saw a group of 100 dots as if it had just 30 dots. Therefore, in much the way that our eyes get used to the sun, they can get used to large numbers, leading to striking visual effects.

Other researchers, among them Frank Durgin of Swarthmore College, questioned whether the adaptation was to number as opposed to texture density (how frequently items appear in a given region of space). As a display of dots increases in number while the area it covers stays the same, it also increases in texture density. But a 2020 study by vision scientists Kevin DeSimone, Minjung Kim and Richard Murray teased these possibilities apart and showed that observers adapt to number independently of texture density. Strange as it sounds, humans see numbers.

NATURAL-BORN ENUMERATORS

DESPITE ABUNDANT EVIDENCE, contemporary empiricists—folks who follow in the tradition of Locke and Mill and believe that all mathematical knowledge is acquired through experience—remain skeptical about the existence of the number sense. After all, the ability to do arithmetic is traditionally considered a hard-won cultural achievement. Now we're supposed to believe babies do math?

Psychologists do have a checkered history when it comes to overinterpreting the numerical abilities of nonhuman animals. Undergraduate psychology majors are sternly warned of the "Clever Hans effect," named after a horse that was prematurely credited with sophisticated arithmetic abilities (not to mention the ability to tell time and spell long words in German). It was later revealed that he was simply responding to subtle cues in his trainer's behavior. Researchers nowadays take great care to avoid inadvertently cueing their subjects, but that doesn't resolve everything.

Rafael Núñez of the University of California, San Diego, argues, for instance, that the number sense simply couldn't represent numbers, because numbers are precise: 30 is exactly one more than 29 and exactly one less than 31. The number sense, in contrast, is imprecise: if you see 30 dots flashed on a screen, you'll have a rough idea of how many there are, but you won't know there are exactly 30. Núñez concludes that whatever the number sense is representing, it cannot be number. As he put it in a 2017 article in *Trends in Cognitive Sciences,* "a basic competence involving, say, the number 'eight,' should require that the quantity is treated as being categorically different from 'seven,' and not merely treated as often—or highly likely to be—different from it."

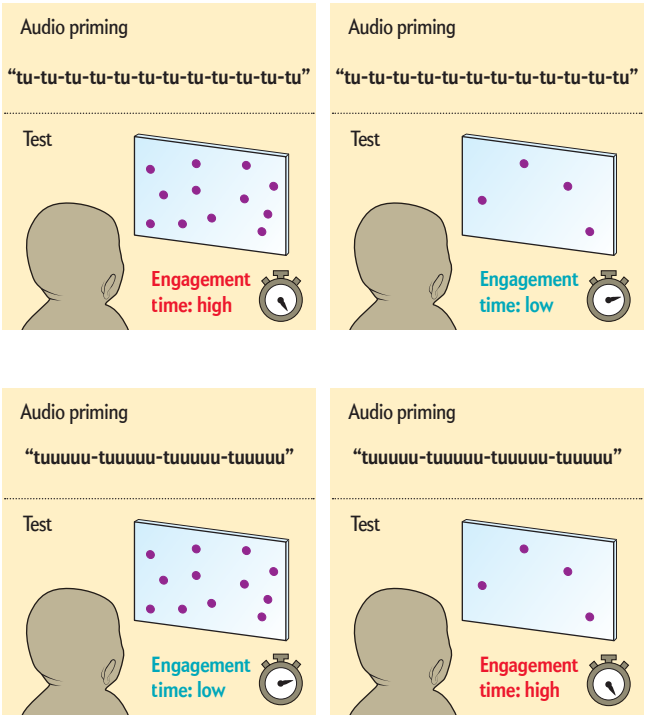
In our 2021 *Behavioral and Brain Sciences* article, we reply that such concerns are misplaced because any quantity can be represented imprecisely. You can represent someone's height precisely as 1.9 meters, but you can also represent it imprecisely as almost two meters. Similarly, you can represent the number of coins in your pocket precisely as five, but you can also represent it imprecisely as a few. You're representing height and number, respectively. All that changes is how you represent those quantities—precisely or imprecisely. Consequently, it's hard to see why the imprecision of the number sense should be taken to suggest that it's representing some attribute other than number.

This may seem like an issue of semantics, but it has a substantive implication. If we follow Núñez in supposing that the number sense doesn't represent numbers, then we need to say what it represents instead. And no one seems to have any good ideas about that. In many studies of the number sense, other variables—density, area, duration, height, weight, volume, brightness, and so on—have been controlled for.

Another reason to think the number sense concerns numbers (as opposed to height, weight, volume or other quantities) comes from late 19th-century German philosopher and logician Gottlob Frege. In his work on the foundations of arithmetic, Frege noted that numbers are unique in that they presuppose a way of describing the stuff they quantify. Imagine you

Newborn Numeracy

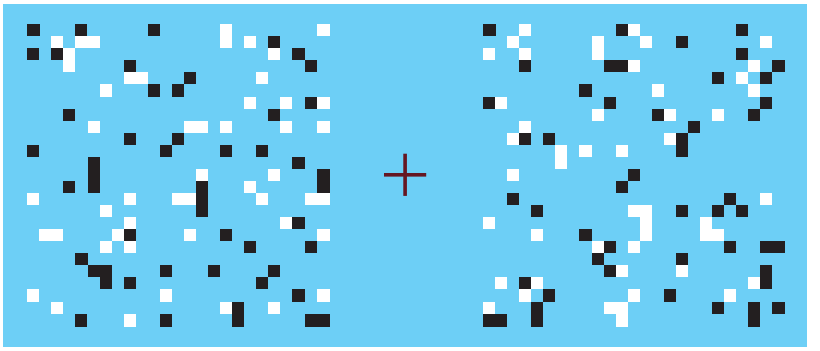
Véronique Izard and her colleagues spent two minutes familiarizing newborn infants to sequences of four or 12 phonemes. The infants were then shown a display containing four or 12 seen items. Fifteen out of the 16 newborn infants who completed the study looked longer when the seen items matched the heard phonemes in number.



Source: "Newborn Infants Perceive Abstract Numbers," by Véronique Izard et al., in *PNAS,* Vol. 106; June 23, 2009 (*reference*)

Seeing Numbers, Part 2

If you kept your eyes fixated on the cross, you probably found that the left-hand array looked more numerous when you first turned the page. Your eyes adapted to the large number of dots on the right in the previous image, giving rise to a striking visual aftereffect.



point to a deck of cards and ask, "How many?" There's no single correct answer. We first need to decide whether we're counting the number of decks (one) or the number of cards (52), even though the 52 cards and the deck are one and the same.

Frege observed that other quantities aren't like this. If we want to know how much the cards weigh, we toss them on a scale and read off our answer. It won't make a difference to their weight if we think of them as a single deck or as a collection of cards. The same goes for their volume. The cards take up the same amount of space whether we describe them as one deck or 52 cards. (Of course, if we remove one card from the deck, it will have a different weight and volume than the full deck does. But then we're changing what we're describing, not just how we're describing it.) If the number sense is sensitive to how stuff is described, we can guess that it truly represents numbers and not other quantities.

This is precisely what we find when we apply Frege's insights. Work by a team of researchers led by Steven Franconeri of Northwestern University gives a vivid illustration. In a 2009 study, they presented subjects with a sequence of two screens containing circles and thin lines. Similar to many of the abovementioned experiments, subjects were asked which screen had more circles. They were also told to ignore the thin lines entirely. But when lines happened to connect two circles, effectively turning the pair of circles into a single dumbbell-shaped object, the subjects underestimated the number of circles on the screen. It seems they couldn't help but see a dumbbell as one object, even when they were trying to ignore the connecting lines and focus only on the circles.

The observers were not simply tracking some other quantity such as the total surface area of the items or the total number of pixels on the screen. After all, whether two circles and a line are connected to make a dumbbell doesn't affect the total surface area or pixel number. What it would, and seemingly did, affect is the perceived number of items in the display. So just as describing something as a deck of cards versus a collection of individual cards influences how you count it, whether you visually interpret something as a single dumbbell or a pair of circles influences how many items you seem to see—exactly as Frege would have predicted for a visual system that tracks number.

None of this is to deny that the mathematical abilities endowed by the number sense differ dramatically from the mature mathematical abilities most human adults possess. If you ask children for exactly 15 jelly beans, only ones who have learned to count in language can honor your request. But that's no reason to suppose their number sense isn't representing number. Just as children can perceive and discriminate distances long before they can think about them precisely, they have the ability to represent numbers before they learn to count in language and think of numbers precisely.

> To understand how an infant develops into an Einstein, we must not underestimate babies' initial grasp of the world.

On their own, these innate mathematical abilities to perceive, add, subtract and operate over numbers are limited. But to understand how an infant develops into an Einstein, we must not underestimate babies' initial grasp of the world. To learn, we need something of substance to build on, and the number sense provides infants with part of the foundation from which new numerical abilities can arise—the ability to track coins and create monied economies, to develop modern mathematics or, more prosaically, to find those missing beers in the back of the fridge. SA

FROM OUR ARCHIVES

Big Answers from Little People. David Dobbs; *Scientific American Mind*, October 2005.

scientificamerican.com/magazine/sa

The number of gumballs in the jar on page 43 is 296.

BIOLOGY

THE SISTERHOOD

OF SPECIES

Studying connections among female animals across the tree of life can improve women's health

By Barbara Natterson-Horowitz

Illustration by Islenia Milien

Barbara Natterson-Horowitz is a cardiologist and evolutionary biologist on the faculties of Harvard University and the University of California, Los Angeles. She studies evolved adaptations in female animals that could improve women's health.

PROJECTED ON THE MASSIVE SCREEN BEHIND ME ONSTAGE, A HERD OF GIRAFFES rushes across a sweep of savanna. With the video set to loop, the giraffes gallop endlessly, giving me time to slowly lean across the podium and ask my audience: "Did you spot the pregnant giraffes?" I am delivering a plenary lecture at the 2019 Nobel Conference in Stockholm. The theme of that year's conference was bioinspired medicine—finding solutions in nature to human health problems—and I wanted to call attention to the connections between women and other female animals.

As a cardiologist and evolutionary biologist, I'd been posing this question about the giraffes to medical students in my courses at Harvard University and the University of California, Los Angeles, for years, so I could tell it had landed as planned. I watched the crowd scan the troop of giraffes for evidence of pregnancy—a baby bump, a lagging mother-to-be. I suspected that few, if any, of the assembled scientists and physicians had considered this question when first taking in the scene. That was precisely my point. Given the importance of female health challenges such as pregnancy to the survival of a species—including our own—shouldn't the realities of female life in the wild be more than an afterthought for doctors and biomedical researchers?

Predators pose a daily threat to survival for all prey species, and they don't give pregnant animals a pass. Even in their final, heaviest days of pregnancy, females must evade predators. To do so, they have evolved impressive physiological adaptations.

Consider a giraffe in the last weeks of her nearly 15-month gestation. She has gained hundreds of pounds—her fetus alone weighs up to 150 pounds, but the load is much heavier when you add in the placenta, extra fluid and fat. Yet pregnant giraffes appear to flee as fast as nonpregnant individuals. If they couldn't, predators would quickly target them as easy prey. That would be the end of the line for that mother, her gestating calf and ultimately the species itself.

As I publicly expressed admiration for the giraffe's gestational athleticism, I privately cringed a bit recalling how unathletic—how un-giraffe-like—I had felt as a cardiologist in the final weeks of my own pregnancies. I was the slowest doctor in the herd of physicians responding to code blue alerts for medical emergencies at the hospital. I'd become so breathless and exhausted rushing up just two flights of stairs that once, on my way to a cardiac arrest, another physician pulled me aside to express concern for my cardiac health.

I understood why they were worried. Late in pregnancy, women are at risk of developing life-threatening diseases such as preeclampsia and heart failure. Even a healthy pregnancy places significant stress on the heart. The volume of blood that is circulating expands nearly 50 percent. To deal with this increased workload, the cardiac cells and pumping chambers of the heart must grow and transform in size and shape. Cardiologists use the term "remodeling" to describe these changes, but when things go wrong, the consequences are far more serious than a misplaced sofa throwing off the feng shui. Problems with how the heart cells get remodeled during pregnancy are linked to reduced cardiac function and even heart failure soon after delivery.

Fortunately, my cardiac health turned out to be fine: the source of my shortness of breath and fatigue was the nearly 40 pounds of fetus, fluid and fat I'd packed on by the end of the third trimester. Slowing down in the last weeks of pregnancy is perfectly nor-

CHEETAHS and other predators need to be able to chase down prey during pregnancy.

StuPorts/Getty Images

mal for humans—including female cardiologists who can use the elevator instead of sprinting up the stairs.

But in the wild, pregnant animals must maintain their speed and stamina to save their lives. For pregnant gazelles, zebras, and other prey species, the ability to flee swiftly protects them from predation. The animals giving chase are often also female and sometimes also pregnant. To avoid starvation, pregnant cheetahs, hyenas, and other predators need to pursue, overtake and capture fleeing prey. A species in which pregnant females can't evade predators or capture food is doomed to extinction.

I've become fascinated by how females of other species have adapted to these challenges. I now study their biology to find possible solutions to women's health issues ranging from heart failure to breast cancer. This field of research is still emerging, but already it is generating insights that could lead to lifesaving treatments for some of the most prevalent human health concerns.

MISSING FEMALES

A MULTISPECIES APPROACH never would have occurred to me as a young professor of medicine in the 1990s. For the first 10 years of my career, I treated many forms of heart disease but always in one species—my own. Then, in 2005, I became a cardiovascular consultant to the Los Angeles Zoo. (Zoo veterinarians occasionally invite physicians to weigh in on diagnoses or assist in medical procedures, especially when the conditions are far more common in humans than in nonhuman animals.) My patient roster expanded to include great apes, bears, lions and raptors, among others. Animal health hadn't been included in my formal medical education, so the learning curve was steep. The zoo's veterinarians and the animals themselves became my teachers as I learned that most of the diseases affecting my human patients—cardiovascular disease and cancer among them—can also develop in other species.

Over the years I grew increasingly convinced that species-spanning medicine could reveal insights for

A CLUSTER of breast cancer cases in beluga whales near Montreal brought attention to a threat to human health.

Paul Souders/Getty Images

my patients that traditional human-centered approaches had not. Partnering with naturalist and science writer Kathryn Bowers, I made it my mission to raise awareness about the relevance of animal health to that of humans, launching educational and professional programs, leading research teams and writing books meant to bring the fields of human medicine, veterinary science and evolutionary biology closer together. The reception to these efforts was mostly positive, but I received a surprising degree of pushback from my own field of medicine. Some physicians seemed resistant to connecting the health of their patients and other species (beyond the transmission of certain diseases from animals to humans). Maybe they took issue with the humbling notion that veterinarians could teach them about their human patients.

Human exceptionalism, I could see, was deeply entrenched in our medical traditions. People haven't always been comfortable accepting that humans are animals. It has been my experience that human health professionals reflexively assume diseases they treat in their patients are unique to our species. (They aren't.)

Anthropocentrism wasn't the only distorted worldview slowing down the progress of medical science. Biomedical research has also long focused on males to the exclusion of females. Until 1993 the National Institutes of Health didn't require the clinical trials they funded to include women—not even studies of diseases known to be more common in women than men. Mind-bogglingly, it wasn't until 2015 that the NIH mandated the inclusion of female laboratory animals in preclinical safety studies of new medical treatments. There were rationales for not including females in biomedical studies: researchers wanted to avoid the potentially confounding effects of the estrus cycle, which can introduce variations in physiology and behavior not seen in males, and they wanted to protect potentially pregnant women, and fetuses, from thalidomide-type tragedies. Yet however well intended these investigators might have been, excluding females from studies proved enormously damaging to women's health.

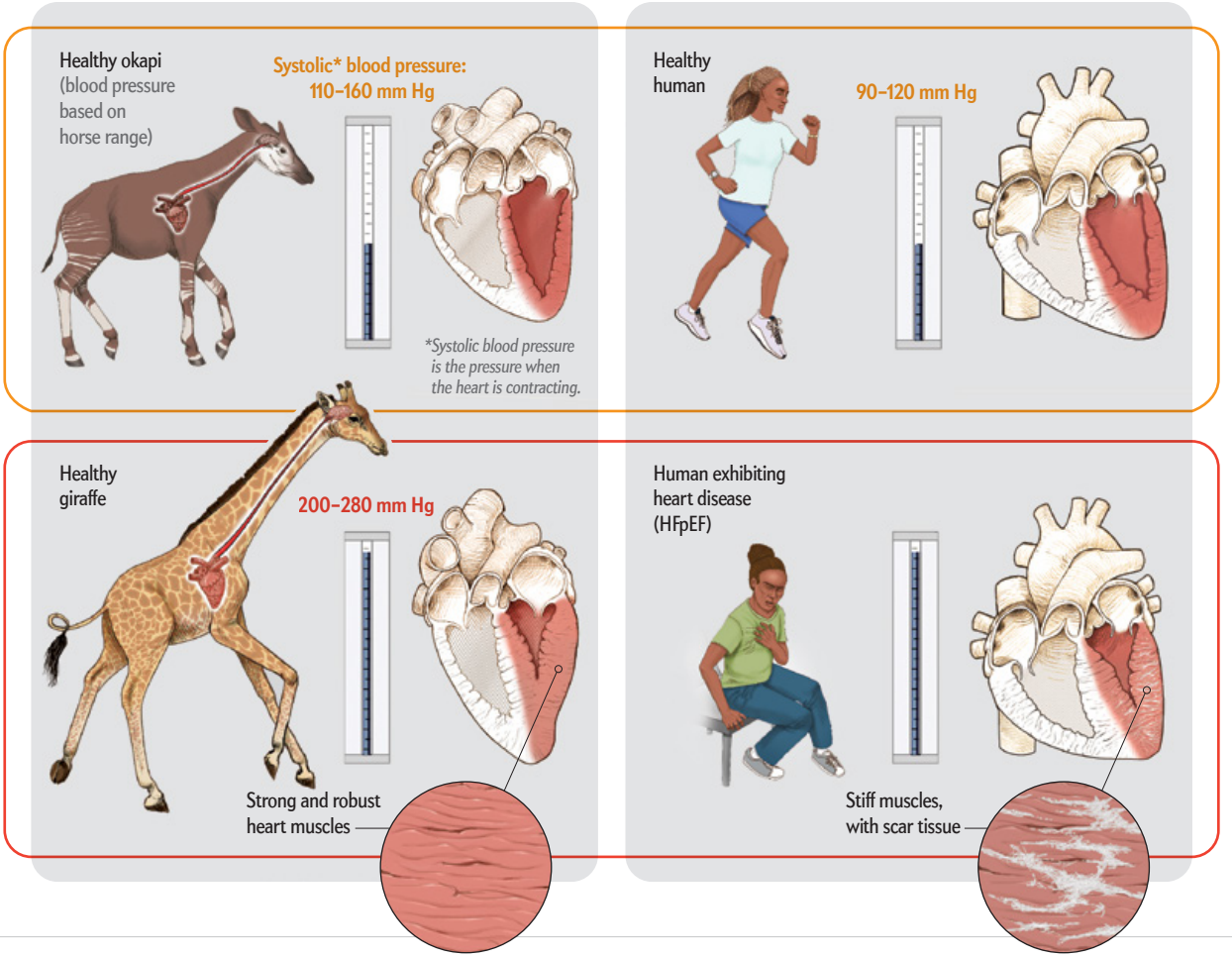
To address the gaps in our medical knowledge, I began to focus my species-spanning research on major challenges in women's health. The health connections between human and nonhuman females weren't hard to find. I've published studies on ovarian cancer in flamingoes, pythons, fish and humans; hosted symposia on menstrual difficulties in great apes (including us), bats and tree shrews; and collaborated with dairy veterinarians who have deep knowledge of lactation in cows to help women with common breastfeeding problems. These experiences have transformed my understanding not only of my patients but of myself as a female. I've learned when it comes to certain aspects of my health, I may have more in common with other female animals than with my husband, brother, son or the other men in my life. I call the shared bond that links human and animal females the "sisterhood of species."

LIONS GET BREAST CANCER

I FIRST GLIMPSED the connection among female animals while examining Cookie, a geriatric lioness, at

Under Pressure

Certain animals have evolved mechanisms that protect them from diseases that kill millions of women every year. The giraffe is one such creature. Its long neck is thought to have evolved as a means of monitoring its grassland habitat for predators and accessing leaves for food. But to pump blood to the brain, the giraffe has to endure high blood pressure. In humans, high blood pressure often leads to cardiac problems, including fibrosis, in which the heart muscle thickens and stiffens. Fibrosis of the heart can slow a person down and damage the organ over time. Despite having much higher blood pressure than a healthy human, the giraffe is able to maintain a large, fibrosis-free heart. The giraffe's closest living relative, the okapi, is a forest-adapted species that did not evolve a long neck. Comparison of the giraffe's genome with the okapi's has shown that the giraffe has mutations in the gene that codes for a growth factor protein called FGFRL1 that may suppress fibrosis of the heart.



the Los Angeles Zoo in 2021. After an operation, a lion's heartbeats sound pretty much the same as those of a human who has been through the same procedure. So the clarity of the lub-dup, lub-dups streaming through the stethoscope I had pressed against Cookie's huge, furry chest reassured me. It meant the dangerous buildup of fluid we had removed from the sac around her heart hadn't returned. The pathology report on the cause of the fluid buildup wasn't back yet, however, and the veterinarians were worried that it might be metastatic breast cancer. There were two reasons for this specific concern. First, breast cancer is one of the tumors that sometimes spreads to the heart, creating inflammation and the kind of fluid buildup that had threatened Cookie's life. The other reason, the veterinarians explained, was that compared with other zoo animals, lions, jaguars, cheetahs, and other cats are especially susceptible to breast cancer.

This connection between human and animal health was personal. Breast cancer is a health concern for many women, and I was no exception. Around the time I first learned about breast cancer in cats, I was being tested for the *BRCA* mutations following several borderline breast biopsies. The *BRCA* mutations are well known to put women at increased risk of

Graphic by Dino Pulerà

THE GIRAFFE'S unique biology shields it from the damaging effects of high blood pressure and could inspire treatments for heart disease in women.

Michel and Christine Denis-Huot/Biosphoto/Minden Pictures

breast and ovarian cancers. To my amazement, I learned that *BRCA* mutations also put some dog breeds, including Cavalier King Charles Spaniels, and certain other carnivores at increased risk. In all my years caring for women, as well as some men, with breast cancer, I hadn't considered what other species might also be vulnerable. In fact, as I showed in a recently published study, breast cancer is a threat across nearly all mammalian lineages, with cases found in creatures ranging from kangaroos and koalas to wombats and water buffalos.

Ultimately Cookie and I were both lucky. Cookie's fluid buildup turned out not to be cancerous, and she went on to live another four years. I tested negative for *BRCA* mutations, and my biopsies did not show breast cancer. Other creatures have not fared so well. But we have learned from their misfortune.

Whales don't usually develop breast cancer—leukemia and lymphoma are the more common cetacean cancers. So when researchers found that 27 percent of the dead belugas they examined in and around the St. Lawrence Estuary near Montreal between 1983 and 1999 had died of breast cancer, their discovery raised questions.

Looking for causes, investigators quickly locked on to several aluminum smelting factories near the estuary that were spewing chemicals known to induce breast and other cancers. The scientists determined that these chemicals probably contributed to the disease not only in the whales but also in humans who lived in the area and exhibited abnormally high cancer rates themselves. Recognizing the breast cancer "epidemic" in mammals living in this urban waterway helped to alert authorities to an environmental hazard that was also threatening human health.

Like the canaries that British coal miners brought with them to detect the presence of hazardous gases in the mines, the female belugas signaled that contaminants were putting humans at risk. Today rising levels of pollution are implicated in many challenges to women's health, including cancers, infertility, premature labor, and other disorders of the female reproductive system. Nonhuman female animals living around human communities are increasingly exposed to the same pollutants as women and girls, as the lines that once separated human and animal environments become blurred. Simply stated, the health of female animals is too important to our own to ignore. All female animals—including women and girls—are now canaries for one another. Our coal mine is the planet we share.

GIRAFFES AVOID HEART FAILURE

THE CONNECTION among female animals extends beyond shared vulnerabilities. Some members of the sisterhood have evolved unique physiologies to defend against disease. The remarkable biology of some female animals prevents them from falling prey to diseases that claim millions of women's lives every year. To understand how and why such unique biology

evolved and how it could save women's lives, consider my new take on the evolution of the giraffe and its improbably long neck.

Rewind to 11.5 million years ago, when the common ancestors of the modern giraffe and its closest evolutionary cousin, the okapi, roamed what is now Africa. Some of those ancestors wandered toward the rain forest and present-day Congo and eventually gave rise to the okapi. Other ancestors migrated toward the savanna and gave rise to the giraffe. Those differing environments helped to produce very different necks in these two lineages. In the rain forest, okapis were able to survive and thrive with perfectly fine albeit unspectacular necks. The ancestral giraffe's environments, in contrast, lacked dense foliage for hiding. A longer neck would have permitted horizon scanning and earlier detection of predators in an open grassland setting. At the same time, getting taller may have given proto-giraffes better access to sometimes limited foliage.

A downside to having a neck that places the head more than 2.5 meters away from the heart is that this all-important muscle must work harder with each beat to push blood vertically to the brain. This greater pressure on the heart is what we call blood pressure, and in a healthy giraffe, systolic blood pressure (the pressure when the heart is contracting) can exceed 250 millimeters of mercury (mm HG), compared with 120 mm HG or less for a healthy human.

Generally the problem with high blood pressure is that when a muscle like the heart works harder, it thickens. In humans and mice, when hearts thicken this way, they develop scarlike tissue, known as fibrosis. Hearts become stiffer than normal, limiting how far or fast an individual can move. To make matters worse, high blood pressure, also known as hypertension, can damage and weaken the heart over time. In humans, it results in a condition called HFpEF (for heart failure with preserved ejection fraction, pronounced "hef-pef"), which leads to exhaustion, shortness of breath and, potentially, death. HFpEF is the leading cause of heart failure in women, responsible for tens of thousands of deaths a year in the U.S. alone.

On the wide-open savanna, such stiffening could slow an animal down, threatening its survival. Hello, lion; goodbye, giraffe. But giraffes have found a workaround. Despite having blood pressure well above the levels that would earn human patients a stern talking-to from their doctor, both male and female giraffes can gallop at lion-evading speeds, and they appear to be resistant to HFpEF. Recent genomic research hints at how giraffes are able to flout the rules that constrain shorter animals.

In the past few years Chang Liu and his colleagues at Northwestern Polytechnical University in Xi'an, China, have published high-quality genomes of giraffe, okapi and other related animals. They discovered several mutations in the giraffe genome that are not found in the other species. One of the affected genes, *FGFRL1,* is linked to high blood pressure, which can lead to heart failure in humans. Could giraffe *FGFRL1* explain the longer-necked species' resistance to diseases associated with increased blood pressure?

To find out, the scientists tested two groups of mice to see how each would respond to an infusion of a hormone that causes blood pressure to rise. The first group of mice were "wild type," meaning that all their genes, including *FGFRL1,* were mouse genes. The second group had their *FGFRL1* sequence edited with CRISPR technology to mimic a giraffe's. After 28 days of exposure to the blood pressure–raising chemical, the wild-type mice had high levels of fibrosis, a common finding in humans with heart failure caused by hypertension. The hearts of the mice with giraffe *FGFRL1,* in contrast, appeared nearly fibrosis-free. This finding suggests that giraffes may have evolved a unique ability to suppress some of the damaging fibrosis of the heart.

Giraffes also appear to have evolved mechanisms to shield against other damaging effects of hypertension, including when it occurs during pregnancy. In humans, gestational hypertension—having high blood pressure during pregnancy—is pathological. A leading cause of fetal and maternal mortality, it occurs in up to 25 percent of pregnancies worldwide and is on the rise. For pregnant giraffes, in contrast, higher blood pressure is normal, and neither mothers nor babies seem to suffer any consequences from it. I've brought together a team of veterinarians, pathologists and OB-GYNs to uncover the unique biology that protects giraffes from gestational hypertension. We are comparing the placentas of giraffe and okapi, looking for clues to the evolution of this trait.

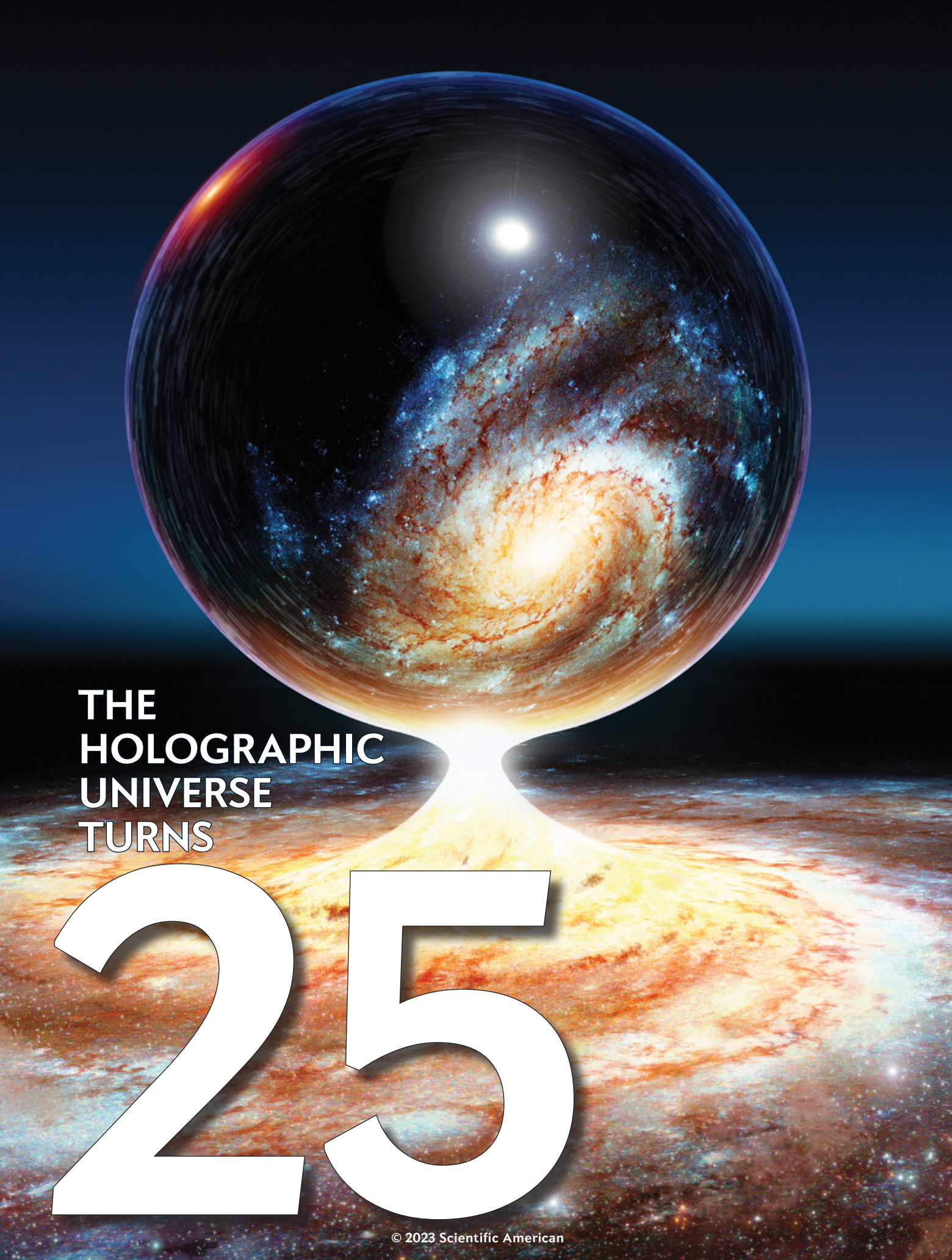
It will take time to figure out how to use the knowledge we obtain from such studies of female animals to prevent diseases in women. The principle is clear, though: many of the greatest threats to women's health may have already been neutralized in other species. The fixes are out there, in the bodies of the animals with whom we share our planet. As ingenious as we humans may be, the natural world is even smarter. Evolution's ability to solve problems is, according to Charles Darwin himself, "immeasurably superior to man's feeble efforts."

Rachel Carson is one of my scientific heroes, not only because she launched the modern environmental movement but also because she recognized the powerful connections across species. "In nature," she wrote, "nothing stands alone." I would add that no female stands alone. Members of the sisterhood of species are linked by common ancestry and the shared challenges and joys of being a female animal. SA

FROM OUR ARCHIVES

Not Just for Men. Marcia L. Stefanick; September 2017.

scientificamerican.com/çmagazine/sa



PHYSICS

The Ads/CFT duality conjecture, which suggests our universe is a hologram, has enabled many significant discoveries in physics

By Anil Ananthaswamy

Illustration by Kenn Brown, Mondolithic Studios

A QUARTER OF A CENTURY AGO a conjecture shook the world of theoretical physics. It had the aura of revelation. "At first, we had a magical statement … almost out of nowhere," says Mark Van Raamsdonk, a theoretical physicist at the University of British Columbia. The idea, put forth by Juan Maldacena of the Institute for Advanced Study in Princeton, N.J., suggested something profound: that our universe could be a hologram. Much like a 3-D hologram emerges from the information encoded on a 2-D surface, our universe's 4-D spacetime could be a holographic projection of a lower-dimensional reality.

Specifically, Maldacena showed that a five-dimensional theory of a type of imaginary spacetime called anti–de Sitter space (AdS) that included gravity could describe the same system as a lower-dimensional quantum field theory of particles and fields in the absence of gravity, referred to as a conformal field theory (CFT). In other words, he found two different theories that could describe the same physical system, showing that the theories were, in a sense, equivalent—even though they included different numbers of dimensions, and one factored in gravity where the other didn't. Maldacena then surmised that this AdS/CFT duality would hold for other pairs of theories in which one had a single extra dimension, possibly even those describing 4-D spacetime akin to ours.

The conjecture was both intriguing and shocking. How could a theory that included gravity be the same as a theory that had no place for gravity? How could they describe the same universe? But the duality has largely held up. In essence, it argues that we can understand what happens inside a volume of spacetime that has gravity by studying the quantum-mechanical behavior of particles and fields at that volume's surface, using a theory with one less dimension, one in which gravity plays no role. "Sometimes some things are easier to understand in one description than the other, and knowing that you're really talking about the same physics is very powerful," says Netta Engelhardt, a theoretical physicist at the Massachusetts Institute of Technology.

In the 25 years since Maldacena proposed the idea, physicists have used this power to address questions about whether black holes destroy information, to better understand an early epoch in the our universe's history called inflation, and to arrive at an astonishing conclusion that spacetime may not be fundamental—it may be something that emerges from quantum entanglement in a lower-dimensional system. These advances all involve the theoretically plausible spacetime of anti–de Sitter space, which is not the de Sitter space that describes our universe. But physicists are optimistic that they'll one day arrive at a duality that works for both. If that were to happen, it could lead to a theory of quantum gravity, which would combine Einstein's general relativity with quantum mechanics. It would also imply that our universe is in truth a hologram.

THE ORIGINS OF HOLOGRAPHY

IN DEVISING THE DUALITY, Maldacena was inspired by work by the late theoretical physicist Joseph Polchinski of the University of California, Santa Barbara. Using string theory, in which reality arises from the vibration of impossibly tiny strings, Polchinski developed a theory of objects called D-branes, which serve as the end points for strings that don't close in on themselves.

Maldacena looked at the conformal field theory describing D-branes without gravity on the one hand and an AdS theory with one more dimension of space and including gravity on the other. Maldacena noticed similarities between the two. Both theories were scale invariant, meaning the physics of the systems the theories described didn't change as the systems got larger or smaller. The lower-dimensional theory also had an additional symmetry—conformal invariance—where the physical laws don't change for all transformations of spacetime that preserve angles. The AdS theory describing the same objects in the presence of gravity showed similar symmetries. "That these two [theories] have the same symmetries was an important clue," Maldacena says.

The differences between the two theories were equally important. Crucially, the quantum field theory of D-branes was strongly coupled, meaning that particles and fields in the theory interacted strongly with one another. The AdS theory was weakly coupled—particles and fields interacted feebly. A lower-dimensional, weakly coupled CFT and its higher-dimensional, strongly coupled AdS counterpart share the same inverse relationship. Making a calculation is simpler in the weakly coupled system, but because the theories are equivalent, the results can apply to the strongly coupled theory without having to do often impossible calculations.

Maldacena described his discovery in a paper that he submitted to a preprint website in November 1997 and eventually published in the *International Journal of Theoretical Physics*. The idea took some time to sink in. "There were hundreds, thousands of papers, just checking [the duality] because at first, it [seemed] so ridiculous that some nongravitational quantum theory could actually just be the same thing as a gravitational theory," Van Raamsdonk says. But AdS/CFT held up to scrutiny, and soon theorists were using it to answer some confounding questions.

One of the first uses of AdS/CFT involved understanding black holes. In the 1970s Stephen Hawking showed that black holes emit thermal radiation, in the form of particles, because of quantum-mechanical effects near the event horizon. Eventually this "Hawking" radiation would cause a black hole to evaporate—which posed a problem. What happens to the information contained in the matter that formed the black hole? Is that information lost forever? Such a loss would go against the laws of quantum mechanics, which say that information cannot be destroyed.

In 2006 physicists Shinsei Ryu and Tadashi Takayanagi, then both at the University of California's Kavli Institute for Theoretical Physics, used the AdS/CFT duality to establish a connection between two numbers, one in each theory. One pertains to a special type of surface in the volume of spacetime described by AdS. Say there's a black hole in the AdS theory. It has a surface, called an extremal surface, which is the boundary around the black hole where spacetime makes the transition from weak to strong curvature (this surface may or may not lie inside the black hole's event horizon). The other number, which pertains to the quantum system being described by the CFT, is called entanglement entropy—it's a measure of how much one part of the quantum system is entangled with the rest. The Ryu-Takayanagi result showed that the area of the extremal surface of a black hole in the AdS is related to the entanglement entropy of the quantum system in the CFT.

The Ryu-Takayanagi conjecture promised something alluring. As a black hole evaporates in AdS, the area of its extremal surface changes. As this area changes, so does the entanglement entropy calculated in the CFT. But however the entanglement changes, the holographic surface described by the CFT evolves according to the rules of quantum mechanics, meaning that information is never lost. This equivalence implied that black holes in AdS were also not losing information. There was a hitch, though. The Ryu-Takayanagi formula works only in the absence of quantum effects in the AdS theory. "And of course, if a black hole is evaporating, it is evaporating as a result of small quantum corrections," Engelhardt says. "So we can't use Ryu-Takayanagi."

In 2014 Engelhardt and Aron Wall of the University of Cambridge found a way to calculate the extremal surface area of a black hole that is subject to the kind of quantum corrections that cause Hawking radiation. Then, in 2019, Engelhardt and her colleagues, along with another researcher working independently, showed that the area of these quantum extremal surfaces can be used to calculate the entanglement entropy of the Hawking radiation in the CFT and that this quantity does indeed follow the dictates of quantum mechanics, consistent with no loss of information. (They also found that the quantum extremal surface lies within the black hole's event horizon.) "This finally gave us a link between something geomet-

Anil Ananthaswamy is author of *The Edge of Physics* (Houghton Mifflin Harcourt, 2010), *The Man Who Wasn't There* (Dutton, 2015), and *Through Two Doors at Once: The Elegant Experiment That Captures the Enigma of Our Quantum Reality* (Dutton, 2018).

ric—these quantum extremal surfaces—and something that's a litmus test of information conservation, which is the behavior of the entropy [when] information is conserved," Engelhardt says. "Without AdS/CFT, I doubt we'd have arrived at these conclusions."

The connection between entanglement entropy in the CFT and the geometry of spacetime in the AdS led to another important result—the notion that spacetime on the AdS side emerges from quantum entanglement on the CFT side, not just in black holes but throughout the universe. The idea is best understood by analogy. Think of a very dilute gas of water molecules. Physicists can't describe this system using the equations of hydrodynamics because the dilute gas does not behave like a liquid. But suppose the water molecules condense into a pool of liquid water. Now those very same molecules are subject to the laws of hydrodynamics. "You could ask, originally, where was that hydrodynamics?" Van Raamsdonk says. "It just wasn't relevant."

Something similar happens in AdS/CFT. On the CFT side, you can start with quantum subsystems—smaller subsets of the overall system you're describing—each with fields and particles, without any entanglement. In the equivalent AdS description, you'd have a system with no spacetime. Without spacetime, Einstein's general relativity isn't relevant, in much the same way that the equations of hydrodynamics don't apply to a gas of water molecules. But when the entanglement on the CFT side starts increasing, the entanglement entropy of the quantum subsystems begins to correspond to patches of spacetime that emerge in the AdS description. These patches are physically disconnected from each other. Going from patch A to patch B isn't possible without leaving both A and B; however, each individual patch can be described using general relativity.

Now, increase the entanglement of the quantum subsystems in the CFT even more, and something intriguing happens in the AdS: the patches of spacetime begin connecting. Eventually you end up with a contiguous volume of spacetime. "When you have the right pattern of entanglement, you start to get a spacetime on the other side," Van Raamsdonk says. "It's almost like the spacetime is a geometrical representation of the entanglement. Take away all the entanglement, and then you just eliminate the spacetime." Engelhardt agrees: "Entanglement between quantum systems is important for the existence and emergence of spacetime." The duality suggested that the spacetime of our physical universe might simply be an emergent property of some underlying, entangled part of nature.

Van Raamsdonk credits the AdS/CFT correspondence for making physicists question the very nature of spacetime. If spacetime emerges from the degree and nature of entanglement in a lower-dimensional quantum system, it means that the quantum system is more "real" than the spacetime we live in, in much the same way that a 2-D postcard is more real than the 3-D hologram it creates. "That [space itself and the geometry of space] should have something to do with quantum mechanics is just really shocking," he says.

TOWARD A THEORY OF QUANTUM GRAVITY

ONCE SPACETIME emerges in a theory, physicists can use it to study aspects of our universe. For example, our cosmos is thought to have expanded exponentially in the first fractions of a second of its existence during inflation. In the standard model of cosmology, theorists start with a spacetime in which particles and fields interact weakly and let inflation proceed for about 50 to 60 "*e*-folds," where each *e*-fold represents more than a doubling of the volume of spacetime (as it increases by a factor of Euler's number *e,* or approximately 2.718). Such inflation can replicate the properties of the observed universe, such as its flatness and isotropy (the fact that it looks the same in all directions).

But there's no reason to think that inflation stops at 60 *e*-folds. What if it goes on for longer? It turns out that if physicists design models of our universe in which inflation goes on for, say, 70 *e*-folds or more, then the initial state of the universe must be strongly coupled—that is, it has to be one in which fields and particles can interact strongly with each other. A model that allows for this prolonged expansion would be more general (meaning it could apply to multiple possible versions of the universe), but calculations involving strongly coupled spacetimes are nearly impossible to compute. And that's where the AdS/CFT approach comes in.

Horatiu Nastase of São Paulo State University–International in Brazil has shown how to use the AdS/CFT duality to study a strongly coupled initial state of the universe. It's possible because the CFT side of the duality turns out to be weakly coupled, making calculations tractable. These calculations can then be used to determine the state of the AdS after, say, 70-plus *e*-folds. Nastase has found that a strongly coupled spacetime that inflates for at least 72 *e*-folds can replicate certain observations from our own cosmos, with some fine-tuning of the model's parameters. In particular, the model can match the kind of fluctuations seen in the cosmic microwave background, the fossil radiation from the big bang. "This is ongoing work," Nastase says. "There are a number of issues that are not yet clear."

Physicists hope that insights like these will get them to a theory of quantum gravity for our own universe. The lack of such a theory is one of the biggest open problems in physics. One fundamental insight from AdS/CFT is that any theory of quantum gravity will most likely be holographic, in that it'll have a dual description in the form of a theory with one fewer dimension, without gravity.

The AdS/CFT community is working hard to generalize the correspondence to spacetimes that are more representative of our universe. In AdS, researchers can create a spacetime with cosmic constituents such as black holes, but the spacetime has to be "asymptotically empty," which means that as one goes farther and farther away from a black hole, space becomes empty. "In describing our own universe, we assume that there's stuff everywhere as far as you go," Van Raamsdonk says. "You're never going to run out of galaxies." Also, in AdS, empty space has negative curvature, whereas the empty de Sitter space of our universe is mostly flat.

As influential as AdS/CFT has proved, the duality still uses a spacetime that does not describe our own reality. Maldacena hopes researchers will find a similar correspondence between de Sitter space—the spacetime we occupy—and a CFT. "I would very much like to have [a] similar statement for de Sitter," he says. "People keep thinking about it, but no clear contender has emerged so far."

Van Raamsdonk is optimistic that such a candidate will emerge. "If it turns out our own universe has some underlying holographic description, if this is really how it works, then I think understanding AdS/CFT will be at the level of understanding quantum mechanics, at the level of understanding general relativity," he says. "[It would be] as big of a leap in our understanding of the universe as anything else that's happened in the history of physics." SA

FROM OUR ARCHIVES

Black Holes, Wormholes and Entanglement. Ahmed Almheiri; September 2022.

scientificamerican.com/magazine/sa

PSYCHIATRY

A Talking Cure for Psychosis

Cognitive-behavioral therapy helps to treat symptoms for which drugs are ineffective

By Matthew M. Kurtz

Schizophrenia is a mental disorder that, at its worst, ravages the totality of everyday life. It is hard to imagine what people with the severest forms of the ailment experience as anything but biologically driven, a direct consequence of aberrant chemical and electrical activity occurring deep within the brain.

As a neuropsychologist, I have often seen convincing evidence of schizophrenia's biological underpinnings in my dealings with patients. To illustrate what I mean, I will describe "Billy"—a composite profile derived from various patients I encountered in my work at the Institute of Living

in Hartford, Conn. Billy exhibits the detachment from reality and emotional agony brought on by a psychotic episode, symptoms experienced by many people with schizophrenia.

Think of Billy as a 35-year-old man who lopes from one corner of a psychiatric hospital to another, gazing down at his feet and repeating, "Billy likes model trains. Billy likes model trains. Billy likes model trains." When a clinician on the unit asks Billy about his treatment goals, he replies, "Saturn is going to crash into Mother Earth." Billy was recently flooded with anxiety as he became convinced that the Blob, the smothering gelatinous substance from the 1958 science-fiction movie of the same name, was about to engulf his neighborhood.

Billy's severe psychotic episodes point to a brain in disequilibrium and, correspondingly, to the need for drugs and treatments to alter this pathology as a basic standard of care. Findings from decades of research and clinical practice support the crucial role of antipsychotic medications, which interfere with the transmission of the brain neurotransmitter dopamine, in the attenuation of delusions, hallucinations and other symptoms that are so apparent in Billy's case.

Yet key features of schizophrenia, such as reduced spoken communication and inappropriate expression of emotions, remain entirely untouched by pharmacological interventions. Similarly, these medications make little difference in the social disability that characterizes the disorder: the chronic unemployment, social withdrawal and isolation, high suicide rates, and abbreviated life spans that typically coincide with a diagnosis. None of these medications has been found to help prevent the onset of the disorder in people at high risk because of family history and mild psychological symptoms that are not severe enough to meet criteria for a diagnosis of schizophrenia.

Research in the psychological sciences and related disciplines is now broadening understanding of both the emergence of schizophrenia and its treatment. These newer approaches focus on psychosocial stress and the patients' own belief systems. Methodologically rigorous, large-scale, population-based studies are delving more deeply into environmental factors linked to disease onset. Other research has shown that talk-based psychotherapy may be able to constrain the aberrant beliefs associated with schizophrenia.

Medical professionals are starting to pair therapy with methods to strengthen thinking skills. For the past 20 years my laboratory has studied ways to measure and improve concentration, memory and problem-solving. The results of these studies show that impairment in these thinking skills, even beyond other, more visible symptoms, often stands in the way of functional improvement for people with schizophrenia and related illnesses. Such work has led to a much more nuanced view of the disorder that highlights psychological factors and complements the biological models that have dominated the field.

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THE PATHOLOGICAL PARENT

FOR MUCH of the 20th century and as recently as 50 years ago, cases such as Billy's were viewed in many professional quarters as resulting from a disorder of the mind that was rooted in pathological parenting styles and influenced by cultural milieus. Sigmund Freud's inordinate influence on psychiatry, particularly in the U.S., led professionals in that field to view illnesses through a lens of environmental factors centered on unresolved family trauma, with talk therapy being the key to relief. But this approach yielded scant success.

The first psychological models of schizophrenia declined in favor for a number of reasons, including stubbornly high psychiatric hospitalization rates and persistently poor outcomes, even among patients with access to the most intensive psychological care and therapy. Charismatic health-care providers developed treatments based on their own theories and supported their claims with isolated case studies rather than exacting scientific data. Many psychotherapists of this era resisted randomized, controlled trials. Solid evidence that the prevailing treatments worked for most patients never materialized.

A watershed event occurred in 1952 with the publication of a clinical trial of chlorpromazine at St. Anne's Hospital in Paris, heralding the arrival of a new class of drugs known as antipsychotic medications. These pharmaceuticals moderated irrational, often paranoid beliefs and hallucinations for many people with schizophrenia, stabilizing them in the hospital and, in many cases, allowing them to reenter the community for the first time in years. The psychological approach to treatment became less dominant as therapists embraced pharmacological therapies targeting the brain.

Three additional factors played a pivotal role in reinforcing the view of schizophrenia as a neuroscientific entity. First there was a new focus on psychiatric illnesses as diseases with consistent signs and symptoms, just like other medical illnesses, which meant they could be studied through rigorous biological analysis. This medical model made it much more likely that patients with similar patterns of symptoms would reliably receive the same psychiatric diagnosis.

The second factor was the emergence of highly detailed imaging technologies that researchers used to look first at the brain's structure and later at the function of its various regions. By the early 2000s it was becoming clear that people with schizophrenia had reductions in brain activity and tissue volume across a broad range of neural systems, particularly in the frontal and side (temporal) brain lobes. Researchers replicated these findings and discerned these changes even in patients experiencing their first episode of schizophrenia, before they had received any antipsychotic therapy.

Third, the mapping of the human genome in the early 2000s and the development of cheaper technology for identifying genetic variants raised the possibility of determining which genes put people at the great-

est risk for schizophrenia. Studies have identified more than 100 locations on DNA that confer increased susceptibility to the disorder. If researchers could use this genetic analysis to identify aberrant protein synthesis, new drugs could be formulated to interfere with this process.

A NEW ERA OF PSYCHOLOGY

SCIENTISTS HAVE MADE undeniable advancements in the neurological and genetic understanding of schizophrenia. But over the past 20 years a growing body of work has suggested yet another revised view of the disorder. Much of this research comes from academic precincts neighboring neuroscience—not just psychology but epidemiology and anthropology. This fresh perspective goes beyond the physiology of schizophrenia to encompass personal belief systems, social interactions and the destructiveness of psychological stress. It also emphasizes the importance of the environment in which a patient lives in explaining the origins of symptoms, not just for schizophrenia but for related psychoses, such as bipolar disorder with accompanying psychotic symptoms.

The field's return to a psychological emphasis is a product, in part, of neuroscience's failure to deliver clear answers about schizophrenia despite its promise for identifying the neural underpinnings of psychiatric conditions. Hundreds of informative structural and functional neuroimaging studies have identified locations in the brains of affected people where there is diminished tissue volume or aberrant activity. But huge genome-wide association studies—which recruit thousands of patients to pinpoint genetic variants that may place people at higher risk for schizophrenia—have failed to define the causes of the illness. So far none of these findings has led to the development of drug treatments that meaningfully alter the course of the disorder.

Evidence from recent studies has helped bolster renewed interest in the psychological underpinnings of schizophrenia. These are rigorous, well-designed, large scientific studies in which researchers carefully quantified patients' experiences, using measures that are consistent over time and that have been validated with other forms of evidence. New psychological therapies undergo testing to minimize biases that might affect whether a treatment is judged effective. Markers of patients' improvement in these studies are standardized and made objective, and study participants and their evaluators often do not know whether participants are in a treatment or a control group. This type of study design helps to ensure that participants don't appear to improve simply because they or their evaluators believe they should be getting better.

Such studies have produced a consensus that adverse experiences and environments contribute in important ways to the development of schizophrenia. For example, rates of psychosis are dramatically higher in some minority immigrant communities compared with those of the native-born populations in their adopted countries. The United Kingdom Aetiology and Ethnicity Study in Schizophrenia and Other Psychoses (AESOP) followed patients who sought clinical treatment starting with their first episode of psychosis. The investigators used census data to obtain estimates of incidence rates, and diagnoses were based on chart notes and a standardized interview and were analyzed by psychiatrists who never learned the patients' ethnicity.

AESOP confirmed previous findings that African-Caribbean and Black African people living in the U.K. were diagnosed with schizophrenia at a rate as much as five to 10 times higher than that of white Britons. A study of the incidence of psychosis in a broader range of immigrant groups—from the Middle East, North Africa, China, Vietnam and Japan—showed that their likelihood of developing psychosis was almost three times greater than that of white Britons. (People from these regions were combined into one study group because the size of each ethnic group alone was too small to be statistically meaningful.) Some aspect of the immigrant experience or a person's minority status, or a combination of these two factors, appeared to be contributing to elevated rates of schizophrenia. More important, these rates were typically much higher than those in the migrants' countries of origin.

Rigorous scientific studies have brought a renewed focus on schizophrenia's psychological roots.

The authors found that psychological and social stresses correlated with the increased incidence of schizophrenia in minority ethnic groups. Separation from a parent during childhood was associated with rates of diagnosis two to three times higher than among people whose families had remained intact. A variety of other markers of social disadvantage, including unemployment, living alone, being single, a lack of formal education and limited social networks, all increased the likelihood of schizophrenia onset in various ethnic groups. White Britons showed similar links between psychosocial stressors and the likelihood of schizophrenia, but immigrant minority groups experienced those stressors more frequently.

Social discrimination may also increase a person's chances of developing schizophrenia. A study from the Netherlands looked at all non-Western immigrants seeking services for a first episode of psychosis in The Hague between 2000 and 2005. The researchers studied minority groups from Morocco, the Antilles, Suriname and Turkey, among other regions, and interviewed members of these groups about the per-

ceived levels of discrimination they encountered. Moroccans, the ethnic group that experienced the most discrimination, showed the highest incidence of psychosis, whereas ethnic groups reporting less bias (Turks, Surinamese and others) had lower rates.

The European Network of National Schizophrenia Networks Studying Gene-Environment Interactions (EU-GEI) took a detailed look at the contribution of immigration in the emergence of psychosis. Using a data set of more than 200 migrants and 200 control participants matched for a variety of variables, including family history of psychosis, the authors defined indicators of social disadvantage for each phase of immigration. In the premigration phase, indicators consisted of parental social class, type of employment and whether the participant lived with their family of origin. In the active migration process, indicators consisted of age, whether the person was detained at any point during immigration and whether they had any plans to return to their country of origin. For the postmigratory phase, the measures included employment during the previous five years, long-term relationships and family structure.

Social disadvantages and adversity in the migrant experience doubled the chances of developing psychosis.

The study found that among first-generation migrants, social disadvantages and adversities during the premigration and postmigration phases doubled a person's chances of developing psychosis even when other risk factors such as cannabis use and age were statistically controlled for. Mismatches between the expectations people held before leaving their native countries and their actual postmigration achievements were also associated with an increased likelihood of psychosis. The risk of illness increased with the number of cumulative adversities. These findings all suggest that providing psychological support to immigrants might alter the onset of schizophrenia in those who are facing high levels of social adversity.

HEARING VOICES

PEOPLE FROM DIFFERENT cultures experience psychosis in distinct ways. Psychological anthropologist T. M. Luhrmann and her collaborators have shown that the emotional tone of auditory hallucinations may vary widely across cultures, suggesting that what one hears may be influenced by cultural expectations. Those in subcultures that have encountered the violence of war or other social upheaval may experience loud or disruptive hallucinations, whereas those with dense family ties may have more benign symptoms.

Luhrmann's research team conducted structured interviews of people diagnosed with schizophrenia, most of them ill for years, from the U.S., Ghana and India. The researchers asked people how many voices they heard, how often they heard them, what their opinion of these voices was and what they believed was the source. In general, the results support the idea that schizophrenia is a biologically based condition that manifests similarly across cultures. Participants in all three countries heard "good" and "bad" voices. Some reported having back-and-forth conversations with the voices they heard, and others thought the voices came from God. At every site, at least some participants disliked their voices and viewed them as an intrusion on their daily mental life.

Many of the symptoms were similar across groups, but the interpretation and consequent emotional tone of these hallucinatory experiences diverged substantially across cultures. Participants in the U.S. were much more likely to use an unadorned clinical diagnostic label—"I am a schizophrenic"—to describe their lives. They tended to report violent imagery associated with their voices more frequently than participants from India or Ghana.

In the other two countries, people were more likely to maintain close relationships with their voices and less apt to describe them as the expression of a mind violated by auditory hallucinations. In Ghana, study participants insisted that voices spoken by an invisible person were controlled by God and that at times evil voices were entirely absent. Rarely did people there describe voices as an intrusion on their everyday mental life. Participants from India often experienced their voices as those of family members. They said the voices conveyed a mix of agreeable and unpleasant utterances but did not have stressful or harsh overtones.

COGNITIVE-BEHAVIORAL THERAPY

IF CULTURAL ATTITUDES exert such a profound effect on the experience of symptoms, that insight holds promise for psychotherapies. It raises the possibility that talking to people with schizophrenia and offering them strategies for changing the way they think about their symptoms can reduce the distress those symptoms cause.

An important question is whether altering beliefs around symptoms can improve people's ability to function in society. A growing body of scientific literature suggests such a goal is achievable. A form of cognitive-behavioral therapy (CBT) has been developed specifically to treat psychosis. It focuses on detrimental thinking—intrusive thoughts that crop up such as "Why even try? I always fail."

The aim of CBT is to help people deal with their emotional and behavioral responses to psychological experiences that cause distress. Atypical or disproportionate responses, which are often among the most

debilitating of schizophrenia's symptoms, can make it difficult to carry out daily tasks. Patients undergoing CBT are taught to think about their symptoms in a new way. They might tell themselves, "The voices in my head don't have to make me anxious; it is the way I think about them that makes me anxious."

People with schizophrenia commonly believe their voices are all-knowing, all-powerful and uncontrollable. CBT can generate alternative explanations for these auditory hallucinations. It can begin a process of interrogating and weakening unhelpful beliefs. A clinician might suggest that a voice a client hears could be that of a family member as opposed to a deity or the devil. The doctor might frame this for the patient in a simple question and statement: "Are we certain that the voice you hear is not your father? Many of the statements the voice makes seem to be similar to ones you have attributed to your father in the past." Such reconsideration of a voice's meaning can lead to a significant decrease in the distress associated with the hallucination.

Other strategies include behavioral tasks to show that voices are not in fact uncontrollable. A therapist might lead a client in an activity—walking outside or listening to music on headphones—to help the person quiet the constant chatter, gain mastery over their symptoms, and disrupt their beliefs about the voices being an inevitable, eternal intrusive presence. The client also might try simply ignoring the stream of commands issued by their inner voices. This can undermine their belief that the commands from hallucinations must be followed or terrible consequences will ensue. When the client discovers that ignoring voices does not produce some feared catastrophe, the realization supports the counterargument that their voices are not all-powerful.

Research provides evidence that this suite of interventions may be effective even for people with the most severe symptoms. In one of the most remarkable demonstrations of the benefits of therapy for psychosis to date, CBT pioneer Aaron Beck, in some of the most influential work he conducted before his death in 2021 at the age of 100, worked with Paul Grant and their colleagues at the University of Pennsylvania to evaluate the impact of a modified approach to CBT that addresses the needs of low-functioning people with schizophrenia. Their study was published in 2012 in *Archives of General Psychiatry*.

The patients they worked with had moderate to high levels of what are labeled negative symptoms of schizophrenia: low motivation, diminished pleasure in life, near absence of spoken language, and reduced emotional expressiveness to the point that they maintained a "wooden" expression during social interactions. Among the most disabling, these symptoms are also the hardest to treat with medication and are disproportionately represented in the most persistently ill patients. People with a high intensity of negative symptoms also typically have the most elevated levels of cognitive distortions and biases. To date, there is no pharmaceutical treatment for negative symptoms.

In the study, participants were randomly assigned to either a control group, in which patients were given standard treatment, including prescribed drugs, or a test group, in which they received CBT in addition to the standard therapy. The CBT was intended to help clients establish long-term goals (seeking independent housing, relationships or a job) as well as intermediate- and short-term goals (calling a friend that day).

Therapy can quiet the train of negative thoughts—beliefs such as "taking even a small risk is foolish because the loss is likely to be a disaster" and "making new friends is not worth the energy it takes." Participants in the CBT group also took part in exercises, games, role-playing and community outings designed to instill belief in their own abilities. The benefits of this therapy persisted for months after treatment ended. Clients assigned to CBT had meaningful improvements in functioning—better motivation and reduced delusions and hallucinations—compared with patients who received only standard treatment.

From what researchers have learned in recent years, adverse experiences increase the likelihood that someone will develop schizophrenia. In addition, the cultural context in which people experience symptoms may affect their ability to come to terms with those symptoms. All these findings support the argument that key aspects of schizophrenia are rooted in the psychology of stress and trauma and in attitudes and biases that are shaped by the persistent lingering of a patient's mental anguish. Treatments designed to address negative biases and societal discrimination and stigma can improve symptoms and functioning in people with schizophrenia, which further highlights the key role that psychology is starting to play in understanding and treating the disorder.

None of these findings throws into question the changes in brain structure that accompany schizophrenia or the genes currently implicated in the disorder. What they suggest is that if methods of prevention and treatment for schizophrenia are to progress, increased public health focus on mitigation of damaging social experiences, along with therapies focused on psychological beliefs and attitudes, is critical.

Psychological therapies need to be prioritized by both practitioners and federal funding agencies and placed on more equal footing with gene and brain-imaging studies. Psychoactive medications will only take a person with schizophrenia so far in adapting to the personal struggles their condition brings. That is why an interaction with a therapist able to question their ideas and basic beliefs is also essential to make peace with the din of voices in their head. SA

FROM OUR ARCHIVES

Listening to Culture. Gary Stix; January 1996.

scientificamerican.com/magazine/sa

Katie Peek is a science journalist and data-visualization designer with degrees in astrophysics and journalism. She is a contributing artist for *Scientific American*.

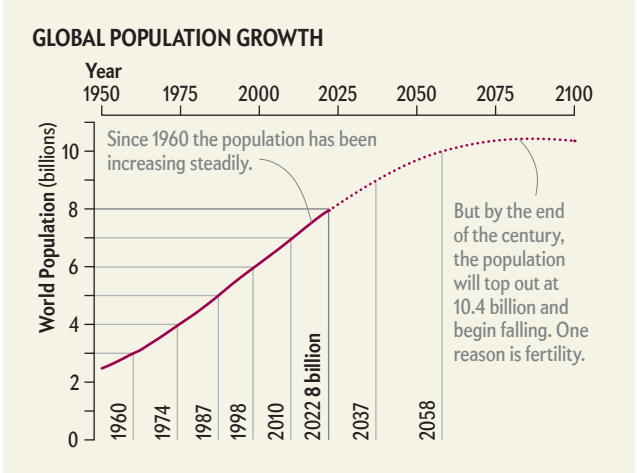
DEMOGRAPHY

Population Growth Is Slowing Down

In 2022 the world's population hit eight billion. But the number of people on Earth will likely top out during this century

Text and Graphics by Katie Peek

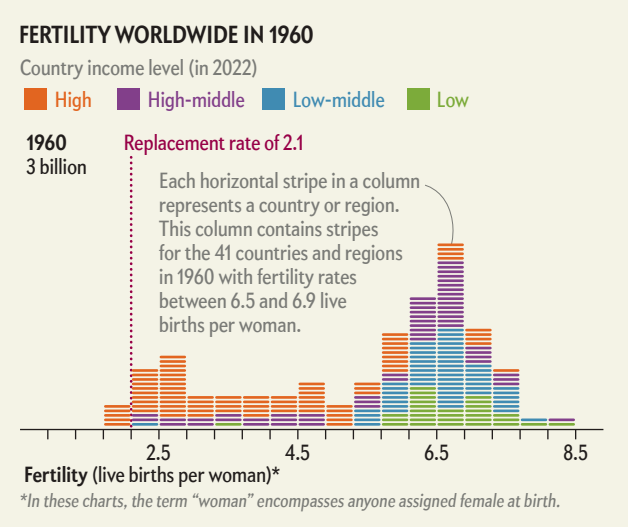
ON NOVEMBER 15, 2022—AS ESTIMATED BY DEMOGRAPHERS—THE COUNT of humans on this planet reached eight billion. Population growth has been steady over the past few decades, with billion-person marks coming every dozen years or so. But that pattern is changing. Growth is beginning to slow, and experts predict the world's population will top out sometime in the 2080s at about 10.4 billion.



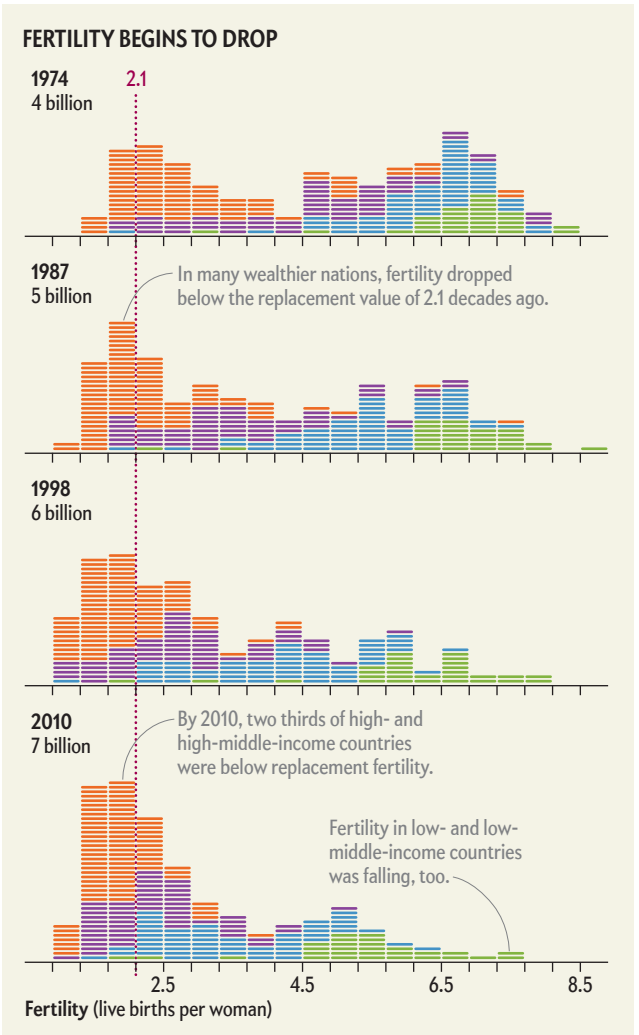
That slowdown is partly the result of a shift toward fewer offspring—a phenomenon that is happening almost everywhere around the world, though at different rates. High-income nations now have the lowest birth rates, and the lowest-income nations currently have the highest birth rates. "The gap has continued to widen between wealthy nations and poorer ones," says Jennifer Sciubba, a social scientist at the Wilson Center in Washington, D.C., who has written about these planetary-scale demographic shifts. "But longer term," she says, "we're moving toward convergence." In other words, this disparity among nations' birth rates isn't a permanent chasm. It's a temporary divide that will narrow over the coming decades.

Many factors contribute to the waxing and waning of the world's population, such as migration, mortality, longevity and other major demographic metrics. Focusing on fertility, however, helps to illuminate why the total number of humans on Earth seems set to fall. Demographers define fertility as the average total number of live births per female individual in a region or country. (In the accompanying graphics, the term "woman" is used to encompass anyone assigned female at birth.) The U.S.'s present fertility rate, for example, is about 1.7; China's is 1.2. Demographers consider a fertility rate of 2.1 to be the replacement rate—that is, the required number of offspring, on average, for a population to hold steady. Today birth rates in the wealthiest countries are below the replacement rate. About 50 percent of all nations fall below the replacement rate, and in 2022 the region with the lowest fertility rate (0.8) was Hong Kong. Over the coming decades most of the rest of the world's countries will likely follow suit. Here's how that might look.

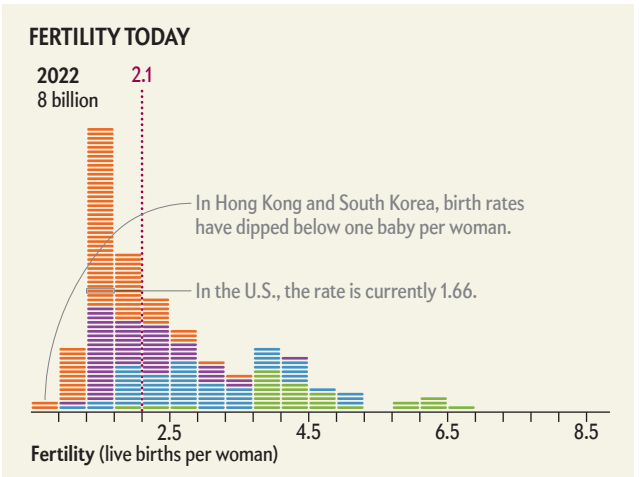
In 1960, when the world's population was three billion, nearly every country had a fertility rate above 2.1 live births per woman.



But over the subsequent decades that began to change. A country's fertility rate tends to be correlated with its average income. Wealthier countries were the first to move toward fewer offspring, but lower-income countries are also following the same trend.

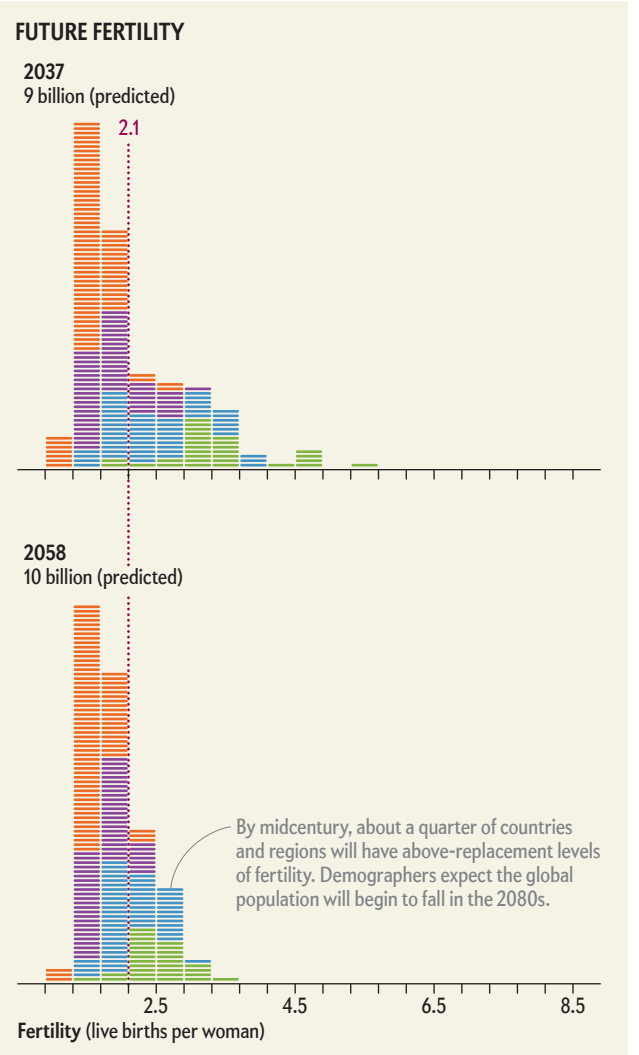


Here's the picture today, as we crest eight billion.



Sources: World Population Prospects 2022, United Nations Population Division (*data*); World Bank (*income categories*)

Fertility was especially disparate in higher- and lower-income countries from the 1990s through today. But by the end of this century fertility rates worldwide will reconverge at a lower number.



These numbers provide insight into how—and where—the population growth rate is changing. But humanity's future clearly depends on many things besides fertility. For example, people in wealthier nations may produce fewer children, but those offspring tend to consume more resources—so rich countries can still have outsize planetary impacts despite their dwindling populations. Organizations such as the United Nations Department of Economic and Social Affairs—which tracks and predicts human population numbers—are working toward policy-based solutions for how all of us can have healthy, satisfying and sustainable lives on Earth. A clear-eyed understanding of population shifts is critical for reaching that bright future. SA

FROM OUR ARCHIVES

Data Captured COVID's Uneven Toll. Amanda Montañez et al.; March 2022.

scientificamerican.com/magazine/sa

Growing Older Means Less Stress

Good news: people report that worries and anxiety drop away as they age

By Daisy Yuhas

No one is a stranger to stress. Decades of research make it clear that major life events, such as the death of a loved one or the start of a new job, can take a lot of our energy and attention. But recently scientists have begun to reveal how smaller daily stressors can create substantial difficulties. David Almeida, a developmental psychologist at Pennsylvania State University, has been following the stressors of daily life in a group of more than 3,000 adults since 1995. Almeida spoke with Mind Matters editor Daisy Yuhas to describe a benefit of aging that he has uncovered: stress levels go down and coping skills may actually go up after people pass their 20s. Still, upsetting national or global events can increase our distress.

[*An edited transcript of the interview follows.*]

You've been tracking people's daily experiences for two decades. How has that shifted your perspective as a psychologist?

In my work, I try to characterize a day in the life of an individual. I look at how people use their time, how they experience stressors and positive events, their mood and their physical symptoms. I chart how this changes from day to day—the ebb and flow of daily experiences. So even though I'm a psychologist, my unit of analysis is a day, not a person.

The more I've dug into this work, the more I've begun to see that people actually differ from themselves day to day as much as you differ from somebody else. Our identity isn't just who we are based on the average of our experiences. Our identities may be in the range in our behavior, the extent to which we're going up and down with our experiences.

How do you track daily stressors?

We ask people to answer a series of structured questions at the end of every day. Originally we used telephone calls, and now we use web-based approaches. We ask about how they spent their time, their mood, their physical symptoms, who they interacted with, and then we ask a lot of questions about the types of stressors they experienced that day. For some studies, we also collect a sample of saliva, which lets us determine the amount of stress hormones in the body.

With that method, we've worked with a large group of people. I want to acknowledge that the wonderful participants in the National Study of Daily Experiences—which is part of a large-scale investigation called Midlife in the United States—have shared their lives with me for the past 20 years. It's been a privilege to follow them.

You recently published findings from an analysis of 2,845 adults—ages 22 to 77 at the start—over 20 years. In that work, you found that people seem less stressed as they grow older. Can you unpack that?

Yes, finally some good news about daily stress! It seems to get a little bit better. We find that younger people report more exposure to stressful events—things they find challenging, upsetting or disruptive—than older people do. So people in their 20s may report stressors on at least 40 to 45 percent of days, but by the time they're in their 70s, that goes down to maybe 20 to 25 percent of days.

In addition, we looked at how much distress people experience or the way they *respond* to stress. Here we see the same type of pattern, with young adults having higher distress on days with stressors than older people. But around 55 years old, that age advantage—where your response to stress gets better with age—starts to taper off and plateau.

Why is there an age advantage in dealing with stress?

I think three reasons could contribute and work together. One has to do with the social roles people inhabit. When you're young, these roles could include being a parent of a young child, starting a job, getting into new relationships. New roles are stressful, as are role conflicts that happen when you have multiple roles going on at once.

A second reason could be that as we grow older, we realize we have only so much life left and want to make the most of it—so we are very motivated to enjoy it.

The third reason, which I am most interested in, is that just by virtue of experiences, opportunities and past stressors, we learn how to deal with them and become more expert in coping with daily stressors as we get older.

Does that explain why research suggests older people are happier than younger ones?

As you grow older, you can list all these things you shouldn't be looking forward to: poorer physical health, loss of friends, being sick and cognitive decline. These are not things you would expect to be related to increased happiness. But we see over and over that as people grow older, they have *increased* life satisfaction.

That said, there is a point when this pattern stops. Much later in life—in someone's 80s or 90s—I think we're seeing a time where things are really tough, and there's a decrease in life satisfaction.

How do things such as economic and political uncertainty affect our day-to-day stress?

We were able to study the effects of the 2008 recession and the postrecession period. From our data, it's fairly clear that compared with people in 1995,

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adults in 2010 had more stressful daily lives and were more upset by their experiences. Our hypothesis is that this reflects historical changes such as the recession and the use of technologies that have changed social interaction. From that, we can speculate on how economic downturn and other changes may affect us. In future work, we hope to see what the pandemic has done—it's possible that we won't see much of an age advantage, for example, in this period.

But what really surprised us from our analysis of the 2008 recession was that this difference in stress seems to be concentrated among people who were in midlife. I'd have thought that younger adults just starting their careers and older adults in retirement would have been worst off, but no: it was adults in their mid-40s through mid-60s who reported higher levels of psychological distress. I think that has to do with the social roles of a midlife adult. They are worried about their kids but also their parents.

On a practical note, should we be trying to remove all stressors from our daily lives?

There's something that might actually be good about having some daily stress. People who report having no stress in their lives—you think they are lucky, happy people. But they also report fewer positive things in their lives. They have fewer people in their lives and perform worse on cognitive tests.

It's the *reactivity* to stress—how you respond to it—that really matters to your health and well-being. It's not the number of stressors but actually your emotional responses that can, for example, raise your risk of cardiovascular disease, increase inflammation and contribute to dying earlier.

How should we manage our responses?

There are things people can do, such as eating well and getting enough sleep. But remember that not everyone can do them. It's not all about individual choice.

We've found that minoritized groups—by race, ethnicity and sexual orientation—have higher stress reactivity. They don't always have the resources to cope with daily stressors. For instance, when your body is experiencing stress, it wants to mobilize energy. So getting up and taking a walk is the best way to stem that emotional response. But many people cannot just get up in the middle of their workday and take a walk somewhere.

We need to start talking about how to provide resources to empower people so they can take care of themselves. SA

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Illustration by Dilek Baykara

Neutrinos Reveal Black Hole Secrets

Particles from an active galaxy show how supermassive black holes gobble matter

By Phil Plait

In the zoo of subatomic particles, neutrinos are strange beasts. Unlike more familiar particles such as electrons and protons, ghostly neutrinos barely interact with other matter at all: they can fly right through a planet as if it weren't even there. This makes it irritatingly difficult to detect them and, for neutrinos streaming in from cosmic objects in the sky, even harder to know exactly where they come from. In a recent study published in *Science,* however, researchers identified an extragalactic source for these subatomic particles.

For the first time, astronomers have confidently detected neutrinos from NGC 1068, a galaxy with a huge and actively feeding black hole in its center. The neutrinos are being created outside the black hole's "point of no return"—its event horizon—although it's not clear just how; several mechanisms are plausible. Scientists are hoping this discovery will change how they understand not just NGC 1068 but *all* such galaxies. As a bonus, they think the finding may have revealed the source of a faint glow of neutrinos we see everywhere we look in the sky.

Material that falls toward a black hole first forms a flattened accretion disk orbiting around it. Friction heats this disk of matter to incredible temperatures, causing it to glow so brightly it outshines the entire host galaxy. We call such galaxies "active," and they are among the most luminous objects in the universe.

In the case of NGC 1068, detecting that brilliant light is difficult because thick clouds of opaque cosmic dust absorb essentially all of it, letting virtually no signal out. This is where neutrinos' most annoying property is an advantage to us: they can pass right through those dust clouds and fly out into space, eventually reaching Earth. Still, we're left with the problem of detecting them. How do you measure neutrinos when they pass unscathed through your detector? The good news is that to neutrinos, matter is only *mostly* permeable. Although it's extraordinarily rare, some do manage to interact with matter—but it takes a very special kind of observatory to see it.

Located almost exactly at Earth's South Pole, the IceCube Neutrino Observatory is just such a place, and it's not your standard astronomical facility. For one thing, it doesn't use a mirror to collect and focus light from cosmic objects as telescopes do; instead it has a series of relatively simple optical sensors hung along dozens of vertical strings, creating a 3-D array of more than 5,000 sensors that can detect the locations and times of flashes of light.

For another, it's buried under more than a kilometer of Antarctic ice. When a neutrino travels through the ice, it has some small chance of slamming into the nucleus of one of the oxygen or hydrogen atoms in that ice. But actual impacts are exceedingly uncommon: trillions of neutrinos pass through every cubic centimeter of matter on Earth every second, but measurable physical interactions with that matter may only happen days apart.

When they do occur, they create high-speed subatomic shrapnel—particles moving away from the nuclear collision site at just under the speed of light. These then plow through the ice as well. Here's the fun part: they actually travel faster than light can move through the ice. No laws of physics are being broken, though. The speed of light in a vacuum is the ultimate cosmic speed limit, but light moves more slowly when it travels through matter. Particles cannot move faster than light in a vacuum, but they can travel faster than light through matter. When they do, they create a kind of photonic boom, like the shock wave created when something travels through air faster than the speed of sound. These faster-than-light events manifest as bright flashes of blue light called Cherenkov radiation. They can be seen for some distance through the clear Antarctic ice and can be picked up by IceCube's detectors.

This phenomenon allows scientists to detect neutrino events from space, but there's a problem with unwanted events that mimic the desired signals. Subatomic particles from other sources in the universe called cosmic rays can hit our atmosphere and create similar flashes of light, confusing the measurements. Scientists can differentiate between the two kinds of signals in a clever way, though: by using Earth itself as an immense filter. Neutrinos coming from space will come from every direction, including up through Earth. Cosmic rays, however, will come only from the sky above the Antarctic observatory because they can't beam straight through Earth as neutrinos do. The detectors in IceCube can measure direction and filter out the events coming from above, thus ensuring scientists keep only the hits from cosmic neutrinos.

IceCube has detected millions of neutrinos overall, but only a few hundred at most appear to have come from bona fide cosmological objects. Some things out there in the universe are the sources of these neutrinos. The question is, What are they?

Looking over data taken from 2011 to 2020, the IceCube Collaboration—a huge collection of scientists, engineers, data analysts, and more—very carefully processed every event detected. Using the directional information from the flashes to trace the trajectories of the incoming cosmic neutrinos, they found several spots on the sky that appeared to be statistically significant sources of neutrinos.

The detection with the largest number of neutrinos? A total of 79 (plus or minus 20 or so) neutrinos over that period coming from the direction of NGC 1068.

This lovely spiral galaxy is relatively close—a mere 47 million light-years from us—and bright enough to be spotted with binoculars. Earlier work analyzing IceCube neutrinos pointed to NGC 1068 as a possible source, but the data weren't strong enough at the time to claim a discovery. These results change that.

The detection of neutrinos ostensibly coming from this active galaxy is a big deal. The neutrinos that the astronomers saw have phenomenally high energy: more than a tera-electron volt each. That is trillions of times the energy of the visible-light photons we see coming from the galaxy. The particles' huge energy must be cre-

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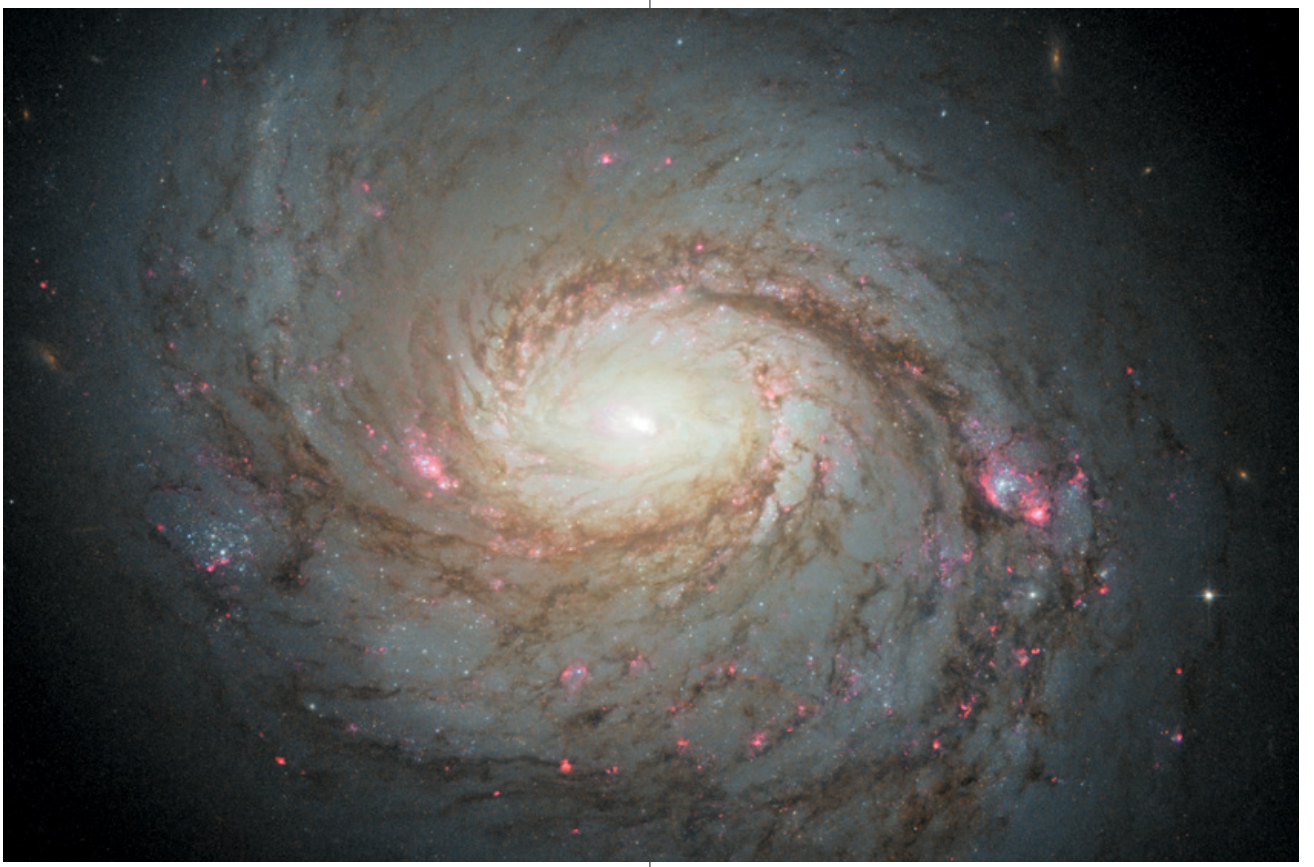

Scientists detected neutrinos from spiral galaxy Messier 77, also known as NGC 1068, seen here in a Hubble Space Telescope image.

NASA/ESA/A. van der Hoeven

ated in an extremely powerful cosmic particle accelerator, and with an actively feeding big black hole, several options are possible.

For example, the turbulent ionized miasma of matter above and below the disk of material around the black hole is infernally hot and contains powerful magnetic fields that can pump vast energies into particles, accelerating them almost to light speed. Another way involves the magnetic field in that accretion disk getting twisted up near the black hole, creating twin vortices such as tornadoes, called jets, that can fling particles away at high speeds. Shock waves generated in the jets as charged particles slam into one another can also produce the energies needed for high-energy neutrinos. Such jets are known to exist in NGC 1068.

Detecting these neutrinos from NGC 1068 will give astronomers insight into the forces involved there, as well as into which specific engines are responsible for them—quite a boon given the hidden nature of black holes.

Fewer than 100 NGC 1068 neutrinos were detected at Earth, but they would have been diluted as they traveled across the vast volume of space. Accounting for this reduction, the astronomers say the total number of neutrinos generated by the black hole must be so huge that they carry away *a billion times* as much energy as the sun emits.

These observations also provide a major clue for another mystery. Neutrinos come to Earth from all over the sky, creating a background glow across the heavens. The source of this glow has been difficult to pin down. Neutrinos from several other active galaxies were also seen in the IceCube data (though with less statistical certainty than for NGC 1068), and there are many millions of these galaxies throughout the universe. The new data indicate that if they emit neutrinos much as NGC 1068 does, these more distant galaxies could be the source of the cosmic neutrino background, similar to how individual stars in the sky blur together to form the continuous glow of the Milky Way you can see from a dark site at night.

Not too long ago we knew of only two astronomical neutrino sources: the sun, where neutrinos are created in the nuclear fires of its core, and Supernova 1987A, a relatively nearby exploding star that emitted a transient flash of neutrinos once and then was gone.

Every big galaxy in the universe has a supermassive black hole in its core, and any of them can potentially be active. Yet, though ubiquitous, they can be difficult to observe. With a positive detection of neutrinos coming from at least one and probably several of them, astronomers have opened up a new window on these prodigious monsters. SA

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NONFICTION

Smart Plants

A controversial invitation to reconsider green intelligence

Review by David George Haskell

Is the potted cactus on your windowsill a cognitive being? When the lettuce in your sandwich was cut from its roots, did it feel pain?

In a provocative new book, *Planta Sapiens: The New Science of Plant Intelligence,* philosopher Paco Calvo, with writer Natalie Lawrence, explores these questions, urging us not to fall into the "zoocentric trap" of believing that intelligence, agency and even consciousness are found only in animals.

Consider the movements of *Mimosa* plants, for example. A poke from a human finger usually causes the plants' leaves to shrink and fold against the stem. This response takes mere seconds—an excellent defense against herbivores. But after a few minutes in a bell jar suffused with anesthetic fumes, *Mimosa* becomes unresponsive. The same drugs quiet the gyrations of pea tendrils and the clenching of Venus flytraps.

Plants don't have nerve cells, but they do thrum with inner electrical signals that connect adjacent cells and transmit information along roots and stems. Networks of chemical messages complement these electrical connections. The effects of anesthetics on plant movement have been known since the 19th century, and recent research shows that they block electrical signals in plant cells, just as they do in animals. Unlike the hierarchical organization of nerves in animal brains, though, message signaling within plants is diffuse, ramifying through modular tissues and netlike vascular conduits. No longer can we think of plants as passive or inert; they are continually sensing and responding to their environments.

Such astonishing findings have led the book's author, among others, to controversially refer to the study of these processes as "plant neurobiology." Calvo goes even further, suggesting that plants are cognitive beings and may have "diffused consciousness."

Planta Sapiens: The New Science of Plant Intelligence
by Paco Calvo, with Natalie Lawrence.
W. W. Norton, 2023 ($28.95)

When a vine sends out tendrils, it does so with intent, he writes, using light and chemicals to explore and then home in on a target. The author claims the plant is not "simply reacting," but it is "making meaning" through inner awareness, perhaps similarly to an octopus whose consciousness seems spread among its arms. Although electrical and chemical signaling inside plants are well established, assertions about plant cognition and possible consciousness are highly contentious. A rebuttal by some animal and plant scientists of Calvo and his colleagues' earlier work states that not only are such ideas wrong, but they harm scientific progress by misleading students and redirecting funding.

The problem is partly perceptual and linguistic. Our senses cannot grasp the rich communicative world of plants. We therefore lack language to describe the "intelligence" of a root tip in conversation with the microbial life of the soil or the "cognition" that emerges when chemical whispers ripple through a lacework of leaf cells. Calvo asks us to apply zoological and psychological concepts and terms to plants. In his view, the parallels between animal and plant biology are so strong that we should expand the boundaries of neurobiological and cognitive science to encompass plants. A better alternative might be to seek a lexicon that honors plants' sophistication without pigeonholing them with animal-derived ideas and words.

Vigorous debate about the nature of plants is surely a sign of a healthy field. Science, at its best, progresses through a reciprocal interplay between speculation and experimentation. Calvo's stimulating book draws us into that process, with an emphasis on the speculative. Could plants suffer, he wonders? When growing roots wriggle away from unexpectedly salty soil, might a psychological experience of distress or surprise direct their physiological response? The experimental evidence for these conjectures is currently scant, so the book repeatedly calls for further investigation.

These arguments would be more powerful if plants themselves were more clearly and frequently foregrounded. When they do appear—young bean plants lunging at poles, hollyhocks anticipating where the sun will rise—the book shines. But this green glow is often muted. In a chapter on ecological cognition, for example, instead of writing about plant communities, Calvo mostly offers analogies with animal behavior and human culture. This is a regrettable omission because if plant cognition does exist, it surely is at its height in biodiverse forests, deep-rooted prairies or thoughtfully tended agricultural landscapes.

Plant life is, above all, decentralized and engaged in reciprocal relationships with other species. And our species has homogenized and destroyed many of these formerly effervescent plant communities, throwing them into crisis. With this erasure, we lose the intelligence—however we choose to speak of it—brought to us by hundreds of millions of years of evolution.

Our human abilities are thus challenged by the rest of the living world: *Look at what your cognition has wrought. Will you sapient apes change your ways?* Instead of being misleading, as critics have claimed, *Planta Sapiens* helps us do so by expanding our imaginations and provoking more creative science. We may not learn whether lettuce has feelings, but we do come away with deeper empathy and admiration for plants.

David George Haskell is a biologist and award-winning author. His most recent book is *Sounds Wild and Broken* (Viking, 2022).

Illustration by London Ladd

NONFICTION

Big Bad Wolves

Tracking an archetype of fear

Staffan Widstrand/Getty Images

In 2011 a wolf known as OR-7 trotted toward the forests of western Oregon, his radio collar broadcasting what would become a years-long, 3,000-mile journey to find a mate and a new home. As he moved into areas that had not seen a wolf in more than 70 years because of government-incentivized extermination campaigns, OR-7 quickly achieved celebrity status, captivating the public and inspiring, according to one headline, "hope and dread." To understand why these canines channel our most visceral emotions, author Erica Berry examines in *Wolfish* what a wolf "brings up beyond itself."

Berry's path of inquiry is a deeply personal one. Struggling with anxiety, she tries to pinpoint its origins in her life and finds in the wolf a new way to explore her relationship with her own fears. Humans have long imbued wolves with coded meaning, and although the specifics of the archetype shift with culture and context, wolves function as "a pressure point in our psyches." Berry explores this role through wide-ranging research, juxtaposing the "wolves" in her life—her fears around personal safety, solo travel and loss of family—

Wolfish: Wolf, Self, and the Stories We Tell about Fear
by Erica Berry.
Flatiron Books, 2023 ($29.99)

with biological wolves and the cultural touchstones they represent.

This unorthodox approach allows for the complexity of both Berry's personal journey and the wolf's status as a rich cultural avatar. In the chapter "Girl v. Wolf," Berry unspools the parallels between her experience attending a college far away from her family and the wolf's quintessential role as a lurking threat to girls who leave home. She describes encounters with Big Bad Wolves that made her feel frightened and uncomfortable, but she also explodes the simplistic lessons of the fairy tale by examining how the story's evolution has distorted its original emphasis on survival rather than victimhood. She reflects poignantly on her connections with other female victims of violence whose fates, like Little Red's, were co-opted to serve others' agendas and to assuage—or exacerbate—their fears.

The book's narrative focus frequently pivots, creating a sense of uncertainty and intrigue not unlike what one would feel while journeying through an unfamiliar wood. Although these paths are occasionally disorienting, Berry is a skillful guide, highlighting the wolf's influence on everything from creation myths to viral memes and from government policies to proverbs.

—Dana Dunham

IN BRIEF

Feed Them Silence

by Lee Mandelo.
Tordotcom, 2023 ($19.99)

Horror, fantasy and science fiction—and even nonfiction, like Erica Berry's *Wolfish,* also out now—have long explored the union of human and wolf, finding surprising correspondence between the civilized and primal. Lee Mandelo's crisp, urgent novella, centered on a study that links the consciousness of a researcher to that of one of North America's last wild wolves, is a new leader of the pack. While Dr. Sean Kell-Luddon's experience of the wolf's perceptions rouses animal hungers that threaten her human relationships, the horror here comes from the fullness with which she understands the cold, hunger and loss animals endure as they fight to survive.

—Alan Schersturhl

Your Brain on Art: How the Arts Transform Us

by Susan Magsamen and Ivy Ross.
Random House, 2023 ($28)

Susan Magsamen and Ivy Ross walk a fine line between expounding the health benefits of participating in art and arguing that such therapeutic effects need not be perfectly understood by science to be useful. Citing enough research to assuage skeptics, *Your Brain on Art* provides abundant ideas for engaging with the arts, ranging from the intuitive (memorizing dance choreography to stave off dementia) to the outlandish (sounding a tuning fork during a business meeting to reduce stress). No single method is for everyone, the authors maintain, but they throw enough spaghetti at the wall to inspire experimentation with new creative practices. *—Maddie Bender*

A Brief History of Living Forever: A Novel

by Jaroslav Kalfař.
Little, Brown, 2023 ($28)

In 2030 biotech researcher Tereza embarks on an expedition across the Czech Republic and the authoritarian U.S. to recover the remains of her long-estranged mother, Adéla, after their reunion is cut short by Adéla's sudden death. Told from the mother's perspective from beyond the grave, the novel traces the way nativism spreads and how morally dubious technologies such as surveillance and immortality science thrive under a fascist, one-party-rule government. Author Jaroslav Kalfař turns an ambitious premise (a person whose body has expired but whose consciousness lives on) into a moving, frightening story about the strength of family bonds. *—Michael Welch*

Naomi Oreskes is a professor of the history of science at Harvard University. She is author of *Why Trust Science?* (Princeton University Press, 2019) and co-author of *The Big Myth* (Bloomsbury, 2023).

The Eight-Billion-Person Bomb

A surging population—and the planet—cannot survive without help

By Naomi Oreskes

The world reached two important milestones toward the end of last year. First, the human population passed eight billion in November, a whopping increase of one billion people since 2011. Then, in December, representatives of 188 governments adopted the Kunming-Montreal Global Biodiversity Framework, promising to conserve and manage at least 30 percent of the planet for biodiversity and restore 30 percent of currently degraded ecosystems.

Press coverage did not generally link these two events, but it should have. The major driver of plant and animal loss is habitat destruction caused primarily by the encroachment of a swelling human population. More people "has meant that ever more natural habitat is being used for agriculture, mining, industrial infrastructure and urban areas," says the Royal Society, one of the world's leading scientific groups. About one million plant and animal species are nearing extinction, and at least 1,000 breeds of mammals used for human food and agriculture are threatened.

We ought to have a plan for slowing the destructive surge in human population. But we don't. In fact, many people defend it. Consider a recent *Washington Post* editorial saying eight billion people is "probably a good thing." The authors' reasoning: Population has "more than doubled since 1968, and living standards around the world have vastly, though unevenly, improved." With an ever increasing population, the editorialists write, "millions of new people—with their new ideas and fresh energy—are on the way," and this will spur innovation that will solve our problems.

This argument is a retread of a theoretical framework that was named cornucopianism in the 1980s. Cornucopians, led by economist Julian Simon and military strategist Herman Kahn, argued that anxiety over limited natural resources is misguided because human ingenuity can overcome any limits. Let populations grow alongside markets operating under minimal government constraints, and people will invent solutions to whatever problems they face.

It's true that technological innovations in the 19th and 20th centuries created more agricultural productivity—enough to feed much of a growing population. But the cornucopian perspective ignores other important facts. For instance, an enormous number of these inventions came into being through government actions. From the canals and railroads of the 19th century to the interstate highways and Internet of the 20th, most large-scale technological achievements have relied, at least in part, on government initiatives and support. Big gains in health and life expectancy stemmed from state investments in scientific research and public health. In the early 21st century the price of renewable solar energy fell dramatically, largely because of state-funded research and policies to help ensure demand.

And although much of our population grew healthily in the 20th century, hundreds of millions died in famines, pandemics and wars. Scientists have been warning us about the risks of anthropogenic climate disruption since the 1950s, but technological progress has not stopped the unfolding climate crisis.

It's both counterfactual and illogical to imagine that more people will solve the problem of too many people. Most population growth is occurring in poor countries, where most people lack educational opportunities that might enable them to develop the kinds of ideas and skills they would need to apply their "fresh energy." And, as the biodiversity agreement makes clear, the issue isn't just living standards as measured by per capita income. It's also quality of life, which is threatened by widespread degradation and destruction of nature.

Population control is a vexing subject because in the past it has generally been espoused by rich people (mostly men) instructing people in poor countries (mostly women) on how to behave. Prior attempts at limiting population surges have been tainted by racism, sexism and class prejudice. But there are reasonable ways to slow growth. For one, women and girls should have greater access to education. Studies show opportunities to learn are an effective means to slow population increases. Focusing on that goal—which has many other benefits—most likely will produce the fresh energy and ideas that we need across the globe. It is much more realistic than fatuously assuring listeners that in the future, somehow, all will be well. SA

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Illustration by Izhar Cohen

MARCH

1973 Eight Billion People

"The human population is now about 3.6 billion. An extrapolation of demographic trends that lies between two extreme projections shows it leveling off at some 8.4 billion by the year 2100."

The United Nations estimates that world population reached eight billion on November 15, 2022. It predicts nine billion people by 2037.

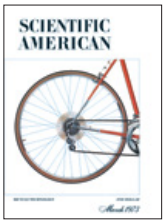
Roe v. Wade Decided

"In the U.S., abortion will henceforth be regulated on the basis of medical standards and practices, rather than according to sociorelegious principles enforced by criminal law. Abortion will nevertheless not become a primary method of fertility control. These are among the conclusions reached by legal and medical specialists in the wake of the U.S. Supreme Court's January decisions striking down almost all provisions of most of the state laws prohibiting and regulating abortion. The Court held that abortion is so safe in the first three months of pregnancy that states may not interfere at all with a decision by a woman and her physician at that stage. In the second and third trimesters states may regulate the practice of abortion, but only in ways 'reasonably related to maternal health.' Some proponents indicated that they would now work for the complete elimination of all criminal legislation, holding that abortion should be treated like any other medical procedure and regulated by the medical profession, civil law and health codes."

On June 24, 2022, the U.S. Supreme Court overturned Roe v. Wade.

1923 Lead Paint Propaganda

"In the recent meeting of the International Labor Congress at Geneva a resolution was passed barring the use of white lead in paints. It was pointed out that these paints are very poisonous and that the white lead pigment can be replaced to good advantage by other white pigments, particularly by titanium white, developed commercially in Norway. There has been a great deal of uncalled-for propaganda against the use of white lead because of its poisonous properties. It is of course true that white lead is poisonous, but so are a great many other substances which are in common daily use. If just the ordinary care is taken with paint, whether it contains white lead or not, there need be no fear of any poisonous or other deleterious effects."



1973

1923


1873

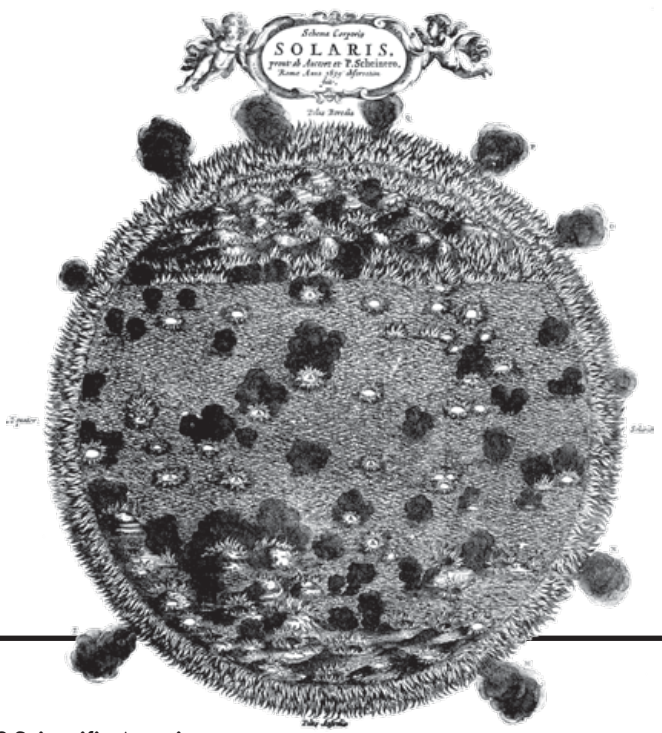
1873 Kant and Goethe Torn Down

"Mere reasoning, not based on sufficient observation of Nature, almost always leads to false conclusions and baseless theories. This was the main fault of ancient philosophers, and is still the fault of that class of moderns. Even some of the most eminent individuals have erred in this way. One such is the famous German philosopher Emanuel Kant, who wrote a volume on dynamics, or rather, on a false imaginary theory of motion, which he calls dynamics. It shows how superficial a thinker Kant was after all. Another illustration is Goethe, who in the latter years of his life wrote a volume on light and colors, in which he proves that he had not the least capability of making experiments, and was still more deficient in his powers of observation. His conclusions are almost all false. We consider it a necessary and progressive step to tear away a portion of the halo which surrounds certain names, owing to the habit people have of regarding their heroes as superior in all respects."

The Best Asbestos

"There are very extensive deposits of this important mineral within the limits of the United States—that found on the eastern slope of the Green Mountains and of the Adirondacks being of the best fineness and tensile strength. The fiber of New York and Vermont asbestos varies in length from two to forty inches and resembles unbleached flax, when found near the surface, but when taken at a greater depth, it is pure white, and very strong and flexible. It is found also, in considerable quantities, in the Tyrol, in Hungary, Corsica and Wales."

1873, Priest Draws Remarkable Sun: "We publish an engraving [based on 1635] cosmographic [observations], written in Latin by Father A. Kircher. His picture shows the dark sun spots, and the faculae; the poles and equator are also indicated. The most remarkable of all are the protuberances. He introduced them more than 200 years before the instruments, which proved their existence beyond a doubt, were invented."



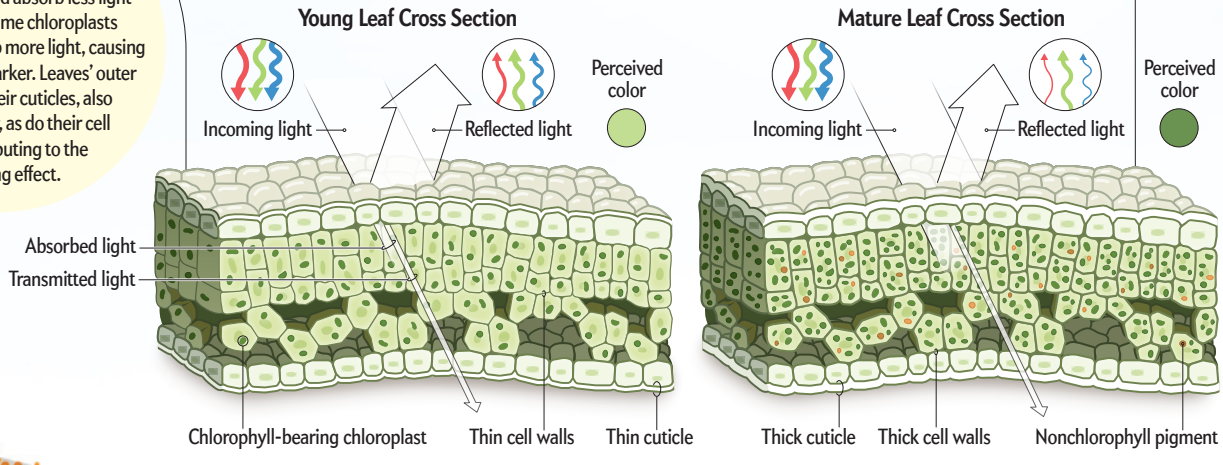
Text by Clara Moskowitz | Graphic by Rebecca Konte

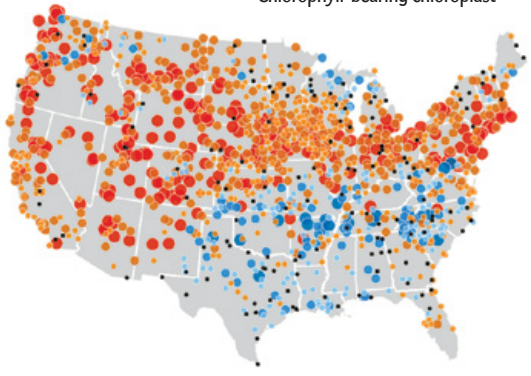
The Science of Spring Green

Leaves darken over the season as chloroplasts grow and mature

Every year trees put on a show in the spring by bursting with bright foliage that seems to celebrate the end of winter. What makes these early leaves so vibrant? The color of a leaf is determined by which wavelengths its cells absorb and which they reflect back at us. The chloroplasts inside these cells, which turn sunlight into energy through the process of photosynthesis, tend to absorb more blue and red wavelengths and less green light. Changes to the number and maturity of chloroplasts within a leaf, as well as to leaves' structures, cause the leaves to appear lighter in the spring and darker later on. "The time it takes to go through this maturity cycle is a couple of weeks at the start of the summer," says Susan Ustin, an ecologist at the University of California, Davis.

The brightness of new leaves stems from their light-absorbing chloroplasts, which are fewer and absorb less light in spring. Over time chloroplasts multiply and soak up more light, causing leaves to appear darker. Leaves' outer layers, called their cuticles, also become thicker, as do their cell walls, contributing to the darkening effect.





Change in First Leaf Date
between 1951–1960 and 2011–2020

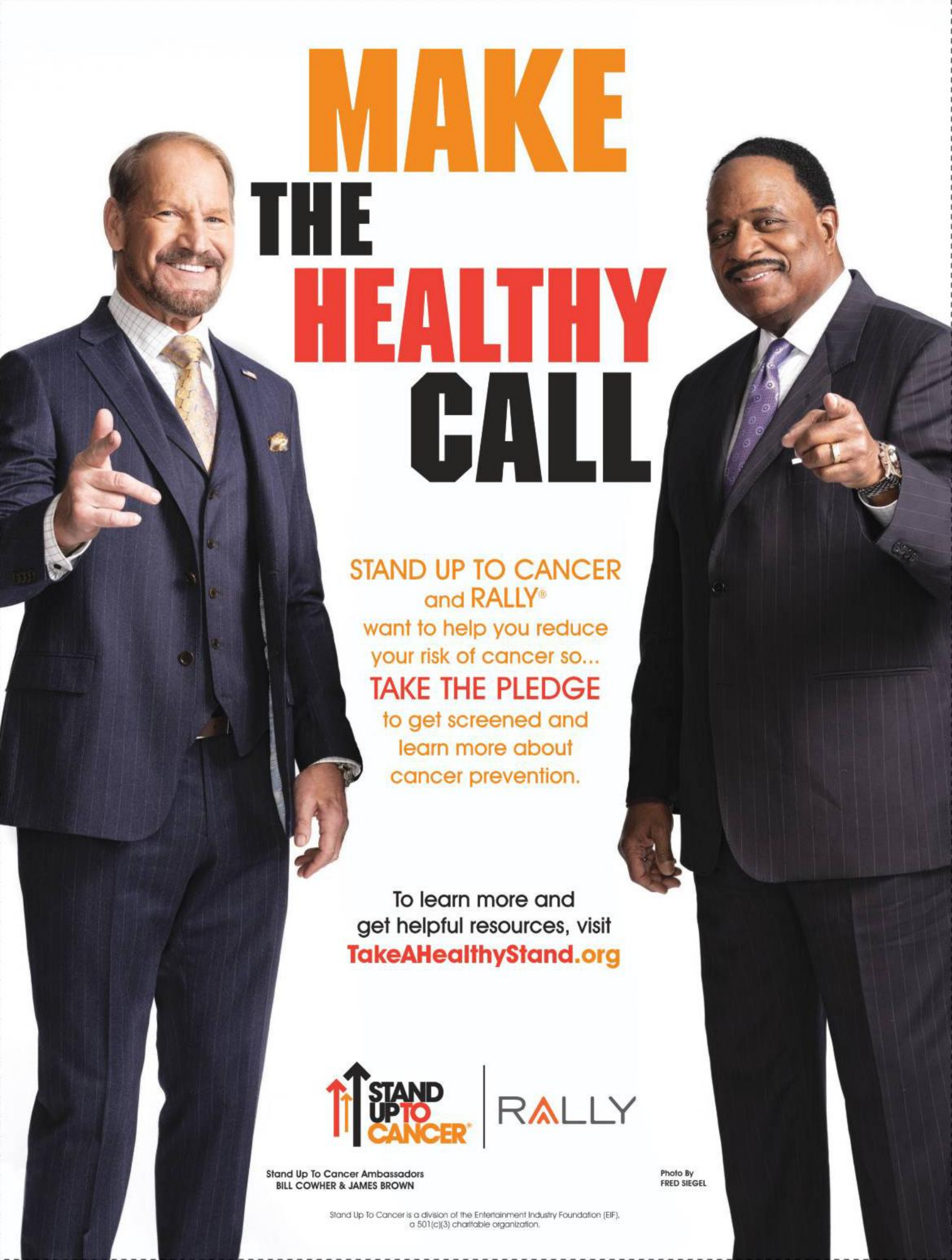
Earlier
- More than 8 days
- 4–8 days
- 1–4 days
- Within a day
- 1–4 days
- 4–8 days
- More than 8 days

Later

Shifting Season

This map shows how lilac and honeysuckle bushes across the U.S. have sprouted their first leaves at different times over the past 60 years as the result of altered temperatures from climate change. The average first leaf date has moved earlier and earlier during the two 10-year periods shown in the West, Midwest and Northeast, whereas the first leaves have appeared later in the South.

Sources: "Climate Change Indicators in the United States," by U.S. Environmental Protection Agency; last updated December 20, 2022 (www.epa.gov/climate-indicators) (*map, restyled for Scientific American by Jen Christiansen*); Mark D. Schwartz 2021 update to data originally published in "Spring Onset Variations and Trends in the Continental United States: Past and Regional Assessment Using Temperature-Based Indices," by Mark D. Schwartz, Toby R. Ault and Julio L. Betancourt, in *International Journal of Climatology*, Vol. 33; 2013 (*data*); Research by Amanda Hobbs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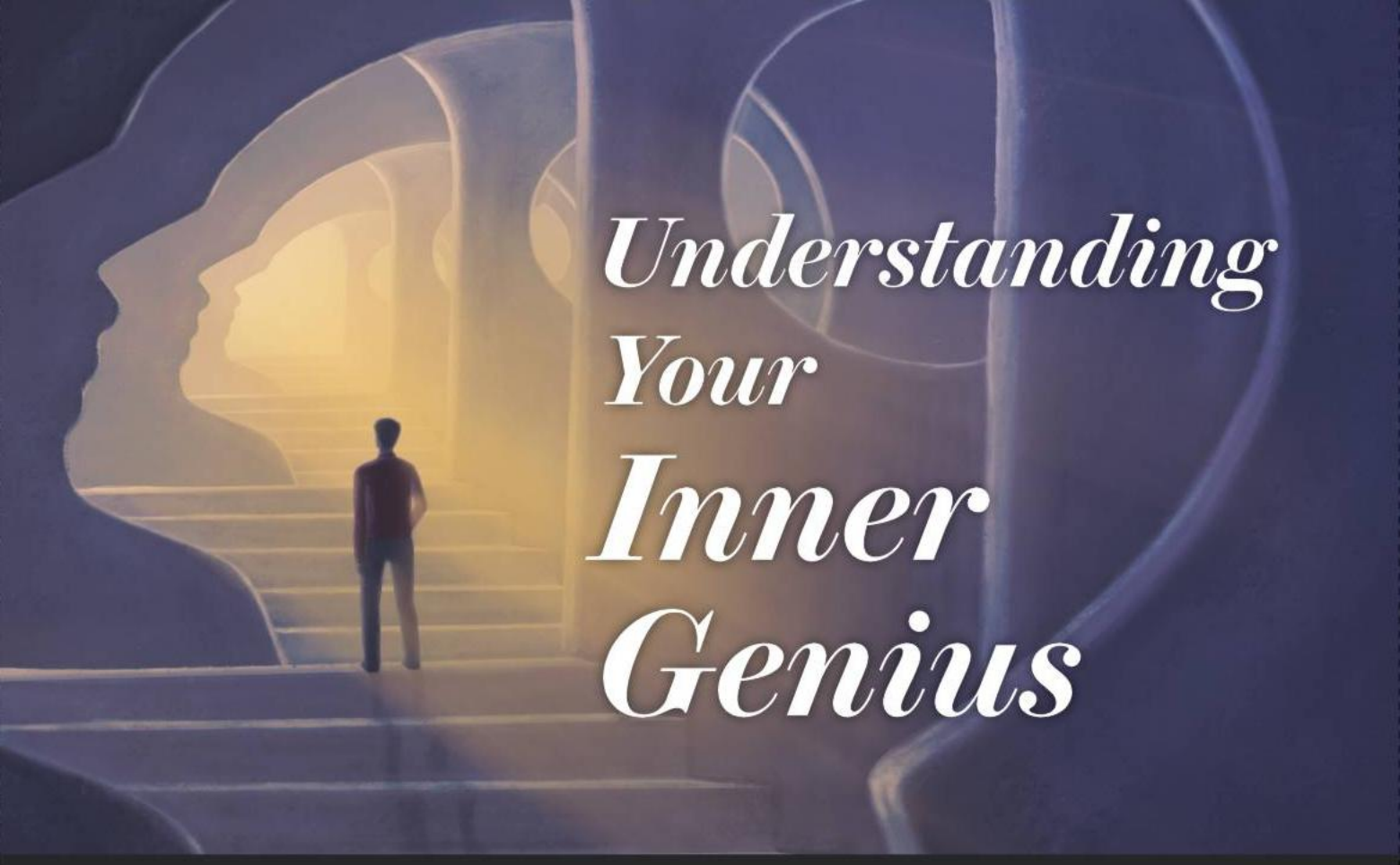

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