

AUGUST 2021

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# SCIENTIFIC AMERICAN

A New  
Understanding  
of Alzheimer's

The Coolest Stars  
in the Universe

The Hype about  
Hypersonic Weapons

## WHY ANIMALS PLAY

The rules of the game  
for dogs, apes  
and elephants



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Animal play is not just a leisurely pursuit. Though fun for the participants, it is also a means of allowing youngsters to practice skills they will need to succeed later in life—such as evading predators, forging alliances and competing for mates—in a safe environment.

**Photograph by Todd Gustafson.**

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ATEM Mini Pro model shown.

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

# Serious Play

**We hope our cover story** this month brings you as much joy reading it as we have had producing it. The author, behavioral ecologist Caitlin O'Connell, has what sounds like one of the best jobs on Earth: observing elephants in the wild and making sense of their behaviors. Some of the silliest behaviors turn out to be surprisingly meaningful. Young elephants play in their water holes much like human children play in swimming pools during summer break. They have toys and games and battles, with older relatives ready to intervene if the play turns dangerous (*page 48*). Many social species, from meerkats to dogs to great apes, engage in ritualized play to hone skills they'll need as adults—and, from everything we can tell, for the joy of it.

Stars and planets are just different ends of a size spectrum, with brown dwarfs in between, astronomer Katelyn Allers explains on page 30. They can't quite sustain fusion like a star does, so they're harder to see, but they emit enough light from heat that astronomers have recently realized they're as abundant as stars in the universe, and they're bizarre. Depending on its age and size, a brown dwarf might have an atmosphere containing titanium oxide or quartz. And Allers has figured out how to measure wind speed on a brown dwarf (2,300 kilometers per hour).

Many of us have lost loved ones to Alzheimer's and desperately hope for a meaningful treatment. Recent research on immune cells called microglia in the brain is leading to some new approaches. Neurologists Jason Ulrich and David M. Holtzman (*page 38*) describe how genetics, mouse models and patient studies point to a two-phase progression of the disease. The story goes into great detail to show exactly where this research stands, with hope but without hype.

As neuroscientist Soo-Eun Chang points out, "speech is one of the most complex motor behaviors we perform." It's no won-

der there are so many ways it can go wrong. Stuttering is one of the most common neurodevelopmental disorders, as *Scientific American* contributing editor Lydia Denworth writes, starting on page 56. It affects about 5 percent of children and 1 percent of adults. In the past few years scientists have identified many of the brain regions and some of the genes involved, and they are rolling out new treatments.

It's refreshing when people who have had a lot of success in their careers recognize the importance of luck. Chemist Jeannette M. Garcia was mixing ingredients in a lab when a reaction went in an unexpected direction and she discovered a new family of polymers. That's a surprisingly common origin story for many scientific advances, but now Garcia (*page 44*) wants to reduce the need for serendipity by using quantum computing to predict the chemically unpredictable.

In our Science Agenda editorial this month (*page 10*), we show that anti-transgender laws are contrary to science as well as cruel. The subject is in the news more than ever these days, but transgender experience is not a fad or an invention. As author Brandy Schillace writes on page 74, the first known transgender health clinic was established in 1919 in Berlin. It thrived until it was destroyed by the Nazis and its library consumed by one of the first Nazi book burnings.

In our November 2020 issue, we ran a Graphic Science column revealing that the Southern Hemisphere's flu season was the mildest ever recorded, an early sign that the 2020–2021 flu season in the North might not be so bad. On page 72, data-visualization designer and *Scientific American* contributing artist Katie Peek follows up with a remarkable series of graphics depicting how flu basically disappeared around the world during the COVID pandemic. The coronavirus is more elusive than flu, in part because it can be spread by those who have no symptoms and don't know they're infected. But if people wash their hands, wear masks in crowded indoor areas and stay home if they're sick, that can stop the flu cold. **SA**

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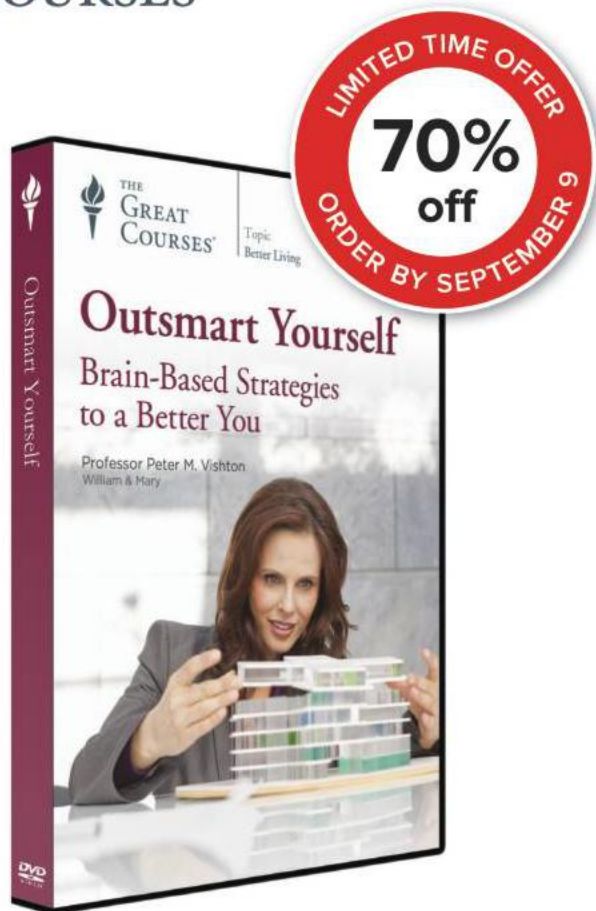
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## Hack Your Brain Using Neuroscience

Feeling the urge to procrastinate? Do nothing for 20 minutes and you'll feel ready to get to work. Come down with a case of the blues? Try eating some fermented foods such as yogurt or sourdough bread.

The brain is an amazing instrument, and neuroscientists today have more information than ever about how it works—as well as strategies for helping us live better every day. The surprising thing is just how counterintuitive some of these strategies can be. Unpack eye-opening insights and more in **Outsmart Yourself: Brain-Based Strategies to a Better You**. Taught by Professor Peter M. Vishton of William & Mary, these 24 practical lectures draw from a wealth of scientific evidence to take you inside your brain and show you why you behave the way you do—and what steps you can take to improve your well-being.

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8. How to Become an Expert on Anything
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April 2021

### PERCOLATION INSPIRATION

It was an absolute delight to read about percolation theory in “The Math of Making Connections,” by Kelsey Houston-Edwards. Please feature more articles by this author and about mathematics as applied to science. I’m not a mathematician, yet I enjoy learning about theory and application. I love the expanse of disciplines you cover.

I am an African-American woman with a biology degree. I used to work as a research assistant in cancer research. That was until the racism that I consistently encountered wore me down, and I just didn’t want to ever work with scientists again. Although I am in another line of work, I haven’t lost my love of the sciences and mathematics. Your magazine provides me with the joy I used to feel but without the heartache.

TRACIE S. JOHNSON *via e-mail*

One approach to developing a theory of quantum gravity is called loop quantum gravity (LQG). It treats space as a discrete substance composed of individual spatial atoms, or nodes, at the Planck distance scale of  $10^{-35}$  meter. They are connected to one another in a way that would seem to lend itself very well to percolation theory, which is precisely geared toward modeling the connections among discrete nodes. Has percolation been applied to advancing LQG and quantum gravity?

EDWARD ROSENBLATT *via e-mail*

**“I haven’t lost my love of the sciences and mathematics. Your magazine provides me with the joy I used to feel but without the heartache.”**

TRACIE S. JOHNSON *VIA E-MAIL*

*HOUSTON-EDWARDS REPLIES: In response to Rosenblatt: In percolation theory, a “dial” controls the local connectivity of a network. When its needle lands on a critical point, a phase transition occurs, and the global connectivity of the network changes dramatically. To apply the theory to LQG, one needs to describe how and why this dial moves to the critical point. But as theoretical physicist Lee Smolin explained in an e-mail to Scientific American, nature exhibits several instances of “self-organized critical phenomena,” in which the dial tunes itself toward the critical threshold. Smolin hypothesizes that such a self-organized phase transition might explain “the emergence of classical spacetime in a quantum theory of gravity,” including loop quantum gravity. He and physicist Mohammad Ansari explored these ideas in the 2008 paper “Self-Organized Criticality in Quantum Gravity.” It is unclear how extensively a “self-tuning” version of percolation could be used for understanding a self-organized phase transition in the case of LQG.*

### CLIMATE PRIORITY

I was troubled by “What to Do about Natural Gas,” Michael E. Webber’s article about ways to decarbonize the natural gas system. Pointing out that the primary alternative, electrification, will be challenging is fair enough. But electrification does not have barriers that are greater than, or even equal to, a zero-carbon gas system, which faces structural limitations. To his credit, Webber names some of these limitations. But his presentation of them as solvable with some tweaks is disingenuous. Even by the gas industry’s own estimates, two decades of scaling up all low-carbon gases would displace only about 13 percent of the U.S.’s existing gas demand. Also, it would squander any genuinely sustainable gases that could be used where we might actually need them, such as chem-

ical feedstocks, shipping and aviation.

Keeping warming within the 1.5 degrees Celsius limit necessary to avoid catastrophic climate destabilization requires us to reach net-zero emissions, meaning we must leave the majority of the world’s existing gas reserves unburned. And whether methane is synthetic, biogenic or fracked, if it’s pumped through the existing distribution network, it will face leakage, adding to atmospheric warming.

Perhaps the most important omission is that decarbonizing gas does not solve the health impacts of combustion. With low-carbon gases, we only get more expensive ways of polluting our homes.

SASAN SAADAT

*Research and policy analyst, Earthjustice*

*WEBBER REPLIES: It seems that we agree that addressing climate change is the most urgent and important challenge of the 21st century. That realization led me to the conclusion that we need every solution possible to get us to carbon neutrality (and carbon negativity!) as quickly, safely and affordably as possible. As I write in the article, I think the first two priorities for decarbonizing the economy are (1) conservation and efficiency and (2) electrification. Because low-carbon fuels play an important role for sectors that are difficult to electrify, we need to make progress on decarbonizing gases as the third step.*

*As someone who invented sensors to measure the emissions from combustion, I’m well aware of its pollution. And as someone who quantitatively analyzes different forms of energy, I’m also aware of the significant ecosystem impacts of some utility-scale renewables. The energy system is all about trade-offs, and there is no one fuel or technology option that is purely villainous or virtuous. Rather we must design a suite of solutions that meets society’s complex needs.*



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## PREDICTIONS AND MEMORY LOSS

In "Prediction Predicament" [Advances], Hannah Seo notes that making predictions impairs people's ability to remember predictive events. I see this a lot in the martial arts. Often when an instructor demonstrates a technique, the students will be busy imagining what comes next and how they think the technique should be performed while failing to see the variation that the instructor is demonstrating. It's like the students are watching to confirm their predictions instead of observing to learn something new.

IAN MCINTYRE *via e-mail*

## RECOVERING FROM ADDICTION

"Hope for Meth Addiction," by Claudia Wallis [Science of Health], encouragingly describes the growing evidence base for contingency management as an effective treatment for stimulant use disorder, particularly in conjunction with bupropion and naltrexone. It notes that one trial of the two drugs found that they helped a significant number of treated users test methamphetamine-free "at least three quarters of the time."

Wallis's piece is to be applauded for its apparent recognition that complete abstinence is not the only recovery pathway. Harm reduction is effective, and reoccurrence of substance use is not unusual for most people as they seek recovery. While abstinence-based approaches may be ideal for some, they don't work for everyone. Contingency management and harm reduction are both important strategies that can lead to improved health and wellness for those who are still struggling with harmful substance use.

ANN HERBST *Interim CEO,*  
*Young People in Recovery*

## ERRATA

In "The Math of Making Connections," by Kelsey Houston-Edwards, the bottom illustration in the box "Square Lattice" should have depicted the white pipe at the top left of the lattice filling with water.

In "Scientists: Admit You Have Values," by Naomi Oreskes [Observatory], the end of the quote attributed to Francis Bacon should have read: "... man prefers to believe what he wants to be true."

# MENDING MIND AND BODY: DIABETES, HEART DISEASE AND MENTAL HEALTH

Those with diabetes are more at risk for heart disease, anxiety, depression and other stresses, which can further worsen health outcomes. Breaking this cycle can offer profound improvements.

By Jeremy Abbate, VP & Publisher, *Scientific American*



As Lawrence Fisher recalls, something profound happened during a visit to his primary care physician.

"After I went through my list of prepared questions," Fisher says, "he looked at me and asked, 'OK, now what is it your wife told you to ask me?'"

Fisher is a professor of Family and Community Medicine at the University of California. He specializes in depression and diabetes care and, more specifically, how clinicians can improve outcomes for patients with chronic diseases. Yet with one small question, his doctor managed to crystalize something Fisher had learned over decades.

**"FRANKLY, I DON'T KNOW OF ANYBODY WITH A CHRONIC DISEASE WHO DOESN'T WORRY ABOUT IT. HOW THEY WORRY, HOW IT'S DEALT WITH, AND HOW PEOPLE INTERACT WITH YOU AROUND IT IS ALL VERY IMPACTFUL."**

—Lawrence Fisher



Sometimes simple gestures that connect with patients to show empathy and understanding can go a long way to relieving the stress of medical interactions.

Mental health has long been known as a determinant of physical health, a fact made painfully obvious during a pandemic. For those living with chronic conditions, such as diabetes, stress, isolation and uncertainty can bring on anxiety and depression, which in turn can lead to poorer self-care and worsening physical conditions. Add to that, diabetes increases the risk for cardiovascular disease—the number-one cause of death for patients with diabetes, according to the American Diabetes Association—and a challenging health picture emerges.

#### From Diagnosis to Daily Life

Receiving a diagnosis of a chronic disease is fraught with emotions, uncertainty and, potentially, heightened anxiety around impending lifestyle changes. In the case of diabetes, meal planning, blood glucose monitoring, insulin dosing and regular exercise become the new normal, and the enormity of confronting the condition can leave patients feeling emotionally drained.

If left unchecked, these emotional and mental burdens—often called diabetes burnout—can start a downward spiral of complications, made all the more serious from the inherent risk of associated heart disease.

Difficult though this may be, methods exist to help manage stress and open more effective channels of communication between health-care providers and patients, as well as between patients and their support networks, including partners, friends and community groups. The challenge is translating that knowledge from physicians' journals to patients.

#### A Fresh Look from the Forum

This past May, *Scientific American's* Custom Media division hosted a virtual salon event supported by Know Diabetes by Heart, a joint initiative of the American Heart Association and the American Diabetes Association, to explore the mental health components of diabetes and heart disease and how best to manage them.

Serving as moderator, I engaged Dr. Fisher at this roundtable event, along with Drs. Paula Trief, Distinguished Service Professor of Psychiatry and Behavioral Sciences and Medicine at the State University of New York Upstate Medical University, and Kenneth Freedland, Professor of Psychiatry and Psychology at the Washington University School of Medicine.

**"HOPELESSNESS IS THE FEELING THAT NOTHING IS EVER GOING TO GET ANY BETTER. HELPLESSNESS IS THE FEELING THAT THERE IS NOTHING A PERSON CAN DO TO MAKE THINGS BETTER."**

—Paula Trief



These three leading experts challenged some of the conventional wisdom and myths around mental health and disease. They explored diabetes and heart disease care management for clinicians and patients through awareness, support, transparency and an appreciation for the power of integrated care.

#### Breaking the Hopeless and Helpless Cycle

One of the most basic obstacles for a patient suffering from chronic disease and depression is to overcome two powerful forces: feelings of hopelessness and helplessness.

"Hopelessness is the feeling that nothing is ever going to get any better," Trief said at the event. "Helplessness is the feeling that there is nothing a person can do to make things better."

When a patient with diabetes is caught in this "hopeless-helpless" mindset, it can be difficult to change deleterious lifestyle habits. Eating well and exercising regularly can seem impossible tasks, while self-administering insulin injections and following health guidelines can slip. "Self-care is impacted by those feelings," Trief said.

Freedland added that for some individuals with chronic disease, particularly those with heart conditions, fear can fuel the inability to adopt better lifestyle habits.

"Part of the challenge is that people often are afraid of doing things they used to do because of their illness," he said. "When someone develops heart disease, they may feel like if they go out for a walk, they might drop dead in this street, so I better stop exercising all together."

Freedland stressed that in such scenarios, clinicians have to remind patients that under the right conditions more exercise is good and will do much to improve their condition. That simple act of communication can start to break the hopeless-helpless cycle. "To help people deal

with self-care," he said, "we need to address fears and uncertainties."

#### Emotions Are as Important as Clinical Conditions

Early in the discussion, Fisher noted that patients do not need a clinically diagnosed condition (depression, clinical anxiety, eating disorders, etc.) for mental health to impact a chronic disease, such as diabetes. The pressure to keep up with diet, keep track of an at times overwhelming number of caregivers or be labeled as a person with diabetes can all increase stress and the risk of diabetes and associated cardiovascular disease.

"Frankly, I don't know of anybody with a chronic disease who doesn't worry about it at some level," Fisher said. "How they worry, how it's dealt with, and how people interact with you around it is all very impactful."

In this regard, caregivers can help patients by simply encouraging transparent dialogue and setting realistic goals for improvement and progress. Fisher, later in the conversation, pointed out that in a typical provider-patient interaction, usually 80 percent of the dialogue is initiated by the health provider. The goal, according to him, should be more like 50 percent or an equal give and take. That can help patients feel more in control of their care and like they have more agency in realizing their potential for improvement.

#### Towards Better Outcomes

In exploring mental health and its impact on diabetes and heart disease, all of the participants advocated for a more integrated structure for health care. Freedland pointed to some models, like the Veterans

**"PART OF THE CHALLENGE IS THAT PEOPLE OFTEN ARE AFRAID OF DOING THINGS THEY USED TO DO BECAUSE OF THEIR ILLNESS."**

—Kenneth Freedland



Administration, in which mental health care is embedded in the total patient experience. The health-care ecosystem needs to include primary care providers, specialists, mental health professionals, community groups and other public resources. Additionally, mental health challenges can stem from economic and social conditions, so greater attention to societal equity can help guide the direction of care.

As all noted in the discussion, we live in an era where health-care professionals are placing a greater focus on the stresses and anxieties of chronic disease than in the past. Entities such as [KnowDiabetesByHeart.org](http://KnowDiabetesByHeart.org) provide clinicians, patients and their allies with many helpful resources to assist in diabetes care, cardiovascular risk mitigation and mental health considerations.

To view the full discussion, visit [sciam.com/kdbh](http://sciam.com/kdbh).

For information and tools to manage type 2 diabetes and heart disease, visit [KnowDiabetesByHeart.org](http://KnowDiabetesByHeart.org).



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# Anti-Trans Laws Are Anti-Health

Bills that restrict access to gender-affirming health care are unscientific

By the Editors

On April 6, the Arkansas state legislature passed a law that would prohibit transgender youth from receiving gender-affirming medical care. It was not alone: before 2021 had even reached the halfway point, at least [35 similar bills](#)—all of them in Republican-controlled states—had been proposed or passed, setting a regrettable record. Advocates for these laws argue that such treatments, which usually involve hormones that delay the changes associated with puberty, are unproven and dangerous and that the legislation is necessary to protect children. That is unscientific and cruel.

The actual danger comes from denying trans people the medical care they need. A 2020 study in the journal *Pediatrics* found that trans kids who wanted hormone treatments and did not receive them faced [greater lifetime odds of suicidal thoughts](#) than those who received “puberty blockers.” These blockers, known as gonadotropin-releasing hormone analogues, are medically safe, and their effects are reversible. The medications have been in use for decades, most often in children who begin puberty too early. For trans kids, they buy some time for young people to explore their gender identity before their bodies develop permanent secondary sex characteristics such as breasts or Adam’s apples. When they are ready, adolescents can decide whether to stop taking the blockers and continue to develop into the gender they were assigned at birth or to take gender-affirming hormones—testosterone or estrogen—to develop the features that match their gender identity.

Anti-trans laws play on fears that children may irreversibly alter their bodies and then come to regret it. But such scare tactics ignore reality for the vast majority of people who receive treatment. Under current guidelines from the Endocrine Society, none of these medical interventions can happen before the onset of puberty. Gender-affirming hormones are usually given in the teen years and only when patients have shown persistent, well-documented distress at the mismatch between their gender identity and their physical sex characteristics, according to the [standards of care set by the World Professional Association for Transgender Health](#). And when it comes to the more significant step of genital surgery, the organization stipulates that it should be an option only for adults who have lived continuously for at least a year in the gender role congruent with their gender identity.

These laws would deny people safe treatments when getting them is already too hard. Many trans people—especially people of color, those from lower-income backgrounds and those who are homeless—do not have the financial resources or support they need to receive care. “If lawmakers are interested in improving the health of young people, including transgender youth, as they of-



ten claim in these debates, a better use of their time might be to focus on improving access to high-quality medical health care for all rather than restricting it for some,” Kristina R. Olson, a Princeton University psychologist who studies the experiences of trans youth, wrote in a [Scientific American](#) opinion essay.

The statehouse war on trans people is not limited to bills restricting health-care access. At least [66 proposed laws](#) would prohibit trans students from participating on sports teams consistent with their gender identity, and 15 would block trans people from using restrooms or locker rooms that match their gender identity, according to the Human Rights Campaign, an LGBTQ rights organization. These callous regulations are just the latest in a long barrage of Republican attacks on gay and trans people. The Trump White House rolled back many LGBTQ protections and even refused to acknowledge Pride Month, traditionally celebrated in June.

In contrast, President Joe Biden issued a [presidential proclamation](#) recognizing Pride Month and signed an executive order on his first day in office [combating discrimination, on the federal level, on the basis of gender identity or sexual orientation](#). These and other acts by the Biden-Harris administration have increased desperately needed protections for the LGBTQ community, but they are just a start. Congress must pass the Equality Act, legislation that would establish nondiscrimination protections for LGBTQ people in employment, housing, credit, education, and other areas. The bill was passed by the House of Representatives in February but had not cleared the Senate at the time of this writing. And state lawmakers would do better to address the many real issues that hurt their constituents rather than enacting laws to combat nonexistent dangers. ■

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# Pesticides Are Killing Our Soils

They harm worms, beetles and thousands of other vital subterranean species

By Nathan Donley and Tari Gunstone

**Scoop up a shovelful** of healthy soil, and you'll likely be holding more living organisms than there are people on Earth. Like citizens of an underground city that never sleeps, tens of thousands of subterranean species of invertebrates, nematodes, bacteria and fungi are constantly filtering our water, recycling nutrients and helping to regulate the planet's temperature.

But under fields covered in tightly knit rows of corn, soybeans, wheat and other monoculture crops, a toxic soup of insecticides, herbicides and fungicides is wreaking havoc, according to our [recent analysis](#) in the journal *Frontiers in Environmental Science*. The study—to our knowledge the most comprehensive review ever conducted on how pesticides affect soil health—should trigger immediate and substantive changes in how the Environmental Protection Agency assesses the risks posed by the nearly 850 pesticide ingredients [approved](#) for use in the U.S.

Regulations currently ignore pesticides' harm to soil species. Our study leaves no doubt that this disregard must change. For our analysis, conducted by researchers at the Center for Biological Diversity, Friends of the Earth and the University of Maryland, we looked at nearly 400 published studies comprising more than 2,800 experiments on how pesticides affect soil organisms. Our review encompassed 275 unique species or types of soil organisms and 284 different pesticides or pesticide mixtures.

In just over 70 percent of those experiments, pesticides were found to harm organisms critical to maintaining healthy soils—harms that have never been considered in the EPA's safety reviews. Pesticide-intensive agriculture and pollution are [driving factors](#) in the precipitous decline of many soil organisms, such as ground beetles and ground-nesting bees. They have been [identified](#) as the most significant driver of soil biodiversity loss in the past decade.

Yet pesticide companies and our pesticide regulators have ignored that research. The EPA, which is responsible for pesticide oversight in the U.S., openly [acknowledges](#) that somewhere between 50 and 100 percent of all agriculturally applied pesticides end up on the soil. Yet to assess pesticides' harms to soil species, the agency still [uses](#) a single test species—one that spends its entire life aboveground in artificial boxes—to estimate risk to all soil organisms: the European honeybee.

The fact that the EPA relies on a species that literally may never touch soil in its entire life to represent the thousands of species



**Nathan Donley** is environmental health science director at the Center for Biological Diversity, headquartered in Arizona. His work focuses on U.S. pesticide regulation and policy.

**Tari Gunstone** is a scientist who, as a research assistant at the Center for Biological Diversity, spent more than a year analyzing studies on pesticide impacts to soil health.

that live or develop underground offers a disturbing glimpse of how the U.S. pesticide regulatory system is set up to protect the pesticide industry instead of species and their ecosystems. What this ultimately means is that pesticide approvals happen without any regard for how those chemicals can harm soil organisms.

To add to this, as principles of regenerative agriculture and soil health gain popularity around the world, pesticide companies have jumped on the bandwagon to greenwash their products. Every [major company](#) now [has](#) Web materials touting its role in promoting soil health, often advocating for reducing tilling and planting cover crops.

As general tenets, both these practices are indeed good for soil health and, if adopted responsibly, are great steps to take. But companies know that these practices are often accompanied by



increased pesticide use. When fields are not tilled, herbicides are frequently used to kill weeds, and cover crops are often killed with chemicals before crop planting. This “one step forward, one step back” approach is preventing meaningful progress to protect our soils. Pesticide companies have so far been successful in coopting “healthy soil” messaging because our regulators have shown no willingness to protect soil organisms from pesticides.

The long-term environmental cost of that failure can no longer be ignored. Soils are some of the most complex ecosystems on Earth, [containing](#) nearly a quarter of the planet's biodiversity. Protecting them should be a priority, not an afterthought. Our research indicates that achieving this will require that we reduce the world's growing and unsustainable reliance on pesticide-intensive agriculture. And it will require that the EPA take aggressive steps to protect soil health. ■

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# ADVANCES





- Ultrawhite paint releases buildings' heat
- Radiation might have sustained underground Martian life
- A new test could distinguish viral from bacterial infections in the doctor's office
- Flashy plants are studied disproportionately

## NEUROSCIENCE

## Brain Typing

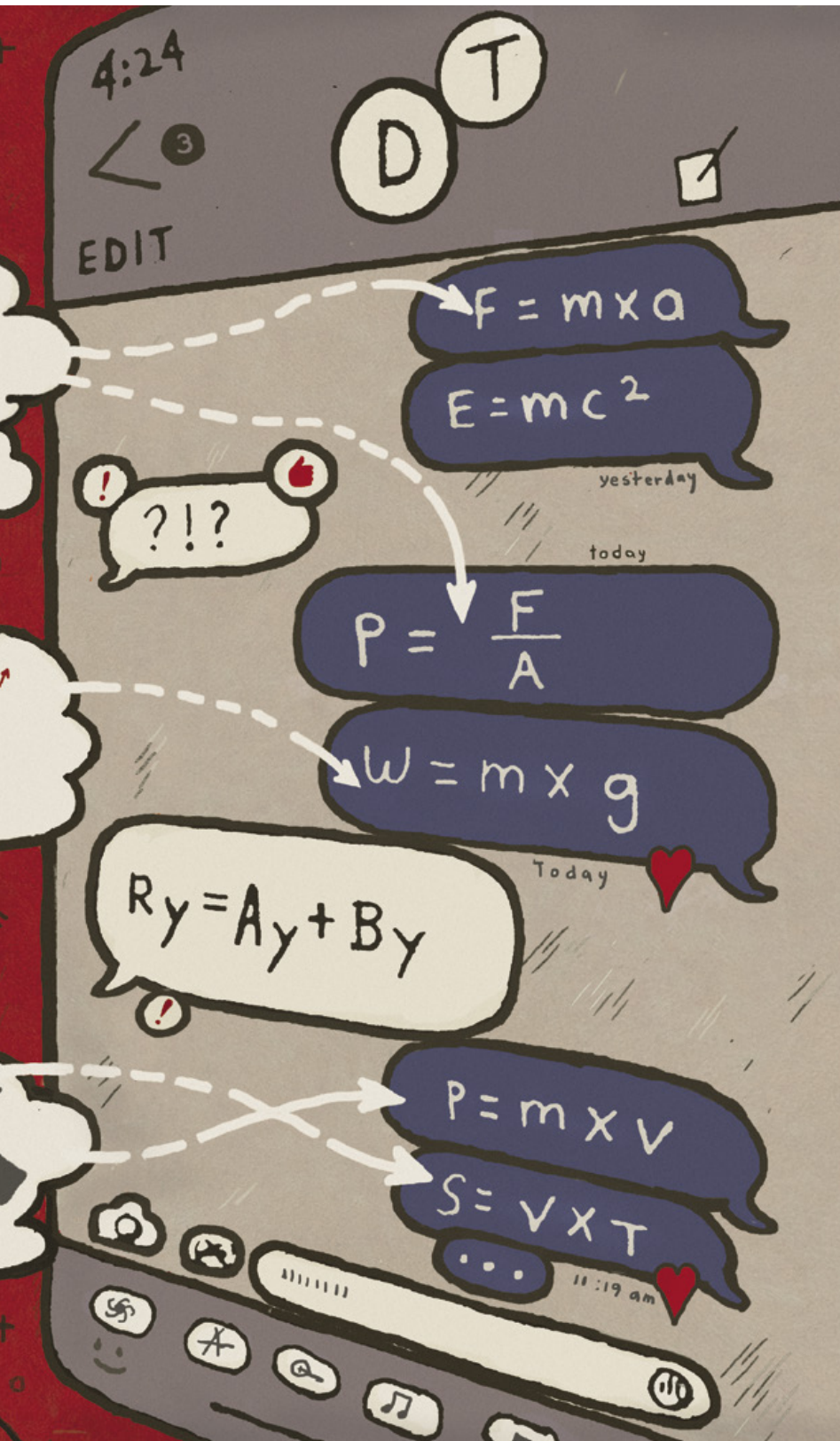
New AI implant turns visualized letters into text

**When you move,** sense, speak, or do just about anything, your brain generates a specific corresponding pattern of electrical activity. For decades, scientists have run these impulses through machines to better understand brain diseases and help people with disabilities. Brain-computer interfaces (BCIs) under development can restore movement in some who have paralysis, and researchers are working on BCIs to treat neurological and psychiatric disorders.

The next frontier in BCIs, however, may be something more like writing a text message. A new study in *Nature* describes a brain implant that could let individuals with impaired limb movement create text using the mind—no hands needed.

For their study, the researchers coupled artificial-intelligence software with electrodes implanted in the brain of a man with full-body paralysis. He was asked to imagine himself writing by hand, and the BCI transformed his visualized letters and words into text on a computer screen. Such technology could potentially benefit millions of people worldwide who cannot type or speak because of impaired limbs or vocal muscles.

Previous work by Krishna V. Shenoy of Stanford University, a co-senior author on the study, had helped analyze neural patterns associated with speech. His software also decoded imagined arm movements, so that those with paralysis could move a cursor around an on-screen keyboard to select and type letters. But this technique let people generate just 40 characters per minute, far lower than the average keyboard typing



speed of roughly 190. The researchers' new work sped up communication speed by using imagined handwriting. Their technique allowed the study subject, who was 65 years old at the time, to mentally type 90 characters per minute. That rate approaches the average for most senior texters, who can typically type about 115 characters per minute on a phone.

"This line of work could help restore communication in people who are severely paralyzed, or 'locked-in,'" says Frank Willett, lead author of the paper and a research scientist at Stanford's Neural Prosthetics Translational Laboratory. "It should help people express themselves and share

## "This study is an important and clear advance for intracortical brain-computer interfaces."

—Amy L. Orsborn,  
University of Washington

their thoughts; it's very exciting."

The study participant had suffered a spinal cord injury in 2007, losing most movement below his neck. In 2016 Stanford neurosurgeon Jaimie Henderson, co-senior author of the paper, implanted two small BCI chips into the man's brain. Each chip had 100 electrodes to sense neuron activity. They were implanted in a region of the motor cortex that controls hand and arm movements, letting the researchers profile brain-activity patterns associated with written language.

"This study is an important and clear advance for intracortical brain-computer interfaces," says University of Washington bioengineer Amy L. Orsborn, who was not involved in the research. "One obvious reason why is because they achieved a huge leap in performance on a challenging but important task like typing. It's also the most significant demonstration to date of leveraging established tools in machine learning, like predictive language models, to improve BCIs."

Mijail D. Serruya, a neurologist at Thomas Jefferson University, who studies BCIs in stroke recovery but was not involved in the new study, is intrigued by the work. "I saw this research initially presented ... in 2019 and think it's great," he says. "I think

it clearly shows that fine-motor trajectories can be decoded from neocortical activity."

Serruya adds that his own research could align with Willett's in helping those who have suffered brain trauma or a stroke. "We have shown that motor-control signals can be decoded [following a stroke], implying that some of the decoding approaches developed by Willett might have applications beyond people with spinal cord injury," he says.

Yet Serruya also has a question about the new research, a hesitation he says he posed to Willett a few years ago: while restoring communication via written letters is intuitive, it may not be the most efficient means of doing so.

"Why not teach the person a new language based on simpler elementary gestures, similar to stenography chords or sign language?" Serruya asks. "This could both boost the speed of communication and, crucially, decrease the mental effort and attention needed."

For now, Willett is focused on mentally decoding more familiar forms of communication—and he wants to repeat the typing experiment, involving more people with paralysis. Translating the brain's control over handwriting may be a significant first step in restoring communication skills, he says. But decoding actual speech—by analyzing what someone intends to say—is still a major challenge facing researchers, given that individuals generate speech more quickly than they write or type.

"It's been a hard problem to decode speech with enough accuracy and vocabulary size to allow people to have a general conversation. There's a much higher signal-to-noise ratio, so it's harder to translate to the computer," Willett says. "But we're now excited that we can decode handwriting very accurately. Each letter evokes a very different pattern of neural activity."

As for when text-and-speech-decoding technology might be available to the public, Willett is cautiously optimistic. "It's hard to predict when our method will be translated into a real device that anyone can buy," he says. "There are companies working on implantable BCI devices now, but you never know when someone will succeed in translating it. We hope it's within years, not decades!" —Bret Stetka

## MATERIALS SCIENCE

### Cool Color

"Whitest white" paint beats the heat

The "blackest black" paint, famed for its thermal camouflage potential, has long absorbed 99.9 percent of public attention. Now it's time to shed some light on the other end of the practical paint spectrum: the "whitest white." Research shows that surfaces coated with a newly formulated white coloring reflect 98.1 percent of sunlight, creating a powerful cooling effect—without plugging in an air conditioner.

This coating absorbs just 1.9 percent of sunlight compared with 10 to 20 percent for conventional white or "heat-reflective" paints, says Purdue University mechanical engineer Xiulin Ruan, co-author of a study on the substance in *ACS Applied Materials & Interfaces*. By reflecting so efficiently, the novel paint can actually help a coated building release the heat inside. The authors calculate that covering a 1,000-square-foot

## GEOLOGY

### Gems of History

Precious information hides in imperfect diamonds

Cloudy, yellowish "fibrous diamonds" are too unsightly for most jewelers. But for scientists, their crystalline structure holds valuable secrets stretching back a billion years or more.

Yaakov Weiss, an earth scientist at the Hebrew University of Jerusalem, and his colleagues crushed portions of South African fibrous diamonds to extract tiny pockets of fluid trapped within. This fluid, from which the diamonds once formed, holds a unique record of long-ago conditions deep within Earth. It also contains uranium and thorium, which decay into the isotope helium 4 and gradually leak out of the diamond's crystalline lattice. But nobody knew the precise leakage rate, which would be needed to determine the diamonds' age and unlock the history within.

roof with their paint could cool a building by about 10 kilowatts. “Our model shows if you’re in, say, Reno or Phoenix, you can save up to 70 to 80 percent on air-conditioning in the summer,” Ruan says.

Scientists have been developing reflective paints for decades, but commercial products still remain at or above the surrounding temperature. In the past 10 years researchers have found greater success with multilayered coatings that incorporate tiny particles of varying sizes, some on the nanoscale, to reflect many wavelengths of light. Teams at Stanford University and the University of Colorado Boulder have shown that such materials can cool a surface to below the ambient temperature. Unfortunately, manufacturing precise layers of multiple substances and applying them to a surface in a set order costs more—and requires a more intensive process—than simply slapping on some paint.

Ruan decided to take a hybrid approach and create an ordinary paint that could easily be brushed or sprayed onto a surface but that would still incorporate a reflective nanomaterial. After testing parti-

cles of several different compounds, he and his colleagues ultimately selected a relatively inexpensive one called barium sulfate. Next they calibrated the necessary concentration to make the paint as reflective as possible, without reducing its ability to stick together. Finally, they made sure the barium sulfate particles came in a variety of sizes to reflect different wavelengths.

“I like this study. I think it’s promising,” says Yuan Yang, a Columbia University materials scientist, who was not involved in the research. “And I think there’s a potential to be commercialized.” Ruan says he hopes to bring a version of his paint to market in a year or two. “The price [of barium sulfate] is comparable to, or even slightly lower than, titanium dioxide that is used in commercial paints,” he adds. “Manufacturing doesn’t involve any expensive nanotechnology. Although it’s still a nanotech, it is a very affordable nanotech.”

There is plenty of competition from other researchers. And Yang notes that any new product like this will need to



stand up to the real world, where grime coats surfaces over time. A manufacturer, he says, would have to grapple with “how to make sure that the paint stays white after 30 years of use.”

Ruan sees his work as a tool to fight the climate emergency. “President [Joe] Biden talked about cutting carbon emissions in half by the end of 2030,” he says. “Our paint can contribute to that goal because it lets us get cooling without using power.”

—Sophie Bushwick

By modeling this decay and how much helium 4 leakage is possible over time, Weiss and his colleagues determined a broad age range for the stones. They then ruled out ages that would be impossible based on known tectonic and thermal conditions in Earth’s mantle and crust at the diamonds’ formation site. Combining these data yielded an upper limit on leakage, which the researchers could apply to all fibrous diamonds they studied. They recently described their results in [Nature Communications](#).

The team dated the fluid back to three separate periods, each coinciding with big changes at the surface. The oldest diamonds were found to be between 750 million and 2.6 billion years old; the scientists narrowed their creation down to about a billion years ago, when tectonic forces were building rugged mountains in what is now South Africa. The next oldest formed 300 million to 540 million years ago, coinciding with the formation of Namibia’s Naukluft Mountains. The youngest formed between 85 million and 118 million years ago, just before a subsurface eruption blasted them

toward the upper crust.

Additionally, the fluid was carbon-rich in the oldest diamonds, heavy in silica in the next oldest, and saline-rich in the youngest. This might also echo significant geologic changes: for instance, the youngest fluids may have come from oceanic crust being pushed deep into Earth as the oceanic plate slid under the continental crust.

No other deep-Earth rock or mineral reaches the surface with as few interior alterations as a diamond, says University of Alberta earth scientist Suzette Timmerman, who was not involved in the study. The fluids thus offer a rare, direct window into the deep lithosphere (crust) and upper mantle. “Whatever is inside is basically a time capsule,” Timmerman says.

Next, the researchers plan to check dia-



A fibrous diamond houses tiny pockets of ancient fluid.

monds from other regions for similar correlations between formation and big surface events, Weiss says: “We’ll need to think about what exactly this says about the evolution of the mantle and the lithosphere.”

—Stephanie Pappas

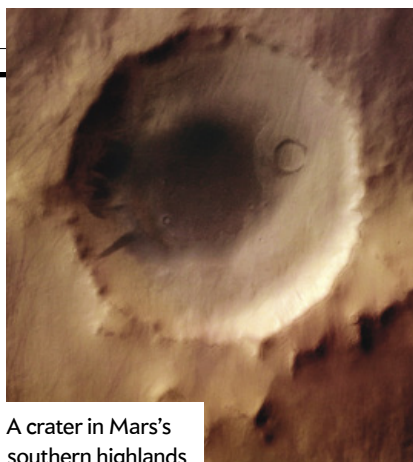
## ASTROBIOLOGY

# Alien Underground

Subsurface radiation could have powered Martian microbes

**Deep below** the ground, radioactive elements disintegrate water molecules, producing ingredients that can fuel subterranean life. This process, known as radiolysis, has sustained bacteria in isolated, water-filled cracks and rock pores on Earth for millions to billions of years. Now a study published in *Astrobiology* contends that radiolysis could have powered microbial life in the Martian subsurface.

Dust storms, cosmic rays and solar winds ravage the Red Planet's surface. But belowground, some life might find refuge. "The environment with the best chance of habitability on Mars is the subsurface," says Jesse Tarnas, a planetary scientist at NASA's Jet Propulsion Laboratory and the new study's lead author. Examining the Martian underground could help scientists learn whether life could have survived



A crater in Mars's southern highlands

there—and the best subsurface samples available today are Martian meteorites that have crash-landed on Earth.

Tarnas and his colleagues evaluated the grain sizes, mineral makeup and radioactive element abundance in Martian meteorites and estimated the Martian crust's porosity using satellite and rover data. They plugged these attributes into a computer model that simulated radiolysis to see how efficiently the process would have generated hydrogen gas and sulfates: chemical ingredients that can power the metabolism of underground bacteria. The researchers report that if water was present, radiolysis in the Martian subsurface could have sus-

tained microbial communities for billions of years—and perhaps still could today.

Scientists have previously studied Mars radiolysis, but this marks the first estimate using Martian rocks to quantify the planet's subsurface habitability. Tarnas and his colleagues also evaluated the potential richness of life in the Martian underground and found that as many as a million microbes could exist in a kilogram of rock. (Geobiologists have found comparable densities in Earth's subsurface.)

The most habitable meteorite samples analyzed appeared to be made of a rock type called regolith breccia. "These are thought to come from the southern highlands of Mars, which is the most ancient terrain on Mars," Tarnas says.

Underground life, as described by this research, would require water—and it remains unknown if groundwater exists on the planet, says Lujendra Ojha, a planetary scientist at Rutgers University, who was not involved in the study. Determining whether the Martian crust contains water will be an important next step, but this investigation helps to motivate that search, Ojha says: "Where there is groundwater, there could be life." —Nikk Ogasa

ESA, DLR, FU Berlin and G. Neukum (CC BY-SA 3.0 IGO)

## HEALTH

# Virus or Bacterium?

New blood test answers a stubborn medical question

**Runny nose, cough, fever:** patients show up in clinics every day with these classic symptoms of respiratory infection. But is the culprit a bacterium, which can be attacked with antibiotics, or a virus, which is harder to target with medication? Often doctors cannot be certain. But researchers say they are closing in on an accurate test that can make the call quickly, right in a physician's office.

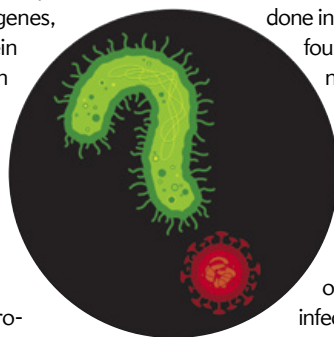
Faced with an unknown infection, doctors sometimes order laboratory tests for common bacteria such as *Streptococcus*. Or they might immediately try antibiotics, basing this decision simply on symptom strength—but antibiotic overuse can lead to dangerously resistant bacterial strains. "When the distinction can be made quickly, we can ensure that antibiotics are not inap-

propriately prescribed," says Duke University infectious disease specialist Ephraim Tsalik. In 2016 he and his colleagues developed a lab test linking common respiratory symptoms to viral, bacterial or noninfectious origins. It works because each pathogen activates a different set of genes, varying their RNA or protein production, and the test can spot these telltale "gene expression" signatures in a small blood sample.

The team recently collaborated with a company called BioFire to speed up this test to produce results within an hour. The new process, tested on more than 600 emergency room patients for a study in *Critical Care Medicine*, identified bacterial infections with 80 percent accuracy and viral infections with nearly 87 percent accuracy. A common lab test Tsalik evaluated had about 69 percent accuracy. Others require time-consuming cultures or can only confirm specific pathogens a doctor decides to test for.

Technology to examine genes' response

to pathogens in a rapid and integrated way was just recently developed, says Stanford University computational immunologist Purvesh Khatri, who was not involved in the study. Amplifying RNA through PCR-based methods, a key analytic step, can now be done in 15 to 20 minutes. Khatri co-



founded Inflammix, a company set to soon release its own rapid test "to tell whether there is an infection and which [pathogen] is likely causing it and also give information about severity."

Tools to help limit antibiotic overuse for respiratory infections "could have a dramatic impact in curbing the rise of antibiotic resistance," says Washington University in St. Louis pediatric infectious disease specialist Gregory Storch, who was not involved in the study. And whereas people from different populations and with certain preexisting conditions might show varying patterns of gene expression, Storch hopes future work will account for such differences to ensure reliable results for all. —Harini Barath

IN THE NEWS

# Quick Hits

By Maddie Bender

## DEMOCRATIC REPUBLIC OF CONGO

Mount Nyiragongo, one of the world's most active volcanoes, erupted for the first time since 2002 and displaced hundreds of thousands of people. A local volcano observatory had warned of a possible eruption last year, but budget cuts and an Internet disruption limited its ability to predict the blast.

## CAMBODIA

A giant pouched rat named Magawa has retired after sniffing out unexploded land mines for five years. Trained by a Belgian non-profit organization, the rodent received a bravery prize previously awarded only to dogs.

## ITALY

Art restorers have cleaned the Medici Chapel in Florence with the help of bacteria. *Serratia*, *Pseudomonas* and *Rhodococcus* ate away at detritus—from visitors and decaying corpses—that had seeped into Michelangelo's sarcophagi.

## GALÁPAGOS ISLANDS

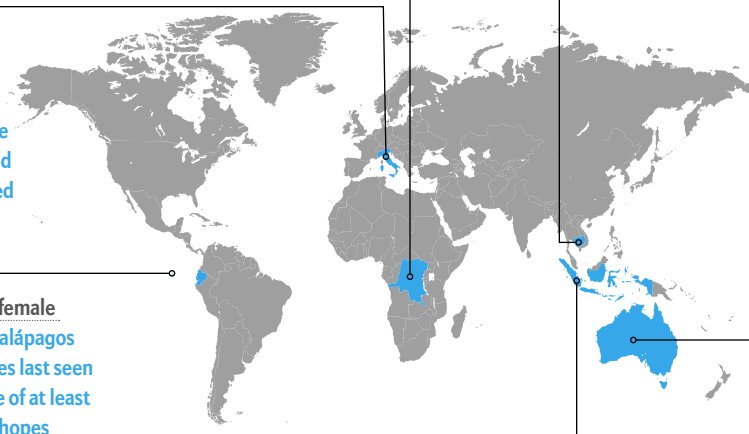
Genetic analysis confirmed that a female giant tortoise, discovered in the Galápagos Islands in 2019, belongs to a species last seen in 1906. Rangers spotted evidence of at least two more of the reptiles, buoying hopes of finding a mate for the female.

## INDONESIA

Researchers found that monsoon seasons lengthened by climate change are damaging some of the world's oldest rock art. The rains most likely increase salt crystal formation in Sulawesi island's limestone caves, breaking up the 20,000- to 45,500-year-old paintings' rocky canvases.

## AUSTRALIA

At least seven Tasmanian devils were born in mainland Australia—the first wild births there in 3,000 years—after the animals were reintroduced last year. Human settlers had long ago brought in dingoes, which wiped out mainland devils and limited their range to the island state of Tasmania.



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## EXTREME WEATHER

# Climate Price Tag

Scientists tally cost of how much global warming worsens disasters

**Superstorm Sandy's** 2012 surge swamped lower Manhattan, unmoored a Jersey Shore roller coaster and pushed the toxic waters of Brooklyn's Gowanus Canal into nearby basements. All told, the storm's floodwaters did more than \$60 billion in property damage in New York State, New Jersey and Connecticut. Although scientists have long known global warming is exacerbating such events by raising sea levels, a recent study calculated just how much of Sandy's bill can be charged to climate change: about \$8 billion.

The study's new modeling method can be extended to any coastal storm or other

flooding event. "It's putting the climate change price sticker on the event where it hasn't been visible," says the new study's lead author Benjamin Strauss, CEO and chief scientist of Climate Central, a non-profit research and news organization.

The team used observations and models to compare our world with one where there is no climate change. Various hypothetical comparisons have already shown how rising temperatures increase the likelihood and severity of extreme weather events, from heat waves to floods. This study, published in *Nature Communications*, goes a step further by tallying the extra damage.

Strauss and his co-authors first calculated that greenhouse gas-driven warming has caused about four inches of sea-level rise over the past century in the New York City area. The team then used computer models to relate various sea levels to flood damage. Sandy's damage was almost entirely from flooding, which let the researchers translate those results to estimates of how much of the tab came from climate change.

Using a sea-level-rise mapping tool developed by Climate Central, the researchers also found that Sandy inundated areas with an additional 71,000 people and 36,000 homes that would have been spared in the absence of global warming. Strauss says his team's method can be used to calculate the damage costs of climate change for any past or future flooding event with sufficient sea-level data. Applying the new method to Sandy alone gives a sense of the already steep cost of the climate emergency, Strauss says. "I think we're paying a lot more than we realize," he adds.

And the new study's calculation is likely an underestimate, says University of Chicago economist Amir Jina, because it does not include nonphysical damage such as the interruption to business. Jina, who collaborates with one of the study's co-authors but was not involved in this project, says such cost estimates can put the price of reducing greenhouse gas emissions into perspective. "Anything that helps us understand the costs of climate change helps us understand how much we get by mitigating it," he says.

—Andrea Thompson

Orjan F. Ellingvag/Getty Images

## MEDICINE

# Blood Secrets

Circulating DNA can pinpoint serious unseen problems

**When a cell dies** in a tumor, a growing fetus or elsewhere in the body, bits and pieces of its DNA enter the bloodstream. A new test that identifies the source of such DNA could

make it easier to find hidden cancers, monitor the success of organ transplants and conduct prenatal screenings. To make this test, the team of researchers figured out how to analyze two types of variation at once to noninvasively pinpoint DNA fragments' origins with near-perfect accuracy.

Circulating DNA is a "diagnostic gold mine," says Cornell University biomedical engineer Iwijn De Vlaminck, who was not involved with the new study. For example, tumor

DNA may appear in the blood before a cancer can be detected using conventional screening methods. But earlier blood tests that looked for circulating DNA were limited by the fact that all the cells in our system have largely the same genome, De Vlaminck adds.

"Our new method will show us where these [DNA] molecules come from with a very high degree of resolution," says Dennis Lo, a chemical pathologist at the Chinese University of Hong Kong and

senior author on the new study in *eLife*.

Along with differences in genetic code—which can indicate whether DNA comes from a transplanted organ or from a growing fetus—the new test (called GETMap, for genetic-epigenetic tissue mapping) also measures a phenomenon called DNA methylation. Cells add molecular groups to certain DNA sequences to turn genes on and off; this so-called methylation fingerprint can reveal the

ENVIRONMENT

# Switchgrass Cleaner

Grass planted on military ranges can sop up a toxic chemical

**Chemicals from munitions** have permeated soil across an estimated 10 million hectares of land used for firing ranges across the U.S. One such chemical, an explosive called RDX, can leach into groundwater and cause seizures and possibly cancer. Now a study in *Nature Biotechnology* shows that genetically modified switchgrass—a plant common in North American prairies—can absorb and break down RDX.

University of York biologists Neil Bruce and Liz Rylott and their colleagues altered a switchgrass variety to carry two genes from a bacterium that produces enzymes capable of reducing RDX into harmless components. After conducting lab tests, the researchers planted the modified switchgrass on New York State's RDX-polluted Fort Drum military base.

For three years the team tested soil and water pumped from plastic-lined plots where modified plants, wild plants or no plants grew, painstakingly removing seeds from the modified switchgrasses to pre-

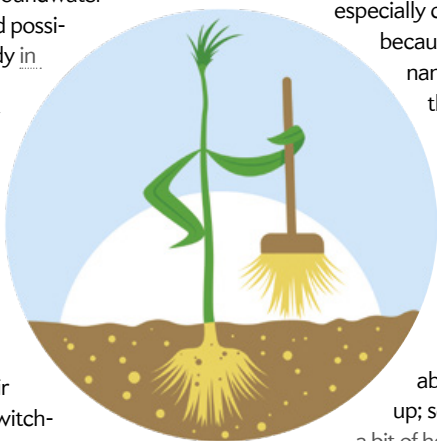
vent cross-pollination with local varieties. They found that the modified plants took up RDX, lowering levels significantly in the surrounding water, and broke it down—RDX did not appear in the modified plants' tissues, but it did in wild plants.

"The evidence is compelling that the transgenic [switchgrass] works very well and grows without the RDX being toxic to the plant," says University of Iowa environmental engineer Jerald Schnoor, who was not involved in the study.

Removing this pollutant has proved especially challenging, partly because unexploded ordnance peppers many of the country's massive firing ranges. Bacteria that break down RDX exist in soil but do not consume the toxin fast enough to keep it from seeping into aquifers.

"Nature has the ability to clean [RDX] up; sometimes it needs a bit of help," Rylott says. "It's a Batman and Robin combo—bacterial Batman, and the plant is Robin." Other researchers have used plants to clean up PDBs, DDT, nickel and arsenic.

The researchers also genetically modified another plant, western wheatgrass, to take up RDX. "If we transform a couple more species," Rylott says, "we can get a toolbox that will be able to take out RDX, but we can also maintain biodiversity across the training range." —Susan Cosier



original tissue source for the DNA.

The researchers tested GETMap in pregnant women, lung transplant recipients and cancer patients. In blood samples from the first group, they could distinguish fetal cell DNA (which has methylation signatures specific to the placenta) from maternal DNA more easily than with current methods.

"If we can determine which of the [circulating]

DNA is coming from the placenta, we could more readily look at specific gene defects," says Virginia Winn, an obstetrician-gynecologist at Stanford University, who was not involved in the study.

In lung transplant recipients, the researchers found that most of the DNA released just after the transplant came from the new lungs' blood vessels, an insight that may be useful in the future for

tracking organ rejection.

And in cancer patients, they pinpointed the sources of tumors, which could reduce the need for full-body scans and allow for more targeted testing and treatment.

GETMap's uses may not stop with blood. Lo says the researchers next plan to test their technique in urine, spinal fluid and other bodily liquids to detect and treat diseases early.

—Anna Goshua

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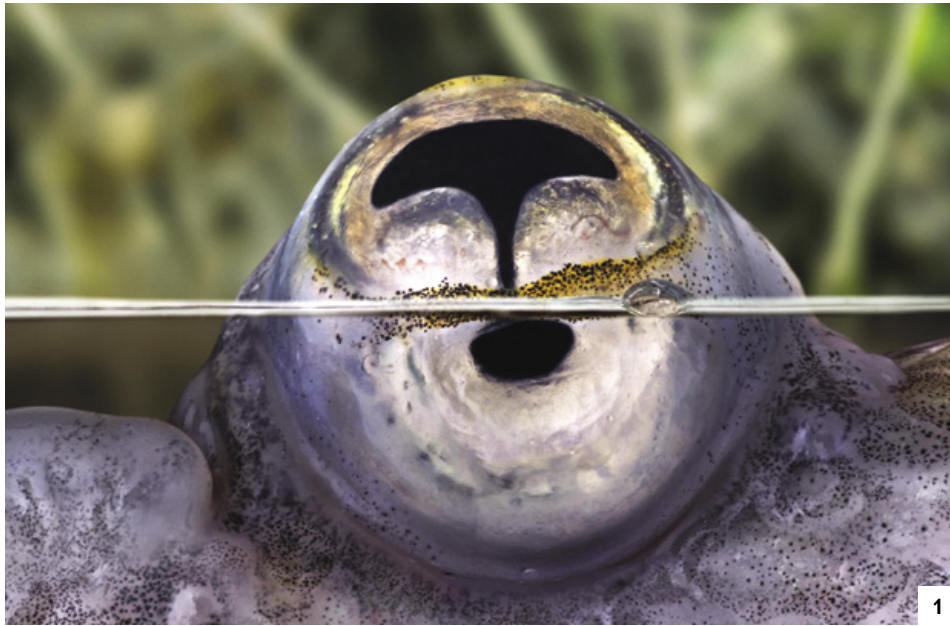


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## ECOLOGY

# Science in Images

By Leslie Nemo

**The first eyes** evolved on Earth more than 500 million years ago, just before a massive biodiversity spike called the Cambrian explosion. The earliest versions might have included the pit eye (an indentation lined with light receptors) and an

eyespot—a simple region of light-detecting tissue. Over time, organisms developed lenses and corneas that bend and focus light. The latter took on special importance for creatures living on land, transforming from a protective cover to an image-forming structure itself.

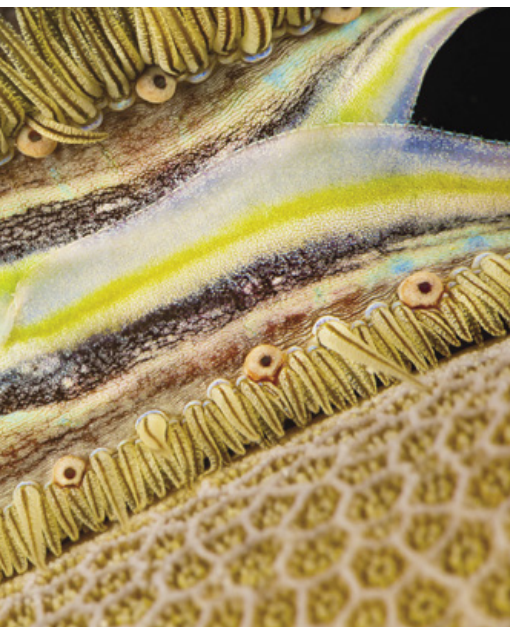
Some organisms stuck with basic structures; today's flatworms and mollusks, for example, still have simple pit eyes. Others, however, have developed mirrored components, elaborate pupil dynamics and arrangements that let their owners see above and below a waterline simultaneously. Even in animals that do not

rely primarily on sight, incredible eye features persist.

- 1 **Four-eyed fish:** A single eye from this species has two lobes. One sits above the waterline and one below as the fish cruises along the surface, searching for floating snacks.
- 2 **Mossy New Caledonian gecko:** The largest gecko species ever recorded, this reptile can grow up to 14 inches long. Like some of its fellow nocturnal relatives, it often slaps its eyes with its tongue to wipe away grime.

Pally Alamy Stock Photo (1); Nature Picture Library and Alamy Stock Photo (2); Steve Bloom Images Alamy Stock Photo (3); David Fleetham Alamy Stock Photo (4)





**3 Indian elephant:** Dissections of both African and Asian elephant eyes show that the gentle giants probably have red-green color blindness just like some humans, meaning they cannot distinguish between the two colors in daytime light.

**4 Coral-boring scallop:** This mollusk's eyes (*11 visible here*) do not focus light with lenses like most animal peepers do. Instead they use reflective crystals—also found in carp scales and chameleon skin—to gather and direct the rays.

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## PUBLIC HEALTH

# Buzz Kill

### Researchers crack the mystery of a natural mosquito repellent

**Mosquito-borne diseases** kill about 700,000 people every year. Lives can be spared by applying insect repellents, including a chrysanthemum flower extract called pyrethrum that humans have used for thousands of years. A new study in *Nature Communications* finally shows how pyrethrum works, with two components acting synergistically to deter the pesky bloodsuckers.

Mosquitoes tend to develop resistance to a specific repellent over time, notes the study's senior author Ke Dong, a Duke University neurotoxicologist. So "new, alternative ones need to be continuously developed to eventually replace current ones," she says. Understanding repellent mechanisms could help. "We're very excited because we are finally beginning to understand how a popular natural insect repellent, used worldwide, keeps mosquitoes from biting people."

To observe pyrethrum's effects, Dong and her colleagues attached tiny electrodes to hairs on mosquitoes' antennae. This let them measure the insects' responses to repellents at the level of individual odorant receptors in nerve cells. Many disease-carrying mosquito species have more than 100 such receptors, but the researchers found pyrethrum activates one in particular called Or31—and they confirmed that mosquitoes would not flinch from the substance if they were genetically modified to lack that receptor.

Unlike many other odorant receptors, Dong says, Or31 just happens to appear in all known disease-carrying mosquito species. Plus, many other natural repellents—unlike pyrethrum—work by activating multiple odorant receptors, and researchers still know very little about

how those other receptors work. Considering these factors, the scientists suggest, Or31 could serve as a clear, universal target for developing better repellents.

The team also used chemical analysis to determine how two of pyrethrum's molecular components—EBF and pyrethrin—elicit the repellent response. Mosquito experiments showed the chemicals work best when combined: EBF activates Or31, and pyrethrins enhance repellency by intensifying nerve signaling.

Dong and her colleagues next plan to investigate the neural circuits behind the repellency induced by pyrethrum and similar natural substances. They will also continue testing other potential repellent molecules, including the main compo-



The Dalmatian chrysanthemum produces a potent repellent.

nent in citronella oil, which they found also activates Or31.

Johns Hopkins University neuroscientist Christopher Potter, who specializes in insect olfaction and was not involved in the research, says the findings could eventually help create "super mosquito repellents." In particular, Potter says, untangling exactly which neurons determine mosquitoes' responses to certain odors could reveal novel ways to manipulate their behavior. "Perhaps one day," he observes, "we could identify how to turn this dial up even further or how to trick mosquitoes into becoming repelled by other odors—such as those that normally attract them to humans."

—Rachel Nuwer

## BOTANY

# A Flashy Focus

Researchers are drawn to tall, bright and showy plants

**Scientists and gardeners** alike seem unable to resist the charms of a flamboyant flower or towering stalk. A new study has found that botanists' research inexorably skews toward showy plants, whereas the drabest, dullest and shortest are often left behind—even if they are endangered.

The analysis, published in *Nature Plants*, reviewed 280 studies conducted from 1975 to 2020 on 113 plant species in the southwestern Alps, a major biodiversity hotspot. Researchers collected data on the plants' morphology (traits such as size and color), as well as their ecology and rarity. A tally of the number of studies conducted on each plant revealed that eye-catching ones attracted far more scientific attention.

Plants with blue flowers, ranging in tone from indigo to cyan, have been studied disproportionately even though blue is one of the least common flower colors, says the study's lead author Martino Adamo, a biologist at the University of Torino in Italy. Plants with red, pink or white blossoms beat those with brown or green flowers, and plants with tall stems also stood out—and not just literally.

“Our findings don't so much suggest that researchers focus on prettier plants,” Adamo says, “but rather that more conspicuous, easy-to-locate and colorful flowering plants are the ones receiving more attention.”

The team had expected to find more endangered species among those most studied, but it did not. This counterintuitive result could have significant implications for plant science, the researchers say. A bias toward “glamorous” plants could mean “we may be missing extraordinary, untold stories of how plants grow, evolve and adapt,” says study co-author Kingsley

Dixon, a botanist at Australia's Curtin University. “Plus, we may be missing species that could be in rapid decline toward extinction, and we don't have even basic information on seed banking for conservation.”

Adamo adds: “These results show that probably our unconscious is stronger than expected in the species model selection; this is not a tragedy, but something to consider” when planning future work. The results echo earlier findings that brightly colored, more charismatic and popular mammals and birds are more often featured in conservation and funding efforts, regardless of scarcity.

University of Melbourne environmental



A highly researched plant (top) and a rarely researched plant (bottom) from the southwestern Alps.

psychology researcher Kathryn Williams, who was not involved in the new study, says the potential consequences of such biases “are important for plant conservation and environmental decision-making more broadly. The availability of data about species, and the strength of the evidence base,” she adds, “will weigh in as difficult decisions are made about where to direct conservation effort and funding.” —Jillian Kramer

Martino Adamo

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## Elizabeth Cabot Agassiz (1822–1907)

*It is perhaps not strange that the Radiates, a type of animals whose home is in the sea, many of whom are so diminutive in size, and so light and evanescent in substance, that they are hardly to be distinguished from the element in which they live, should have been among the last to attract the attention of naturalists.*

They say I came to science  
through marriage. As though  
I wouldn't have, otherwise.

As though I was dragged, by accident,  
like a jellyfish caught in a net.

The truth is I married for science.

It was a way in. Like  
a radiate, I got what I wanted  
without attracting undue attention.

*Nothing can be more unprepossessing than a sea-anemone when contracted. A mere lump of brown or whitish jelly, it lies like a lifeless thing on the rock to which it clings, and it is difficult to believe that it has an elaborate and exceedingly delicate internal organization, or will ever expand into such grace and beauty as really to deserve the name of the flower after which it has been called ... the whole summit of the body seems crowned with soft, plummy fringes.*

We are all lumps, aren't we, before we find  
the thing we love? The things?  
My husband and I, lumped together,  
blossomed into beauty. I know  
that sounds maudlin. Let me try again.

*Author's Note: All italic quotations are from Agassiz's Seaside Studies in Natural History (1865). In addition to her scientific research, Agassiz collaborated with her husband, natural historian Louis Agassiz, on marine expeditions. She was a co-founder and the first president of Radcliffe College.*

*These animals ... thrive well in confinement.*

For some women, marriage is a prison.  
They enter it willingly. It keeps them  
safe from the world. Our marriage  
was more like a boat.

*They may also multiply by a process of self-division.*

We had no children. I took notes.

Another way of saying it is I wrote books.

At every point in our studies  
of sea creatures and each other,  
I was in charge of the words.

*The name Jelly-fish is an inappropriate one, though the gelatinous consistency of these animals is accurately enough expressed by it; but they have no more structural relation to a fish than to a bird or an insect.*

Jellyfish are neither jelly nor fish,  
as I was not truly wife nor scientist.  
Have you seen them move?  
It looks as if they move by breathing.



Jessy Randall's books include *How to Tell If You Are Human: Diagram Poems* (Pleiades), *Suicide Hotline Hold Music* (Red Hen), and, forthcoming in 2022, *Mathematics for Ladies: Poems on Women in Science* (Gold SF).



*Encountering one of those huge Jelly-fishes, when out in a row-boat one day, we attempted to make a rough measurement of his dimensions upon the spot. He was lying quietly near the surface, and did not seem in the least disturbed by the proceeding, but allowed the oar, eight feet in length, to be laid across the disk, which proved to be about seven feet in diameter. Backing the boat slowly along the line of the tentacles, which were floating at their utmost extension behind him, we then measured these in the same manner, and found them to be rather more than fourteen times the length of the oar...*

As I write these lines I remember that day in the boat and how happy we were. A person could measure our happiness in oars. A person could lay down oar after oar and still need more oars.

Our laughter echoing over the waves. No one to hear it besides each other—and the biggest jellyfish we ever saw.



Bruce Shafer - Stocktrek Images and Science Source



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*.

# With Antibiotics, Less Is Often More

For many common infections, fewer days on the drugs does the trick

By Claudia Wallis

**My husband has this bad habit.** When prescribed a week or two of antibiotics, he rarely completes the full course. Once his symptoms subside, he tosses out the rest of the pills, despite warnings on the bottle to finish the prescription. Ignoring doctors' orders is not a good idea, yet in this case he may be onto something.

Dozens of studies show that for many bacterial infections, a short course of antibiotics, measured in days, performs as well as the traditional course, measured in weeks. Shorter courses also carry a lower risk of side effects. In April the strength of this research persuaded the American College of Physicians to issue new "best practice advice" for four kinds of infections: pneumonia (the kind acquired in the community rather than in a hospital), "uncomplicated" urinary tract infections (UTIs), skin infections known as cellulitis (provided there is no pus) and acute bronchitis in people with chronic obstructive pulmonary disease. "These are some of the most common infections that internists are treating on a weekly basis and where there's a lot of unnecessary treatment," says Rachael Lee, first author of the advice statement and an infectious disease specialist at the University of Alabama, Birmingham. The big question going forward is: Will the medical profession heed the call and change its ways?

The driving force behind the push to use antibiotics more sparingly is the worldwide threat of treatment-resistant microbes, which have evolved rapidly with excessive use of these drugs. The dangerous organisms include the dreaded "flesh-eating" MRSA (methicillin-resistant *Staphylococcus aureus*), as well as drug-resistant strains of microbes that cause UTIs, tuberculosis and malaria. Yet many physicians have the mistaken belief that a longer course of antibiotics forestalls resistant strains. "Think of it as an urban legend with no substance," says infectious disease specialist Brad Spellberg, chief medical officer at the Los Angeles County/U.S.C. Medical Center. Doctors used to prescribe antibiotics for only as long as it took to get an infection under control and the patient out of danger, Spellberg says. "But durations kept creeping longer with the misguided belief that 'if I treat for longer, I'll pre-

vent relapse due to resistant pathogens'—which is absolutely false."

Spellberg is a vigorous advocate for the shorter-is-better approach. His Web site ([bradspellberg.com/shorter-is-better](http://bradspellberg.com/shorter-is-better)) tracks randomized controlled trials that show how short courses of antibiotics compare with longer courses. This spring the site listed more than 70 studies of 14 infectious diseases that demonstrated that shorter courses get the job done equally well, although in some trials the short-course antibiotic was different from the long-course drug. Some of those studies also tie briefer use to reduced emergence of drug-resistant microbes. Spellberg likes to point out that it is inherently absurd to prescribe in units of one or two weeks, which he refers to as "Constantine units" for the Roman emperor who decreed in A.D. 321 that a week lasts seven days. There's nothing biologically valid about this metric, he observes.

The evidence supporting shorter courses is especially strong for community-acquired pneumonia. At least 12 randomized con-

trolled trials in adults have shown that three to five days of antibiotics works as well as five to 14 days, and a [2021 study](#) found the same holds true for children. More than 25 studies have shown that short courses also work well for sinus infections and acute flare-ups of chronic bronchitis. Spellberg notes these two conditions can be caused by viruses, in which case antibiotics would not help at all. "If you are going to give antibiotics to people who don't need them, at least do us the courtesy of doing it for a brief period," he says.

Shorter drug courses have other advantages. They may do less harm to helpful bacteria that are part of our microbiome (one reason fewer pills cause fewer side effects). And short prescriptions get better patient

compliance. "It's a lot easier to remember to take your pills for five days than for 10," says Helen Boucher, chief of infectious diseases at Tufts Medical Center and treasurer of the Infectious Diseases Society of America (IDSA). But surveys show that old prescription-pad habits die hard. A [2019 study of antibiotic prescribing](#) among 10,616 family physicians in Ontario found that 35 percent of the scripts were for nine or more days.

Some infections do require prolonged therapy. A study published in [May](#) found that six weeks of antibiotics for infections around prosthetic joints was less effective than 12 weeks. And although antibiotics tend to be overprescribed for childhood ear infections, a longer course is more effective for kids younger than two.

Right-sizing antibiotic prescriptions is a critical part of the battle against drug-resistant "superbugs," Boucher says: "It's a message that we at the IDSA have been working to drive home for years." As patients, we can also do our part. Ask your doctor about shorter durations and if a pill is really likely to speed your recovery. ■



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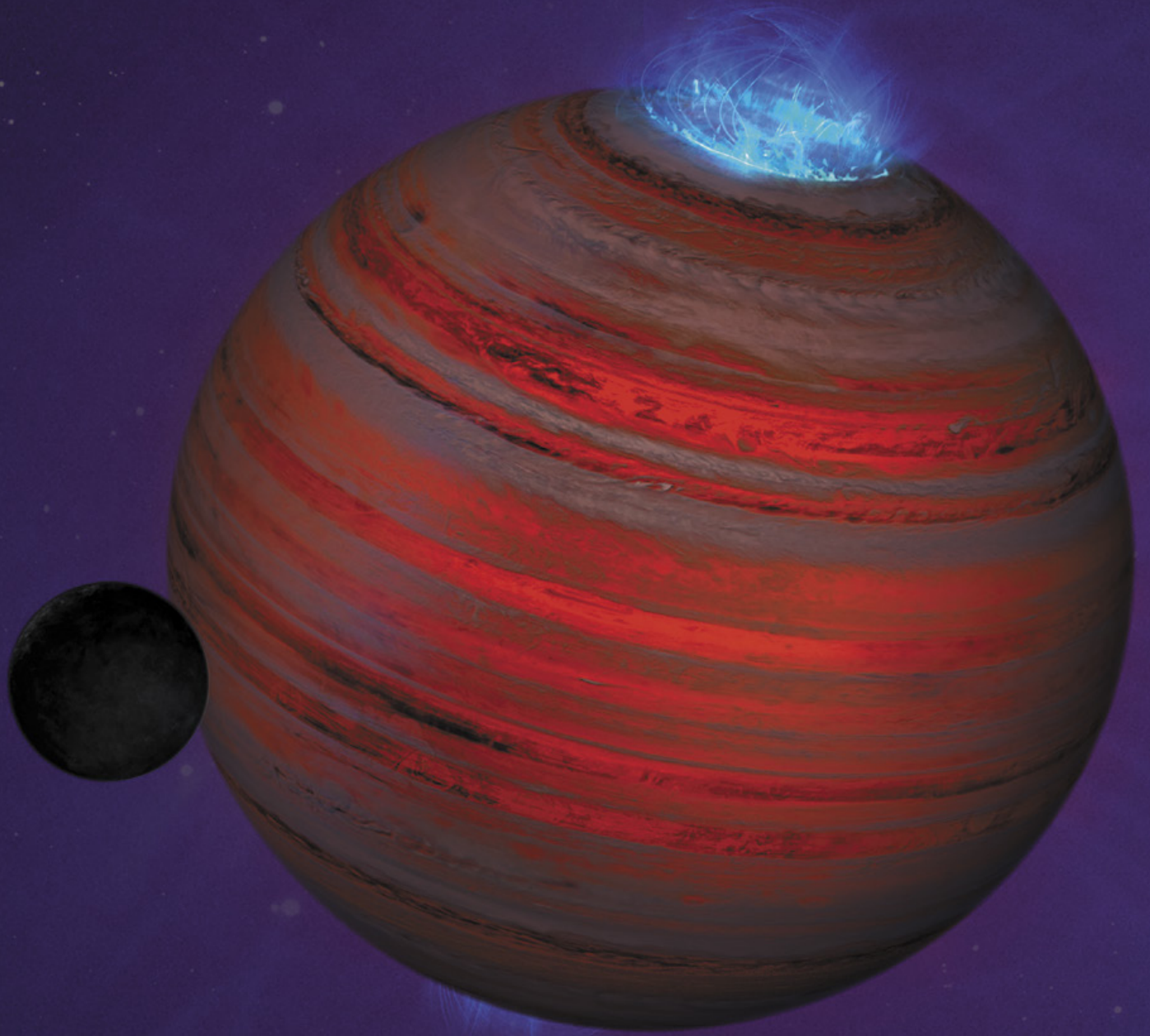
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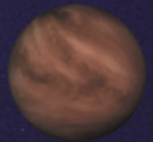
ASTRONOMY

# Not Quite Stars

Brown dwarfs straddle the line  
between stars and planets, and they might  
help solve mysteries about both

*By Katelyn Allers*

*Illustration by Mark Ross*



**Katelyn Allers** is an astronomer whose research focuses on low-mass stars and brown dwarfs. Until recently, she was a professor at Bucknell University. She now produces digital-training materials at Northwest Registered Agent.



**B**REATHE. BREATHE. I REPEATED THESE WORDS TO MYSELF LIKE A MANTRA. At 18,400 feet, my body was craving oxygen, and I had to concentrate on pulling enough air into my lungs. I was on the summit of Cerro Toco, a stratovolcano overlooking Chile's Chajnantor Plateau, now home to the Atacama Large Millimeter/submillimeter Array, one of the world's premier radio telescopes. Between the thin atmosphere and the barren red terrain of the mountain, it felt like I was on Mars. My colleagues and I were testing the atmospheric conditions on Cerro Toco. If they were good enough, they might justify taking on the technical challenges of building an observatory at such a remote, high-altitude site.

Earth's atmosphere is a problem for astronomers, and clouds frustrate many an observer. Atmospheric turbulence smears starlight, making stars appear to dance and flicker when close to the horizon. Molecules such as water vapor and carbon dioxide in the atmosphere absorb incoming starlight, particularly infrared light. With more than half of Earth's air below the summit of Cerro Toco (a point repeatedly raised by my burning lungs), we hoped that new and exciting insights could come from a dedicated infrared telescope there.

The sense of adventure that had led me to this summit had also sparked my fascination with infrared astronomy, where scientists peer at the cosmos in light too red for the human eye to see. Infrared light tends to come from the dimmest and most distant objects observable. One class of objects best seen in the infrared is brown dwarfs. When I was in graduate school in the early 2000s, these bodies had only recently been discovered, and they presented many tempting mysteries. I came to be captivated by these uncanny orbs, which, in terms of their classification, occupy a boundary zone between stars and planets. I wondered where and how they formed and what they were like. I learned through my research that in addition to being interesting in their own right, brown dwarfs serve as an important bridge to our understanding of both planets and stars, with temperatures and masses intermediate between the two. Now I and other brown dwarf astronomers are enjoying a sweet spot for research—there are still many brown dwarfs waiting to be discovered, and we can build on the wealth of

previous research to uncover new details of physical processes at work on these objects. We finally have the technological tools to study the atmospheres of brown dwarfs, for example, as well as their wind and rotation speeds, and to try to determine whether they might even host planets of their own.

#### IN-BETWEEN OBJECTS

MOST STARS are powered by the fusion of hydrogen into helium, a wonderfully stable process that keeps stars burning at the same temperature and brightness for billions of years. But if a would-be star never reaches high-enough temperatures or pressures to sustain hydrogen fusion, it is a brown dwarf, with a maximum mass of 8 percent of our sun's, or about 80 times the mass of Jupiter.

Recent studies indicate that brown dwarfs are nearly as common as stars, and they are everywhere. Brown dwarfs have been found in stellar nurseries alongside young protostars. They have been found in binary systems paired with white dwarfs, having survived potential engulfment by the white dwarf's previous red giant form. (Our sun, a yellow dwarf star, will one day turn into a bloated red giant, and after it dies, it will become a white dwarf.) Some of the closest stellar systems to our sun are brown dwarfs—the third and fourth nearest extrasolar systems, at 6.5 and 7.3 light-years, respectively (the closest are Alpha Centauri and Barnard's star). And yet, despite their ubiquity, most people have never heard of brown dwarfs.

Although they lack hydrogen fusion, brown dwarfs do emit light—thermal radiation from the heat within

them. They start out relatively hot (around 5,000 degrees Fahrenheit), and over the subsequent billions of years, they cool and dim. Brown dwarfs never die; they spend eternity cooling off and fading away. The coldest known brown dwarf checks in at a temperature below the freezing point of water. Because they are so cool, most of the light they emit is at infrared wavelengths. They are far too faint for the unaided human eye to see in our night sky, but if we could look at them up close, they would probably have a dull orange-red or magenta hue.

In the more than two decades since astronomers began studying brown dwarfs, we have formed a fairly clear picture of their basic characteristics. Like our sun, brown dwarfs are composed almost entirely of hydrogen. The temperatures in their upper atmospheres are cool enough, however, that a variety of molecules can form. Signatures of water vapor are seen in nearly all brown dwarfs. As they cool further, their atmospheric chemistry changes, and different molecules and clouds become predominant. The evolution of a brown dwarf's atmosphere depends on its mass and age. Imagine a brown dwarf with a mass 40 times that of Jupiter, for instance. For the first 100 million years, it will have an atmospheric composition similar to that of a red dwarf star, with titanium oxide and carbon monoxide present in the mix. Between 100 million and 500 million years, the atmosphere will cool, and dusty clouds made of minerals such as enstatite and quartz will form. Roughly a billion years after that, the clouds will break up and sink, and methane will become the dominant molecular species in the upper atmosphere. The coolest known brown dwarf shows evidence of water-ice clouds, as well as water vapor and methane. We expect its atmosphere to contain significant amounts of ammonia, similar to what we see on Jupiter.

Beyond these properties, however, there are many things about brown dwarfs that we do not yet know. The mysterious nature of these objects has inspired some far-fetched ideas. Brown dwarfs were once considered to be a possible reservoir of dark matter, although this idea was quickly abandoned when it became clear that brown dwarfs emit light (that is, they are not dark) and that their contribution to the total mass of our galaxy is small. More recently, scientists proposed that life could form in the cool upper regions of brown dwarfs' atmospheres—an idea that brown dwarf experts quickly squashed because the dynamics are such that any life-form would cycle into deeper layers of the atmosphere that are hot and inhospitable.

And then there was the hoax of the Nibiru cataclysm, a prophecy put forward in 1995 that predicted an imminent, disastrous encounter between Earth and a brown dwarf. Astronomers would be very excited to see a brown dwarf up close, but there is no scientific evidence to support this doomsday scenario, and a brown dwarf would be visible for hundreds or thousands of years prior to any close encounter.

## THE FIRST BROWN DWARFS

SCIENTISTS PREDICTED brown dwarfs in the 1960s based on what they knew about how stars and planets form. It seemed that this intermediate category should exist, but astronomers were not finding any such objects in the sky. It turned out that brown dwarfs are simply very, very faint, and most of the light they emit is infrared. And infrared technology was still in its infancy—just not up to the task. Then came the year 1995, a big one for astronomy. Astronomers Michel Mayor and Didier Queloz found 51 Pegasi b, the first exoplanet known to be orbiting a regular star. Perhaps more important, at least to this highly biased author, the first brown dwarfs were discovered.

Teide 1 was identified in the famous Pleiades star cluster. Astronomers Rafael Rebolo López, María Rosa Zapatero-Osorio and Eduardo L. Martín first spotted it in optical images from the 0.80-meter telescope at the Teide Observatory in the Canary Islands. The object was young, still glowing slightly from its formation. The team observed the signatures of several molecules in its atmosphere, including lithium. Stars usually burn up lithium as soon as they form, so this amazing detection proved that nuclear fusion was not occurring. They published their finding in September 1995.

Two months later astronomers announced the discovery of a second brown dwarf, Gliese 229B, a companion to another star. A group of astronomers at the California Institute of Technology and Johns Hopkins University first saw the object in an infrared image from the Palomar Observatory. They immediately knew that it was strange. It had unusual colors and displayed the signature of methane in its atmosphere. Conditions must be very cold for methane to be present because the highly reactive molecule usually turns into carbon monoxide at higher temperatures. Later observations revealed that the brown dwarf is about the same width as Jupiter, with a diameter of nearly 129,000 kilometers, but much denser, with 70 times as much mass.

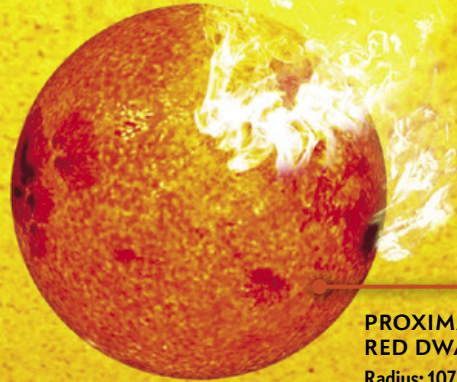
By the time I started graduate school in 2000, we knew of more brown dwarfs, though not that many. I was focused on building infrared instruments, and I needed a subject for my research topic. My Ph.D. adviser studied star formation, so I decided to search for brown dwarfs in star-forming regions. I ended up discovering a good number of brown dwarfs in my thesis work, including some that were the first known to have masses putting them near the range of planets. At the time we had no idea how these things formed, and we did not know whether there was a lower-mass threshold, but we started finding smaller and smaller objects.

All in all, my thesis work published fewer than 20 new brown dwarf discoveries, but they made a significant contribution to the total number known. Since then, new instruments have found many, many more. The main contributors were the 2 Micron All Sky Sur-

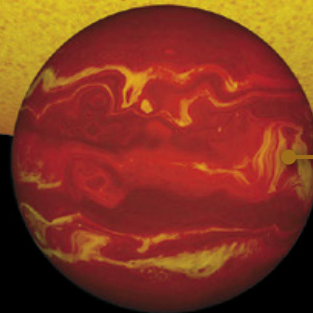
# A Guide to Brown Dwarfs

Ubiquitous throughout space, brown dwarfs are dim and compact objects that share some similarities with stars and others with planets. With masses at least 13 times that of Jupiter but less than 80 Jupiters, they occupy their own category. New research on their formation processes, their atmospheres, and more helps to elucidate these strange, in-between objects.

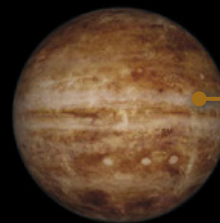
**SUN,  
YELLOW DWARF**  
Radius: 696,000 kilometers  
Mass: 1,050 × the mass of Jupiter



**PROXIMA CENTAURI,  
RED DWARF**  
Radius: 107,000 km  
Mass: 130 × the mass of Jupiter



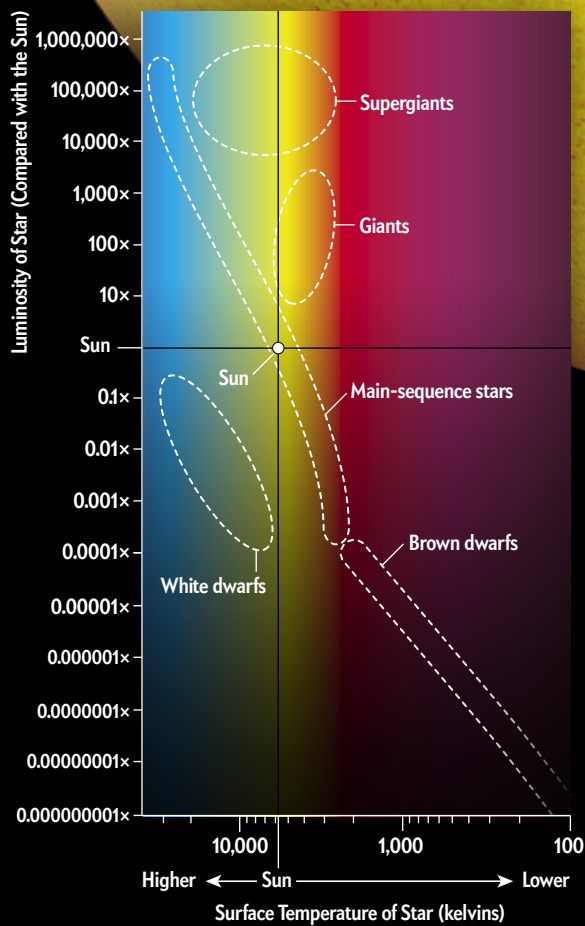
**PSO J318.5-22,  
BROWN DWARF**  
(Spectral class L)  
Radius: 105,000 km  
Mass: 8.3 × the mass of Jupiter



**WISE 0855,  
BROWN DWARF**  
(Spectral class Y)  
Radius: 72,000 km  
Mass: 3-10 × the mass of Jupiter



**JUPITER,  
GAS-GIANT PLANET**  
Radius: 71,500 km



## H-R DIAGRAM

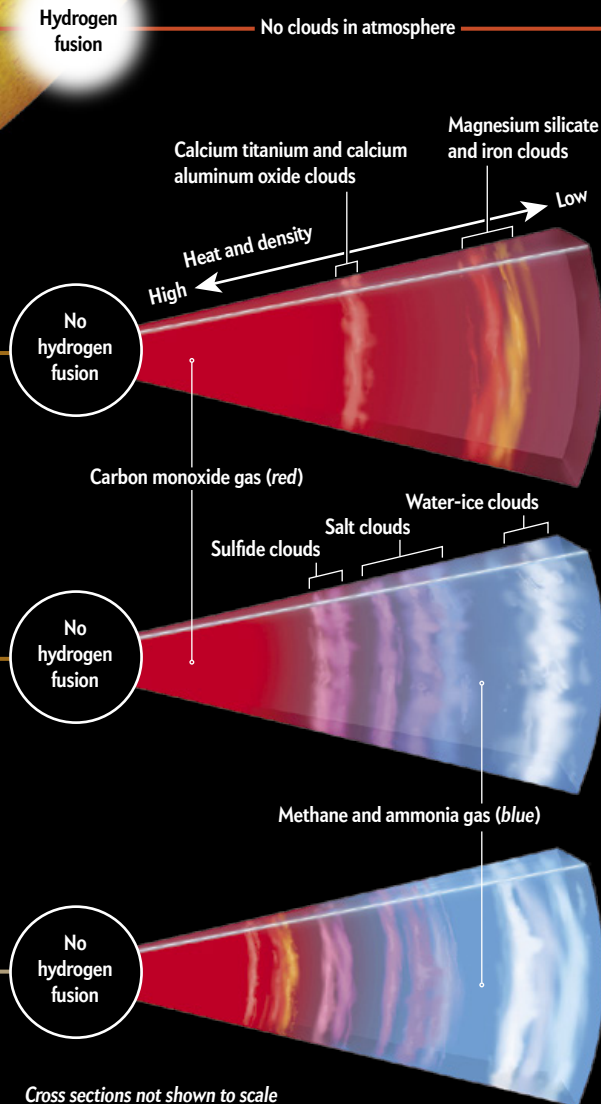
This plot of stellar temperature versus brightness, known as a Hertzsprung-Russell (H-R) diagram, is a classic tool for astronomers to characterize classes of stars. At the bottom right, brown dwarfs represent a cooler and dimmer category than any of the star types shown.

### INTERIOR ENGINES

Stars are powered by hydrogen fusion, but brown dwarfs are too small to sustain this process. Instead they glow with heat left over from their formation. Planets such as Jupiter reflect light from their parent stars in addition to emitting formation heat.

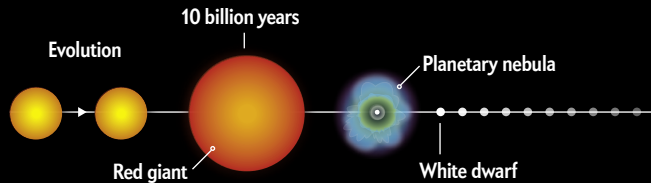
### ATMOSPHERES

Stars, planets and brown dwarfs each have their own atmospheric trends. A brown dwarf, scientists have recently learned, goes through stages: at first, its atmosphere will resemble that of a red dwarf star. As it ages and cools, clouds made of minerals can form, and later in life these clouds will sink, and its upper atmosphere comes to resemble that of a gas-giant planet.



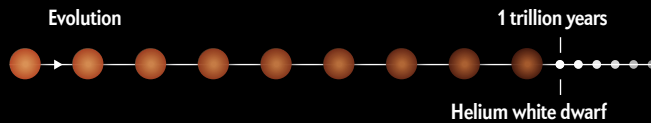
### YELLOW DWARF (STAR)

Our sun is an example of a yellow dwarf star. These stars burn hydrogen into helium for around 10 billion years, until most of the hydrogen is gone. Then they puff up into much larger, redder "red giant" stars, which fuse helium into carbon and other heavier elements. Eventually they run out of fuel for nuclear fusion and cast off their outer gaseous layers to produce glowing planetary nebulae, while their cores collapse into dense and hot white dwarfs.



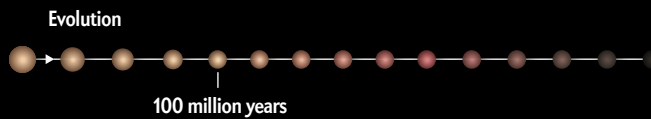
### RED DWARF (STAR)

By far the most abundant type of star in the Milky Way, red dwarfs are dimmer and cooler than stars like the sun. They, too, fuse hydrogen into helium, but they age much more slowly than yellow dwarfs and can go for a trillion years before running out of hydrogen. When they eventually do exhaust their fuel, they, too, become white dwarfs.



### BROWN DWARF

These bodies are not stars, because their mass is too small to generate enough pressure to ignite nuclear fusion. They shine with the leftover heat of their creation and gradually dim and cool over time. They will never die, nor will they transform into another class—they will simply get darker and colder forever.



### GAS GIANT (PLANET)

Rather than arising when a gas cloud condenses, as stars and brown dwarfs do, planets grow up around stars from the leftover rubble that forms a planetary disk around a nascent star. The gas giants Jupiter and Saturn are the largest planets in the solar system and are made primarily of hydrogen and helium. Like brown dwarfs, gas giants do not host nuclear fusion in their cores.

vey (2MASS), an infrared survey conducted in the early 2000s, and the Wide-field Infrared Survey Explorer (WISE), a space telescope launched in 2009. The current tally of brown dwarfs is about 3,000. There are many more to be found, though—estimates suggest that the Milky Way contains between 25 billion and 100 billion brown dwarfs.

### FORMATION SCENARIOS

AS THE LOWEST-MASS outcome of the star-formation process, brown dwarfs offer astronomers a unique chance to deepen our understanding of the basic steps involved in the birth of stars and planets. Stars form in complexes of gas (mostly molecular hydrogen) and dust known as molecular clouds. If a molecular cloud contains enough mass, gravity can overcome the gas pressure supporting the cloud and cause it to collapse into a star. During the collapse, any small amount of rotation in the cloud becomes amplified, much like how ice skaters spin faster when they pull their arms in. This rotation of the cloud material leads to the formation of a circumstellar disk of matter surrounding the nascent star, which then becomes a crucible for planet formation.

When brown dwarfs were first discovered, astronomers assumed they might form in a process similar to that for stars, but they were perplexed as to how the gravity from such a small mass was able to overcome gas pressure and initiate a collapse. In writing this article, I looked back over some grant and telescope proposals from early in my career, most of which were aimed at better understanding the formation mechanism of brown dwarfs. At the time there were several competing ideas. Some theories involved disrupting the formation of a star before it had reached its final mass. Perhaps some process physically removed the brown dwarf or burned off its natal environment, leaving behind a miniature star?

Other hypotheses invoked a scaled-down version of star formation or a scaled-up version of planet formation. This is a lovely example of using a variety of possible theories to make distinct, testable predictions. As we discovered the ubiquity of circumstellar disks around brown dwarfs, determined the distribution of stellar and brown dwarf masses in a variety of environments, and mapped the orbits of brown dwarfs in binary pairs, it became clear that most brown dwarfs seem to form like scaled-down stars—but from a smaller reservoir of gas. And the fact that brown dwarfs form circumstellar disks raises the tantalizing possibility that they host planets. Although we have never seen any for sure, it is very likely that planets grow in these disks just as they do around stars. Scientists hope the coming years will finally see the confirmed discovery of worlds orbiting brown dwarfs.

Recently researchers discovered isolated brown dwarfs with masses similar to those of giant planets (less than 13 times the mass of Jupiter), which again raised the question of how they might have formed. Could some of these planetary-mass brown dwarfs

have arisen in the circumstellar disks of more massive stars—in other words, formed just as planets do?

To test the mechanism for the formation of planetlike masses, my colleagues and I proposed a survey with the Hubble Space Telescope. Because Hubble is in orbit, it avoids the smearing and absorption of light by Earth's atmosphere, which makes it ideal for imaging binary pairs of brown dwarfs. Through this survey, in 2020 we discovered a unique system of brown dwarfs that strongly supports a starlike-formation mechanism for planetlike masses. The system, Oph 98 AB, is very young in cosmic terms (three million years old), and its two components weigh in at 15 and eight times the mass of Jupiter. These extremely low-mass objects are separated by 200 times the distance between Earth and the sun. Because Oph 98 A and B are so light and so widely separated, the system has the lowest gravitational binding energy of any known binary pair. The weak binding energy means that these bodies must have formed in their current orientation, rather than originating elsewhere and later becoming a pair, which points to a starlike-formation mechanism. And the young age of the system (yes, we consider three million years young!) means that planetary-mass objects apparently do not take any longer to form than stars.

### NEW INSIGHTS

BROWN DWARF science has now reached a stage where we are able to make more precise measurements and ask more detailed questions than ever before about these still mysterious objects. Among the most interesting recent discoveries are the coldest brown dwarfs, known as Y dwarfs. These objects have temperatures ranging from 350 degrees F down to  $-10$  degrees F. I love to joke when working on Y dwarfs that I am studying the coolest systems in the galaxy! Though not quite as cold as Jupiter ( $-234$  degrees F), these Y dwarfs have enabled us to make the first meaningful comparison between brown dwarfs and the atmospheres of the giant planets in our solar system. Y dwarfs are difficult to observe because they are both cool and very dim. The light they do emit is predominantly in the infrared range, at wavelengths of three to five microns, where Earth's atmosphere makes observations difficult.

Regardless, my colleagues and I have published spectra of several Y dwarfs and used theoretical models to infer the presence of water-ice clouds, as well as a significant amount of vertical mixing in the atmosphere. In this same wavelength range, Jupiter emits its own light (rather than just reflecting the light of our sun) and shows significant vertical mixing as well. Our hope is that by studying Y dwarfs, we will be able to disentangle properties of Jupiter that come from its planetary nature—in other words, the fact that it formed in the circumstellar disk of our sun and is constantly illuminated by sunlight—and properties that may be ubiquitous among cool gaseous objects, be they planets, exoplanets or brown dwarfs. Thus far our studies are showing that highly dynamic atmospheres tend to be the norm.

These insights about brown dwarf atmospheres have led to a new subfield: exometeorology. Although brown dwarfs are too far away for us to visually examine their atmospheric features, we can see their imprint through changes in brightness. As a cloud or other feature rotates in and out of view, it changes the light coming from the brown dwarf. Astronomers have analyzed the brightness variations of brown dwarfs over many rotations and have created maps of their spots and bands, which look remarkably like the familiar stripes and storms on the giant planets in our own solar system. Some brown dwarfs have been found to change in brightness by up to 25 percent over one rotation. The results of these studies are leading us to better understand atmospheric processes more generally—we have found that brown dwarfs with temperatures at which clouds break up show large variations in brightness and that young objects tend to show greater variability in brightness.

Scientists have also discovered other similarities between brown dwarfs and gas giants. Both, for example, tend to have strong magnetic fields and aurorae, as revealed by radio observations of the signatures of charged particles spiraling in their magnetic fields. The measured magnetic field strengths for brown dwarfs are 1,000 times stronger than Jupiter's magnetic field and 10,000 times stronger than Earth's. I like to imagine what the night sky might look like from one of these brown dwarfs—given the beauty of Earth's aurora borealis, it would likely be a spectacular sight.

Recently a student's question prompted another project to examine how the atmospheres on brown dwarfs compare with those on planets. When I teach courses in introductory astronomy, we cover the planets of the solar system (and of course, I sprinkle in a lot of information about brown dwarfs as well). A tidbit I present is that the length of a Jovian day depends on how you measure it. If you clock the motion of visible features in Jupiter's equatorial region, you measure a rotation period that is five minutes shorter than the rotation period measured in the radio signal, which probes its interior rotation. A student asked me why this difference in rotation period occurs, and I replied that it was because Jupiter's equatorial features are pushed along by strong zonal winds. The winds on Earth are driven by the redistribution of solar energy, but we are not sure to what degree this applies to Jupiter's winds.

After the lecture, I started thinking about this further. Astronomers have measured radio emission in brown dwarfs, which occurs via the same mechanism as Jupiter's radio emission, so we can measure an interior rotation period. And we can use our method of monitoring brightness changes to measure the atmosphere's rotation period. Thus, I hatched an idea to measure the wind speed on a brown dwarf for the first time. The best candidate we had to try out the technique was a methane brown dwarf with con-

firmed radio emission. To determine the wind speed, we would need to measure both periods to a precision of less than 30 seconds. My colleagues and I submitted a proposal to use the Spitzer Space Telescope to measure the brown dwarf's brightness variations and applied to use the Karl G. Jansky Very Large Array in New Mexico to measure a more precise radio period. It still feels like a small miracle that our measurements revealed a period difference of just more than a minute, which equates to a wind speed of 2,300 kilometers per hour. We published our findings last year in the journal *Science*. This high wind speed on an iso-

**Between 100 million and 500 million years after a brown dwarf forms, its atmosphere will cool, and dusty clouds made of minerals such as enstatite and quartz will form.**

lated brown dwarf means that atmospheric winds are not always driven by the redistribution of solar energy, leaving open the question of whether Jupiter's winds are driven by the sun.

Astronomers continue to search for more brown dwarfs. Some surveys focus on identifying large samples of brown dwarfs via deep imaging surveys of the whole sky such as 2MASS, WISE, and the Panoramic Survey Telescope and Rapid Response System (Pan-STARRS). Citizen scientists have also become involved in the search through projects such as Backyard Worlds, which allows anyone to examine WISE data for signs of brown dwarfs and other moving objects. We expect that upcoming large surveys with the Vera C. Rubin Observatory (due to begin observing early next year) and the Nancy Grace Roman Space Telescope (launching in 2025) will work to further complete our census of brown dwarfs.

Sadly, we could not get funding for the telescope on Cerro Toco, and it was never built. But once the James Webb Space Telescope is launched later this year, astronomers will have an unprecedented look at brown dwarfs in the infrared, without interference from Earth's atmosphere. The first cycle of observations planned includes programs to study the atmospheric chemistry of Y dwarfs and the cloud composition of dusty brown dwarfs and even a search for planetary systems around brown dwarfs. Exciting times are certainly ahead for those of us who study some of the cosmos's most overlooked objects. ■

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#### FROM OUR ARCHIVES

The Discovery of Brown Dwarfs. Gibor Basri; April 2000.

[scientificamerican.com/magazine/sa](https://www.scientificamerican.com/magazine/sa)

NEUROLOGICAL DISEASE

# A NEW UNDERSTANDING OF ALZHEIMER'S

**Immune cells called microglia have become a promising target for researchers looking for leads to treat the neurodegenerative disease**

*By Jason Ulrich and David M. Holtzman*

*Illustration by Ruaida Manna*

IN 1907 GERMAN PSYCHIATRIST ALOIS ALZHEIMER PUBLISHED A CASE REPORT OF AN UNUSUAL ILLNESS AFFECTING the cerebral cortex. A 51-year-old woman living in an asylum in Frankfurt am Main exhibited symptoms that are all too familiar to the millions of families affected by what is now known as Alzheimer's disease. There was memory loss, confusion and disorientation.

After the patient died, Alzheimer examined her brain and made a few key observations. First, it was smaller than average, or atrophic, with a corresponding loss of neurons. Next, there were tangles of protein fibers within neurons and deposits of a different protein outside brain cells. For the next 100 years, these two pathological proteins—known as tau and amyloid—were the focus of research into the causes of the disease.

But there was an additional, often forgotten clue that Alzheimer noted in the autopsy. Under the microscope lens, he saw clear changes in the structural makeup of certain nonneuronal cells. Called glia, they constitute roughly half of the brain's cells.

After being studied by only a small number of scientists since

Alzheimer's discovery, glia have now entered the spotlight. One type, called microglia, is the main kind of immune cell in the brain and may influence the progression of the disease in different ways during both early and later stages. Microglia might also explain the complex relation between amyloid and tau, the aberrant proteins that lead to neuron degeneration and memory loss.

Research in the past decade has identified new molecular risk factors that implicate these brain immune cells in Alzheimer's disease. Guided by powerful genetic-sequencing methods, we are beginning to gain an understanding of microglia and of the role of the immune system and its inflammatory processes in Alzheimer's.

Although we have learned a lot about the biochemistry of tau





and amyloid proteins, as well as about some of the genetic and lifestyle factors that can influence a person's risk of Alzheimer's, there are virtually no treatments to stop or slow the progression of the disease. On June 7 the U.S. Food and Drug Administration approved a new drug, aducanumab, that removes amyloid from the brain. But it is unclear how effective it is in improving patients' waning cognitive skills. More interventions are still needed. Recent insights about microglia have suggested potential new therapies for the disease, and several are being developed now, with some already being tested in clinical trials.

### PLAQUES, TANGLES AND GENES

ALZHEIMER'S DISEASE is the leading cause of dementia worldwide, and its multiple pathologies accumulate and converge over the course of decades. Alzheimer's has two distinctive molecular hallmarks. The first is plaques made up of one form of amyloid called beta-amyloid. These peptides, or small proteins, are found in the spaces between cells.

The second is the contorted, or misfolded, forms of the tau protein, to which large numbers of phosphate groups get attached in a process known as hyperphosphorylation. This increase in tau phosphorylation has been linked to increased aggregation and toxicity of the protein. Tau is present in twisted clumps, called neurofibrillary tangles, in the cell bodies of neurons. Some tau also turns up adjacent to amyloid plaques in swollen, damaged axons, the long protrusions from the main bodies of neurons. This form is known as neuritic plaque tau.

Both tau and the larger protein from which amyloid is derived have normal roles in cell functioning that get corrupted by the disease process in people with Alzheimer's. Extensive efforts to understand the pathological forms of amyloid and tau have led to the conclusion that we should consider Alzheimer's in two stages. The first is a presymptomatic phase of 15 to 25 years during which amyloid builds up in the cerebral cortex, the brain's outermost layer, in the absence of cognitive symptoms. In the second phase, tau tangles develop in the cortex, and neurodegeneration begins, with cognitive dysfunction appearing as brain cells die.

The Alzheimer's research community has known for decades that genetic risk factors strongly influence a person's likelihood of developing Alzheimer's and that genes provide valuable insight into mechanisms underlying the disease. The foremost risk gene associated with Alzheimer's is *APOE*. It encodes the protein apolipoprotein E, which is involved in fat and cholesterol metabolism. (The alphanumeric designations for genes are typically italicized, whereas those for the proteins they encode are presented as regular text.)

The gene's association with Alzheimer's, first reported in 1993, relates to one version of it, known as an allele, that dramatically increases the risk of illness. The three common *APOE* alleles in the human population are *APOE2*, *APOE3* and *APOE4*. *APOE3* is the most common, constituting approximately 78 percent of all alleles, followed by *APOE4* at around 14 percent and *APOE2* at around 8 percent. Every person has two *APOE* alleles, and about 25 percent of people carry at least one *APOE4* allele. But among those with Alzheimer's, about 60 percent have at least one *APOE4* allele.

People with a single allele of *APOE4* have a threefold to fourfold increased risk of developing Alzheimer's, and individuals with two copies of *APOE4* have an approximately 12-fold increased risk compared with people who have two alleles of *APOE3*. *APOE4* carriers have earlier and more abundant deposition of amyloid

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David M. Holtzman is professor and chair of neurology, scientific director of the Hope Center for Neurological Disorders at Washington University in St. Louis and associate director of the Knight Alzheimer's Disease Research Center. He is co-founder of C2N Diagnostics and has consulting arrangements with and research grants from various other companies.



plaques because their version of apolipoprotein E decreases clearance of beta-amyloid from the brain and facilitates aggregation of the protein. Conversely, people who are *APOE2* carriers are at lower risk for developing Alzheimer's and are much less likely to develop amyloid pathology.

Despite the strength of *APOE4*'s effect, it does not account for all of the genetic susceptibility to Alzheimer's. Geneticists have doggedly pursued other risk factors that might explain this "missing heritability," using advances in gene-sequencing technology to screen thousands of people for changes in DNA associated with a higher or lower risk of developing Alzheimer's.

Wide-scale screening has identified genetic regions and genes that appear to influence disease risk. Among them are variants of genes—*CD33*, *BINI*, *CR1* and *MS4A6A*—that encode proteins with various functions. For instance, *CD33* and *CR1* provide the genetic instructions for receptors on the cell surface that detect signals from other cells. These genes discovered by screening across populations have relatively modest effects on disease risk.

Researchers have also sequenced the genomes of thousands of people with Alzheimer's to look for rare variants that might exert a strong effect on disease risk. Several of these risk genes are expressed predominantly by microglia, the brain's major immune cells. In 2013 two studies identified a rare variant in *TREM2*, a gene encoding a receptor that traverses the cell membrane in microglia, as strongly increasing the risk of developing Alzheimer's.

The sequencing data revealed a variant that substituted an amino acid called histidine for arginine. This mutation was found to impair microglia's functioning and increase the risk of developing Alzheimer's roughly twofold to fourfold. Interestingly, like several of the other new risk-factor genes, *TREM2* is expressed exclusively by microglia in the brain. These genetic clues suggested that microglia could actively contribute to the disease process, but how?

### SURVEILLANCE SQUAD

MICROGLIA ARE RELATED to immune cells called macrophages that patrol the body to combat pathogens or help repair injured tissue. Researchers are learning that they are involved in everything from defense against infection to pruning excess synapses—the junctions where neurons meet—in the developing brain. Under normal conditions, microglia have small cell bodies with branchlike protrusions that extend throughout brain tissue. The immune cells gobble up—or, more formally, phagocytose—unnecessary synapses and debris, and they look for signs of injury or invasion by pathogens.

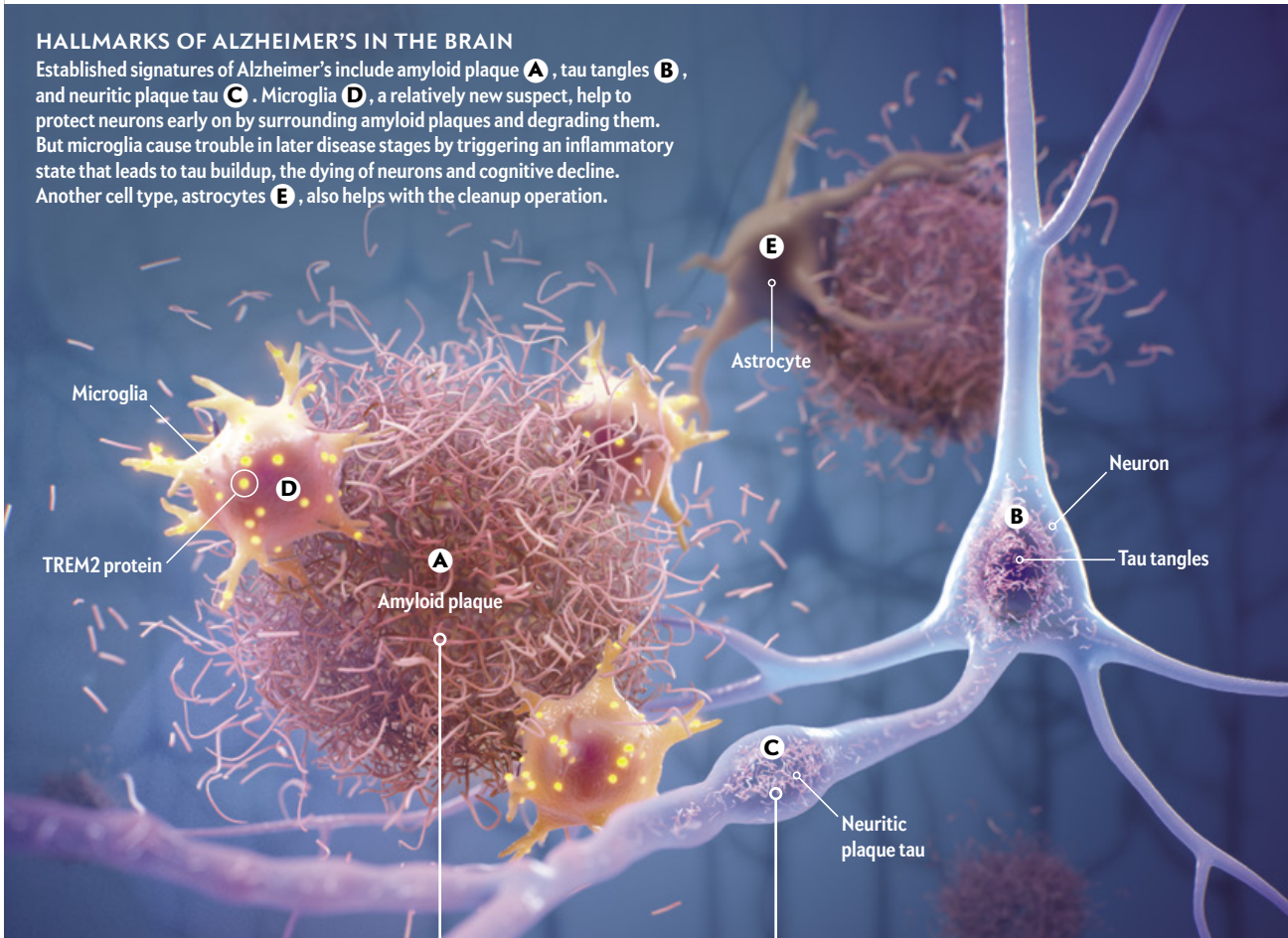
If injury does occur, the shape and function of microglia change. The cell bodies get larger, and the branches extending from them shorten and decrease in number. Microglia migrate to the site of an injury to initiate an inflammatory response. For decades research-

# A Genetic Trail to the Roots of Alzheimer's

Frustrated by failures with new therapies, many Alzheimer's researchers have turned their focus to genes such as *TREM2*, which encodes an immune protein, and *APOE4*, the strongest known genetic risk factor for Alzheimer's. Understanding these genes is generating new ideas to help the more than six million people in the U.S. with a fateful diagnosis.

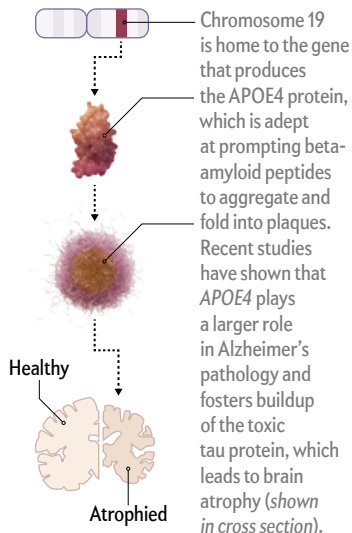
## HALLMARKS OF ALZHEIMER'S IN THE BRAIN

Established signatures of Alzheimer's include amyloid plaque **A**, tau tangles **B**, and neuritic plaque tau **C**. Microglia **D**, a relatively new suspect, help to protect neurons early on by surrounding amyloid plaques and degrading them. But microglia cause trouble in later disease stages by triggering an inflammatory state that leads to tau buildup, the dying of neurons and cognitive decline. Another cell type, astrocytes **E**, also helps with the cleanup operation.



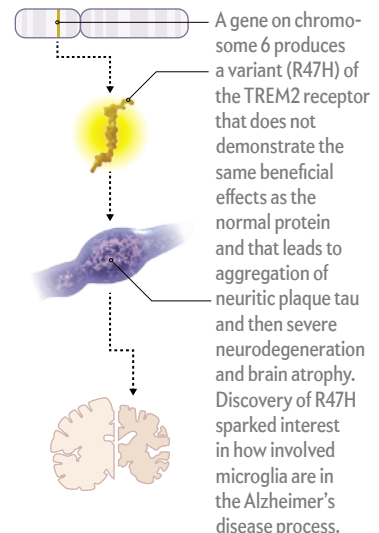
### Old Timer: *APOE4*

A variant of a gene involved in fat metabolism, *APOE4*, makes a protein that gets secreted from microglia and astrocytes. *APOE4* is a leading risk gene for the form of Alzheimer's disease that arrives late in life. First reported in 1993, its role in the pathology of Alzheimer's has been only partially understood. New research has begun to paint a clearer picture.



### New Suspect: *TREM2*

An Alzheimer's risk gene expressed by microglial cells, called *TREM2*, codes for a receptor protein on the cells' surface. The protein produces paradoxical effects depending on the stage of disease progression. Early on, *TREM2* signaling helps reduce amyloid damage and the advance of tau. But later it may drive damage to neurons and ultimately lead to their demise.



ers had observed microglia surrounding amyloid plaques. It was unknown, though, whether they helped to limit amyloid buildup or initiated toxic inflammation. The relation between microglia and tau also was not well understood.

Some studies have indicated that microglia act on neurons to damage axons and synapses, jamming signals transmitted along axons and resulting in an accumulation of tau in cells.

Other research shows that inflammatory proteins called cytokines that are secreted by microglia dramatically increase the destructive process of hyperphosphorylation. The discovery of genetic risk factors such as *TREM2* and *CD33* pointed to distinct molecules in microglia that could be involved in Alzheimer's. Researchers hope that understanding how these proteins function will provide insight into the broader role these cells play in the disease process.

Experimental mice are valuable tools for studying how genetic factors can influence the kinds of brain changes seen in human Alzheimer's dementia. So far there are few experimental animals that reproduce all aspects of Alzheimer's (for example, a mouse with amyloid-plaque buildup followed by the spread of pathological tau and accompanying neurodegeneration). But researchers have created several dozen "models"—genetically engineered mice that develop either amyloid plaque or tau.

By crossing these transgenic mice with mice engineered to express alterations in Alzheimer's risk genes, researchers can determine how a gene variant influences different aspects of Alzheimer's-like pathology. For example, two decades ago amyloid mouse models engineered to express human APOE4 protein were shown to develop more amyloid plaques than mice with the *APOE3* or *APOE2* gene variants. In recent years researchers have assessed the role of the human *TREM2* protein in Alzheimer's by deleting the *Trem2* gene in mouse models of amyloid pathology. Several laboratories consistently identified a dramatic reduction in the number of microglia surrounding amyloid plaques in such mice.

A series of studies from the lab of Marco Colonna at Washington University in St. Louis found that in mice without the *Trem2* gene, microglia were unable to properly ramp up their metabolism. When near amyloid plaques, they did not produce sufficient adenosine triphosphate, or ATP, a molecule that fuels cellular activity. Starved of energy, the cells were unable to surround amyloid plaques. Researchers then saw an increase in swollen, injured axons, known as dystrophic neurites, caused by damage from amyloid.

These key observations—fewer microglia surrounding plaques and increased damage to axons—were also seen in postmortem brain sections from people with Alzheimer's who had a rare mutation in the *TREM2* gene known as R47H, the one that had been discovered in 2013. This finding boosted the confidence that the observations in mice could be relevant to how *TREM2* works in humans. In addition, work by Jaime Grutzendler's group at Yale University showed that the fewer microglia that surrounded a plaque, the more damaged the nearby axons were.

That study provided further evidence of the potential role of microglia in protecting against amyloid's toxic effects in local areas around plaques. It also showed that microglia interact with the ends of tiny amyloid fibers, potentially halting their growth or shielding the surrounding neurons from amyloid's ill effects.

## TOXIC SEEDS

IF MICROGLIA PROTECT AXONS from amyloid plaque damage, might they also safeguard against tau pathology? If so, dangerous *TREM2* mutations such as R47H might exacerbate Alzheimer's pathology by making it easier for neuritic plaque tau to develop near amyloid plaques. Testing this hypothesis remains challenging, but some clues have come from research exploring how tau pathology is able to spread similarly to prions, the proteins that characterize diseases such as Creutzfeldt-Jakob disease, one form of which is associated with "mad cow" disease.

Over the past decade or so researchers have found that tau and amyloid fold up into aberrant shapes similar to a prionlike "seed" that then causes normally structured forms of the proteins to misfold as well. In this manner, pathological tau can propagate to connected brain regions as Alzheimer's progresses. A series of papers by Virginia Man-Yee Lee's lab at the University of Pennsylvania showed that injecting normal mouse brains with aggregated tau seeds isolated from brains with Alzheimer's pathology resulted in the misfolding of mouse tau into neurofibrillary tangles. Mice that already had amyloid pathology developed neuritic plaque tau, the axon-damaging form of the protein. The latter process resembles the chain of events in Alzheimer's. Although the mice did not develop significant neurodegeneration, the "seeding" approach provided a reliable method to study both amyloid and tau pathology.

When it is not contributing to Alzheimer's pathology, tau is normally located in the axons of neurons, where it helps to stabilize structural proteins called microtubules that aid in the transport of cellular materials from one part of a neuron to another. Lee's team found that tau in swollen axons near amyloid plaques became disengaged from microtubules, leaving it potentially more prone to contortion. In essence, these damaged axons turned into fertile soil in which pathological tau seeds in the surrounding amyloid-laden cortex could take root.

Because the detrimental R47H-mutant type of *TREM2* protein on microglia increases axon damage, we reasoned that the more common *TREM2* form might help the immune cells shield axons near amyloid plaque, preventing tau seeds from spurring further tau accumulation or invading other areas of the cortex. In a study led by Cheryl Leyns and Maud Gratuze, then members of our lab, we injected tau seeds from an Alzheimer's brain into mouse models with and without genes expressing functional *TREM2* protein and found that mice without the protein developed far more neuritic plaque tau in the swollen axons. That damage spread to other regions in the brain through networks of connected neurons.

We also used mouse models developed by Colonna that expressed either normal human *TREM2* or the R47H form. Again, amyloid mouse models with the R47H variant developed more neuritic plaque tau pathology near amyloid plaques when injected with tau seeds. To confirm the findings from mouse models, we also examined human brains and found that people with Alzheimer's-associated *TREM2* variants had more neuritic plaque tau. From these observations, we concluded that normal *TREM2* and perhaps microglia in general protect against amyloid-induced seeding and spreading of tau throughout the brain.

Microglia seem to be protective against the spread of tau pathology in the amyloid-laden cortex typical of the first phase of Alzheimer's. But are they still protective once neurofibrillary tangles develop in the cortex and neurodegeneration begins during the symptomatic phase of the disease? Two influential studies—one

from Ido Amit's lab at the Weizmann Institute of Science in Rehovot, Israel, and the other from Oleg Butovsky of Brigham and Women's Hospital and his colleagues—looked at changes in the activity of microglial genes in mouse models of different neurodegenerative diseases and identified remarkable similarities in how those genes are activated.

They found that microglia in mouse brains with neurodegenerative injuries similar to those that occur with tau pathology switched on diverse genes, many of which encode proteins for degrading unwanted materials in the cell. Microglia at this point strongly increased expression of a mouse version of the *APOE4* risk gene. It seems then that both APOE and TREM2 play key roles in determining whether a microglial response is activated when neurons start to die and symptoms first appear.

That discovery led us to cross mice expressing different versions of human APOE with a mouse model that develops both tau pathology and severe neurodegeneration. In a study led by Yang Shi at our lab at Washington University in St. Louis, we found that a tau mouse model that expressed APOE4 had far more neurodegeneration and more advanced tau pathology than mice with APOE3 or APOE2. Next we assessed cell death in people with Alzheimer's or other neurodegenerative diseases with large accumulations of tau. We found that *APOE4* carriers suffered greater damage in the brain than those who carried other alleles.

Additionally, Alzheimer's patients who were *APOE4* carriers declined faster than those who were not. This came as a surprise to us and other researchers because for many years, it had been thought that the primary effect of *APOE4* was the accumulation of large amounts of amyloid. These studies, however, pointed to a role for *APOE4* not only in regulating amyloid pathology but also in dictating how fast neurons die in response to tau pathology. This implies that the "Alzheimer's gene," as *APOE4* is known, influences not only amyloid deposition but also neurological damage because of tau accumulation, the two major disease stages.

The expanding understanding of *APOE4* led to the next mouse experiment. We found that deletion of the mouse version of the *APOE* gene was strongly protective against neurodegeneration and delayed the progression of tau pathology—and, more important, the brain damage caused by tau buildup. If deletion of the *APOE* gene is neuroprotective in mouse models, then perhaps decreasing APOE levels in the human brain would slow down neurodegeneration, particularly in people carrying the *APOE4* variant.

In another experiment, we used the tau mouse model, which also expressed human *APOE4*, to test whether reducing levels of the apolipoprotein variant would protect against neurodegeneration. We collaborated with Ionis Pharmaceuticals to use antisense oligonucleotides, short stretches of modified DNA that degrade messenger RNA (the molecular instructions for a cell to make a specific protein) to reduce the amount of APOE4 in the mice's brains by half. We found that lowering APOE4 levels when tau pathology was starting to take hold preserved neurons and diminished inflammation and microglial activation in the mice's brains.

An emerging picture suggests that microglia play two different roles during the progression of Alzheimer's dementia. In mouse models of amyloid pathology, increased microglial activity around plaques appears to protect the brain. In mice with tau pathology, aberrant tau strongly increases the expression of microglial genes associated with neurodegeneration, and APOE4 seems to further inflame the brain. All of this indicates a strong

immune response by microglia to tau pathology that correlates with increased damage, not protection of the brain.

Of course, correlations do not equal causation, and at that point in our research it was unclear whether the strong immune response seen in tau models that expressed APOE4 was driving the degeneration or was simply a response to it. We next asked whether the loss of TREM2, the receptor on the surface of microglia, would increase neurodegeneration and inflammation in the brain. It would not have been entirely surprising if microglia helped to protect neurons, even at that relatively late stage of the disease.

Again, an experiment lowering gene activity was in store. Knocking out TREM2 in tau mouse models decreased the microglial response and diminished neurodegeneration levels. This finding suggested that reducing microglial activity resulted in less damage and brain atrophy from tau pathology.

## A DOUBLE-EDGED SWORD

MORE EVIDENCE implicating microglia as drivers of the neuron loss that leads to cognitive decline later in the disease process came from two 2019 studies. Giving mice a drug that blocked the critical protein colony-stimulating factor 1, which microglia need to survive, was shown to remove around 90 percent of microglia in the brain. In tau mouse models, mice that received the drug exhibited dramatically reduced tau pathology and neurodegeneration, indicating that microglia are required for tau-dependent neurodegeneration. These findings demonstrate that TREM2 signaling appears to produce paradoxical effects—either protective or detrimental—depending on the stage of disease progression.

From this research, it seems likely that TREM2 signaling during the presymptomatic and possibly the early symptomatic phases of Alzheimer's, when amyloid accumulates, helps to reduce the amount of damage amyloid can inflict on nearby axons and synapses. It also impedes the advance of tau through the cortex. Once tau pathology is clearly established, however, microglia may drive synapse loss and the death of neurons.

Assuming that the damaging effect of microglia in mouse models of tau pathology holds true in human Alzheimer's—still a big assumption—targeting microglia might be a viable treatment strategy. It might be best to promote microglial activation, particularly around amyloid plaques, in the presymptomatic and early symptomatic phases of the illness. Conversely, in more advanced stages of tau pathology, decreasing the microglia response might slow neurodegeneration, as well as the rate of cognitive decline.

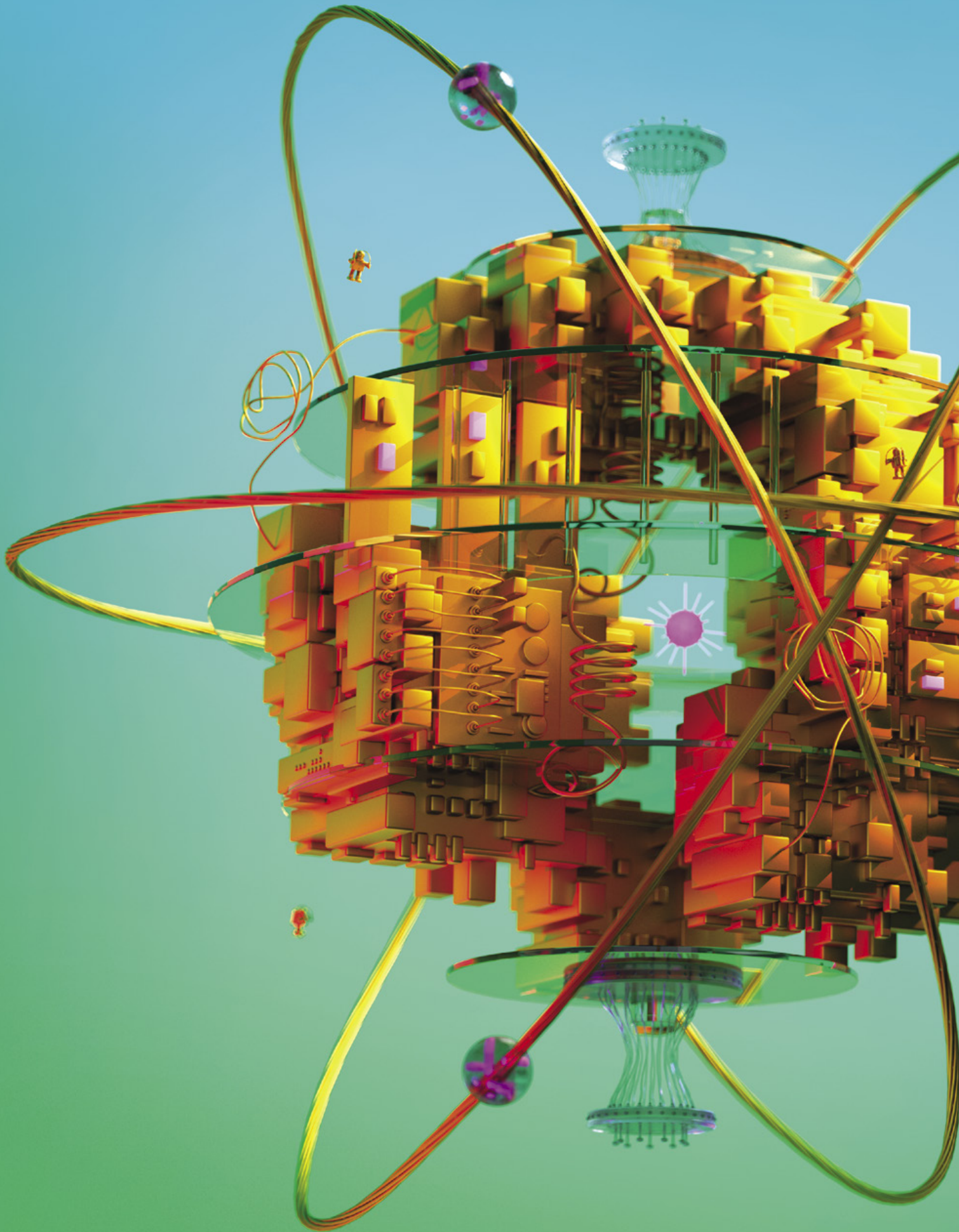
Perhaps as we learn more about how microglia behave in response to amyloid and tau pathology, new targets can be identified for the development of therapies to treat this devastating disease. A human clinical trial is currently testing whether TREM2 activation can slow the course of early-stage Alzheimer's, and multiple other microglia-targeted therapies are entering drug-development pipelines. If these approaches prove successful, it may turn out to be the third, overlooked finding in Alzheimer's famous autopsy—after the better-known plaques and tangles—that proves instrumental in decreasing the terrible impact on patients' brains. ■

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QUANTUM COMPUTING

# Chemistry's Quantum Future

Quantum computers will bring molecular modeling to a new level of accuracy, reducing researchers' dependence on serendipity

*By Jeannette M. Garcia*

*Illustration by Richard Borge*

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**I**N MY CAREER AS A CHEMIST, I OWE A HUGE DEBT TO SERENDIPITY. IN 2012 I WAS IN THE RIGHT PLACE (IBM's Almaden research laboratory in California) at the right time—and I did the “wrong” thing. I was supposed to be mixing three ingredients in a beaker in the hope of creating a known material. The goal was to replace one of the usual ingredients with a version derived from plastic waste, in an effort to increase the sustainability of strong plastics called thermoset polymers.

Instead, when I mixed two of the ingredients together, a hard, white plastic substance formed in the beaker. It was so tough I had to smash the beaker to get it out. Furthermore, when it sat in dilute acid overnight, it reverted to its precursor materials. Without meaning to, I had discovered a whole new family of recyclable thermoset polymers. Had I considered it a failed experiment and not followed up, we would have never known what we had made. It was scientific fortuity at its best, in the noble tradition of Roy Plunkett, who accidentally invented Teflon while working on the chemistry of coolant gases.

Today I have a new goal: to reduce the need for serendipity in chemical discovery. Challenges such as the climate crisis and COVID-19 are so big that our responses can't depend on luck alone. Nature is complex and powerful, and we need to be able to model it precisely if we want to make the scientific advances we need. Specifically, if we want to push the field of chemistry forward, we need to be able to understand the energetics of chemical reactions with a high level of confidence. This is not a new insight, but it highlights a major constraint: predicting the behavior of even simple molecules with total accuracy is beyond the capabilities of the most powerful computers. This is where quantum computing offers the possibility of significant advances in the coming years.

Modeling chemical reactions on classical computers requires approximations because they can't perfectly calculate the quantum behavior of more than just a couple of electrons—the computations are too large and time-consuming. Each approximation reduces the value of the model and increases the amount of lab work that chemists have to do to validate and guide the model. Quantum computing, however, works differently. Each quantum bit, or qubit, can map onto a specific electron's spin orbitals; quantum computers can take advantage of

quantum phenomena such as entanglement to describe electron-electron interactions without approximations. Quantum computers are now at the point where they can begin to model the energetics and properties of small molecules such as lithium hydride—offering the possibility of models that will provide clearer pathways to discovery than we have now.

### MODELING REACTIONS

QUANTUM CHEMISTRY as a field is nothing new. In the early 20th century German chemists such as Walter Heitler and Fritz London showed that the covalent bond could be understood through quantum mechanics. In the late 20th century the growth in computing power available to chemists made it practical to do some basic modeling on classical systems.

Even so, when I was working toward my Ph.D. in the mid-2000s at Boston College, it was relatively rare that bench chemists had a functional knowledge of the kind of chemical modeling computers could do. The disciplines (and skill sets involved) were so different. Instead of exploring the insights of computational approaches, bench chemists stuck to trial-and-error strategies, combined with a hope for an educated but often lucky discovery. I was fortunate enough to work in the research



group of Amir Hoveyda, who was early to recognize the value of combining experimental research with theoretical research.

Today theoretical research and modeling of chemical reactions to understand experimental results are commonplace—a consequence of the theoretical discipline becoming more sophisticated and bench chemists gradually beginning to incorporate these models into their work. The output of the models provides a useful feedback loop for discoveries in the lab. To take one example, the explosion of available chemical data from a trial-and-error-based experimental method called high-throughput screening has allowed for the creation of well-developed chemical models. Industrial uses of these models include drug discovery and material experimentation.

The limiting factor of these models is the need to simplify. At each stage of the simulation, you have to pick a certain area where you compromise on accuracy to stay within the bounds of what the computer can practically handle. In the terminology of the field, you are working with “coarse-grained” models. Each simplification reduces the overall accuracy of your model and limits its usefulness in the pursuit of discovery. The coarser your data, the more labor-intensive your lab work.

The quantum approach is different. At its purest, quantum computing would enable us to model nature as it is, with no approximations. In the oft-quoted words of Richard Feynman, “Nature isn’t classical, dammit, and if you want to make a simulation of nature, you’d better make it quantum-mechanical.” We’ve seen rapid advances in the power of quantum computers in recent years. IBM doubled its quantum volume—a measure of the quantity and quality of qubits in a system—twice in 2020 and is on course to produce a chip with more than 1,000 qubits by 2023, compared with single-digit figures in 2016. Others in the industry have also made bold claims about the power and capabilities of their machines.

### LAYING THE GROUNDWORK

SO FAR WE HAVE EXTENDED the use of quantum computers to model energies related to the ground states and excited states of molecules. These types of calculations will lead us to be able to explore a variety of reaction pathways as well as molecules that react to light. In addition, we have used them to model the dipole moment in small molecules, a step in the direction of understanding how electrons are distributed between atoms in a chemical bond, which can also tell us something about how these molecules will react.

Looking ahead, we have started laying the foundation for future modeling of chemical systems using quantum computers and have been investigating different types of calculations on different types of molecules solvable on a quantum computer today. For example, what happens when you have an unpaired electron in the system? This adds spin to the molecule, making calculations tricky. How can we adjust the algorithm to get it to match the expected results? This kind of work will enable us to someday look at radical species—molecules with unpaired electrons—which can be notoriously difficult to analyze in the lab or simulate classically.

To be sure, this work is all replicable on classical computers. Still, none of it would have been possible with the quantum

technology that existed five years ago. The progress in recent years holds out the promise that quantum computing can serve as a powerful catalyst for chemical discovery in the near future.

I don’t envision a future where chemists simply plug algorithms into a quantum device and get a clear set of data for immediate discovery in the lab. What is feasible—and may already be possible—is incorporating quantum models as a step in the existing processes that currently rely on classical computers. In this approach, we use classical methods for the computationally intensive part of a model. This could include an enzyme, a polymer chain or a metal surface. We then apply a

## Quantum computers are now at the point where they can begin to model the energetics and properties of small molecules such as lithium hydride.

quantum method to model distinct interactions, such as the chemistry in an enzyme pocket, explicit interactions between a solvent molecule and a polymer chain, or hydrogen bonding in a small molecule. We would still accept approximations in certain parts of the model, but we would achieve much greater accuracy in the most distinct parts of the reaction.

We have already made important progress through studying the possibility of embedding quantum-electronic structure calculation into a classically computed environment. This approach has many practical applications. More rapid advances in the field of polymer chains could help us tackle the problem of plastic pollution, which has grown more acute since China cut its imports of recyclable material. The energy costs of U.S. recycling remain relatively high; if we could develop plastics that are easier to recycle, we could make a major dent in the waste being produced. Beyond the field of plastics, the need for materials with lower carbon emissions is ever more pressing, and the ability to manufacture substances such as jet fuel and concrete with a smaller carbon footprint is crucial to reducing our total global emissions.

The next generation of chemists emerging from graduate schools around the world possesses a level of data fluency that would have been unimaginable in the 2000s. But the constraints on this fluency are physical: classically built computers simply cannot handle the level of complexity of substances as commonplace as caffeine. In this dynamic, no amount of data fluency can eliminate the need for serendipity: you will always need luck on your side to make important advances. But if future chemists embrace quantum computers, they are likely to be a lot luckier. ■

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ANIMAL BEHAVIOR

WHY ANIMALS

# PLAY

Frolicking hones physical fitness and cognition, allowing creatures to develop skills needed to survive and reproduce

*By Caitlin O'Connell*

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IT WAS LATE AFTERNOON IN THE WINTER SCRUB DESERT WITHIN NAMIBIA'S ETOSHA NATIONAL Park when I spotted a family of elephants on the southern edge of the clearing. I was scanning the horizon from the observation tower where my colleagues and I conduct our research at Mushara water hole. Wind had deterred elephant families from visiting the water hole earlier—it interferes with their efforts to keep tabs on one another vocally—but with the air now still, our first customers of the day had finally appeared.

Judging from how many trunks were stretched high, sampling the air, the group was itching to break cover and run for the water. The young males were particularly anxious to get going. Not only were they thirsty, but they had a lot of sparring to catch up on. As winter wears on, the environment dries out, and elephants have to venture farther from water to find enough to eat. Several days may pass before they can return to the water hole for a drink and a reunion.

I could see why this group was holding back, however. Another elephant family was amassing in the southeastern forest and heading our way, and the adult females were wary. They stood with their feet firmly planted, ears held straight out, as they sniffed what little remained of the prevailing wind for any potential danger. Not only would exiting the security of the forest expose the family to predators, but an encounter with a higher-ranking elephant family could result in an aggressive interaction. For the youngsters in the group, however, more families meant more opportunities to play. So after thoroughly assessing the clearing, the matriarch gave the word with a rumble and an ear flap, and the family began its approach to the water.

Late afternoon is my favorite time of day during our field season in the austral winter—the air cools fast as the sun sinks low in the sky, painting the elephants a radiant pink. My colleagues and I stand in the observation tower with a celebratory drink in hand, our binoculars trained on the horizon, hoping for a sunset visit like this one from one of our beloved resident families. During these daily visits, I always learn a new lesson about elephants—particularly when they play.

I have witnessed the important role of play in calf development and family politics by watching members of my favorite elephant groups frolic at this water hole at sunset. These often chaotic observations inspired me to want to understand more about how animals play and what advantages this behavior might confer, not just to elephants but to all social creatures, including humans. It turns out that play, like other forms of interaction, has rules of engagement. And it is essential for developing the physical and cognitive faculties that animals need to survive and reproduce.

#### **RULES AND REGULATIONS**

PEOPLE TEND TO THINK of play as an activity one engages in at one's leisure, outside of learning import-



ant skills needed to succeed later in life, such as hunting, mating, and evading predators. But although playing is fun for all involved—and fun for those who are watching—play behaviors evolved as ritualized forms of survival skills needed later in life, providing the opportunity to perfect those skills.

Engaging in play allows animals to experiment with new behaviors in a protected environment without dangerous consequences. The unwritten code of conduct surrounding play lets them explore many possible outcomes.

Animals learn the rules of engagement for play at a very young age. Among dogs, the bow is a universal invitation to engage in silliness that triggers the same bowing down and splaying of the front legs in the receiver of the signal—invariably followed by chasing and pretend biting. Chimpanzees and gorillas motivate others to romp by showing their upper and lower teeth in what primatologists refer to as a play face, which is comparable to human laughter.

When a young male elephant wants to play with another male of similar age, he holds his trunk up and presents it to the other as an invitation. Most often his next move would be to place his trunk over the other's head, which in adults signals dominance but in calves is guaranteed to precipitate a spirited sparring match. These encounters run the gamut

from gentle shoving to intense headbutting and pushing back and forth with trunks entwining and tusks clacking. The fun continues for seconds to minutes for youngsters; for older teens and young adults, it can go on much longer. The sparring matches provide bulls with the opportunity to test their fighting ability so that they might successfully compete for a female when they reach sexual maturity and enter the hormonal state of musth around the age of 25.

When a young male elephant is feeling particularly adventurous, he may venture far away from Mom's protection to invite a distant relative to spar. If his foray takes him too far away or if a spar turns unexpectedly rough, the brave calf will lose his nerve and often will run quickly back to Mom's side with ears flapping and trunk yo-yoing as he retreats.

Occasionally an older sister will oversee a play bout between youngsters. These ever watchful siblings form part of an extended caretaking network that facilitates play, but its members also will intervene if a calf crosses an invisible bloodline and gets deflected with a trunk slap by an overly protective, high-ranking mother.

#### FORMS OF PLAY

SCHOLARS OF ANIMAL BEHAVIOR recognize three main categories of play. The first is social play, which is

**PLAY SHARPENS SURVIVAL SKILLS:** Elephant calves extend an invitation to play by placing their trunk over another's head (*bottom right*). Sparring is an important play behavior that helps build strength and test new defense maneuvers in a safe zone (*left*). An older elephant may kneel down to provide an opportunity for a young male relative to spar (*top right*).

any kind of antic that involves others. The second is locomotive play—including running, walking, jumping and pouncing—which facilitates lifelong motor skills. In prey species, locomotive play helps perfect predator-avoidance tactics such as the springbok’s “pronking” high into the air while running as a herd and landing in unpredictable spots. In elephants, it hones predator-avoidance skills, as well as strategies for escaping an aggressive suitor or a competitor looking to inflict a mortal wound. Conversely, young predators such as lion cubs use locomotive play to sharpen their hunting ability. Chasing and tripping littermates and then giving them a good chew on the spine or throat are rehearsals of the skills needed to catch prey animals and dispatch them by severing their spinal cord or choking them.

Many species, including our own, engage in the mock-fighting variety of locomotive play, which allows them to test their strength in a safe environment where everyone understands the rules. A playful spar in elephants is just like an arm wrestle between human peers. When play becomes more elaborate and determined, it turns from an arm wrestle into something akin to martial arts, allowing both participants to practice skills and develop innovative solutions that could help them avoid mortal combat later in life. Play fighting also provides opportunities to test boundaries, gauge who can be trusted and learn important body language.

The third main category of play is object play, which incorporates objects from the environment into the cavorting. For an elephant, this object might take the form of a stick or branch that the elephant explores, carries or throws with its trunk. In captivity, elephants enjoy playing with balls or hauling inner tubes around for fun. Alternatively, the object could be another animal, such as a zebra or giraffe, that offers an irresistible opportunity for a chase. In one case, a four-year-old male calf named Leo taught his baby brother, Liam, just how fun such a chase can be, leaving Liam scrambling to keep up

## Play provides an environment for experimenting with risk.

with Leo’s charge as a giraffe made a quick escape.

Two other forms of play have only been documented in great apes, including humans. One of these, game playing, combines social, locomotive and object play. Sports such as soccer, field hockey, lacrosse and polo are examples of traditional games that became formalized as sports with specific sets of rules (among nonhuman great apes, only captive individuals raised in human contexts play formal games). The other variety of play that appears to be



unique to great apes is make-believe. For example, a wild chimpanzee may carry around a small log, pretending it is an infant. A human child might play with an invisible toy or set up an invisible barrier that they want adults to acknowledge.

### NOT JUST FUN AND GAMES

PLAY PROVIDES AN ENVIRONMENT for experimenting with risk. When a lion cub deliberately gives up some control over its body, it puts itself at a disadvantage, allowing others to succeed in pouncing on it. Marc Bekoff of the University of Colorado Boulder and his colleagues have proposed that play increases the versatility of movements used to recover from

a loss of balance and enhances the ability of the player to cope with unexpected stressful situations. The goal is not to win but to improve skills, sometimes by self-handicapping.

Once a cub has been tackled by its littermates, roles might reverse such that a littermate handicaps itself, allowing the other cub to tackle it in return. Self-handicapping is risky and requires trust, but it is a great way to develop strength and agility. It is also an important exercise in building cooperation. In the Sawtooth wolf pack raised by Jim and Jamie Dutcher in the Sawtooth Mountains in Idaho, the dominant wolf would slow down to allow a close companion that happened to be a subordinate to catch up and tackle him. In elephants, on a number of occasions I have seen older male calves crouch down to allow a much



younger calf to spar with them. This is akin to an older brother handicapping himself during an arm wrestle by not using all of his strength to let his little brother win.

Being silly is another important aspect of play, one that gets us outside our comfort zone and forces us to test new strategies. Silliness in our movements, behavior and even language helps us think much more broadly and creatively. Problem-solving derived from the silliness of play has been demonstrated in many species and even in robots. When computer scientist Hod Lipson of Columbia University gave his artificial-intelligence robots a chance to play—by dancing around in random movements—they outperformed other robots when challenged with the unexpected. The positioning information garnered from moving around randomly led one robot to come up with creative solutions for maintaining its balance after losing a limb. Likewise, when sea lions play in the surf, they often project themselves high into the air midway down the face of monster waves, like those that roll into Santa Cruz. These are just the kinds of behaviors needed to avoid an attack by a great white shark—their primary predator apart from killer whales and humans.

Play also builds trust. Thomas Bugnyar of the University of Vienna in Austria and his colleagues found that ravens pretend to cache highly valued food items and then watch how other ravens respond, apparently to determine whom they can trust. Learning how to differentiate competitors from likely reliable collaborators early on has obvi-

ous advantages, whether one wants to gain allies or build a coalition within a group—or repair broken relationships.

#### FAMILIES REUNITED

“INCOMING FROM THE SOUTHEAST!” I called out from the Mushara tower as my elephant field team narrowed in on what looked like a dusty line of pinkish-gray boulders amassing on the edge of the clearing one afternoon during our 2018 field season. The search for identifying features began. A missing tusk, a notch in the bottom of the left ear, or a V-shaped cut in the top of the right ear would give the family away. Whoever identified the elephant family first would get an extra sundown drink.

That day the incoming family turned out to be the Actors. It was our first sighting of the group that season, and we were excited to see a new addition to the family: high-ranking Susan, identified by her daggerlike left tusk, had a new male calf, Liam. And low-ranking Wynona, who was missing her left tusk, had her two-year-old calf Lucy in tow. We had been following the contentious dynamic between these two mothers very closely over the years, particularly during the 2012 season when each had a calf—Leo and Liza, respectively.

Susan had relentlessly tormented Wynona all the way up to the end of her pregnancy, aggressively charging her whenever she got close to the water to drink. The tension was so high that when Wynona broke away from the family to give birth, surrounded by her daughter Erin and their calves, I worried for

**ANIMALS LEARN** the rules of engagement for play early on. Among dogs, the “bow” is a universally understood invitation to play (*left*). Young predators such as lion cubs use play to develop their hunting skills (*right*).

her baby's life if a reunion were to take place. Sure enough, there was no fanfare and no reunion that we witnessed to present her new baby to the rest of the family. I assumed then that Wynona's days as a member of the Actor family were numbered.

As predicted, Wynona did separate from the larger family and became the matriarch of her own core family. It went on like that for four years until the arrival of Wynona's newest baby, Lucy, in 2016 yet again changed the dynamic of the larger extended family group. Play appeared to be an important contributing factor in reuniting the family.

Lucy's older sister, Liza, had been a shy baby who stuck to her mom and her very close relatives. Wynona timed her movements to avoid too much overlap with the larger family group when they went to

**AMONG WILD ELEPHANTS,** play is almost always a group affair. For youngsters, it often includes piling on top of siblings, cousins or, if permitted, even older family members.

experiments with independence. But the arrival of Lucy showed us that the story was not that simple.

Lucy spent a lot of time a great distance away from her mom and played with calves of mothers of all ranks. When it came time to leave the water hole and go in separate directions, as dictated by the prevailing family politics, Lucy made that impossible. She was so busy playing with other calves that there was no extracting her, leaving Wynona no choice but to modify her behavior.

Instead of continuing on her premeditated departure route, in the opposite direction from the Actor family, Wynona, her eldest daughter Erin and their calves turned around and followed the rest of the family so that Wynona did not risk losing her new calf. There was no guarantee that the other mothers would protect Lucy, much less allow her to suckle, as that would mean fewer precious nutrients for their own calves. But by 2018 Wynona was fully reintegrated into the Actor family, whether she wanted to be or not.

Every time I see this dynamic unfold, it makes me smile. How often is it the

case in our own families where grudges of older generations are put aside because of the bonds forged by the next generation through play?

Play should be on our daily agenda. Smiling and laughing are contagious behaviors that facilitate bonding, are curative and, most important, do not have to take up much time. The next time you feel like you are too busy to play a frivolous game at work or you don't want to face that family reunion, make the time and muster the will. You might be surprised at the outcome, whether it be a better idea for a pitch meeting or the dissolution of a long-standing barrier between you and a contentious relative thanks to a good giggle.

Our highly adaptable and innovative nature is rooted in play. I am grateful to my favorite elephant, Wynona, and her daughter Lucy for reminding me that there is always something new we can learn from it—and that we are never too old to internalize those lessons. A good romp can pay off in ways I hadn't anticipated. It forges new bonds, reunites divided families, improves coping skills and overall health, and facilitates cooperation and innovation. Given all these benefits, how could we afford not to play? ■

## How often in our own families do grudges of older generations get put aside because of bonds forged by the next generation through play?

Mushara water hole to drink. They tended to be one day behind or ahead of the Actor family, usually behind. On the rare occasion that they did overlap just at the end of the extended family visit, Liza did not stray to interact with the larger family. And who would blame her? Susan was right there with a quick jab with her dagger tusk or a trunk slap, whichever was more convenient, making it clear that the low-ranking babies had no place on the playground with royalty. There was hardly a chance for calves of Wynona's small but growing family to get to know members of the extended family.

Lucy changed all that. From the start, she was quite the extrovert. Maybe being born into a very small family made her all the more curious and excited by the opportunity to engage with the extended family on the infrequent occasion of their overlapping. And she was not deterred by the admonishments of high-ranking moms within the extended family, much to the seeming annoyance of the ever watchful Susan.

Now the two-year-old Lucy knew just how to run through adults' legs and out of trunk's reach, navigating potential minefields and dodging her mom's attempts to rein her in. She behaved more like Susan's calf, Leo, who was her older sister Liza's contemporary. When we scored Leo's distance from his mom at the water hole, he always had a much higher score than Liza. We had assumed that was attributable mainly to his sex and the male elephant's early

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### FROM OUR ARCHIVES

**When Animals Fight.** Gareth Arnott and Robert W. Elwood; August 2019.

[scientificamerican.com/magazine/sa](https://www.scientificamerican.com/magazine/sa)





NEUROSCIENCE

# THE STUTTE MIND

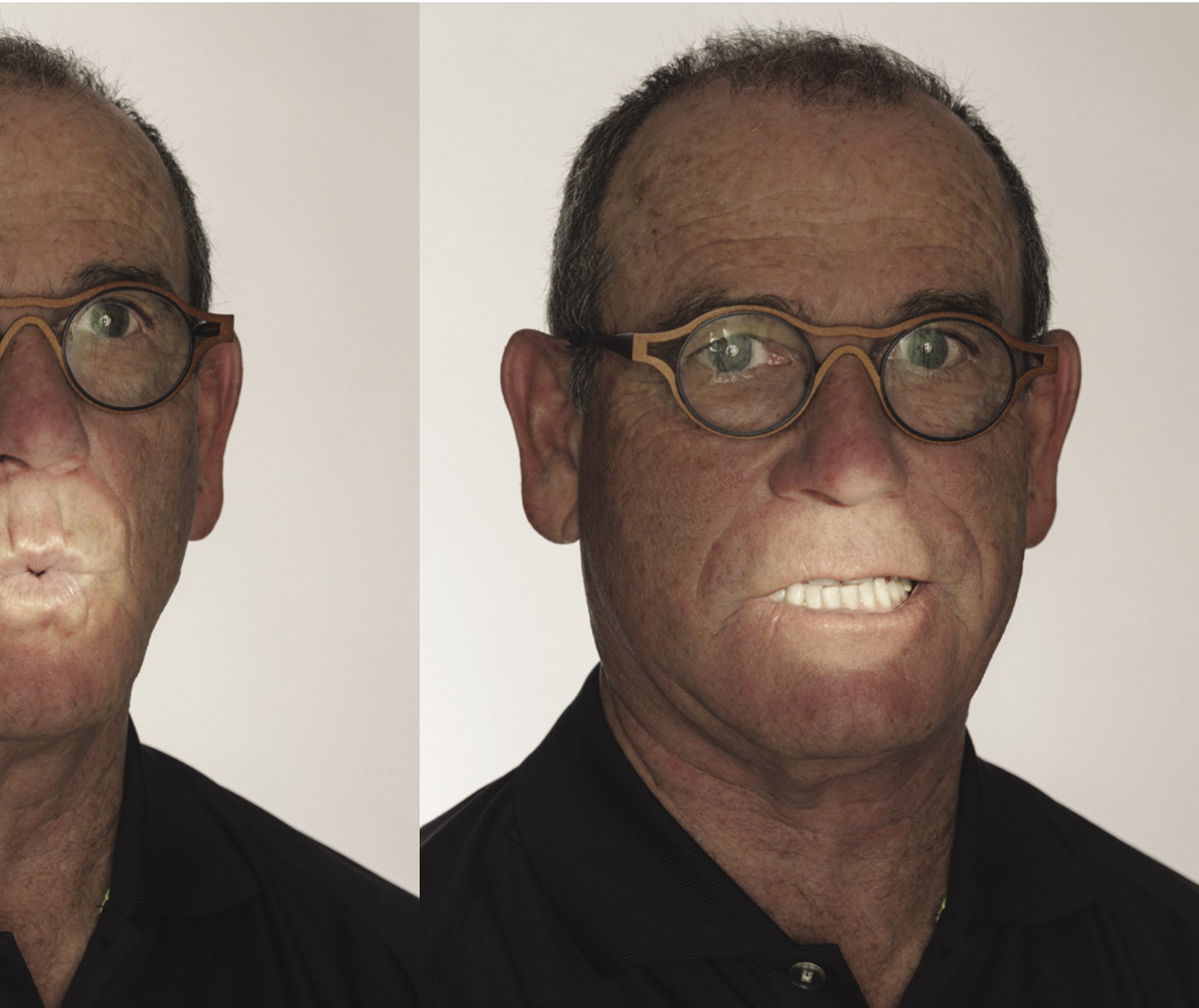


# RING

Once blamed on personalities or parents, this speech disorder originates from neurological wiring and genes. New findings are pointing to new treatments

*By Lydia Denworth*

*Photographs by Anthony Francis*



LEE REEVES, who stutters, demonstrates three sounds that trip him up: “L” (left), “W” (center) and “ST” (right). Reeves says that relaxing when he forms the sounds reduces a lot of his speech stumbles.

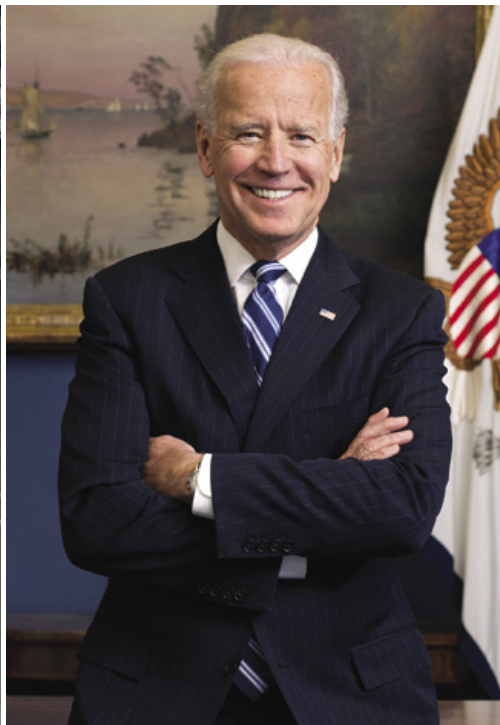
**Lydia Denworth** is a Brooklyn, N.Y.-based science writer, a contributing editor for *Scientific American*, and author of *Friendship: The Evolution, Biology, and Extraordinary Power of Life's Fundamental Bond* (W. W. Norton, 2020).



**L**EE REEVES ALWAYS WANTED TO BE A VETERINARIAN. WHEN HE WAS IN HIGH SCHOOL in the Washington, D.C., suburbs, he went to an animal hospital near his house on a busy Saturday morning to apply for a job. The receptionist said the doctor was too busy to talk. But Reeves was determined and waited. Three and a half hours later, after all the dogs and cats had been seen, the veterinarian emerged and asked Reeves what he could do for him.

Reeves, who has stuttered since he was three years old, had trouble answering. "I somehow struggled out the fact that I wanted the job and he asked

me what my name was," he says. "I couldn't get my name out to save my life." The vet finally reached for a piece of paper and had Reeves write down his



name and add his phone number, but he said there was no job available. “I remember walking out of that clinic that morning thinking that essentially my life was over,” Reeves says. “Not only was I never going to become a veterinarian, but I couldn’t even get a job cleaning cages.”

More than 50 years have passed. Reeves, who is now 72, has gone on to become an effective national advocate for people with speech impairments, but the frustration and embarrassment of that day are still vivid. They are also emblematic of the complicated experience that is stuttering. Technically, stuttering is a disruption in the easy flow of speech, but the physical struggle and the emotional effects that often go with it have led observers to wrongly attribute the condition to defects of the tongue or voice box, problems with cognition, emotional trauma or nervousness, forcing left-handed children to become right-handed, and, most unfortunately, poor parenting. Freudian psychiatrists thought stuttering represented “oral-sadistic conflict,” whereas the behavioralists argued that labeling a child a stutterer would exacerbate the problem. Reeves’s parents were told to call no attention to his stutter—wait it out, and it would go away.

These myths and misconceptions have been debunked. Over the past 20 years, and especially in the past five to 10, a growing body of research has established that stuttering is biological in nature. Specifically, it looks like a neurodevelopmental disorder. In most of the more than 70 million people

worldwide who stutter, the condition appears early in life, when children are learning to talk. Looking at the brains of people who stutter, scientists have uncovered subtle variations in both structure and function that affect the fluidity of speech. Compared with those who do not stutter, those who do have differences in neural connectivity, changes in how their speech and motor systems are integrated, and alterations in the activity of crucial neurotransmitters such as dopamine.

There is also a genetic component: researchers have identified four genes that dramatically increase the likelihood of this speech problem. Just as a flickering lightbulb is sometimes the result not of a bad filament but of faulty wiring throughout a room, these differences add up to what neuroscientists call “a system-level problem” in the brain.

These neurobiological revelations are already inspiring new treatments. A drug that targets dopamine overactivity is in a clinical trial, and others are in development. Several recent studies have shown benefits from brain stimulation. And given the importance of neuroplasticity in very young children, specialists now advise the opposite of a wait-and-see approach. “The brain findings affirm the idea that we want to get involved as early as we can,” says speech language pathologist J. Scott Yaruss of Michigan State University.

Some aspects of stuttering remain a puzzle. The condition affects about 1 percent of adults but roughly 5 percent of children, up to 80 percent of

**FAMOUS PEOPLE** who had to overcome stutters include (from left to right) King George VI of England, U.S. President Joe Biden, and actors Samuel L. Jackson, Marilyn Monroe, James Earl Jones and Emily Blunt.

PA Images and Alamy Stock Photo; White House Photo and Alamy Stock Photo; Michael Mella Alamy Stock Photo; Shawshank and Alamy Stock Photo; Everett Collection, Inc., and Alamy Stock Photo; Everett Collection, Inc., and Alamy Stock Photo (from left to right)



whom recover fluent speech. (So, yes, Reeves might well have outgrown it.) Scientists—and parents and therapists and, most dearly, people who stutter themselves—would like to know what accounts for the difference between persistent stuttering and recovery. Therapy can help but does not appear to explain it. Long-term studies of children may shed light on this, and such studies are just beginning to show results. And although a few genes linked to stuttering have been identified, their precise role in the disorder has not yet been pinned down.

But as more pieces fall into place, researchers

## Antipsychotic drugs that block dopamine receptors in the brain improved fluency in some people who stutter. But they came with the risk of severe side effects such as movement disorders.

and therapists hope the recognition of these biological causes will help to change society's prejudices about stuttering. Although some people who stutter or have other speech impediments go on to accomplish great things—President Joe Biden struggled to get words out, as did the poet who recited at his inauguration earlier this year, Amanda Gorman—others have difficult lives. Many are underemployed and suffer from social anxiety and mood disorders. Psychiatrist and neuroscientist Gerald A. Maguire of the University of California, Riverside, School of Medicine stutters himself and has devoted his career to understanding the condition and developing pharmacological treatments for it. His brother, who also stuttered, died by suicide. “If we understand the biology, then we're open to all sorts of treatments, and hopefully the stigma is less,” Maguire says.

### FROM PEBBLES TO PET SCANS

STUTTERING HAS BEEN RECOGNIZED for thousands of years and exists in every language and culture. In addition to Biden, well-known people who have stuttered include Greek orator Demosthenes, who put pebbles in his mouth to practice speaking; King George VI of England, whose unconventional speech therapy was immortalized in the 2010 film *The King's Speech*; and actor Samuel L. Jackson, who used curse words to improve his fluency. It is distinct from occasional or habitual word stumbles. Repeating words or peppering sentences with “um” or “ah” indicates hiccups in planning speech, whereas the underlying neurological differences in

people who stutter disrupt a more basic level of speech production. “Everybody is dysfluent, but only some people stutter,” Yaruss says.

There are three types of stutters people experience: prolongations, stretching out a sound (*mmm-man*); repetitions, in which syllables or sounds are repeated (*my-my-my-myself*); and blocks, in which the speaker initially cannot get any sound out at all. If a child continues to stutter past the age of about eight, they are likely to stutter throughout life.

Reeves describes the experience of stuttering as an unexpected loss of control. “You know what you want to say and how to say it—the words, the phrases, the sentence structure, the inflection—but all of a sudden you get stuck,” he explains. “You can't move forward. You can't move backward. All of the muscles are just locked.”

The first suggestion that stuttering might be neurological came in 1928. Samuel Orton and Lee Travis, a physician and speech

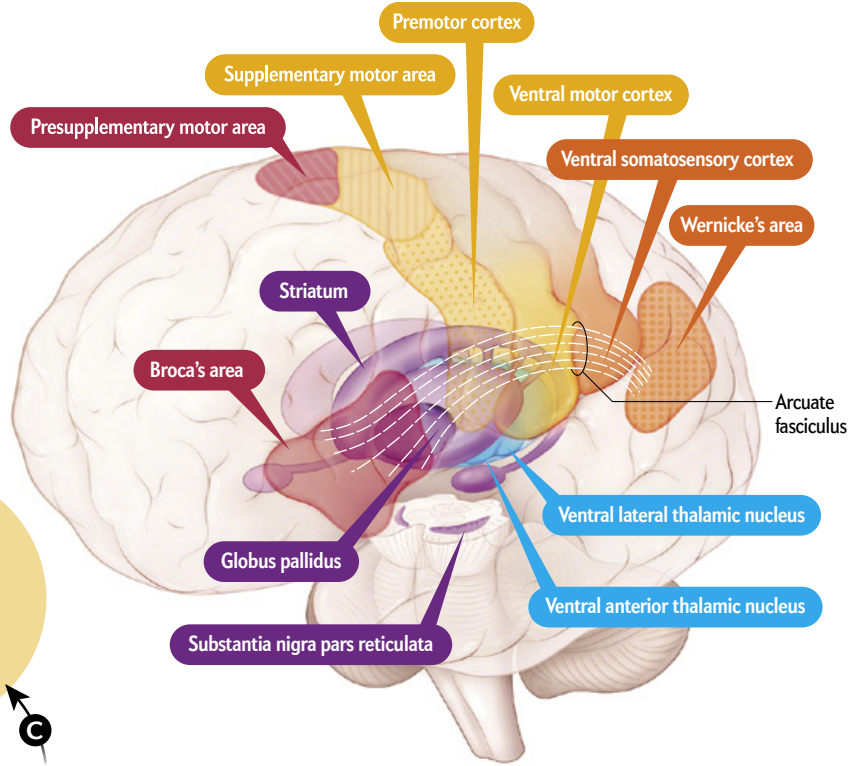
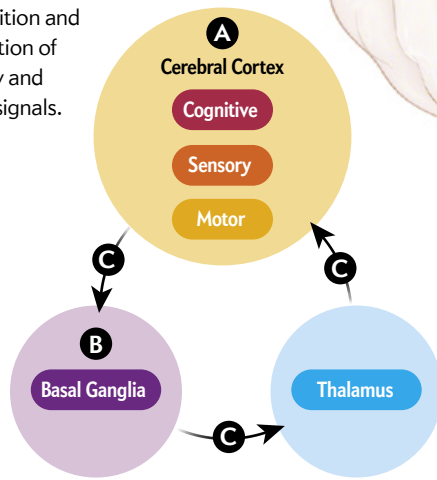
language pathologist, respectively, theorized that stuttering was the result of competition between the brain's two hemispheres. “They were on the right track,” Maguire says. But it took the arrival of sophisticated brain-imaging techniques in the 1990s to reveal neural differences in people who stutter. In 1995 Maguire and his colleagues published the first positron-emission tomography (PET) study of the problem, scanning the brains of four people who stutter, and reported consistent decreases in neural activity in language areas. Other small early studies found increased levels of dopamine in the striatum, a critical piece of the brain's reward circuitry.

Building on this type of work, researchers tested antipsychotic drugs that block dopamine receptors and found the medications improved fluency in some people, although the drugs came with the risk of severe side effects such as parkinsonian movement disorders. Still, there were plenty of skeptics who were convinced stuttering had nothing to do with the brain. When Maguire presented his theory that stuttering was a brain disorder at a scientific conference in the late 1990s, he recalls, “I was kind of booed off the stage.”

The newest research uses high-tech scanners and advanced analytical techniques, and it proves these early researchers were onto something. In most people, language is predominantly supported in the left hemisphere. Adults who stutter show less activity in the left-hemisphere areas that support speech production and more activity in the right hemisphere than adults who do not stutter. For example,

# Stuttering Circuit

Speech is one of the most sophisticated human behaviors, involving millisecond-by-millisecond coordination among multiple parts of the brain. Stuttering has been linked to weakness in the fibers that carry nerve impulses among these areas. The areas fall into three regions: the thalamus, which relays sensory signals; the basal ganglia, which coordinates movements; and the cerebral cortex, which is involved in cognition and integration of sensory and motor signals.



There are many connections within and among these areas. In the cortex **A**, a key fiber link is the arcuate fasciculus, which shows deficiencies in people who stutter. Other potentially poor connections are within the basal ganglia **B** and in the network linking all areas, the cortico-basal ganglia-thalamocortical loop **C**.

cognitive neuroscientist Kate Watkins of the University of Oxford identified an area in the left hemisphere close to speech regions, the ventral premotor cortex, that did not activate when people who stutter were speaking.

That area sits directly above an important white matter fiber tract linking auditory- and movement-control areas where Watkins and others have found structural differences in people who stutter. White matter is made up of axons, long neuronal projections that transmit impulses. “It’s all of the cables and wires that allow communication,” Watkins says.

That communication needs to be timed perfectly. To pull that off, axons are insulated with myelin, a fatty substance that speeds transmission. Well-myelinated axons in tracts usually run in the same direction, like the fibers in stalks of celery. But a kind of brain scan called diffusion-weighted imaging reveals that in people who stutter, the axons most likely crisscross.

Moreover, fluid and neurotransmitters should travel through white matter bundles much like

water would flow through celery, along parallel fibers. In these brain scans, the flow is quantified in a measure called fractional anisotropy (FA)—the higher the FA, the more tightly organized the white matter. People who stutter have consistently lower FA values in this tract. Watkins suspects that means that brain areas the white matter was meant to feed sometimes are not getting the message and do not activate. (Parts of other white matter tracts in people who stutter, such as the corpus callosum that connects the cerebral hemispheres, show similar reductions in white matter integrity.)

Functionally, people who stutter appear to have deficits in a brain circuit called the cortico-basal ganglia-thalamocortical loop, which also underlies auditory, speech and motor integration. As the name implies, the circuit connects structures deep in the brain—the basal ganglia, which includes the striatum, and the thalamus—with areas in the cortex closer to the brain’s surface. “Speech is one of the most complex motor behaviors we perform,” says neuroscientist Soo-Eun Chang of the University of

Source: “Involvement of the Cortico-Basal Ganglia-Thalamocortical Loop in Developmental Stuttering,” by Soo-Eun Chang and Frank H. Guenther, in *Frontiers in Psychology*, January 28, 2020 (loop reference)

Michigan. “It relies on millisecond coordination among neural circuits as well as muscles. Among other things, this loop supports smooth and timely initiation of movement patterns.”

It is not yet clear exactly why the breakdown occurs, but even subtle deficits could lead to difficulty producing fluent speech. “Everything’s pointing to the basal ganglia being the switchboard,” Maguire says. “If anything along that pathway is disturbed, it can lead to stuttering symptoms.”

Differences such as these could be at the root of stuttering. Or they could be compensatory changes, the effect of the brain trying to adapt to the experience of stuttering. Chang is trying to distinguish cause from effect by tracking more than 250 children beginning at the age of three and following them for at least four years. Some of the children recover from stuttering, and some do not.

In 2017 Chang and her colleagues reported that compared with children who did not stutter, children who did began with a weakness in white matter integrity in the left-hemisphere tract connecting auditory and motor regions. But in children who recover, white matter integrity became better organized over time. “That was increasing and normalizing in recovered kids, and it was completely plateaued or even going downward in persistent kids,” Chang says.

In both adults and children who stutter, she has found weakness on the left side of the brain. More consistently in adults so far, she has also discovered a pattern of overactivity on the right side, suggesting it is an adaptive, late-occurring change. The “million-dollar question,” Chang says, is whether there are detectable differences from the start between children who go on to recover and those whose stutters persist. “Having that objective marker early on would be critical,” she says, because it would indicate who is at greatest risk for continued stuttering.

#### ALL IN THE FAMILY

MUCH OF THAT RISK is handed down with family DNA. Studies of twins and adopted children suggest genes explain anywhere between 42 and 85 percent of the risk of stuttering. Identical twins share a lot more genes than do fraternal twins, and in one study, 63 percent of identical twins both stuttered versus 19 percent of fraternal same-sex twins. The remaining risk may be caused by environmental factors (one indication of such nongenetic influence is that not every pair of identical twins both stutter), although some environmental factors can combine with genetic predisposition. Exactly what those environmental factors are is not known.

But some of the genes have been identified, thanks to work that geneticist Dennis Drayna of the Na-

tional Institute on Deafness and Other Communication Disorders began some 20 years ago. Drayna traveled to Pakistan, where it is common to marry cousins, a practice that can strengthen the effects of genes within families. “It was easy to find great big families with lots and lots of cases of stuttering,” Drayna says.

In 2010 Drayna and his colleagues reported three stuttering genes: a mutation in *GNPTAB*, a gene that was previously identified in a severe genetic disorder entirely unrelated to stuttering, and mutations in genes called *GNPTG* and *NAGPA*. And then Drayna got an online question from a man in Cameroon asking about the prevalence of stuttering in his family—out of 71 individuals Drayna later met, 33 stuttered—and it led the geneticist to a fourth stuttering gene, *AP4E1*. (A report of a fifth gene is still unpublished.) Together those genes might at best account for 20 to 25 percent of cases, Drayna says. The high family prevalence of the problem indicates there are more genes to find, and to look for them, a consortium of 22 research groups led by Australian scientists is conducting a new genome-wide association study (GWAS) of people who stutter.

All the genes identified so far have to do with intracellular trafficking, or the transport of molecules within cells. In a 2019 study, Drayna and his colleagues found that mice carrying a mutation of the gene *GNPTAB* had abnormally long pauses in their vocalizations, similar to stuttering. And in those mice, they identified a deficit in astrocytes, a type of brain cell widely found in white matter tracts that interconnect the two cerebral hemispheres. It could be that mutations in lysosomal genes, which help to remove waste products, are one link between genetics and the neurology of stuttering.

#### ENDING STIGMA

THE GENETIC ORIGINS of stuttering do not mean it cannot be treated. Already the newer research is informing therapy for stuttering. Pharmacological approaches are being fine-tuned. Maguire and his colleagues believe that medications that lower dopamine activity in certain brain circuits are the most promising approach to date. Antipsychotic drugs do just that. Maguire has successfully tested risperidone, olanzapine and lurasidone, all of which reduced the severity of stuttering, although none has received approval from the Food and Drug Administration. Unfortunately, these drugs can also cause unpleasant side effects such as weight gain and impaired movement. Still, some people, including Maguire, take them off-label.

Maguire is now leading a larger, randomized clinical trial of a drug called ecopipam, which is also being tested to treat Tourette’s syndrome. Ecopipam



targets a different set of dopamine receptors than earlier drugs. In a small pilot study, the drug improved fluency and quality of life and had no significant side effects. But any pharmacological treatment for stuttering that wins FDA approval is unlikely to work for everybody. “I think our next path will be personalized medicine, figuring out what’s really going on in [each] person,” Maguire says. “We’re learning now that stuttering is not going to be one condition.”

Brain stimulation with mild electric currents also appears promising. At Oxford, Watkins combined noninvasive transcranial stimulation with known speech-fluency strategies such as getting a group of people to read together in chorus or asking people to speak to the beat of a metronome. Such techniques have been shown to temporarily improve fluency in people who stutter, probably because they take advantage of external cues to initiate speech.

In a group who had combined treatment, Watkins found that the portion of their speech with repeated or prolonged syllables—or some other features of stuttering—dropped from 12 to 8 percent. But this percentage did not change in a control group who did not receive stimulation. Given the small size of the study and its short duration (five days), even that limited impact was enough to suggest they were on to something.

Adding brain stimulation to speech therapy may strengthen learning. “We were kind of consolidating that pathway, making it work more efficiently by stimulating it,” Watkins says. For now, many people who stutter have only traditional speech therapy to turn to, if they choose. The techniques usually involve practicing speech production but also learning to communicate effectively with a stutterer. Speech therapy can be very effective but does not necessarily last—most people relapse at some point.

Partly in recognition of that fact and partly because of changing cultural awareness, the goal of therapy for people who stutter has shifted in recent years from trying to eradicate stuttering to trying to make it easier to accept and manage. “There’s a huge component that is coping-related,” Yaruss says. He likens it to learning to ice skate. The first time you strap on skates and go out on the ice, you’ll flail around and feel like you’re slipping or falling. But as you learn to tolerate that slipping feeling, you respond more expertly. “You can say, I know what to do when this happens; you move through a moment of stuttering more expertly.”

That shift in emphasis is a welcome one. Cathe-

rine Moroney, 54, is a physicist and software engineer at the NASA Jet Propulsion Laboratory. As a child, she says, “I basically couldn’t make myself understood.” Speech therapy greatly improved her fluency but only temporarily because she finished her therapy just as she was in the midst of a punishing physics degree program. Stress and anxiety do not cause stuttering, but they can make it worse.

Moroney, whose stutter is moderate now but used to be more severe, was fortunate to find a boss who cared only for the quality of her work, which involves studying clouds and their role in the climate system. She now takes the antipsychotic olanzapine off-label. “It just makes daily life a little bit easier.” But what really changed Moroney’s life was joining what she calls “my stuttering family.” “It may be

**“Speech is one of the most complex motor behaviors we perform. It relies on millisecond coordination among neural circuits as well as muscles.”**

—Neuroscientist Soo-Eun Chang,  
*University of Michigan*

counterintuitive, but the loudest and noisiest place in the world is a stuttering conference,” she says with a laugh. “Nobody ever shuts up. It is so freeing for those few days to be in the majority.”

Lee Reeves, a former chair of the board of the National Stuttering Association and an early advocate of the self-help movement in stuttering, agrees wholeheartedly. Speech therapy did improve his fluency, but the fact that his therapist was a clinical psychologist who addressed the mental stress of the condition was absolutely critical to his success. “I learned to stutter in a way that was acceptable to me,” he says.

Nor did his stutter stop him from becoming a veterinarian. Three weeks after he visited that animal hospital as a teenager, the vet—his name was Peter Malnati—called back and offered Reeves a job. Reeves worked for that clinic through the rest of high school and college and went on to a five-decade career as a small-animal vet, much of it in Plano, Tex. Now his days of frustration and embarrassment are long gone. “I still stutter. I stuttered yesterday, and I stuttered today,” Reeves says. “I hope I stutter tomorrow because it means I’m still alive.” ■

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#### FROM OUR ARCHIVES

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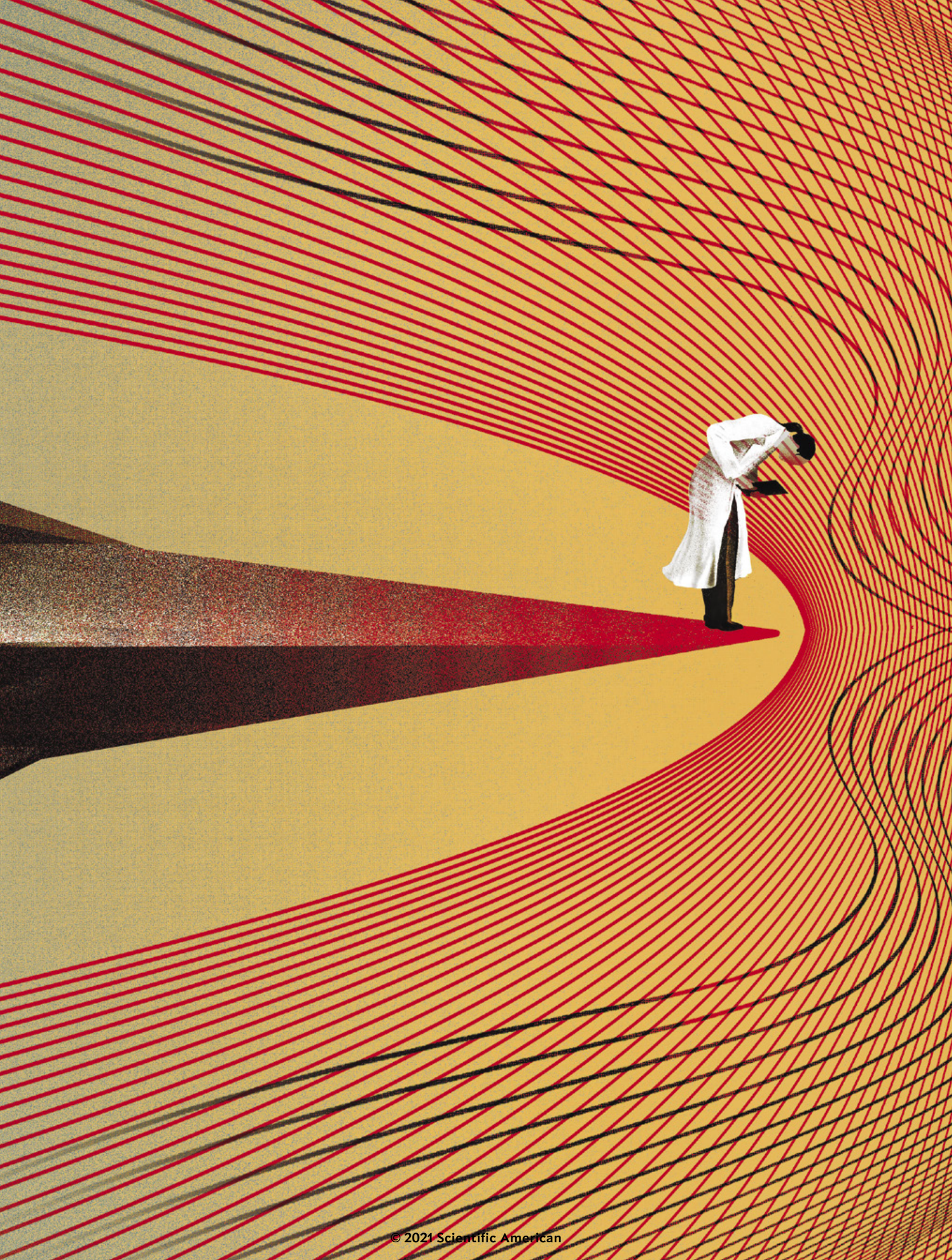
SECURITY

# Overhyped

Physics dictates that hypersonic weapons cannot live up to the grand promises made on their behalf

*By David Wright and Cameron Tracy*

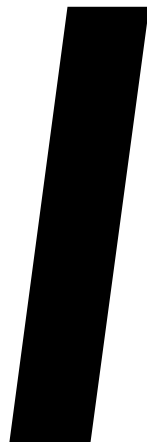
*Illustration by Brian Stauffer*



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**Cameron Tracy** is a Global Security Fellow at the Union of Concerned Scientists. An engineer and materials scientist, he researches hypersonic weapons and nuclear waste management.



**I**N A TELEVISED ADDRESS TO RUSSIA'S FEDERAL ASSEMBLY IN 2018, PRESIDENT VLADIMIR PUTIN announced an escalation of the ongoing arms race with the U.S., which had withdrawn from the Anti-Ballistic Missile (ABM) Treaty in 2002. Having rejected the decades-long arms-control agreement, the U.S. had developed and begun building a network of defenses to intercept long-range ballistic missiles, threatening Russia's ability to deter attacks on its homeland. He had warned Americans that Russia would be forced to respond to these deployments, Putin told his audience, but they had refused to listen. "So listen now!"

Among other systems, Russia was developing new hypersonic weapons, Putin declared: missiles that fly long distances through the atmosphere at more than five times the speed of sound, or faster than Mach 5. (Mach 1 is the local speed of sound. Speeds between Mach 1 and Mach 5 are supersonic, whereas those exceeding Mach 5 are hypersonic.) According to him, one of these, called Avangard, was a highly maneuverable missile that could glide thousands of kilometers with an initial speed greater than Mach 20, making it "absolutely invulnerable to any air or missile defense system."

Putin's announcement, accompanied by intimidating simulations of the new weapons snaking across the globe at unbelievable speeds, added fuel to a dangerous new arms race. The weapons involved in this competition are touted not only for their speed but also for their stealth and maneuverability. Intercontinental ballistic missiles, which follow an elliptical path into space before plunging down toward their target, reach speeds above Mach 20, but they have predictable trajectories for most of their flight and typically can maneuver only briefly, after they reenter the atmosphere. In contrast, hypersonic weapons would fly deep within the atmosphere most of the time, using lift generated by airflow to weave around and try to evade interceptors. Approaching at such low altitudes, these weapons would avoid detection by ground-based radar systems until close to their target, making them more difficult to stop.

In an assessment after Putin's speech, U.S. military officials stated that hypersonic weapons, which China was also developing, would "revolutionize warfare." The Pentagon, which had been working on similar systems for a decade and a half, ramped up its own efforts; last year Congress dedicated \$3.2 billion to the research and development of hypersonic weapons and defenses. Russia and China now claim to each have deployed at least one such system. The U.S. has six known

hypersonic programs, divided among the air force, army and navy. Proponents say that these weapons are incredibly fast and agile and virtually invisible.

We disagree. We belong to a small but vibrant community of physicists and engineers scattered around the globe who study new weapons systems to understand their potential impacts on global security. This tradition is deep, going back to participants in the Manhattan Project and Russian scientists such as Andrei Sakharov, who sought to mitigate the danger to the world from the nuclear weapons they had helped create. As investigative physicists, we glean what information we can about new and usually secretive technologies, analyze it and share our evaluations with the public.

Our studies indicate that hypersonic weapons may have advantages in certain scenarios, but by no means do they constitute a revolution. Many of the claims about them are exaggerated or simply false. And yet the widespread perception that hypersonic weapons are a game-changer has increased tensions among the U.S., Russia and China, driving a new arms race and escalating the chances of conflict.

#### FITS AND STARTS

MILITARIES HAVE PURSUED hypersonic aircraft for almost a century, though with limited success. In the late 1930s Austrian engineer Eugen Sänger and German physicist Irene Bredt designed the first hypersonic aircraft, a glider called the Silbervogel. It was to be launched from a rocket, fly primarily within the atmosphere and, like any other glider, stay aloft using aerodynamic lift, but Nazi planners decided it would be too difficult and expensive to build.

During World War II, German engineers developed rocket engines, which burn propellant, a mixture of fuel and chemical oxidizer, to release an intense burst of energy. In subsequent

# The Hypersonic Realm

Armed vehicles that fly faster than five times the speed of sound (Mach 5) and for long distances, using lift from the atmosphere to maneuver, are described as hypersonic weapons. Ballistic missiles are accelerated by rocket boosters and fly at speeds of up to about Mach 20, but they do not fall into this category. The world's militaries are pursuing hypersonic weapons of two types. One is a cruise missile,

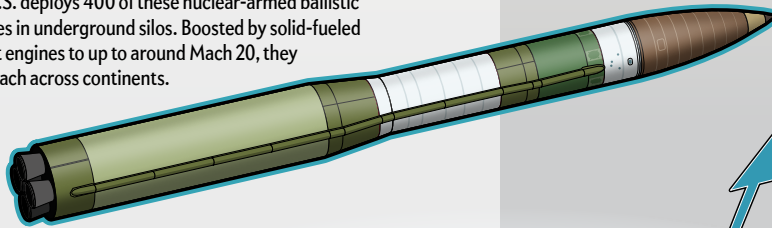
powered throughout its flight, but engines that can propel these weapons faster than Mach 5 are still being developed. The other type, which Russia and China claim to have deployed, are "boost-glide" weapons. Boosted to hypersonic speeds by rockets, these are supposed to glide through the atmosphere for long distances, using lift from airflow to maneuver.

An intercontinental ballistic missile on a "minimum-energy" trajectory arcs high above Earth, avoiding the resistance of the atmosphere for almost all of its path. A boost-glide hypersonic weapon, in contrast, flies mostly through the atmosphere, enabling it to maneuver. It would be faster than a ballistic missile on a high-altitude trajectory, but a ballistic missile on a lower, or "depressed," trajectory can deliver its warhead just as fast or faster.

## BALLISTIC MISSILES

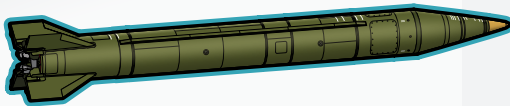
### Long-Range Example: Minuteman III

The U.S. deploys 400 of these nuclear-armed ballistic missiles in underground silos. Boosted by solid-fueled rocket engines to up to around Mach 20, they can reach across continents.



### Short-Range Example: Scud-B

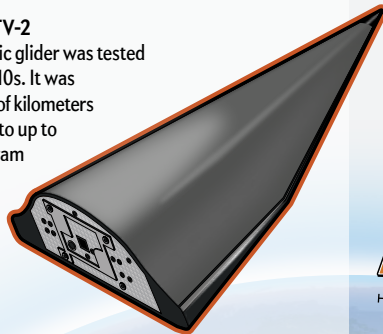
Many countries now own these 300-kilometer-range ballistic missiles, developed by the Soviet Union in the 1960s. They are boosted by liquid-fueled rocket engines.



## HYPERSONIC MISSILES

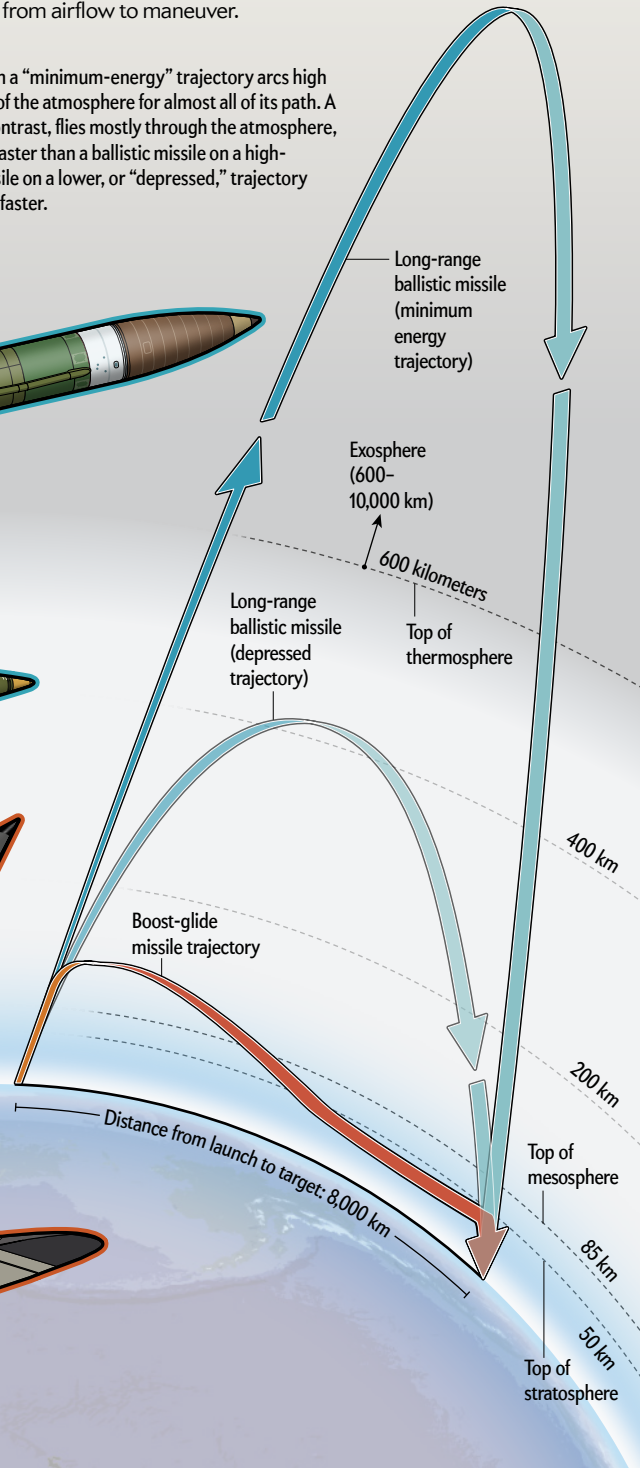
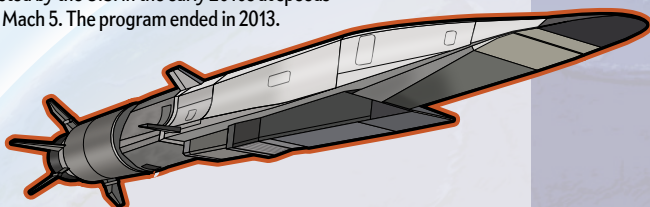
### Boost-Glide Example: HTV-2

This long-range hypersonic glider was tested by the U.S. in the early 2010s. It was designed to fly thousands of kilometers when boosted by a rocket to up to about Mach 20. The program was shelved around 2014.



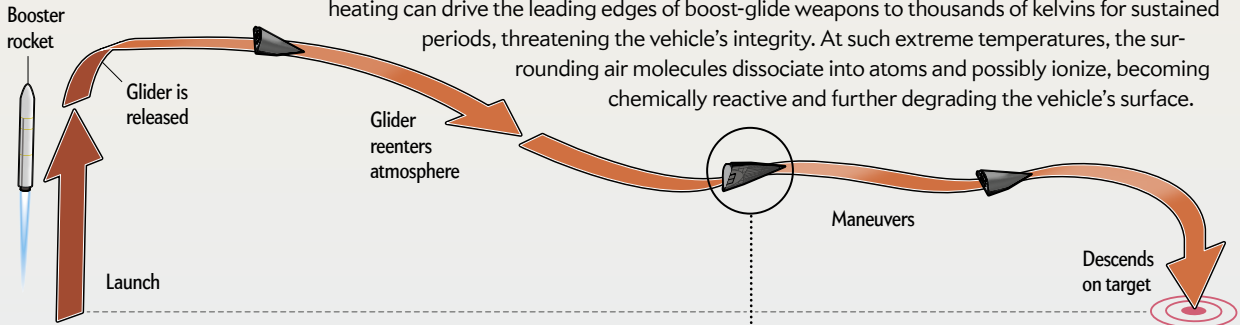
### Cruise Example: Boeing X-51

This vehicle, powered by a jet engine, was tested by the U.S. in the early 2010s at speeds of Mach 5. The program ended in 2013.



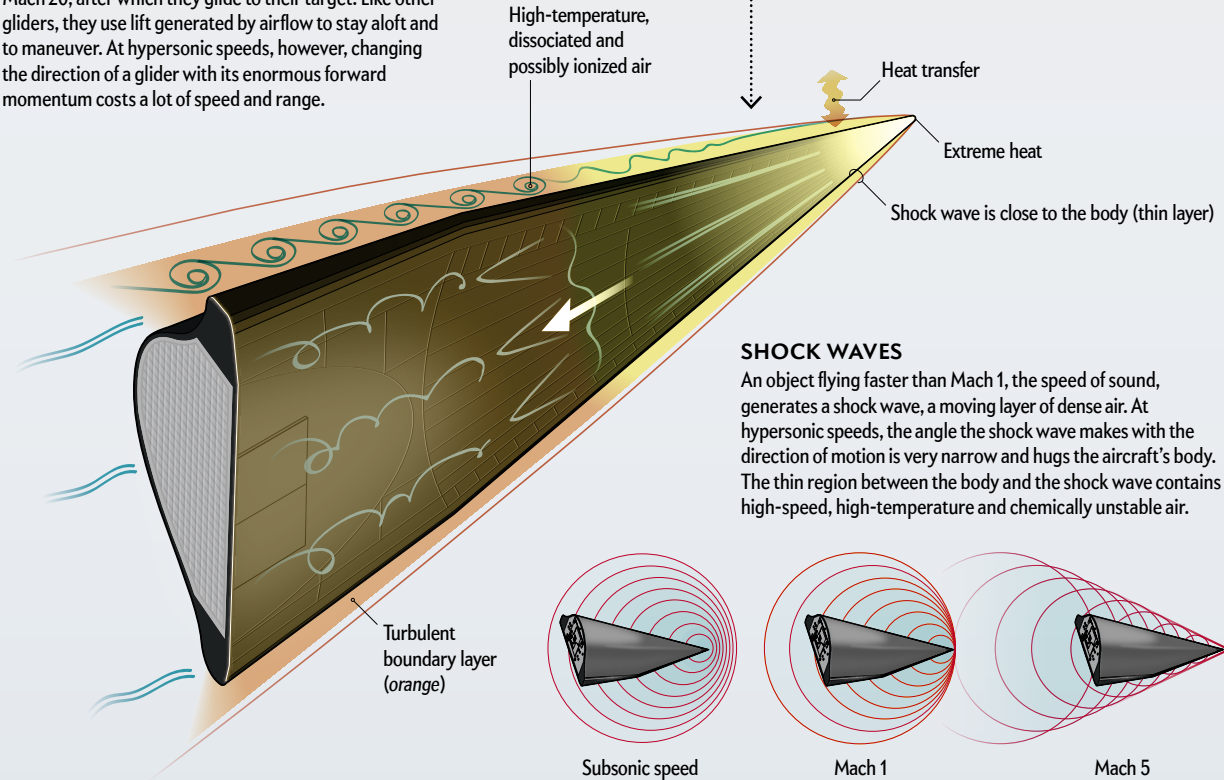
# The Problem of Drag

The drag, or resistance faced by an object as it pushes through a fluid, increases in proportion to the square of its speed. As a result, it poses an enormous obstacle to hypersonic flight, slowing down gliders and making them harder to maneuver. Making matters worse, drag drains kinetic energy from the vehicle, converting it to shock waves and thermal energy in the surrounding air. The intense heating can drive the leading edges of boost-glide weapons to thousands of kelvins for sustained periods, threatening the vehicle's integrity. At such extreme temperatures, the surrounding air molecules dissociate into atoms and possibly ionize, becoming chemically reactive and further degrading the vehicle's surface.



## BOOST-GLIDE BASICS

Hypersonic gliders are boosted by rockets to up to about Mach 20, after which they glide to their target. Like other gliders, they use lift generated by airflow to stay aloft and to maneuver. At hypersonic speeds, however, changing the direction of a glider with its enormous forward momentum costs a lot of speed and range.

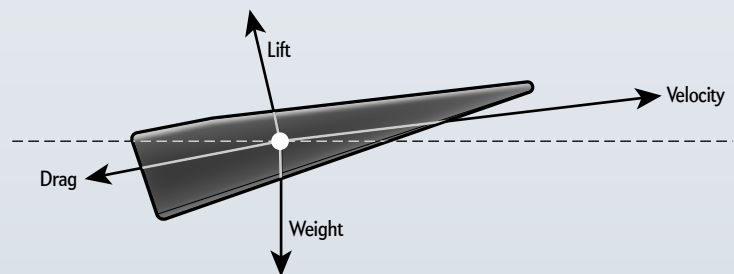


## SHOCK WAVES

An object flying faster than Mach 1, the speed of sound, generates a shock wave, a moving layer of dense air. At hypersonic speeds, the angle the shock wave makes with the direction of motion is very narrow and hugs the aircraft's body. The thin region between the body and the shock wave contains high-speed, high-temperature and chemically unstable air.

## LIFT AND DRAG

An aircraft stays aloft and maneuvers using lift (L), a force perpendicular to the velocity with respect to the air. The lift increases as the square of the velocity—but so does the drag (D). The ratio  $L/D$  is therefore a key marker of performance of an aircraft. But it is exceedingly difficult to design aircraft that have high  $L/D$  at hypersonic speeds. Commercial aircraft, which travel at subsonic speeds, have  $L/D$  of about 20, but the HTV-2, an experimental hypersonic glider tested by the U.S. in the early 2010s, achieved  $L/D$  of only 2.6.



Source: "Supersonic Combustion in Air-Breathing Propulsion Systems for Hypersonic Flight," by Javier Urzay, in *Annual Review of Fluid Mechanics*, Vol. 50, January 2018 (boost-glide weapon flow physics reference)

decades, experimental rocket-powered aircraft broke speed record after speed record. In October 1947 the rocket-propelled X-1 became the first piloted aircraft to officially break the sound barrier—crossing Mach 1—and in the 1960s the X-15 reached Mach 6.7 during tests. The strong g-forces produced by rocket engines placed extreme demands on human physiology, so piloted rocket-propelled aircraft never became more than experiments. But rocket technology enabled the U.S. and the Soviet Union to build arsenals of nuclear-armed ballistic missiles that are boosted to more than Mach 20 to reach across continents.

Another technology developed in this era, the jet engine, became the workhorse of military and commercial travel, however. Drawing in atmospheric oxygen to continuously burn fuel, a jet engine does not carry the extra weight of an oxidizer. It enables long-distance transport and maneuverability without the extreme acceleration of rocket engines. Today the fastest official speed for a piloted jet aircraft stands at approximately Mach 3, which the Lockheed SR-71 Blackbird reached in July 1976. Jet engines also power cruise missiles—maneuverable and pilotless aircraft, the fastest of which can achieve supersonic speeds.

Meanwhile hypersonic gliders continued to soar—and drop. In 1963, after spending over \$5 billion (in current dollars) developing the X-20 Dyna-Soar hypersonic glider, the U.S. abandoned the design. But after the Al Qaeda attacks on September 11, 2001, President George W. Bush directed the development of hypersonic missiles that could quickly and accurately disrupt terrorist activities on different continents with nonnuclear warheads. (Ballistic missiles could do the job, but the launch of such a weapon could be mistaken for a nuclear attack, provoking a nuclear war.)

Bush also withdrew from the Anti-Ballistic Missile treaty, which the U.S. and the Soviet Union had signed in 1972. The treaty had stopped the adversaries from constructing defensive shields against each other's ballistic missiles—and thereby halted a race for technologies to build shields and break through those of the other side. Instead the Bush administration proceeded to develop and deploy interceptors to protect against long-range ballistic missiles. Fearing that their ability to deter a U.S. nuclear attack would be compromised, Russia and, more recently, China, began to pursue diverse stratagems for surmounting the U.S. shield. The most recent of these devices are hypersonic missiles, which fly too low to be blocked by current U.S. interceptors of long-range ballistic missiles. In sum, the 9/11 attacks provoked a series of hasty decisions that have brought the three superpowers to the present situation, in which they are all racing to develop hypersonic weapons based on various technologies and designed for various purposes.

### DRAG AND LIFT

HYPERSONIC SYSTEMS deployed in the near term will be “boost-glide” weapons, which would be launched by a rocket booster and then glide long distances without propulsion. (The U.S. and other countries are also working to build hypersonic cruise missiles, but their engines are still under development.) Yet our studies indicate that hypersonic gliders encounter severe challenges. Physics gets in the way.

Designers of hypersonic vehicles face a daunting adversary: drag, the resistance a fluid offers to anything moving through it.

The drag on a flying object increases in proportion to the square of its velocity, making it particularly debilitating at hypersonic speeds. A glider at Mach 5 is subjected to 25 times the drag force than when it flies at Mach 1, for example, and one at Mach 20 faces 400 times the drag of when it is at Mach 1.

Even more severe is the energy drain from an aircraft as it pushes the molecules of air forward and aside: it increases as the cube of the velocity. So a glider flying at Mach 5 will lose energy 125 times faster than at Mach 1; one flying at Mach 20 will lose energy 8,000 times faster. Just as problematic, the kinetic energy flowing from the glider to the surrounding air transforms to thermal energy and shock waves. Some of that energy transfers back to the vehicle as heat: leading edges of boost-glide weapons flying at Mach 10 or above can reach temperatures above 2,000 kelvins for sustained periods. Protecting a vehicle from this intense heat is one of the biggest problems facing engineers.

At the same time, like any other glider, a hypersonic one must generate lift—a force perpendicular to its direction of motion—to stay aloft and to turn. (A glider turns by banking or otherwise inducing a horizontal component of the lift force.) As it happens, lift is also proportional to the square of the velocity. Moreover, the aerodynamic processes that produce lift also unavoidably generate drag. The ratio of the lift force,  $L$ , to the drag force,  $D$ , is called the lift-to-drag ratio,  $L/D$ , a key marker of a glider's performance.

Achievable values of  $L/D$  for hypersonic vehicles are much lower than for conventional aircraft. For subsonic aircraft, the ratio can be 15 or larger. Yet after decades of research and development, U.S. hypersonic weapons tested in the past decade appear to have  $L/D$  values less than three. Such low  $L/D$  ratios mean low lift and high drag—which limits the speed and range of a hypersonic glider, reduces its maneuverability and increases surface heating.

As if that were not enough, the physics and chemistry of air flowing past an object become radically different at hypersonic speeds. Heated to thousands of degrees, the surrounding air dissociates, converting molecular oxygen into free atoms that can ionize and scour away the surface of the vehicle. Even if the missile survives the roasting, the heating produces a bright infrared signal that satellites can see.

### NO SILVER BULLET

IN THE EARLY 2010s the U.S. flight-tested a long-range glider, the Hypersonic Technology Vehicle 2 (HTV-2). It was designed to glide up to 7,600 kilometers after being boosted to an initial speed of Mach 20 by a rocket. We combined data from these tests with other information about the vehicle to construct detailed computer simulations of hypersonic flight. We also compared the performance of boost-glide weapons with long-established technologies, such as ballistic or cruise missiles, on the three abilities in which hypersonic weapons are said to be exceptional—delivery time, maneuverability and stealth.

Hypersonic weapons are often said to reduce the time needed to deliver a warhead, but this claim is largely based on a misleading comparison with subsonic cruise missiles or with ballistic missiles on longer trajectories. The most energy-efficient path for a ballistic missile, called a minimum-energy trajectory, sends a warhead arcing high above Earth before it falls to its tar-

get. The warhead avoids atmospheric drag over most of its flight but follows a much longer path than a hypersonic glider would, so it can take somewhat longer to reach the same target.

Yet a ballistic missile can instead fly at lower altitude, called a depressed trajectory—long seen as a way of delivering quicker nuclear attacks from submarines. Such a path would be much shorter than a minimum-energy one, and a warhead following it would also avoid drag over most of its trajectory. In contrast, a hypersonic glider spends significantly more time within the atmosphere, where drag reduces its speed. Our calculations show that a ballistic missile on a depressed trajectory can deliver a warhead with an equal or shorter flight time than a hypersonic weapon over the same range.

Maneuvering is another advertised advantage of hypersonic weapons. Again, the reality is more complicated. The U.S. has developed and tested maneuvering reentry vehicles (MaRVs)—warheads that use aerodynamic forces to change direction as they near the target, helping to increase accuracy and evade missile defenses—for ballistic missiles for decades: maneuverability is not unique to hypersonic weapons. To be sure, MaRVs typically twist and turn only late in flight. They cannot snake around during their entire course as hypersonic gliders are supposed to do. But the maneuverability of hypersonic gliders is constrained by the great forces needed to turn a vehicle flying at such tremendous speeds.

To change direction, a hypersonic glider must use lift forces to impart a horizontal velocity—which might itself have to be hypersonic. For example, to turn by 30 degrees, a glider flying at Mach 15, or 4.5 kilometers per second, must generate a horizontal velocity of Mach 7.5, or 2.3 kilometers per second. (Because the speed of sound changes with density and altitude, flight engineers often take Mach 1 to be about 300 meters per second, and so do we.) At the same time, the glider must retain enough vertical lift to stay aloft. Such maneuvers can cost significant speed and range.

To generate the extra lift needed to change direction, the vehicle could dive to a lower altitude to use the greater push from denser air. It would make its turn before returning to a higher altitude, with less drag, to resume its flight. Going to lower altitudes would reduce the

time needed to turn but also increase the drag that the vehicle experiences. For example, at Mach 15 a glider such as the HTV-2 would fly at an altitude of about 40 kilometers. If it drops by about 2.5 kilometers, then turning by 30 degrees would take about seven minutes, during which it would travel along a vast arc, with a radius of some 4,000 kilometers. The extra drag that comes from traveling in denser air, even for such a short time, would reduce the glider's speed by about Mach 1.3, causing it to lose about 450 kilometers of range out of the 3,000 kilometers it might otherwise have traveled.

Some amount of midcourse maneuvering, such as for selecting a new target, can be useful, and gliders could likely make larger maneuvers than ballistic missile warheads can. Still, MaRVs can already maneuver by hundreds of kilometers during reentry, so it is hard to see how this ability is revolutionary.

Another common claim is that because gliders travel at lower altitudes than a ballistic warhead, they would be “nearly invisible” to early-warning systems. A ground-based radar system can spot a warhead at an altitude of 1,000 kilometers from about 3,500 kilometers away, but because of the earth's curvature it would not see a glider approaching at a height of 40 kilometers until it was only about 500 kilometers away. But both the U.S. and Russia have early-warning satellites with sensitive infrared sensors that could spot the intense light that gliders emit because of their extreme temperatures. Our analysis indicates that currently deployed U.S. satellites would be capable of detecting and tracking gliders traveling through the atmosphere at speeds covering most of the hypersonic regime.

Glider deployable in the foreseeable future might avoid being seen by U.S. satellites if they fly at the low end of the hypersonic range—below about Mach 6. This concern appears to be motivating U.S. research into new constellations of satellite sensors. But a boost-glide vehicle similar to the HTV-2 with an initial speed of Mach 5.5 would travel less than 500 kilometers, so flying at these speeds would significantly limit its range. Hypersonic cruise missiles could conceivably maintain these low speeds over longer distances. Such slow speeds may, however, negate another key argument for hypersonic weapons—their ability to avoid terminal missile defenses.



HTV-2 GLIDER (top), shaped like an arrowhead and shown prior to its launch from a rocket, was tested by the U.S. military in the early 2010s but failed to perform as advertised. A rocket booster (bottom) launches a different hypersonic glider the Pentagon is developing, based on a 1970s conical design.

Volgi Archive and Alamy Stock (top); Oscar Sosa and U.S. Navy (bottom)



Russia and China seem to be developing hypersonic weapons largely because of their ability to evade U.S. missile defense systems. The U.S. Ground-based Midcourse Defense and ship-based Aegis SM-3 systems, which are intended to defend the U.S., Japan, and other countries, intercept above the atmosphere and are unable to engage hypersonic weapons flying in at lower altitudes. Hypersonic gliders with sufficient speed and maneuverability could also evade defenses of shorter range that work within the atmosphere, such as the U.S. Patriot, SM-2 and THAAD systems. These interceptors protect small regions, tens of kilometers across, around military sites and ships, using lift forces for turning to intercept incoming weapons. Their efficacy depends on their being more maneuverable than the missile they are trying to hit, which in turn depends strongly on flight speed. Patriot interceptors, for example, use rocket boosters to reach speeds of up to Mach 6. A hypersonic weapon could likely outmaneuver these interceptors if it maintained high speeds—but could become vulnerable to them when flying below about Mach 6. Thus, almost as soon as a hypersonic glider becomes invisible to satellites (but possibly visible to ground radar), it can become susceptible to interception.

Moreover, the ability to penetrate defensive shields is not unique to hypersonic gliders. Interceptors that operate outside the atmosphere are particularly vulnerable to being fooled by decoys and other countermeasures, which Russia and China have developed and likely deployed. Ballistic missiles of short and medium range, launched from an aircraft, could fly at altitudes low enough to avoid such “exo-atmospheric” defenses. Similarly, equipping ballistic missiles, including missiles of short and medium range, with MaRVs could allow them to outmaneuver and penetrate defenses that operate within the atmosphere.

Today the U.S. has shifted its focus from developing long-range gliders such as the HTV-2 toward hypersonic systems of shorter range, of up to a few thousand kilometers. This change is motivated not only by the shortcomings of the prototype HTV-2 glider, which the tests had revealed, but also by a new mission: to use weapons in a local, or “theater,” conflict to penetrate and destroy defensive systems. In terms of capabilities, however, these shorter-range hypersonic gliders are virtually indistinguishable from MaRV-tipped ballistic missiles flying on depressed trajectories. The similarity became obvious in 2018, when the U.S. Department of Defense announced its choice of design for a hypersonic vehicle intended for joint use by the army, navy and air force. Rather than opting for a wedge shape like that of the HTV-2, which would increase the value of L/D, the Pentagon chose an older conical design based on an experimental MaRV originally developed in the 1970s. This weapon would have a lower range and less maneuverability, the Pentagon acknowledged, but the technology was less risky.

A design from the 1970s is hardly revolutionary. It looks to us like the Pentagon is using the hype about hypersonic weapons to secure funding from Congress while reverting to a technology developed half a century ago for its main system. While the Pentagon is putting some funds into other designs, its focus is not the revolutionary systems that were advertised.

#### WAVERIDER

SIGNIFICANTLY ENHANCING L/D, if possible, would reduce the technical barriers to long-range hypersonic flight. Theoretically,

“waverider” designs can increase the L/D values of hypersonic vehicles to six or higher. These use a wedge shape that matches the shock-wave pattern of the airflow around the glider at a given speed and altitude, enclosing part of the shock wave under the vehicle to provide additional lift.

This concept dates from the late 1950s but has proved difficult to transform into working vehicles. The HTV-2 was in fact based on such a design—but achieved an L/D value of only 2.6. Even so, in 2020 the air force withdrew from the Pentagon’s joint hypersonic program and announced that it would pursue a wedge design like that of the HTV-2 for a short-range glider. Increasing L/D to four or six would help reduce heat loads and increase a glider’s range. But would such improvements open new possibilities for military uses?

We think not. Heating remains a major challenge because the surface temperature of a vehicle falls rather slowly with increases in L/D. Our calculations show, for example, that increasing L/D from 2.6, the value that the HTV-2 achieved, to 6 would reduce a glider’s surface temperature at a given speed by at most 15 percent. Preventing material damage during long-range flights would therefore still be difficult. Such an increase in L/D would also reduce the infrared signature of a missile and potentially increase the speed at which it could fly undetected (by current satellites) to up to Mach 7. Increasing L/D could in addition provide somewhat higher maneuverability—but that could be more easily boosted by relatively small increases in a glider’s initial speed. (Recall that maneuverability depends on lift, which increases as the square of the velocity.) For such reasons, it does not look like foreseeable advances in hypersonic gliders, such as increasing L/D, would give hypersonic weapons revolutionary capabilities.

Despite this reality, the hype around hypersonic weapons has driven big increases in spending on these systems and heightened fear, distrust and the risk of conflict among the U.S., Russia and China. The prospect of fast and potentially undetected attacks, even if exaggerated, could prompt these countries to react quickly and rashly to warnings, either real or mistaken, increasing the chances of blundering into conflict.

By providing technical analyses of new military systems, independent scientists and engineers such as ourselves seek to help the public and policy makers make sound decisions about them. Our ranks are thinning, however. Although funds for designing and building novel weapons seem inexhaustible, resources for such impartial research into their abilities and impacts is shrinking—creating daunting barriers for early-career researchers who might otherwise be inclined to join the field. We believe that the unbiased and informed studies we provide are vital, however, and policy makers should heed them. The U.S. Congress and the Pentagon need to dispense with the hype and make a careful, realistic and technically informed appraisal of the potential benefits and costs of hypersonic weapons. Failure to fully assess these factors is a recipe for wasteful spending and increased global risk. ■

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#### FROM OUR ARCHIVES

*Broken Shield.* Laura Grego and David Wright; June 2019.

[scientificamerican.com/magazine/sa](https://www.scientificamerican.com/magazine/sa)

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EPIDEMIOLOGY

# The Year Flu Disappeared

Public health measures meant to slow the spread of COVID-19 essentially defeated influenza

*Text and Graphics by Katie Peek*

SINCE THE NOVEL CORONAVIRUS BEGAN ITS GLOBAL SPREAD, INFLUENZA CASES REPORTED TO THE WORLD Health Organization from the Northern and Southern Hemispheres have dropped to minute levels. The reason, epidemiologists think, is that the public health measures taken to keep the coronavirus from spreading—notably mask wearing and social distancing—also stop the flu. Influenza viruses are transmitted in much the same way as SARS-CoV-2, the virus that causes COVID-19, and they are less effective at jumping from person to person.

As *Scientific American* reported in November 2020, the drop-off in flu numbers following COVID's arrival was swift and global. Since then, cases have stayed remarkably low. "There's just no flu circulating," says Greg Poland, who has studied the disease at the Mayo Clinic for decades. The U.S. saw about 700 deaths from influenza during the 2020–2021 season. In comparison, the Centers for Disease Control and Prevention estimates there were approximately 22,000 U.S. deaths in the prior season and 34,000 deaths two seasons ago.

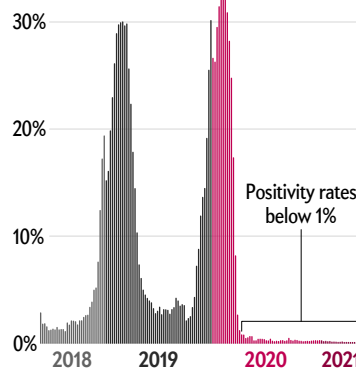
Because each year's flu vaccine is based on strains that have been circulating around the world during the past 12 months, it is unclear how the upcoming 2021–2022 vaccine will fare should the typical patterns of infection return. The WHO made its flu strain recommenda-

tions in late February as usual, but they were based on far fewer cases than normal. Yet with less virus circulating, there is a reduced chance of mutation, so the upcoming vaccine could be especially effective.

Public health experts are grateful for the reprieve in cases. If the future includes more hand washing, face covering and temporary social distancing when people become sick, perhaps flu seasons can be less severe, even as health restrictions lift and groups gather together again. ■

◀ SINCE MARCH 2020 fewer people have been tested for influenza, but that is not the reason for fewer recorded cases. The percentage of samples that have tested positive (the positivity rate) has also plummeted.

U.S. Flu Positivity Rate by Week

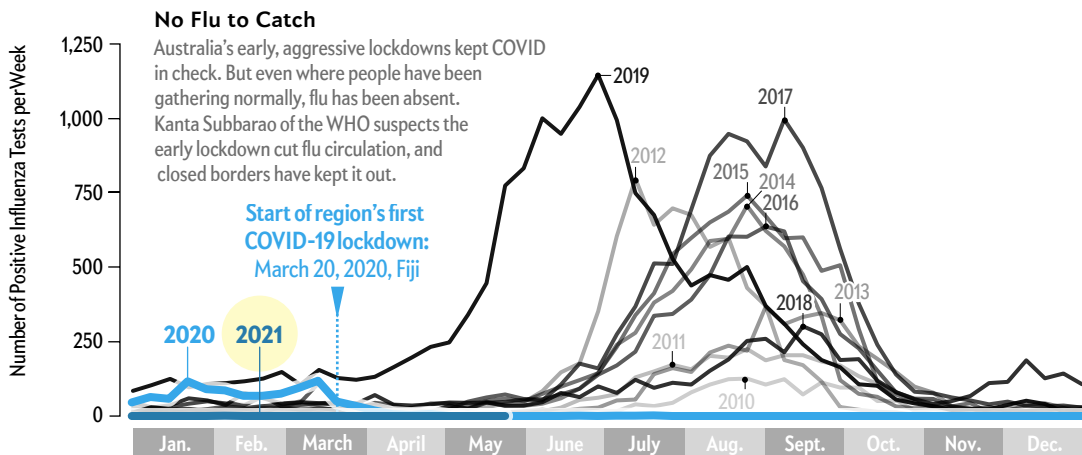
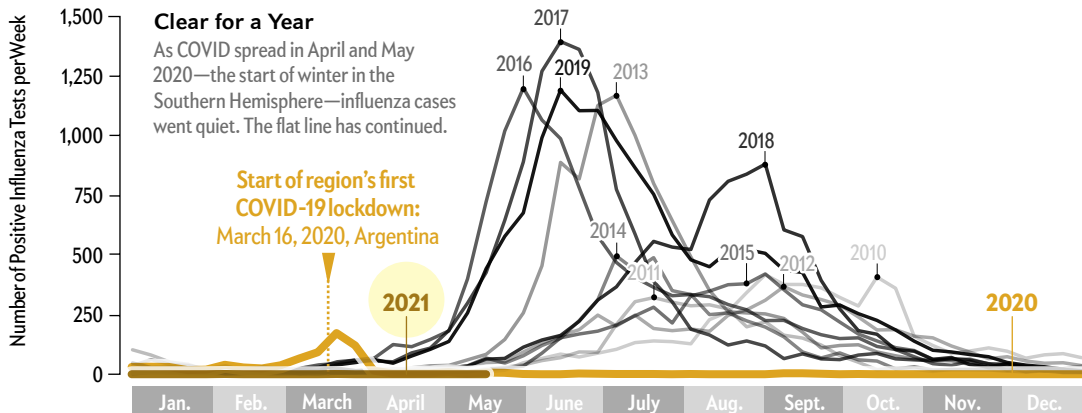
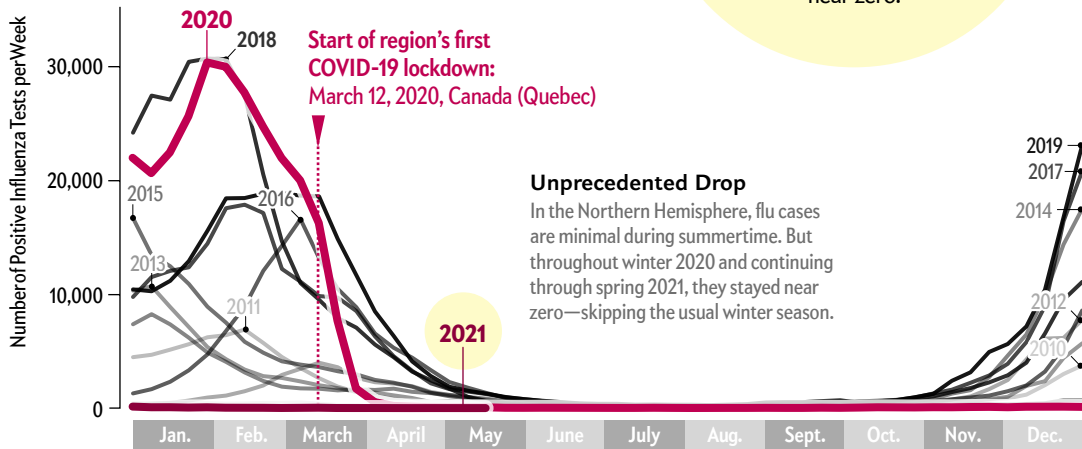


## WEEKLY INFLUENZA CASES (2010–2021)

The World Health Organization tracks influenza activity in 18 transmission zones. In temperate regions, cases are generally high in winter and low in summer, but they have been extremely low for a year. The weekly tally counts only people who are tested for influenzalike illnesses—typically about 5 percent of those who fall ill.

### KEY

— Cases before COVID-19    — Cases during 2020 and 2021    All data as of June 1, 2021



**Gone Missing**

When *Scientific American* first published influenza data in November 2020, the 2020–2021 flu season looked like a possible no-show. Since then, cases around the world have remained near zero.

Source: FluNet/Global Influenza Surveillance and Response System at the World Health Organization (data)



COSTUME PARTY at the Institute for Sexual Research in Berlin, date and photographer unknown. Magnus Hirschfeld (*in glasses*) holds hands with his partner, Karl Giese (*center*).



GENDER STUDIES

# The World's First Trans Clinic

In Germany,  
the Institute  
for Sexual Research  
would be a  
century old  
if it hadn't  
been destroyed  
by the Nazis

*By Brandy Schillace*

L

ATE ONE NIGHT ON THE CUSP OF THE 20TH century, Magnus Hirschfeld, a young doctor, found a soldier on the doorstep of his practice in Germany. Distraught and agitated, the man had come to confess himself an *Urning*—a word used to refer to homosexual men. It explained the cover of darkness;

to speak of such things was dangerous business. The infamous “Paragraph 175” in the German criminal code made homosexuality illegal; a man so accused could be stripped of his ranks and titles and thrown in jail.

Hirschfeld understood the soldier’s plight—he was himself both homosexual and Jewish—and did his best to comfort his patient. But the soldier had already made up his mind. It was the eve of his wedding, an event he could not face. Shortly after, he shot himself.

The soldier bequeathed his private papers to Hirschfeld, along with a letter: “The thought that you could contribute to [a future] when the German fatherland will think of *us* in more just terms,” he wrote, “sweetens the hour of death.” Hirschfeld would be forever haunted by this needless loss; the soldier had called himself a “curse,” fit only to die, because the expectations of heterosexual norms, reinforced by marriage and law, made no room for his kind.

These heartbreaking stories, Hirschfeld wrote in *The Sexual History of the World War*, “bring before us the whole tragedy [in Germany]; what fatherland did they have, and for what freedom were they fighting?” In the aftermath of this lonely death, Hirschfeld left his medical practice and began a crusade for justice that would alter the course of queer history.

Hirschfeld sought to specialize in sexual health, an area of growing interest. Many of his predecessors and colleagues believed that homosexuality was pathological, using new theories from psychology to sug-



MAGNUS HIRSCHFELD, director of the Institute for Sexual Research, in an undated portrait.

gest it was a sign of mental ill health. Hirschfeld, in contrast, argued that a person may be born with characteristics that did not fit into heterosexual or binary categories and supported the idea that a “third sex” (or *Geschlecht*) existed naturally. Hirschfeld proposed the term “sexual intermediaries” for nonconforming individuals. Included under this umbrella were what



**Brandy Schillace** is editor in chief of *BMJ’s Medical Humanities* journal and author of the recently released book *Mr. Humble and Doctor Butcher*, a biography of Robert White, who aimed to transplant the human soul.

Magnus-Hirschfeld-Gesellschaft e.V., Berlin (preceding pages and this page)

he considered “situational” and “constitutional” homosexuals—a recognition that there is often a spectrum of bisexual practice—as well as what he termed “transvestites.” This group included those who wished to wear the clothes of the opposite sex and those who “from the point of view of their character” should be considered as the opposite sex. One soldier with whom Hirschfeld had worked described wearing women’s clothing as the chance “to be a human being at least for a moment.” He likewise recognized that these people could be either homosexual or heterosexual, something that is frequently misunderstood about transgender people today.

Perhaps even more surprising was Hirschfeld’s inclusion of those with no fixed gender, akin to today’s concept of gender-fluid or nonbinary identity (he counted French novelist George Sand among them). Most important for Hirschfeld, these people were acting “in accordance with their nature,” not against it.

If this seems like extremely forward thinking for the time, it was. It was possibly even more forward than our own thinking, 100 years later. Current anti-trans sentiments center on the idea that being transgender is both new and unnatural. In the wake of a U.K. court decision in 2020 limiting trans rights, an editorial in the *Economist* argued that other countries should follow suit, and an editorial in the *Observer* praised the court for resisting a “disturbing trend” of children receiving gender-affirming health care as part of a transition.

But history bears witness to the plurality of gender and sexuality. Hirschfeld considered Socrates, Michelangelo and Shakespeare to be sexual intermediaries; he considered himself and his partner Karl Giese to be the same. Hirschfeld’s own predecessor in sexology, Richard von Krafft-Ebing, had claimed in the 19th century that homosexuality was natural sexual variation and congenital.

Hirschfeld’s study of sexual intermediaries was no trend or fad; instead it was a recognition that people may be born with a nature contrary to their assigned gender. And in cases where the desire to live as the opposite sex was strong, he thought science ought to provide a means of transition. He purchased a Berlin villa in early 1919 and opened the *Institut für Sexualwissenschaft* (the Institute for Sexual Research) on July 6. By 1930 it would perform the first modern gender-affirmation surgeries in the world.

### A PLACE OF SAFETY

A CORNER BUILDING with wings to either side, the institute was an architectural gem that blurred the line



1926 PORTRAIT of Lili Elbe, one of Hirschfeld’s patients. Elbe’s story inspired the 2015 film *The Danish Girl*.

between professional and intimate living spaces. A journalist reported it could not be a scientific institute, because it was furnished, plush and “full of life everywhere.” Its stated purpose was to be a place of “research, teaching, healing, and refuge” that could “free the individual from physical ailments, psychological afflictions, and social deprivation.” Hirschfeld’s institute would also be a place of education. While in medical school, he had experienced the trauma of watching as a gay man was paraded naked before the class, to be verbally abused as a degenerate.

Hirschfeld would instead provide sex education and health clinics, advice on contraception, and research on gender and sexuality, both anthropological and psychological. He worked tirelessly to try to overturn Paragraph 175. Unable to do so, he got legally accepted “transvestite” identity cards for his patients, intended to prevent them from being arrested for openly dressing and living as the opposite sex. The grounds also included room for offices given over to



feminist activists, as well as a printing house for sex reform journals meant to dispel myths about sexuality. “Love,” Hirschfeld said, “is as varied as people are.”

The institute would ultimately house an immense library on sexuality, gathered over many years and including rare books and diagrams and protocols for male-to-female (MTF) surgical transition. In addition to psychiatrists for therapy, he had hired Ludwig Levy-Lenz, a gynecologist. Together, with surgeon Erwin Gohrbandt, they performed male-to-female surgery called *Genitalumwandlung*—literally, “transformation of genitals.” This occurred in stages: castration, penectomy and vaginoplasty. (The institute treated only trans women at this time; female-to-male phalloplasty would not be practiced until the late 1940s.) Patients would also be prescribed hormone therapy, allowing them to grow natural breasts and softer features.

Their groundbreaking studies, meticulously documented, drew international attention. Legal rights and recognition did not immediately follow, however. After surgery, some trans women had difficulty getting work to support themselves, and as a result, five were employed at the institute itself. In this way,

**ONE OF THE FIRST and largest Nazi book burnings destroyed the library at the Institute for Sexual Research.**

Hirschfeld sought to provide a safe space for those whose altered bodies differed from the gender they were assigned at birth—including, at times, protection from the law.

### **LIVES WORTH LIVING**

THAT SUCH AN INSTITUTE existed as early as 1919, recognizing the plurality of gender identity and offering support, comes as a surprise to many. It should have been the bedrock on which to build a bolder future. But as the institute celebrated its first decade, the Nazi party was already on the rise. By 1932 it was the largest political party in Germany, growing its numbers through a nationalism that targeted the immigrant, the disabled and the “genetically unfit.” Weakened by economic crisis and without a majority, the Weimar Republic collapsed.

Adolf Hitler was named chancellor on January 30, 1933, and enacted policies to rid Germany of *Lebensunwertes Leben*, or “lives unworthy of living.” What began as a sterilization program ultimately led to the extermination of millions of Jews, Roma, Soviet and Polish citizens—and homosexuals and transgender people.

Ullstein Bild and Getty Images



# Although the Nazi newsreels still exist, and the pictures of the burning library are often reproduced, few know those iconic images feature the world's first trans clinic.

When the Nazis came for the institute on May 6, 1933, Hirschfeld was out of the country. Giese fled with what little he could. Troops swarmed the building, carrying off a bronze bust of Hirschfeld and all his precious books, which they piled in the street. Soon a towerlike bonfire engulfed more than 20,000 books, some of them rare copies that had helped provide a historiography for nonconforming people.

The carnage flickered over German newsreels. It was among the first and largest of the Nazi book burnings. Nazi youth, students and soldiers participated in the destruction, while voiceovers of the footage declared that the German state had committed “the intellectual garbage of the past” to the flames. The collection was irreplaceable.

Levy-Lenz, who like Hirschfeld was Jewish, fled Germany. But in a dark twist, his collaborator Gohrbandt, with whom he had performed supportive operations, joined the Luftwaffe as chief medical adviser and later contributed to grim experiments in the Dachau concentration camp. Hirschfeld's likeness would be reproduced on Nazi propaganda as the worst kind of offender (both Jewish and homosexual) to the perfect heteronormative Aryan race.

In the immediate aftermath of the Nazi raid, Giese joined Hirschfeld and his protégé Li Shiu Tong, a medical student, in Paris. The three would continue living together as partners and colleagues with hopes of rebuilding the institute, until the growing threat of Nazi occupation in Paris required them to flee to Nice. Hirschfeld died of a sudden stroke in 1935 while still on the run. Giese died by suicide in 1938. Tong abandoned his hopes of opening an institute in Hong Kong for a life of obscurity abroad.

Over time their stories have resurfaced in popular culture. In 2015, for instance, the institute was a major plot point in the second season of the television show *Transparent*, and one of Hirschfeld's patients, Lili Elbe, was the protagonist of the film *The Danish Girl*. Notably, the doctor's name never appears in the novel that inspired the movie, and despite these few exceptions the history of Hirschfeld's clinic has been effectively erased. So effectively, in fact, that although the Nazi newsreels still exist, and the pictures of the burning library are often reproduced, few know they feature the world's first trans clinic. Even that iconic image has been decontextualized, a nameless tragedy.

The Nazi ideal had been based on white, cisgender (that is, cisgender and heterosexual) masculinity masquerading as genetic superiority. Any who strayed were considered as depraved, immoral, and worthy of total eradication. What began as a project of “protecting” German youth and raising healthy families had become, under Hitler, a mechanism for genocide.

## A NOTE FOR THE FUTURE

THE FUTURE DOESN'T always guarantee progress, even as time moves forward, and the story of the Institute for Sexual Research sounds a warning for our present moment. Current legislation and indeed calls even to [separate trans children](#) from supportive parents bear a striking resemblance to those terrible campaigns against so-labeled aberrant lives.

Studies have shown that supportive hormone therapy, accessed at an early age, lowers rates of suicide among trans youth. But there are those who reject the evidence that trans identity is something you can be “born with.” Evolutionary biologist Richard Dawkins was recently stripped of his “humanist of the year” award for [comments comparing trans people to Rachel Dolezal](#), a civil rights activist who posed as a Black woman, as though gender transition were a kind of duplicity. His comments come on the heels of legislation in [Florida](#) aiming to ban trans athletes from participating in sports and an [Arkansas](#) bill denying trans children and teens supportive care.

Looking back on the story of Hirschfeld's institute—his protocols not only for surgery but for a trans-supportive community of care, for mental and physical healing, and for social change—it's hard not to imagine a history that might have been. What future might have been built from a platform where “sexual intermediaries” were indeed thought of in “more just terms”? Still, these pioneers and their heroic sacrifices help to deepen a sense of pride—and of legacy—for LGBTQ+ communities worldwide. As we confront oppressive legislation today, may we find hope in the history of the institute and a cautionary tale in the Nazis who were bent on erasing it. ■

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### FROM OUR ARCHIVES

On the Basis of Testosterone. Grace Huckins; February 2021.

[scientificamerican.com/magazine/sa](https://www.scientificamerican.com/magazine/sa)

## NONFICTION

# Driven to Cooperate

Can our instinct to work together override what polarizes us?

Review by Dana Dunham

Society is built on a foundation of cooperation, with lessons on its importance starting as early as *Sesame Street*. It may be tempting to look at our ability to cooperate—however imperfectly—as evidence that humans have transcended our baser instincts. But in her energetic analysis, psychologist Nichola Raihani recontextualizes cooperation within the framework of evolution and reveals the competition for survival that still bubbles below its surface.

According to Raihani, cooperation is “not just about what we do, but who and what we are.” As multicellular beings, we literally embody cooperation. As individuals, we gravitate toward others. The same instincts that lead us to live in tight-knit family groups drive us to help those who are not part of our immediate circles, even when our assistance will never be reciprocated. While this may not seem to square with “survival of the fittest,” Raihani accounts for this evolutionary puzzle and illuminates how cooperation has shaped such disparate phenomena as cancer, monogamy, menopause, hatred toward vegans, and people leaving dirty dishes in the office sink.



## The Social Instinct: How Cooperation Shaped the World

by Nichola Raihani.  
St. Martin's Press,  
2021 (\$29.99)

Raihani explains the breathtaking intricacies of natural selection yet does not shy away from addressing the field's current controversies (such as whether human societies should share the status of “superorganisms” with bee and ant colonies) or touching on its outermost frontiers, including the “mind-bendingly bonkers” possibili-

ties of microchimerism, the presence of cells of two individuals in one body. She compares human behaviors with those of other intensely social animals. For instance, meerkats teach their young how to handle food safely through scaffolded lessons, and the bluestreak cleaner wrasse polices its cleaning station to prevent conflict that might scare off fussy client fish.

Raihani offers insight into how our hardwired drive to cooperate could help us meet the challenges rushing at us, from pandemics to climate change. We can “change the rules” of our society to favor large-scale cooperation—a welcome idea as we confront living in the Anthropocene.



MEERKATS, like humans, are intensely social.

## IN BRIEF

### Secret Worlds: The Extraordinary Senses of Animals

by Martin Stevens.  
Oxford University Press, 2021 (\$25.95)

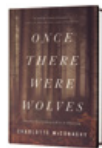


Ecologist Martin Stevens catalogs animals' sensory systems and how they exceed our own while informing—and challenging—our reality as humans. The book has a narrative and inquisitive style that will appeal to a wide audience. Stevens explores dozens of sensory systems through examples of the amazing capabilities they allow, from nocturnal dung beetles that orientate by using the Milky Way to sea turtles that navigate currents by reading the earth's magnetic fields. *Secret Worlds* is filled with lessons on how different species evolved to perceive the world.

—Jen St. Jude

### Once There Were Wolves

by Charlotte McConaghy.  
Flatiron Books, 2021 (\$27.99)



Australian writer Charlotte McConaghy (author of *Migrations*) delivers a suspenseful and poignant novel about a woman named Inti Flynn and her team of biologists who reintroduce gray wolves into Scotland's remote Highlands. At first, the wolves seem to thrive, but when a farmer gets mauled, locals blame the animals. Inti, however, reaches a different—and tragic—conclusion: she suspects the man she loves. Her story unfolds as a meditation on the social and scientific consequences of influencing ecosystems, while reminding us that humans and animals alike can break our hearts.

—Amy Brady

### The Shimmering State

by Meredith Westgate. Atria Books, 2021 (\$27)



Memoroxin, a personalized pill that replaces memories in people with Alzheimer's, is being abused as a recreational drug. Unmoored from reality, Lucien and Sophie meet at a “Mem” rehab center in Los Angeles, where personal traumas can be snipped away along with foreign memories. They feel drawn to each other; have they met before? Like the film *Eternal Sunshine of the Spotless Mind*, *The Shimmering State* explores whether the joys and pains of love can ever be fully erased. Through interconnected relationships, the novel delves into some of the moral dilemmas of a technology that can catalog and edit consciousness.

—Jen Schwartz

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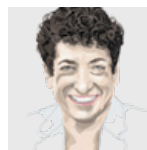
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**Naomi Oreskes** is a professor of the history of science at Harvard University. She is author of *Why Trust Science?* (Princeton University Press, 2019) and co-author of *Discerning Experts* (University of Chicago, 2019).

# The Appeal of Bad Science

Nonreplicable studies are cited strangely often

By Naomi Oreskes

A recent paper makes an upsetting claim about the state of science: nonreplicable studies are cited more often than replicable ones. In other words, according to the report in *Science Advances*, bad science seems to get more attention than good science.

The paper follows up on reports of a “replication crisis” in psychology, wherein large numbers of academic papers present results that other researchers are unable to reproduce—as well as claims that the problem is not limited to psychology. This matters for several reasons. If a substantial proportion of science fails to meet the norm of replicability, then this work won’t provide a solid basis for decision-making. Failure to replicate results may delay the use of



science in developing new medicines and technologies. It may also undermine public trust, making it harder to get Americans vaccinated or to act on climate change. And money spent on invalid science is money wasted: one study puts the cost of irreproducible medical research in the U.S. alone at \$28 billion a year.

In the new study, the authors tracked papers in psychology journals, economics journals, and *Science* and *Nature* with documented failures of replication. The results are disturbing: papers that couldn’t be replicated were cited more than average, even after the news of the reproducibility failure had been published, and only 12 percent of postexposure citations acknowledged the failure.

These results parallel those of a 2018 study. An analysis of 126,000 rumor cascades on Twitter showed that false news spread faster and reached more people than verified true claims. It also found that robots propagated true and false news in equal proportions: it was people, not bots, who were responsible for the disproportionate spread of falsehoods online.

A potential explanation for these findings involves a two-edged sword. Academics valorize novelty: new findings, new results, “cutting-edge” and “disruptive” research. On one level this makes sense. If science is a process of discovery, then papers that offer new and surprising things are more likely to represent a possible big advance than papers that strengthen the foundations of existing knowledge or modestly extend its domain of applicability. Moreover, both academics and laypeople experience surprises as more interesting (and certainly more entertaining) than the predictable, the normal and the quotidian. No editor wants to be the one who rejects a paper that later becomes the basis of a Nobel Prize. The problem is that surprising results are surprising because they go against what experience has led us to believe so far, which means that there’s a good chance they’re wrong.

The authors of the citation study theorize that reviewers and editors apply lower standards to “showy” or dramatic papers than to those that incrementally advance the field and that highly interesting papers attract more attention, discussion and citations. In other words, there is a bias in favor of novelty. The authors of the Twitter study also point to novelty as a culprit: they found that the false news that spread rapidly online was significantly more unusual than the true news.

Novel claims have the potential to be very valuable. If something surprises us, it indicates that we might have something to learn from it. The operative word here is “might” because this premise presupposes that the surprising thing is at least partly true. But sometimes things are surprising and wrong. All of which indicates that researchers, reviewers and editors should take steps to correct their bias in favor of novelty, and suggestions have been put forward for how to do this.

There is another problem. As the authors of the citation study note, many replication studies focus on splashy papers that have received a lot of attention. But these are more likely than average to fail to hold up on further scrutiny. A review focused on showy, high-profile papers is not going to be reflective of science at large—a failure of the norm of representativeness. In one case that I have discussed elsewhere, a paper flagging reproducibility problems failed to reveal the researchers’ own methods, yet this paper has been—yes—highly cited. So scientists must be careful that in their quest to flag papers that couldn’t be replicated, they don’t create flashy but flimsy claims of their own. ■

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AUGUST

## 1971 How Locusts Control Yaw

“Like an airplane, an insect can roll around its longitudinal axis, pitch around a horizontal axis or yaw around a vertical axis. It appears that locusts have two different yaw-correcting strategies: (1) a rapid change in wing twist, abdomen position and leg position controlled by wind-sensitive hairs on the head, and (2) a slower, subtler movement of the same general character evoked by cervical receptors. It seems that the change in wind angle, indicating a yaw, is integrated somewhere in the locust’s central nervous system, and is followed by independent motor commands to the wings, legs, abdomen and head.”

## 1921 Tasty Radio

“Two engineers recently conducted experiments to determine the feasibility of reception of radio signals by the sense of taste. Electrodes were placed under the tongue to cause a taste sensation when a source of [electrical] potential was connected to them. Tests were made, using low-potential direct current and 60-cycle alternating current, to ascertain the amount of energy and potential necessary for taste reception. The reception of actual signals from an antenna was tried. It was found impossible, [even with] four stages of amplification. The results indicate that while from an electrical standpoint it is possible to receive radio signals by the sense of taste, it is much inferior to that of hearing, or even of sight.”

## Orange Tree Never Quits

“An ever-bearing orange tree which citrus fruit growers believe is destined to revolutionize the orange industry has been discovered by horticulturists in a small grove at Avon Park, Florida. To protect the specimen, its purchasers have placed around it a heavy wire fence

20 feet in height and stationed guards day and night. The tree has been in bearing continuously eight years, but until recently its existence was known only to the owner and several neighbors, who, according to citrus experts, did not realize its value but regarded it merely as a freak of nature. A syndicate has been formed to propagate the tree so that a large number of trees may be set out in groves in 1923.”

## 1871 Early Fake Leather

“Enameled cloth enters into many uses as a substitute for leather. Its most important use is that of covering for carriage tops, for traveling bags and trunks, and not rarely is it worked up into rainproof coats and pants. The foundation is cotton cloth, which is slowly passed through a machine’s iron cylinders. It first receives a coating of a black, disagreeable-looking substance composed of oil, lampblack, resin and other ingredients, boiled to-

gether till about the consistency of melted tar. Then the cloth is wound upon a huge wooden frame that is passed into a heater to dry. It then is laid on long tables, and workers sprinkle with water and rub with pumice stone, till the whole surface is made perfectly smooth. The fabric is thoroughly varnished, and again passed through the heater. It is now a piece of cloth with a thick, shining coat of black, very much resembling patent leather.”

## Wonders of Chloroform

“Chloroform is the best known solvent for camphor, resins and sealing wax; it also dissolves the vegetable alkaloids. As a solvent it will remove greasy spots from fabrics of all kinds, but its chief use is as an anesthetic. There are several other volatile organic bodies which possess similar properties, but none produce the total unconsciousness and muscular relaxation that follow the inhalation of chloroform.”



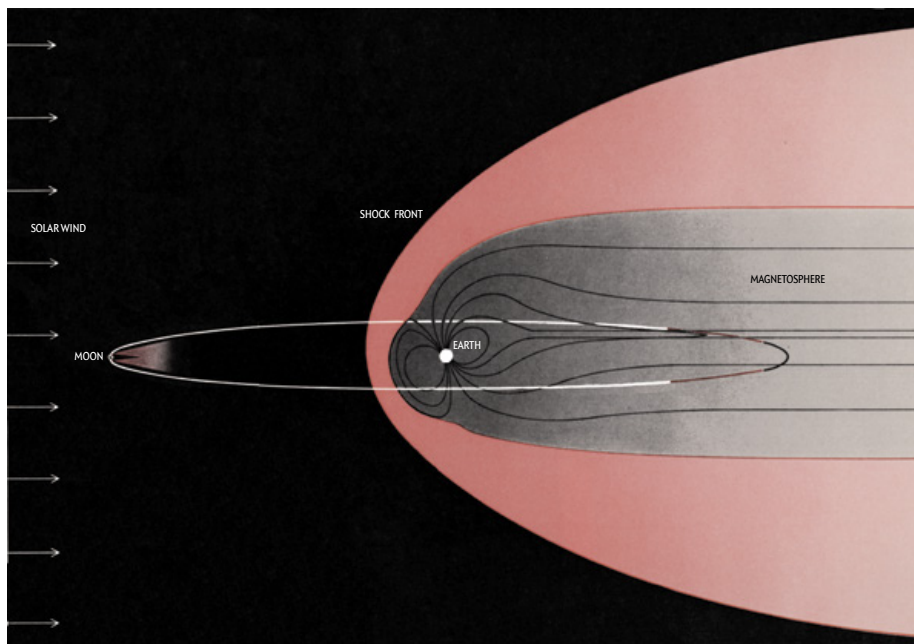
1971



1921



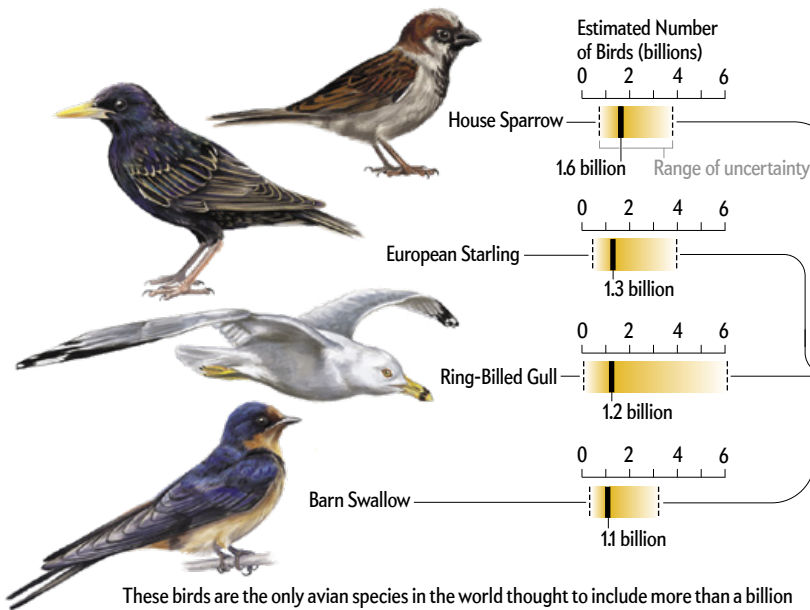
1871



1971: “The ‘solar wind’ of particles sweeps the earth’s magnetic field into a magnetosphere (gray). It in turn causes a shock front (red). When the moon is in the magnetosphere, its magnetic environment is dominated by the earth’s. The intermediate magnetosheath (light-colored area) has erratic solar-particle flow and the most turbulent fields of the lunar orbit.”

# GRAPHIC SCIENCE

Text by Clara Moskowitz | Graphic by Jen Christiansen (chart) and Liz Wahid (birds)



These birds are the only avian species in the world thought to include more than a billion individuals worldwide. Their abundance estimates appear above (shown as black lines), along with a scale of how uncertain those estimates are (shown in orange). The uncertainty ranges reflect the relative difficulty of gathering data on each species—those which inhabit a larger geographic range, for instance, tend to be harder to count.

## Counting Birds

There are many rare species and comparatively few common species

**Comparing the relative sizes** of bird species has long seemed an impossible task—too many species simply lack reliable counts. A recent influx of citizen science data, however, allowed researchers to make global abundance estimates for 9,700 species, about 92 percent of all birds on Earth. Biologists Corey T. Callaghan, Shinichi Nakagawa and William K. Cornwell, all at the University of New South Wales in Australia, combined scientific data for 724 well-studied species with counts from the app eBird, where people around the world can submit bird sightings. The researchers used an algorithm to extrapolate estimates for all species in their sample. The results, published recently in the *Proceedings of the National Academy of Sciences USA*, confirm a common pattern among animals: across the globe there are many species with small populations isolated in niche habitats and relatively few species that have managed to expand over a wide territory and grow their population into the hundreds of millions or billions. Eventually the findings could help with conservation efforts. “The next step is, Which species are rare because that’s just the way Mother Nature made them, and which species are rare because we [humans] screwed up?” Callaghan asks. This project did not try to answer these questions, but it is a “necessary first step” toward doing so, he says.

1,180 species (12% of all 9,700) are estimated to have populations of fewer than 5,000 individuals (hatched area). This includes species such as the Great Spotted Kiwi (377 individuals) and the Malaita Fantail (fewer than 100 individuals).

Circle size indicates the number of bird species with population sizes that fall within the range indicated

**Number of Species**  
Global population size

4  
More than 1 billion

8  
500 million–1 billion

13  
250 million–500 million

37  
100 million–250 million

78  
50 million–100 million

190  
25 million–50 million

436  
10 million–25 million

563  
5 million–10 million

737  
2.5 million–5 million

1,434  
1 million–2.5 million

1,478  
500,000–1 million

5,022  
Fewer than 500,000

Estimated global population size

1 billion

900 million

800 million

700 million

600 million

500 million

400 million

300 million

200 million

100 million

1 million

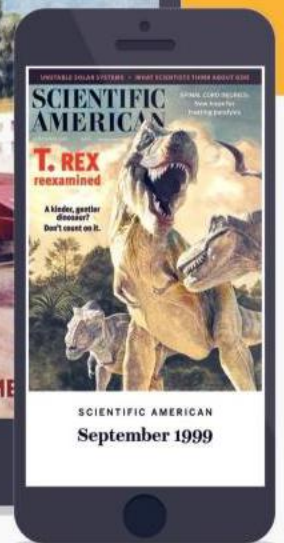
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Source: “Global abundance estimates for 9,700 bird species,” by Corey T. Callaghan, Shinichi Nakagawa and William K. Cornwell, in *PNAS*, Vol. 118, May 25, 2021 (data)

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