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Psychedelics to Treat Trauma

Surprisingly Sophisticated Neandertals

Teaching Kids to Spot Disinformation

THE ORIGINS OF SPACE AND TIME

Does spacetime emerge from a more fundamental reality?

FEBRUARY 2022

VOLUME 326, NUMBER 2

SCIENTIFIC AMERICAN

Andrew Hetherington

ON THE COVER

Space and time seem like the bedrock of the universe, but what if they are not fundamental? Several different theories of physics are converging on the idea that spacetime may instead be "emergent"—an artifact of deeper underlying elements of the universe. If scientists can figure out where spacetime comes from, they may be able to achieve one of the biggest goals in physics—a theory of everything. Illustration by Stefania Infante.

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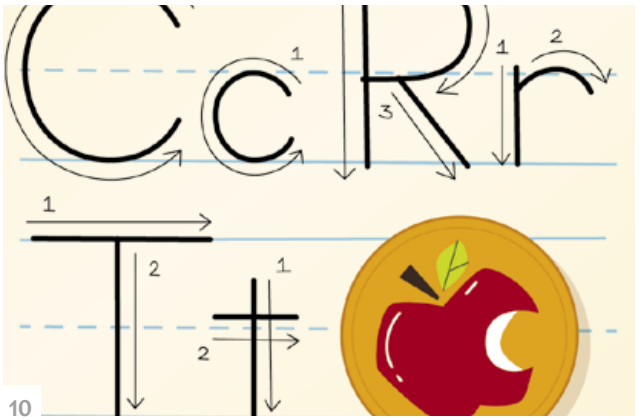

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Laura Helmuth is editor in chief of *Scientific American*.
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Big Questions

What *are* space and time? Where do they come from? Physicists have treated them as fundamental properties of the universe, but scientists are finding intriguing evidence that they could just be expressions of something even more fundamental. Author Adam Becker, in our cover story starting on page 26, takes us on a romp through this mind-bending research that could potentially lead to a theory of everything.

There are a lot of weird vertebrates in the world—zippy hummingbirds, absurdly long-necked giraffes, bipedal apes—but some of the strangest are salamanders. They can regenerate limbs and even brains, and some species stay in their larval form and never grow up. But one of the strangest things about salamanders is their genomes, which are enormous, so big that salamander cells become swollen just to contain all the DNA. Now, as journalist Douglas Fox writes on page 40, scientists have figured out that salamanders' oversized genomes seem to account for many of the other amazing features of their lifestyles.

Kids are vulnerable to misinformation and conspiracy theories, and teaching them how to sort truth from fiction is an increasingly urgent educational need. On page 34, author Melinda Wenner Moyer explores how education experts are struggling to design and evaluate the best techniques for teaching students this defense against the dark arts.

Bringing any new drug to market is an arduous process, and it is especially so for agents that are classified as dangerous addictive substances. Neurology professor Jennifer M. Mitchell, on page 56, shares how scientists, regulators, physicians and patient volunteers have demonstrated that MDMA, also known as Ecstasy, can be used safely to treat mental health problems.

Real Neandertals were a lot more sophisticated than pop culture Neandertals. Anthropologist David W. Frayer and museum curator Davorka Radovčić, on page 50, detail how Neandertal artifacts and sites show evidence of symbolic thinking and sophisticated behaviors that developed independently of modern humans.

One of the many reasons it's so important for as many people as possible to get vaccinated is that by slowing the circulation of infectious disease, vaccines protect people with compromised immune systems. Many people who have immune system diseases or organ transplants or who are in treatment for cancer have not responded robustly to COVID vaccines, as health and medicine senior editor Tanya Lewis explains on page 62. Fortunately, boosters and new approaches may help them.

People who jump to conclusions, as researchers Carmen Sanchez and David Dunning discuss on page 68, are also likely to make bad bets, endorse conspiracy theories and be overconfident (and misguided) in their judgments.

We're proud to share that *Scientific American* won two big journalism awards from the American Geophysical Union, the largest organization of Earth and space scientists in the world. Freelancer Jonathan O'Callaghan won the Excellence in Science Journalism—Features award for his "The Curious Science of Chondrules," in the March 2021 issue, about dust from asteroid Ryugu brought back to Earth by Japan's Hayabusa2 mission. Senior sustainability editor Mark Fischetti, who has been with *Scientific American* for more than 15 years, won the most prestigious award, for Sustained Achievement in Science Journalism. The awards committee observed that Mark has a "sixth 'science sense' that appears to lead him to important scientific work well ahead of other journalists."

We're honored to publish Mark and Jonny in our pages, along with other excellent journalists who devote their careers to finding urgent, insightful, fascinating stories to share with us all. SA

Illustration by Nick Higgins


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We're on the Ground in Wide Sky Country
We deliver skilled health care providers, relevant research and crucial services to some of the most remote places in America.
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• Center for Disabilities advances independence for people with disabilities living in rural locations or on tribal reservations.
The landscape here is vast.
The challenges are immense.
Every person is deserving.
usd.edu

October 2021

MUON MATTERS

In "The Unseen Universe," Marcela Carena describes apparent discrepancies between the observed behavior of muons—one of the three types of charged leptons—and calculations based on the Standard Model of particle physics. If the discrepancies for muons are real, I would also expect discrepancies for tau leptons.

VAN SNYDER *La Crescenta, Calif.*

As a shade-tree quantum mechanic, I wonder if the vibrations of muons are the effect of waves of gravity—the crests and troughs of the waves.

JIM JAKUBCIN *via e-mail*

In her article, Carena states, "Starlight is the result of the electromagnetic force acting between the charged protons and electrons, liberating light energy at the hot surface of the star. The heat source of these stars, including our sun, is the strong force, which acts on the protons and neutrons to produce nuclear fusion."

I wonder what heat is. Are heat and heat energy the same? Is the gluon the source of the heat of nuclear fusion? I also wonder what light is. Are light and light energy the same? Is light a photon traveling through space?

HIROYUKI UCHIDA *Tokyo*

CARENA REPLIES: Snyder brings up a very good question. Indeed, the simplest explanation for the results of the Muon g-2 experiment introduces a new force that affects both muons and tau leptons but not electrons (the third type of charged lepton). This is because the rules of quantum mechanics are not consistent with the simplest kind of new force unless that force affects at least one other kind of particle besides the muon. Several other explanations for the Muon g-2 results also involve tau leptons, so it is important to think about how we might see something in an experiment with these particles. Tau leptons are much more unstable than muons and harder to produce in the first place, but one could imagine building a particle accelerator optimized for producing them—a "tau factory"—in the future.

A shade-tree quantum mechanic sounds like a very nice occupation! We think the effects of gravitational waves are too weak to be relevant to the Muon g-2 experiment, but what Jakubcin suggests is not far away from what string theorists are trying to do. They claim that everything we see is the result of vibrating strings, such that gravity is one kind of vibration, whereas the effects we see with muons are other kinds. If such a unified picture turns out to be correct, it might ultimately be the explanation for why there should be new exotic particles or forces affecting Muon g-2.

Uchida asks questions that deserve long answers, but here is a short summary: When we say "heat," we almost always mean the kinetic energy of particles, which could be atoms, molecules or a plasma of charged elementary particles. Kinetic energy just means that the particles are rapidly moving. Charged particles (such as electrons) can emit photons, which are particles of light. This is a way to convert energy in the form of heat into energy in the form of light, as occurs in an old-fashioned lightbulb or at the surface of the sun.

Heat in our sun originally arose from gravity, which, billions of years ago, caused the gas that the sun is made of to collapse into a giant hot ball. Once this hot ball formed, however, the sun began to produce heat from a process called nuclear fusion.

In the first step of this fusion process, two protons inside the sun fuse into a deuteron while giving off a neutrino and a positron—the antiparticle of the electron. Then the deuteron captures another proton to form a helium isotope and emits a gamma-ray photon. The deuteron is a bound state of a proton and a neutron, and the binding comes from the strong force, which is carried by gluons. So indeed, fusion energy production in the sun requires gluons.

In addition, because one of the two protons must be converted to a neutron, the process requires a W *boson, the carrier of what we call the weak force. It is actually a good thing for us that the weak force is weak because this is why the first step of fusion in the sun proceeds very slowly—meaning our home star will shine steadily for billions of years instead of exploding in a much shorter time.*

AGE AND FALLING RISKS

"When Health Takes a Tumble," by Claudia Wallis [The Science of Health], discusses a recent increase in dangerous falls among the elderly. As a 78-year-old retired physician, I think that perhaps one of the causes of these falls is the gradual diminution of proprioception—at least it is in my case. My balance is good (I walk on uneven, rocky ground every day), and my strength, though certainly decreased, is still adequate. But I have noticed my proprioception is off by just a bit, which is enough to cause problems. I drop items because my grip is not quite tight enough and stub my toe on thresholds and throw rugs. I also tend to bang plates and cups when placing items on the counter.

> "Perhaps one of the causes of falls among the elderly is the gradual diminution of proprioception."
>
> PATRICK LAUGHLIN *VIA E-MAIL*

PATRICK LAUGHLIN *via e-mail*

WALLIS REPLIES: Research confirms that proprioception—the sense of where one's body is in space—does decline with age, as

do other senses. It also suggests that appropriate physical activity can slow this decline—just another way that well-targeted exercise can reduce the risk of falling.

FEEDING FUTURE POPULATIONS

"More Food, Less Waste," by Chad Frischmann and Mamta Mehra, started out with a major punch: given the current rate of population growth and economic development, by 2050 an area at least equivalent to India would have to be added to our global food production systems to meet expected needs. The article describes potential improvements to the efficiency of food use, mainly by reduction of waste, to tackle that issue, and they seem to be well worth attempting to achieve. But what about addressing the rise in food demand by trying to lower or reverse human population growth?

Whereas more efficient food usage makes sense for a variety of reasons, it might target the symptom rather than the cause. Perhaps *Scientific American* could present us with another article on how much food demand, as well as many other environmental problems, might be reduced if people across the globe adopted practices that would move total human population downward.

Scott T. Meissner *via e-mail*

SCI-FI HISTORY

Gabrielle Bellot's review of *Black Sci-Fi Short Stories* in "Exploring Black Sci-Fi" [Recommended; July] reminds me that about the time my first fantasy novel appeared with Warner Books, my editor, Betsy Mitchell, oversaw the publication of *Dark Matter: A Century of Speculative Fiction from the African Diaspora* (Warner Books, 2000). The anthology, which won a 2001 World Fantasy Award, was edited by Sheree R. Thomas. I was lucky enough to get a copy signed by Thomas, which she kindly addressed to my son.

James Stoddard *via e-mail*

ERRATUM

In "Infinite Math," by Emily Riehl, the arrows in the illustration "Compositions Are Associate and Unital" are incorrect. The arrow $g \circ f$ should point from A to C, and the arrow h should point from C to D.

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NOT ALL PATIENTS WITH DIABETES ARE TREATED EQUALLY

For those living with type 2 diabetes, care and health outcomes can vary widely between racial, ethnic and economic groups. What can be done to reduce these disparities?

Across the US, those living with type 2 diabetes regularly face obstacles to care. Perhaps they can't afford treatment and have to choose between rent and diabetes medications. Perhaps they can't understand their doctor's instructions because they don't speak the same language or are hard of hearing. Or perhaps their doctor's instructions run counter to cultural beliefs or norms.

"These are just a few of the challenges facing patients," says Michelle Litchman, a Researcher and Medical Director of the Intensive Diabetes Education and Support Program at the Utah Diabetes and Endocrinology Center. Litchman investigates real-world management of diabetes and other chronic diseases.

"We see that [people] want to take care of themselves," she says, but they often have to choose between care and say, cost or stigma or taking time from work. Opting out of care only worsens diabetes and can heighten the risk of cardiovascular disease (CVD), which is already the leading cause of death for those living with type 2 diabetes.

An estimated 34.1 million adults in the U.S. have diabetes, according to the US Centers for Disease Control and Prevention, and between 90 and 95 percent of them have type 2 diabetes. That is about 13 percent of the 18+ population. The figure doubles to 26 percent when looking at populations of 65 and older.

Higher still is the incidence of type 2 diabetes among minority and economically disadvantaged populations, when compared with non-Hispanic white people or the wealthy. Deaths from CVD among type 2 diabetes patients within those communities can be up to seven times greater than wealthier ones.

Such inequities have been studied for decades, and it's clear that addressing them will relieve suffering and prolong life for those living with type 2 diabetes. The question is how best to do so.

Discussing disparities

In October, *Scientific American*'s Custom Media division hosted a virtual event to examine disparities in care and outcomes among those living with type 2 diabetes. It was part of a series supported by Know Diabetes by Heart, a joint initiative of the American Heart Association and the American Diabetes Association.

Three experts took to the virtual stage: Michelle Litchman; Dr. K.M. Venkat Narayan, the Ruth and O.C. Hubert Chair of Global Health and Director of the Global Diabetes Research Center at Emory University; and Dr. Enrique Caballero, Faculty Director of International Innovation Programs at Harvard Medical School.

At the event, the panelists explored ways to reverse the compound threats that certain demographics face from diabetes and heart disease. They examined bias in diagnosis and treatment; genetic, cultural and sociological risk factors; and they outlined ways that health care providers can better meet the needs of patients who have faced discrimination or exclusion.

Not-so-simple communication

As comprehensive as the U.S. health care system is, type 2 diabetes patients regularly encounter gaps or obstacles

"WE KNOW THAT REFERRALS TO DIABETES CARE AND EDUCATION SPECIALISTS DIFFER BASED ON RACE AND ETHNICITY."
—Michelle Litchman

CREDIT: MICHAEL GIBBS

that can derail care. "We know that referrals to diabetes care and education specialists differ based on race and ethnicity," Litchman said at the event. That heavily impacts patients' abilities to manage their health. Data show that minority populations are also less likely to be prescribed – or get – necessary follow-up testing.

With better communication, patients' conditions can improve. Caballero highlighted a successful program instituted by the Kaiser Permanent group, in California, that paired Spanish-speaking patients and doctors. Medically-trained interpreters can also help.

But not enough interpreters or multilingual health care providers exist to meet demand. Caballero emphasized the need for medical educators to actively recruit minorities. But he also called clinicians to account. "I think that every health care professional should embrace the need to communicate better and understand the culture of our patients," he said.

The deaf and hearing impaired, who have higher rates of diabetes and cardiovascular disease than others in the same age bracket, also need special consideration, often in the form of online resources.

Systemic inequities

Caballero noted that society is quick to blame patients for not taking good care of themselves or ignoring medical recommendations. He places significant responsibility on the health care system, noting that "even if people have access to health care, the quality of care that is provided to underserved communities is much lower than what is provided to the white population."

A large, inclusive study by the US National Institutes of Health revealed that with equitable care, everyone benefited regardless of age, ethnicity, race or gender. "That should take away the myth that it is the patient's fault," Narayan added. "It really is the system's fault."

The panelists expressed concern about bias, both conscious and unconscious, among doctors and those in the health care system. While pervasive, they said, it was clearly evident in U.S. clinical research. Historically, most studies and clinical trials have been heavily weighted toward white, male populations, leaving minorities, women, and other underrepresented groups unaccounted for.

Diabetes is a complex disease, with genetic and lifestyle underpinnings and such racial and ethnic disparities in research, and can blind caregivers to potential issues. For example, Narayan noted, there seems to be greater insulin resistance among Hispanic, African American, and South Asian communities, and up to 60 percent of some Native American and Alaska Native communities may have diabetes. Asian Americans may develop both diabetes risk and cardiovascular disease at a far lower body mass index than other groups. Without such groups accounted for in clinical research and trials, doctors and patients are at a disadvantage.

The way forward

While addressing disparities among type 2 diabetes patients is complex, every panelist stressed that it is also feasible. More equitable research and clinical trials along with greater access to interpreters and translated information are good steps, but the panelists had a number of others.

Since there is sometimes mistrust towards health care professionals, Litchman emphasized the important role that community health workers play in facilitating successful treatment. They can see patients at home or in the neighborhood; explain doctors' recommendations; offer healthy, culturally appropriate recipes; and coach patients as they adopt a healthier lifestyle and control their blood glucose.

She also noted that the vast expansion of telehealth, sparked by the COVID-19 pandemic, has greatly expanded access to care. It has allowed health care providers to communicate with patients in their homes via cell phone, virtual appointments and text messaging. The key is to make these resources accessible to all.

Caballero urged health care providers to include social and cultural considerations in their clinical practices. "Think about transportation, housing, financial challenges, safety in [patients'] neighborhoods, availability of foods and where people are going to be able to implement your recommendations," he said.

Perhaps most importantly, Lichtman said, providers need to acknowledge that disparities exist. With increased awareness, "We need to move into action," she said, to improve diagnosis, testing, referrals, treatment, research and patient education. "Every patient that comes to the door has unique needs. We need to address them on a case-by-case basis."

For information and tools to manage type 2 diabetes and heart disease, visit KnowDiabetesByHeart.org.

THE EXPERTS WEIGH IN

- **Michelle Litchman**, *Researcher and Medical Director of the Intensive Diabetes Education and Support Program at the Utah Diabetes and Endocrinology Center.*
- **Venkat Narayan,** *the Ruth and O.C. Hubert Chair of Global Health and Director of the Global Diabetes Research Center at Emory University*
- **Enrique Caballero,** *Faculty Director of International Innovation Programs at Harvard Medical School*

"THAT SHOULD TAKE AWAY THE MYTH THAT IT IS THE PATIENT'S FAULT, IT REALLY IS THE SYSTEM'S FAULT."
—Venkat Narayan

"EVEN IF PEOPLE HAVE ACCESS TO HEALTH CARE, THE QUALITY OF CARE THAT IS PROVIDED TO UNDERSERVED COMMUNITIES IS MUCH LOWER THAN WHAT IT IS PROVIDED TO THE WHITE POPULATION"
—Enrique Caballero

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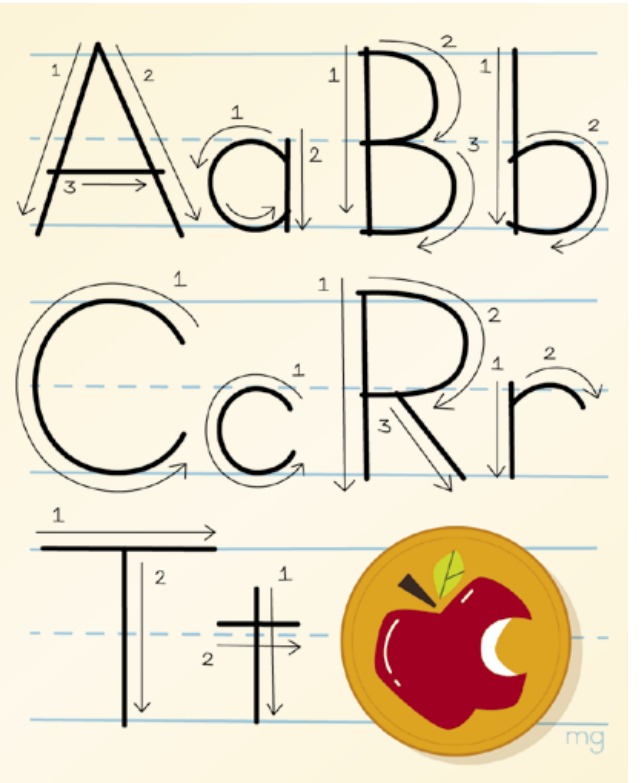
American History Should Teach Reality

Lessons about racism are essential to a fact-based education

By the Editors



Elected officials who campaigned against critical race theory (CRT), the study of how social structures perpetuate racial inequality and injustice, are being sworn into office all over the U.S. These candidates captured voters' attention by vilifying CRT, which has become a catch-all to describe any teaching about racial injustice. Lessons about the genocide of Native Americans, slavery, segregation and systemic racism would harm children, these candidates argued. Calling its inclusion divisive, some states have enacted legislation banning CRT from school curricula altogether.

This regressive agenda threatens children's education by propagating a falsified view of reality in which American history and culture are outcomes of white virtue. It is part of a larger program of avoiding any truths that make some people uncomfortable, which sometimes allows in active disinformation, such as creationism. Children are especially susceptible to misinformation, as Melinda Wenner Moyer writes in "Schooled in Lies," on page 34.

It is crucial for young people to learn about equity and social justice so they can thrive in our increasingly global, multilingual and multicultural society. When students become aware of the structural origins of inequality, they better understand the foundations of American society. They are also better equipped to comprehend, interpret and integrate into their worldviews the science they learn in their classrooms and experience in their lives.

Pondering racial, ethnic and socioeconomic disparities helps students understand, for example, why COVID death rates among Black, Latino and Native American people were much higher than those of white people as the pandemic began. They can better comprehend why people of color are far more likely to be subjected to the ravages of pollution and climate change or how a legacy of U.S. science that experimented on Black and Indigenous Americans may have led to distrust of doctors and health care.

Removing conversations around race and society removes truth and reality from education. This political interference is nothing new—political and cultural ideologues have fought for years to remove subjects such as evolution, Earth history and sex education from classrooms and textbooks, despite the evidence that sex ed helps to prevent unwanted pregnancy and sexually transmitted diseases, that evolution explains all life on Earth and that the world is older than a few thousand years.

Many of the school districts that brought in anti-CRT board members are the same ones that refuse to mandate masks, despite the evidence that masks can prevent the spread of COVID. These school officials also rail against vaccine mandates as a violation of personal choice. It is the same prioritization of individuals over community and a discomfort with hard truths that characterize the movement against the teaching of true history.

Fortunately, efforts to limit children's education face stark opposition. The American Civil Liberties Union describes initiatives to quash discussions of racism in classrooms as "anathema to free speech." And the U.S. Department of Education is debating a series of American History and Civics standards that include introducing "racially, ethnically, culturally, and linguistically diverse perspectives into teaching and learning." Caught in the middle are teachers who are trying to educate children during a pandemic.

While many parents of school-aged children supported anti-CRT campaigns, voters with no connection to the classroom helped significantly to tip these elections. Parents and educators must bring the conversation back to teaching children about reality. EdAllies, a Minnesota-based educational-support nonprofit, is encouraging teachers to reach out to parents and administrators to explain the necessity of antiracist content in their lessons, as a way to build community support.

All over the U.S., school board meetings are being taken over by fear of the inclusion bogeyman. And after our recent elections, more board members have the power to act against lessons they dislike. Today, tomorrow and for as long as these elected officials are in office, it is the children and the teachers who will pay the price for an incomplete education. We must work toward a school experience that includes narratives of discrimination, social justice and inequality as truths we can learn from so that history might not repeat itself. SA

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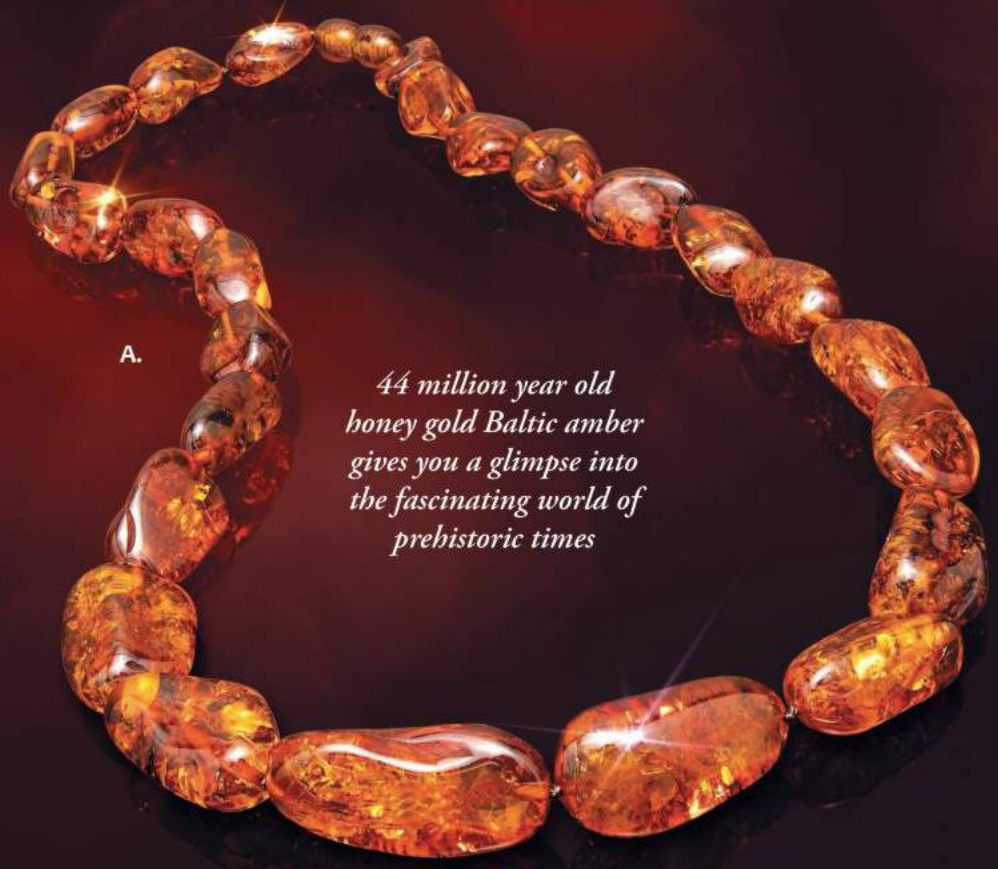
Illustration by Martin Gee



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Kyle Wiens is a right-to-repair advocate and CEO of iFixit, a free repair-manual Web site. He has dedicated his life to defeating the second law of thermodynamics.

Freedom to Tinker

The U.S. Congress needs to uphold the right to repair electronic devices

By Kyle Wiens

My trusty Xbox is out of warranty. Although it has been a real workhorse for many years, all that swapping of discs is eventually going to kill its optical drive. I'm a fixer, and if the disc drive failed in a different kind of product, I could easily repair it by installing a new part. But this particular fix is beyond hard—it is illegal. Or at least it was until late last year.

Fighting for the right to fix such problems has taken me down a decade-long rabbit hole of work on federal policy, including an obscure section of U.S. copyright law, Section 1201. It blocks the breaking of digital locks used to guard access to devices' software. Cell phones, for example, are locked to the mobile carrier from which they were purchased, so if owners want to switch carriers, they first need to remove the baseband lock. But any product with a microcontroller has software, and such locks protect that software in everything from coffee machines to game consoles.

Unlocking Section 1201 is an essential part of the broader right-to-repair movement, which aims to combat the measures that make it difficult or impossible to improve or fix electronics. Limiting the ability to repair a broken device destroys independent repair shops and encourages consumers to dispose of a machine instead of fixing it. This is bad for device owners, and it contributes to the rising tide of electronic waste around the world.

The proposed solution is simple: create an ecosystem of professional and do-it-yourself fixers by removing the obstacles to repair that many manufacturers have built into their products. With the iPhone 13, for instance, a digital lock pairs the screen to the device, and replacing a cracked screen will disable the critical Face ID feature. (Responding to criticism, Apple announced last November that it will make software and spare parts for repairing its products available to U.S. consumers sometime this year.) Similarly, John Deere refuses to provide farmers with the software they need to work on the electronics embedded in their equipment. Sony and Microsoft likewise withhold access to the tools required to repair new optical drives in game consoles.

In 2021 public demand induced at least 27 U.S. states to propose legislation for enabling repairs. These laws would require manufacturers to open up access to proprietary tools and parts and make service information and schematics available to consumers. States cannot fix copyright law, however: giving my Xbox a tune-up will have to be legalized at the federal level.

When Congress passed Section 1201 as part of the Digital Millennium Copyright Act in 1998, its intent was to prevent DVD piracy. Legislators wrote the text quite broadly. As a result, anything with software and a digital lock falls under Section 1201—and any

repairs that require the breaking of a digital lock are illegal. But there is an escape hatch: every three years you can petition for the right to break certain kinds of locks.

Last year a coalition that included iFixit, an online repair community that I co-founded, asked the U.S. Copyright Office to make fixing things by bypassing software locks legal. Hedging our bets, we also asked for a more specific exemption: working around antipiracy schemes when replacing the disc drives on video game consoles such as Xboxes and PlayStations. Thanks to these efforts, since October 28 it has been legal to break locks for the purposes of "diagnosis, maintenance, and repair" on any "software-enabled device that is primarily designed for use by consumers," as well as on vehicles, marine vessels and medical devices.

This is a big win. But the new exemptions do not cover "modifications"—such as, say, changing the settings on your cat's smart litter box—or nonconsumer devices such as laboratory equipment. And there is an even bigger catch: they do not allow the distribution of repair tools that circumvent manufacturers' digital locks. According to Section 1201, the Copyright Office lacks the authority to grant permission to sell or distribute the necessary software. Without easy access to these tools, the new rules have no teeth. For example, if you want to repair your Xbox legally, you will have to whittle your own set of digital picklocks from scratch. That just does not scale—most gamers are not security engineers.

Clearly, the system is broken. It is time for Congress to step in and permanently exempt repair, and especially repair tools, from Section 1201. I hope they get it done before my Xbox needs a fix. SA

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Illustration by Jacob Stead

ADVANCES

Islands, by area

5 hectares
77 islands

10 hectares
165 islands

Black squares compare island areas.

100 hectares
55 islands

1,000 hectares
22 islands

10,000 hectares
7 islands

100,000 hectares
1 island

Islands with extant pests (93)

Each line represents one island. Gray means no data are available.

For each island, dots tally the status of each pest species.

Black rings mark failed eradication attempts.

Empty circles mark where a species was removed.

TARGET SPECIES

Norway rats
Native to China, Norway rats are ground hunters that can swim up to a mile between islands.

Ship rats (black rats)
Smaller than Norway rats, ship rats hunt both on the ground and in treetops, but they're not as strong swimmers.

Polynesian rats
Also called kiore, these small rats served as a food source for Polynesian explorers.

Stoats
Members of the weasel family, stoats are agile hunters. They're also strong swimmers, making island reinvasion a concern.

Australian possums
Brushtail possums were introduced from Australia in 1837 because they were (and remain) a source of fur. But they also eat bird eggs.

MAINLAND EFFORTS

Ground-based poisons
Cereals laden with vertebrate pesticides, distributed by hand.

Aerial poisons
Pesticides released from buckets underneath helicopters.

Traps
Baited boxes with kill mechanisms that dispatch pests.

Fenced areas
Cleared zones with barriers to prevent pest reentry.

The Ambitious Kiwi Quest

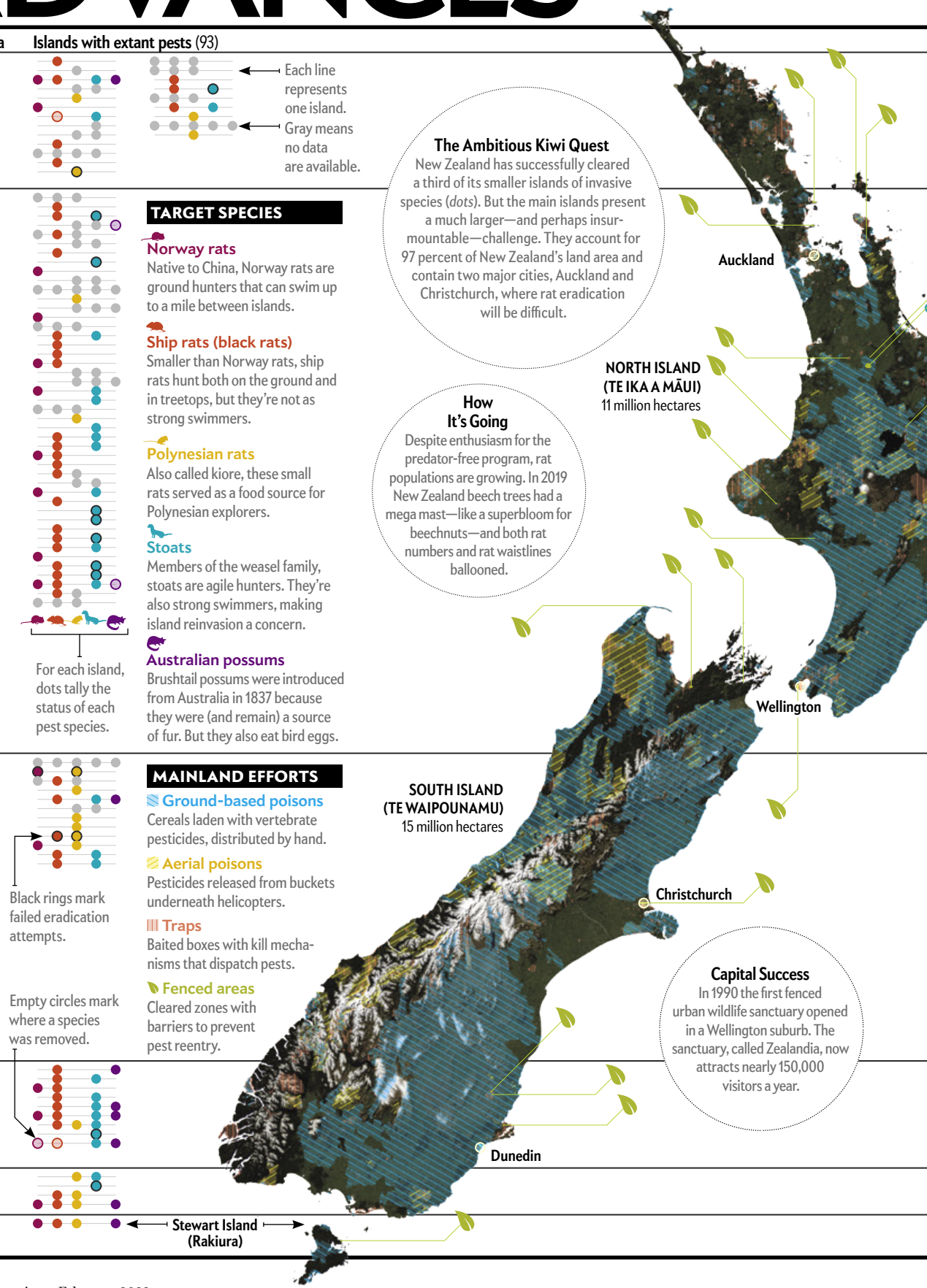
New Zealand has successfully cleared a third of its smaller islands of invasive species (*dots*). But the main islands present a much larger—and perhaps insurmountable—challenge. They account for 97 percent of New Zealand's land area and contain two major cities, Auckland and Christchurch, where rat eradication will be difficult.

How It's Going

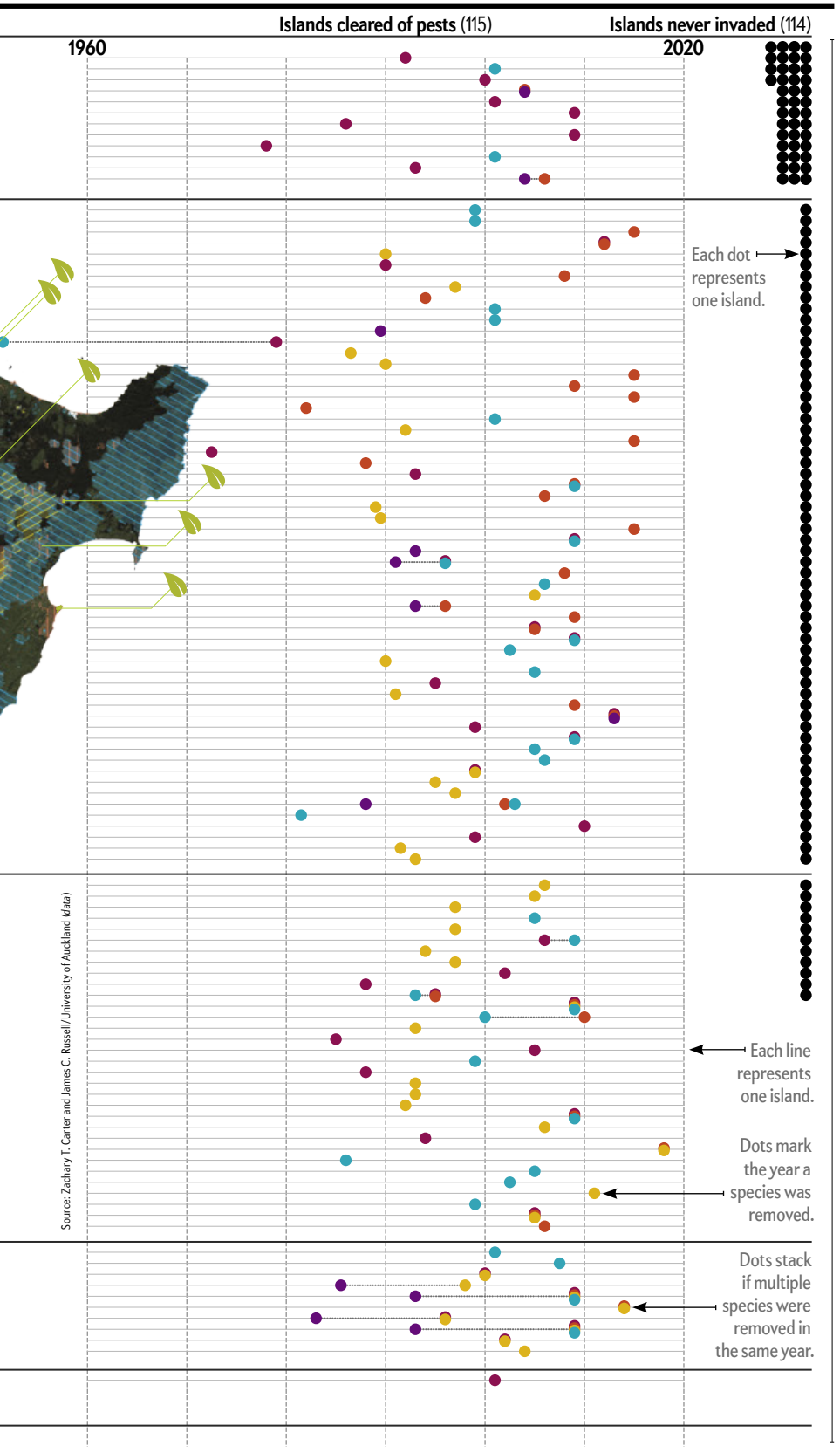
Despite enthusiasm for the predator-free program, rat populations are growing. In 2019 New Zealand beech trees had a mega mast—like a superbloom for beechnuts—and both rat numbers and rat waistlines ballooned.

Capital Success

In 1990 the first fenced urban wildlife sanctuary opened in a Wellington suburb. The sanctuary, called Zealandia, now attracts nearly 150,000 visitors a year.



Graphic by Katie Peek



INSIDE

CONSERVATION

Taking Back Nature

New Zealand's audacious antipredator drive gains ground

A thousand years ago the islands that today form New Zealand were riotously wild. Birds, reptiles and invertebrates flourished in lush forests hundreds of miles from any other landmass. Māori settlers in the 1200s brought Polynesian rats for food, and together the humans and the rodents began to shift the ecological balance. Native species started to go extinct.

Enter European ships, bearing new carnivores: more aggressive rat species, plus mice, stoats, and others. These ground-based predators hunted differently from the falcons and other aerial threats New Zealand wildlife had evolved with. Native birds that slept in burrows made easy prey for prowling mammals. Invasive predator populations exploded, devastating native wildlife.

But in the past 60 years humans have intervened to help old New Zealand ecosystems claw their way back. First, a single five-acre (two-hectare) islet called Maria Island (Ruapuke in Māori) was declared rat-free by ecologists in 1964, five years after volunteers set poisoned bait. It was a special case. The white-faced storm petrels at risk there were especially charismatic—they appear to walk on water—and easily gained public support. The ample baiting effort also got particularly lucky with its placement, ecologists say. Nevertheless, the serendipitous success kicked off decades of eradication efforts.

Since then, New Zealand ecologists have cleared island after island of invasive pests. About two thirds of the country's smaller islands are now pest-free, as are 27 fenced forest fragments on the main islands (which

make up 97 percent of New Zealand's land area). Native life surrounded by fence or sea is rebounding. And in 2016 the prime minister announced a first-of-its-kind nationwide goal: Predator-Free 2050.

The initiative aims to remove rats, stoats and possums from all New Zealand's 600-plus islands by that year. "Those three animal predators are basically just eating our native wildlife out from under us," says program director Brent Beaven.

Killing stoats and possums might startle some nature lovers, but University of Auckland ecologist James Russell describes the situation as an ecological trolley problem: "If we choose not to kill the mammals," he says, "we're essentially choosing to let the birds die."

Russell describes the initiative as a broad social movement. "It's not something that the government proposed," he says. "The government adopted something for which there was a groundswell already." In Predator-Free 2050, the government coordinates actions by universities, nonprofits, wildlife sanctuaries, habitat-rehabilitation programs, and people with traps in their backyards. These groups are removing the predators while developing better-targeted poisons, restoring native plant life, reintroducing native species and inventing new ways to keep predators out.

Predator-Free 2050 also relies on Māori tribes, says Tame Malcom, who works for the environmental nonprofit group Te Tira Whakamātaki: they have been trapping rats for centuries, and Māori partnership has increased the program's effectiveness and reduced costs. "Our language is proving almost vital to ecological restoration efforts," Malcolm adds, "because the names of places give a clue about what the place used to be like." The location name Paekākā, for example, comes from "horizon" and a type of parrot, indicating the place was once rich with that species.

For everyone focused on eradication, the basic blueprint is the same: choose an island or sanctuary, intensively kill invasive animals, then monitor to make sure they stay away. But reality, of course, is more complex. Massey University conservation biologist Doug Armstrong, who heads the Oceania section of the International Union for Conservation of Nature's reintroduction specialist group, notes that not all native species take off quickly once an area has been cleared. Learning and catering to struggling species' habitat needs will take time. And with their competition so helpfully removed, mice can balloon in number as they feast on native lizards and frogs.

Then there is cost. "Our standard eradication practices at the moment are $600 to $1,000 [NZD] a hectare, and we just can't sustain that as a country," Beaven says. Program leaders hope technology will help. Last year biologists finished sequencing all target species' genomes, which could lead to targeted baits or gene-editing approaches akin to recent mosquito-control projects elsewhere. (New Zealanders, many of whom worked to ban genetically modified organisms in the early 2000s, are still debating whether to pursue gene editing.) Engineers are developing traps that identify species by their footsteps, and researchers are building drones to distribute bait and monitor large areas for reinfestation. The country's innovations are already rippling outward: Armstrong says the bulk of international invasive species eradication efforts have New Zealanders somewhere at the helm.

But as researchers tackle the challenges of clearing invasive predators from an entire country, some ecologists question the initiative's premise, even for somewhere as geographically isolated as New Zealand. Wayne Linklater, an environmental scientist at Sacramento State University, suggests fully removing invasive predators is unattainable. Instead he advocates for mitigation, such as protected breeding zones or a network of sanctuaries to conserve threatened species more effectively. Such tactics have met with success in Australia and South Africa.

Beaven, however, sees those approaches as stopgaps requiring constant human involvement. Eradication, he says, lets native flora and fauna truly thrive. That's what program fieldworker Scott Sambell would like to see. A few times a year Sambell uses a rat-sniffing dog to monitor islands that have previously been cleared. His circuit includes some places that, like Maria Island/Ruapuke, have been pest-free for five decades. "You get into these areas, and you feel like a stranger," he says. "This is the birds' domain. And it's *awesome*." —*Katie Peek*

ANIMAL BEHAVIOR

Shark Feels

Fish species around the world deliberately rub against sharks

Lacey Williams was using a drone to follow a great white shark in South Africa's Plettenberg Bay when a school of leerfish began actively pursuing the predator—and then started rubbing their bodies against its tail as though it were an exfoliating pumice stone. "We were just really gobsmacked," says Williams, a marine biology graduate student at the University of Miami.

Numerous past studies have confirmed that a whole host of marine organisms, including sharks themselves, chafe on sand and rocks—presumably to remove parasites and bacteria. But even though there were anecdotal reports of other fish chafing on sharks' sandpapery skin, no one had ever undertaken a formal study of the behavior.

Williams and fellow graduate student Alexandra Anstett compiled all the records they could uncover of such chafing—including drone footage, photographs, diver video feeds and anecdotal reports. They found 47 incidents involving eight different shark species being chafed by 12 species of fish and one species of shark (the last being silky sharks seen rubbing against a whale shark). These examples spanned 13 locations in three

OPTICS

Out of Sight

Holographic camera tech can reconstruct hidden objects

A new imaging technique might one day help physicians peer into human tissue and behind bones, let mechanics inspect moving machinery such as airplane turbines for tiny defects, or enable automated vehicles to see through dense fog or around blind corners. A study detailed in *Nature Communications* shows how the process, called synthetic wavelength holography, can capture detailed and nearly instant snapshots of objects hidden from view.

Light scatters when it bounces around a corner or travels through a cloudy material, says Atul Ingle, an electrical engineer at Portland State University who was not involved in the study. To see what lies on the

oceans, from Massachusetts to Mexico to the Galápagos. The findings, published in *Ecology*, show that fish-on-shark chafing is more pervasive and widespread than previously recognized. "It must serve some ecological function to have evolved across so many species," Williams says.

The duration of the chafing events ranged from a fleeting eight seconds to more than five minutes. Sometimes a lone fish was involved; at other times, an entire school of 100 or more individuals took part. Many sharks seemed not to care that they were being used as a living back scratcher, but some of the great white sharks contorted, wiggled their bodies or did corkscrew dives, seemingly trying to shake the other fish off. To the researchers' surprise, sharks were not observed trying to eat the fish.

Jonathan Balcombe, an independent animal behavior biologist and author of *What a Fish Knows*, says chafing "is consistent with the awareness, intelligence and opportunism of fishes as shown by a growing body of research on their cognitive and emotional capacities." It is possible the fish simply enjoy the sensation of rubbing against sharks' rough skin, adds Balcombe, who was not involved in the study. There is "both anecdotal and scientific support for a therapeutic role of touch in relieving stress in fishes and other taxa."

The authors acknowledge that the study raises more questions than it answers—including whether sharks get any benefit or are harmed from chafing and why fish specifically choose sharks to rub against rather than sticking with inert (and seemingly much safer) rocks or sand. After all, Anstett says, "you don't see a lion's prey scratching up against a lion." —*Rachel Nuwer*

other side of such obstacles, he says, "you need to undo the scattering and resolve the [hidden] structures with very high resolution." The technique overcomes those challenges at frame rates fast enough for video, Ingle adds.

The process involves firing laser beams with slightly different wavelengths past obstructions—be it off a wall or through some translucent material—to strike a hidden target. The wavelengths that reflect back are captured and superimposed to produce an interference pattern that reveals the distances of objects hidden from direct view. This process draws from a technique called interferometry, which scientists have used to precisely measure the size and shape of stars and cell structures. Other forms of "non-line-of-sight" imaging struggle with simultaneous speed, high resolution and broad field of view. "Our method combines all these attributes at the same time in one method," says Northwestern University physicist Florian Willomitzer, lead author on the new study.

Willomitzer and his colleagues demonstrated that they could capture images of millimeter-sized letters beyond corners as well as through hazy plastic plates. Whereas previous imaging methods iteratively scanned thousands of pixels to compose a scene, this process required only two exposures (each taking just 23 milliseconds to capture) to scan a near-hemispherical field of view.

Combining this technique with ultrasound imaging could eventually let doctors see around bones or view tiny blood vessels under skin, Ingle suggests. Both researchers say, however, that more work and testing are needed to turn that vision into reality. Probing a slab of living tissue is harder than peering through thin plastic—but in 10 or more years, Ingle says, this research could yield a practical, commercially available way to look beyond the line of sight. —*Nikk Ogasa*

Illustration by Scott Brundage

BIOLOGY

Polar Night Light

Even without the sun, Arctic crustaceans follow a day-and-night rhythm

During Arctic winter, the sun disappears below the horizon for long weeks of "polar night." But new research shows that tiny crustaceans in the Arctic Ocean somehow maintain their daily rhythms during these extended periods of darkness.

Most living creatures use sunlight to time their biological processes and behaviors. This becomes a challenge when there is effectively no sunrise or sunset—and even more so under the sea, where water dims what little light there is. But small, shrimplike animals known as Arctic krill, an important food source for many aquatic species, have developed a crafty adaptation to maintain their habits during the polar night. Even underwater they can detect extremely subtle changes in light from the sky as the sun shifts position below the horizon, researchers report in *PLOS Biology*.

"Biological clocks are how our bodies anticipate what's going to happen next, like how we know to start getting hungry around lunchtime," says University of Delaware marine biologist Jonathan Cohen, lead author on the new study. Krill behavior shows that the polar night has enough light to keep this biological timer ticking in some creatures.

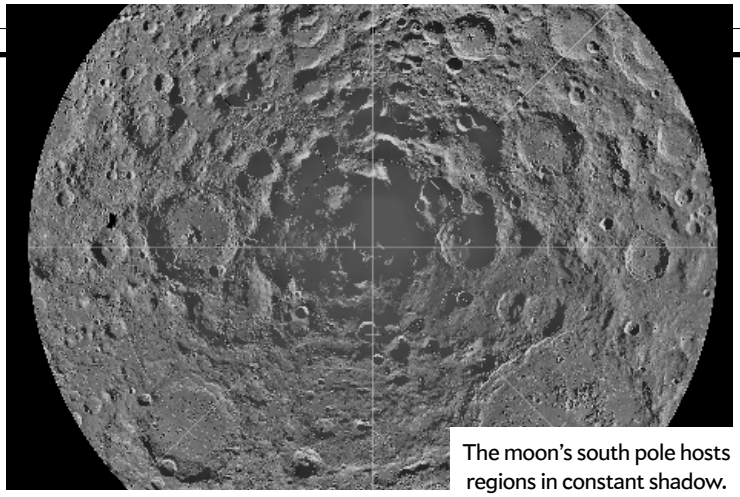
Arctic krill

Jonathan Cohen

Cohen and his colleagues studied the krill species *Thysanoessa inermis* in the laboratory and in its natural Arctic Ocean habitats off the Svalbard archipelago. They found not only that krill could detect minimal shifts in very scant light but that the electrical activity in their eyes heightened at night, suggesting increased light sensitivity. Moreover, the crustaceans were using the faint light variations to coordinate their movements through the water column, gliding to the surface to search for food in the darkest times and retreating to the depths during the "brighter" hours to evade predators. So far scientists know of only a few other animals, including flies and mice, that can tune biological clocks with such low levels of light, Cohen says.

The researchers are still unsure why krill continue swimming up and down during the very darkest nights. "If there's no light, there's no primary production and algal blooms—so there's nothing for them to eat," says Emma Cavan, a marine biologist at Imperial College London who was not involved in the study. "So why are they moving to the surface? It's one of the big mysteries of vertical migrations."

—Daniela Mocker and Nikk Ogasa



The moon's south pole hosts regions in constant shadow.

NASA/JPL/USGS

TECH

Lunar Shadowlands

New algorithm illuminates the moon's murky polar regions

Certain areas near the moon's poles linger perpetually in shadow, never receiving direct sunlight. Recent studies suggest these so-called permanently shadowed regions (PSRs) contain rich ice reservoirs that could reveal details about the early solar system; they could also help future visitors make fuel and other resources. But these areas are hard to photograph from satellites orbiting the moon and thus are a challenge to study. The few photons PSRs do reflect are often overwhelmed by staticlike camera noise and quantum effects.

Now researchers have produced a deep-learning algorithm to cut through the interference and see these dark zones. "Our images enable scientists to identify geologic features, such as craters and boulders … as small as three meters across for the first time—a five- to 10-fold increase in resolution compared to previous efforts," says Valentin Bickel, a planetary scientist at the Max Planck Institute of Solar System Research in Germany and lead author of a *Nature Communications* study testing the new algorithm.

The researchers used more than 70,000 images of completely dark lunar areas—with no light signal—paired with details about the camera's temperature and position in orbit to train their algorithm to recognize and filter out camera noise. Next they tackled residual noise, such as quantum effects on traveling photons; this algorithm stage learned from millions of sunlit lunar photos, paired with simulated versions of the same images in shadow. Ignacio Lopez-Francos, a study co-author and engineer at the NASA Ames Research Center, says using this simulated shadow was necessary because sunlit PSR images do not exist. A similar technique is also used in low-light digital camera photography.

"It's an interesting application of machine-learning technology, and the noise model seems realistic and useful for this real case," says computer scientist Chongyi Li, who uses similar strategies to enhance underwater images at Singapore's Nanyang Technological University and was not involved in the study.

The researchers used their algorithm to analyze the size and distribution of craters and boulders in several PSRs that might be explored by NASA's Artemis moon program. They also evaluated the likely origins of some boulders and plotted a potential route for a rover through a PSR on the moon's Leibnitz plateau, avoiding obstacles and slopes steeper than 10 degrees.

"There's a lot of interest in the poles—not just from the human exploration standpoint but also the topography of the ground surface," says University of Texas at El Paso geologist Jose Hurtado, who was not involved in the study. Ice might either be interspersed in the lunar soil or stored in more concentrated layers, deforming the landscape, he says. "And so this kind of image processing offers a way of testing some of those hypotheses."

—Connie Chang

CLIMATE

Breaking Up

Albatross "marriages" cool as the climate warms

Few animals appear more affectionate than the black-browed albatross. These large seabirds, whose dark eyebrows shadow their eyes like mascara, are socially monogamous and often mate for life. Their romantic-seeming "marriages" have a practical purpose: staying with the same partner builds trust, which is essential as the pair alternates between lengthy foraging trips and egg-incubation duties.

But "divorce" is not unheard of. As is the case with other monogamous animals, a female albatross will leave a partnership that lacks breeding success. The process is relatively understated and free from noisy squabbles, says University of Lisbon biologist Francesco Ventura. Often when a female deems the partnership unsuccessful over the course of a year, she will simply appear with a different male in the following breeding season.

Although divorce is natural among these birds, Ventura recently began noticing that its rates seemed to vary from year to year for the roughly 15,500 pairs of black-browed albatross breeding on New Island, a rocky outcrop in the Falkland Islands. "There were clearly years in which more pairs split up, compared with the previous years," says Ventura, whose team combed through about 15 years of breeding data.

To investigate, the group focused on two environmental variables vital to albatross: wind speed and sea-surface temperature. Each affects the birds in different ways. Higher winds make it easier for them to soar for greater distances to gather food. Increasing sea-surface temperatures, on the other hand, limit the nutrients available to foraging albatross by curbing the production of phytoplankton, which has cascading effects on the rest of the marine food web. As a result, albatross must travel farther and struggle more to find enough food. This throws breeding schedules into disarray and increases stress levels among partnerships—both factors that can decrease breeding success.

In a paper published in the *Proceedings of the Royal Society B*, Ventura and his team concluded that warmer sea temperatures are linked to higher divorce rates among New Island's black-browed albatross—providing the first evidence of environmental conditions increasing such rates among a wild monogamous animal population, the researchers say.

Warmer sea conditions were associated with more albatross divorcing because of breeding failures. And digging deeper, the team found that in warmer years female albatross were more likely to leave their mate even after successful breeding attempts.

"Previous successful females are the ones that are most affected by this [warming]," Ventura says. "They divorced more often, when in theory they should have remained together with their previous partner." This may be a manifestation of what Ventura calls the "partner-blaming hypothesis," in which the female conflates the stress caused by environmental conditions with poor performance by a partner.

Ventura hypothesizes that similar patterns may manifest in other seabird populations and possibly among some monogamous mammals, highlighting a potentially overlooked consequence of climate change. According to Natasha Gillies, a researcher at the University of Liverpool in England, who studies seabird-breeding behavior and was not involved in the new study, similar scenarios could have "profound" impacts on smaller populations of birds by decreasing breeding options. "If you have a situation where increasing sea-surface temperature is leading to higher divorce rates, that reduces breeding success for the population as a whole," she says. "Ultimately you're sending fewer albatrosses out into the world, and that's going to impact the population more widely." —*Jack Tamisiea*

Enrique Aguirre Aves/Getty Images

IN THE NEWS

Quick Hits

By Nikk Ogasa

GERMANY

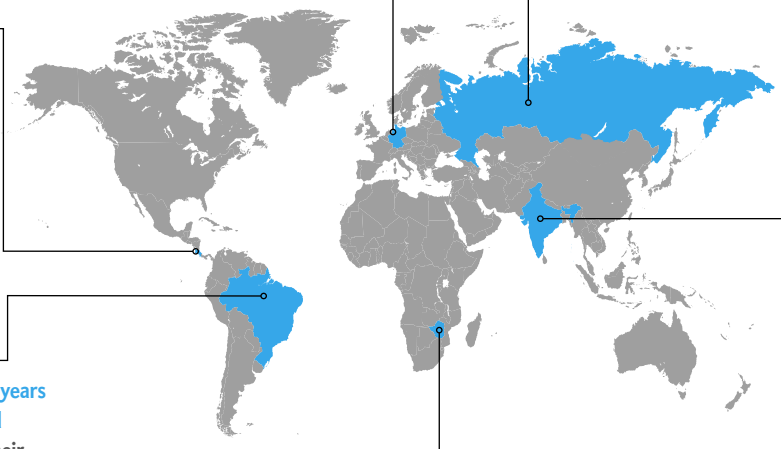
Silver-studded blue butterflies naturally favor grassland habitats, but researchers recently found four times as many in active mining quarries than in similar-sized meadows. The insects lay their eggs on certain plants, which mining operations may help thrive by eliminating larger, competing vegetation.

RUSSIA

While analyzing DNA found in Siberian sediments, scientists discovered that mammoths survived there until around 4,000 years ago—much later than previously thought. This finding means humans may have coexisted with the beasts for thousands of years without overhunting them.

COSTA RICA

Scientists found that meat-eating "vulture bees" have evolved more acidic guts that harbor acid-tolerant bacteria, similar to those found in vultures and hyenas, letting the insects safely consume carrion.



INDIA

Geologists found groups of rocks in India to be about 3.2 billion years old. The rocks consisted of sediments eroded from land, which suggests that large landmasses emerged from the sea more than half a billion years earlier than many researchers believed.

BRAZIL

Measurements over the past 40 years revealed that 77 Amazonian bird species lost 0.1 to 2 percent of their average weight each decade. Researchers suggest the birds may have adapted leaner shapes to cope with climate warming; 61 species also developed longer, more efficient wings.

For more details, visit www.ScientificAmerican.com/feb2022/advances

ZIMBABWE

Investigators recently determined the age of one of Africa's most famous trees, a 25-meter-tall baobab named "Big Tree." Because baobabs do not form regular tree rings, scientists analyzed Big Tree's carbon decay to determine it was an impressive 1,150 years old.

NEUROSCIENCE

Sated Brain

A surprising brain area helps to curb overeating

People with a rare genetic disorder known as Prader-Willi syndrome never feel full, and this insatiable hunger can lead to life-threatening obesity. Scientists studying the problem have now found that the fist-shaped structure known as the cerebellum—which had not previously been linked to hunger—is key to regulating satiation in those with this condition.

This finding is the latest in a series of discoveries revealing that the cerebellum, long thought to be primarily involved in motor coordination, also plays a broad role in cognition, emotion and behavior. "We've opened up a whole field of cerebellar control of food intake," says Albert Chen, a neuroscientist at the Scintillon Institute in California.

The project began with a serendipitous observation: Chen and his team noticed they could make mice stop eating by activating small pockets of neurons in regions known as the anterior deep cerebellar nuclei (aDCN), within the cerebellum. Intrigued, the researchers contacted collaborators at Harvard Medical School. Scientists there had gathered data using functional MRI to compare brain activity in 14 people who had Prader-Willi syndrome with activity in 14 unaffected people while each subject viewed images of food—either immediately following a meal or after fasting for at least four hours.

New analysis of these scans revealed that activity in the same regions Chen's group had pinpointed in mice, the aDCN, appeared to be significantly disrupted in humans with Prader-Willi syndrome. In healthy individuals, the aDCN were more active in response to food images while fasting than just after a meal, but no such difference was identifiable in participants with the disorder. The result suggested that the aDCN were involved in controlling hunger. Further experiments on mice, conducted by researchers from several different institutions, demonstrated that activating the animals' aDCN neurons dramatically reduced food intake by blunting how the brain's pleasure center responds to food. The findings were recently detailed in *Nature*.

For years neuroscientists studying appetite focused mainly either on the hypothalamus, a brain area involved in regulating energy balance, or on reward-processing centers such as the nucleus accumbens. But this group has identified a novel feeding center in the brain, says Elanor Hinton, a neuroscientist at the University of Bristol in England who was not involved with the study. "I've been working in appetite research for the past 15 years or so, and the cerebellum has just not been a target," Hinton says. "I think this is going to be important both for Prader-Willi syndrome and, much more widely, to address obesity in the general population."

Multiple colleagues of Chen's are now planning to test whether they can manipulate this circuit in healthy people by using a noninvasive intervention known as transcranial magnetic stimulation. If that is successful, Chen says, the researchers hope to eventually conduct a clinical trial.

—Diana Kwon

INFECTIOUS DISEASE

Social Insect Distancing

Honeybees balance separation with caring for infected individuals

Redmond Durrell/Alamy Stock Photo

Humans are not the only animals that practice social distancing to deal with a deadly pathogen: A new study shows honeybees change their behavior and use of space to avoid spreading *Varroa destructor* mites, which feed on bees' organs and can harbor nasty viruses. Researchers observed these changes in wild and caged bees infected with the mites, which are one of the biggest global threats to honeybees.

The team found that in the infected wild populations, older forager bees would perform foraging dances—which they use to show other bees where to find food—near the periphery of the hive. These actions seemed intended to avoid sickening the young nurse bees and larvae in the hive's center. The infected wild bees also groomed one another for parasites more intensely in the center of the hive, among the more valuable young bees. The findings were reported in *Science Advances*.

"We interpreted this change in the social organization as a possible strategy to limit the spread of the parasite within the hive," says lead study author Michelina Pusceddu, an agricultural scientist at the University of Sassari in Italy.

As predicted, the infected bees in cages received more grooming than uninfected bees. But contrary to expectations, the infected bees engaged in more socializing as well, such as touching antennae and sharing regurgitated food. This may reflect a trade-off between limiting disease spread and maintaining communication, the authors say. "Probably social distancing is too costly at a small scale or within the same cohort," notes senior study author Alberto Satta, also at the University of Sassari.

The study provides an example of how "we can find evidence for really complicated behavioral changes that [social animals] have—like the social distancing phenomenon—to deal with the special challenges of living in a big social group," says Adam Dolezal, an entomologist at the University of Illinois at Urbana-Champaign, who was not involved with the new study. Dolezal's own research has shown that honeybees reduce their contact with bees infected with a pathogen called Israeli acute paralysis virus, which the insects can detect by smell.

Black garden ants, lobsters, birds and nonhuman primates also show social distancing behavior. But for any social animal, keeping one's distance comes with a cost.

—Tanya Lewis

GENETICS

Science in Images

By Susan Cosier

Every April for the past decade, systems biologist Rodrigo Gutiérrez has driven 1,600 kilometers (1,000 miles) to reach one of the driest places on Earth: Chile's Atacama Desert, parts of which receive less than three millimeters of rain annually. His team collected plants and soil from nearly two dozen sites each year, froze the samples in liquid nitrogen, and brought them back to his laboratory at the Pontifical Catholic University of Chile. For a new study in the *Proceedings of the National Academy of Sciences USA*, Guitérrez and his colleagues analyzed the plants' genes and the microorganisms that help them thrive in such extreme conditions.

"We knew almost nothing about how these plants survived," Gutiérrez says. "There was great potential to study these wild species, which is now a little easier with all the genomic tools that we have." His team investigated 32 plant species, some closely related to grains, legumes and potato crops, from three altitude ranges.

Scientists usually conduct genetic studies on lab-grown plants, which lets researchers tightly control factors such as the amount of nutrients and light the plants receive. But sampling plants in nature captures critical differences based on their varied living conditions. This study "merges the genomics with ecological understanding of how plants behave in their natural environment," says University of California, Davis, plant biologist Neelima Sinha, who was not involved in the research. "That just by itself makes it very significant."

To identify genes that contribute to the plants' survival, Gutiérrez worked with ecologists, plant biologists, genomics experts and computer scientists to compare the genetic codes of the sampled Atacama species with those of closely related plants. In what the researchers describe as a "genetic gold mine," they traced genomes' evolutionary changes and identified adaptive mutations related to stress response, metabolism and energy production. These mutations might help desert plants tolerate intense solar radiation, optimize water capture and adjust flowering times. The researchers also discovered an abundance of bacteria that live on the desert plants' roots and convert nitrogen from the air into a usable form, aiding growth in nitrogen-poor soils.

Researchers could potentially insert newfound genes into food plants and grasses used for biofuel, Gutiérrez says, giving such species better survival odds when planted in saltier soils and areas experiencing drought—conditions expected to become more severe with climate change.

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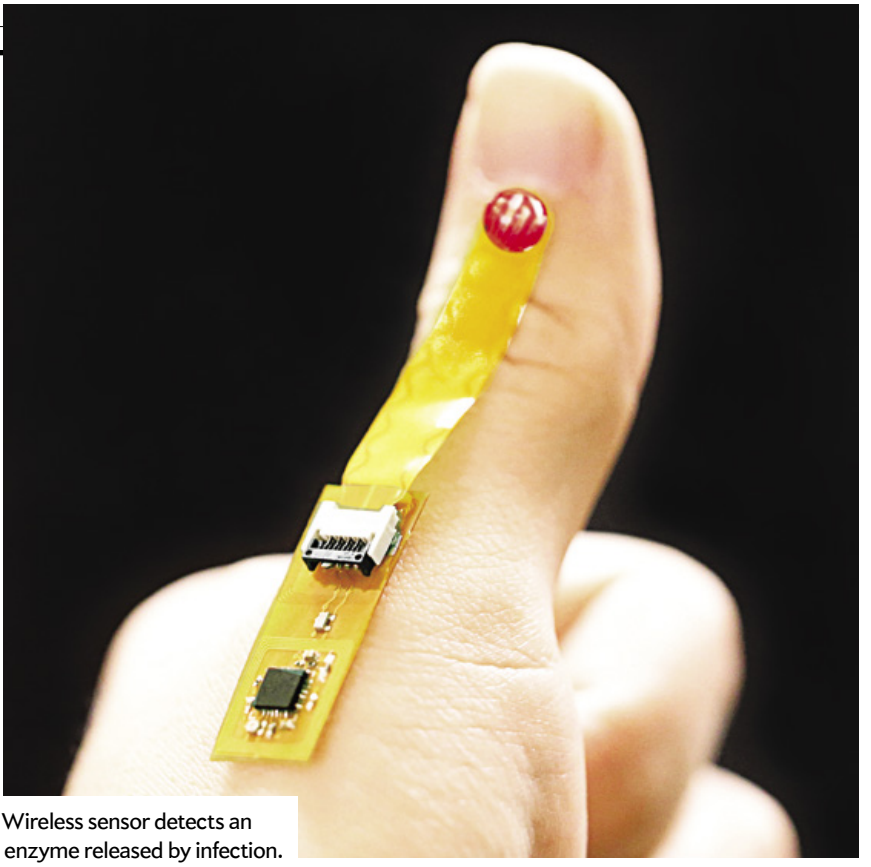
Atacama Desert, on the western edge of the Andes

HEALTH

Wound Guard

Gel-based sensor can send infection alerts to a smartphone



Wireless sensor detects an enzyme released by infection.

Ze Xiong

When bacteria make their way into wounds, they literally threaten life and limb—unless they are detected as quickly as possible. Now a new sensor can nestle in bandages and alert a nearby smartphone when the bacterial population tips over into dangerous territory.

Healthy human skin is covered with bacteria that are quick to colonize an open wound, such as *Staphylococcus aureus* and *Escherichia coli*. To prevent these organisms from spreading through the body, which can permanently injure or kill a person, the infected wound may need to be cleaned and treated with antibiotics or—in the most extreme situations—an affected limb may require amputation. Medical professionals typically identify infections by unwrapping and observing a wound or by swabbing it and conducting a laboratory test. But removing a wound's dressing can slow down the healing process. Plus, observations are subjective, swab tests take time, and both require that a patient be physically present.

To address these issues, some research teams are developing devices that sit under bandages and continuously monitor indirect signs of infection, such as changes in wound temperature or acidity. And scientists at the National University of Singapore have now created an even more direct infection sensor.

This sensor can detect an enzyme called deoxyribonuclease, or DNase. The enzyme acts as a reliable infection indicator because disease-causing bacteria produce it in large amounts inside wounds, whereas bacteria on healthy skin do not—so testing for the substance reduces the chance of a false positive result. Furthermore, DNase builds up before other infection signs appear. The new alert system (dubbed the "wireless infection detection on wounds," or WINDOW, sensor) was detailed in *Science Advances*.

WINDOW's enzyme-sensing parts rely on a gooey material called DNA hydrogel, or DNAgel, made of entangled chains of DNA. The researchers developed a particular kind of DNAgel that remains stable in watery environments, such as the human body, but begins to break down in the presence of DNase. They connected this gel to a chip that senses when the gel decays and responds by sending a signal to a smartphone. This signal is broadcast using a battery-free wireless process called near-field communication, the same technology that allows people to make a payment with the tap of a credit card.

"By coupling this DNAgel with that sensor [chip], we can make a completely battery-free device that can fit under a bandage on the wound," says study co-author John Ho, an electrical engineer at the National University of Singapore. A person with a chronic wound or someone sent home after a surgical operation might monitor their own status by tapping a smartphone next to their dressing a couple of times a day. If the phone receives an infection alert, it can send a message to a doctor or tell the patient to return to the hospital for an antibiotic treatment.

Other researchers have tried different approaches to infection detection, including high-tech imaging to monitor bacterial spread and "electronic noses" to sniff out an infection's chemical signals. "There's a raft of stuff out there that people, in principle, have proved" works, says June Mercer-Chalmers, a project manager at the University of Bath in England, who was not involved with the new study but worked on a team that developed a low-cost ultrafast swab test for infections. The issue, Mercer-Chalmers says, comes down to a tool's practicality: whether it requires a lot of cumbersome equipment, if it has steep barriers to legal approval, and how cost-effective it is. She points out that the WINDOW sensor requires electronic parts and smartphone access, which might put it out of reach for some people and hospitals systems. Ho says the material cost of each WINDOW sensor is under $10, noting that it could be constructed with existing electronic manufacturing methods.

Thus far Ho's team has exposed the DNAgel to wound swabs from 18 people's diabetic foot ulcers, some with *S. aureus* infections, to see how much the material degraded in the presence of the bacteria. The researchers also used the device on six living lab mice whose wounds were exposed to the same bacterial species, and it successfully detected infections within 24 hours—before any physical signs had become visible. Because the WINDOW sensor is still in its early days, Ho plans to continue testing it on larger groups of patients and on wounds infected with other kinds of bacteria. "Hypothetically, this should work with many other types of strains as well [because they] have similar DNase-secreting mechanisms," he says.

—Sophie Bushwick

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Despite a childhood determination to become a biophysicist writing novels on the side, **Judith K. Liebmann** earned a Ph.D. in comparative literature at Yale University and became a poet. Her work has appeared in the journals *Cream City Review,* the *Laurel Review* and *Orim,* as well as in the *New York Times.*

Elective Affinities: Ghazal of the Muon

"Long-Awaited Muon Measurement Boosts Evidence for New Physics"
—*Scientific American,* April 7, 2021

The Muon's aberrant behavior, an extended quantum particle wobble,
upends the Standard Theory, creating in Physics an existential wobble.

Normally a wavelike excitation, spinning through Higgs's gravitational field, unless
caught and entangled in a moment of viable wobble,

endowed with inertia and mass by its fellow particles' embrace—a short-
lived liaison, alas, for it soon dissipates in an unavoidable wobble.

Mathematical equations calculate how long the Muon dance goes on,
what fraction of a millisecond until its final metaphysical wobble.

The calculations are precise, just wrong. Held in the mesh of gravity and spin, a skein of
quantum magnetic charge, the Muon persists, outlives its foreseeable wobble.

In the pull and twitch of particle affinities—knitting and purling the fabric of the universe—
something has not been accounted for that prolongs the Muon's mortal wobble.

This flouting of what we think we know requires us to think again, to ponder what unknown
matter, lepton, quark or boson explains the Muon's extendable wobble.

The enigma entwines us all. In our own life's brief entanglement, anchored between infinities
small and large, we, too, hover, then fade, in a final fatal wobble.

Do we then spin on, subatomized, in the quantum particle soup? Does
immortality in fact exist in the blips of an electromagnetic celestial wobble?

Yuichiro Chino/Getty Images

NOTE: A ghazal (pronounced "guzzle") is an ancient Arabic poetic form that usually treats a theme of love or loss. Each couplet in a ghazal ends with the same word or phrase.

CHANGE IS POSSIBLE

Fact: You have options when facing a lung cancer diagnosis.

Learning all that you can about a diagnosis and what options are available can bring more than just hope. It can be the key to accessing treatments that help make long-term survival possible.

Lung cancer clinical trials may be the right option for you or a loved one.

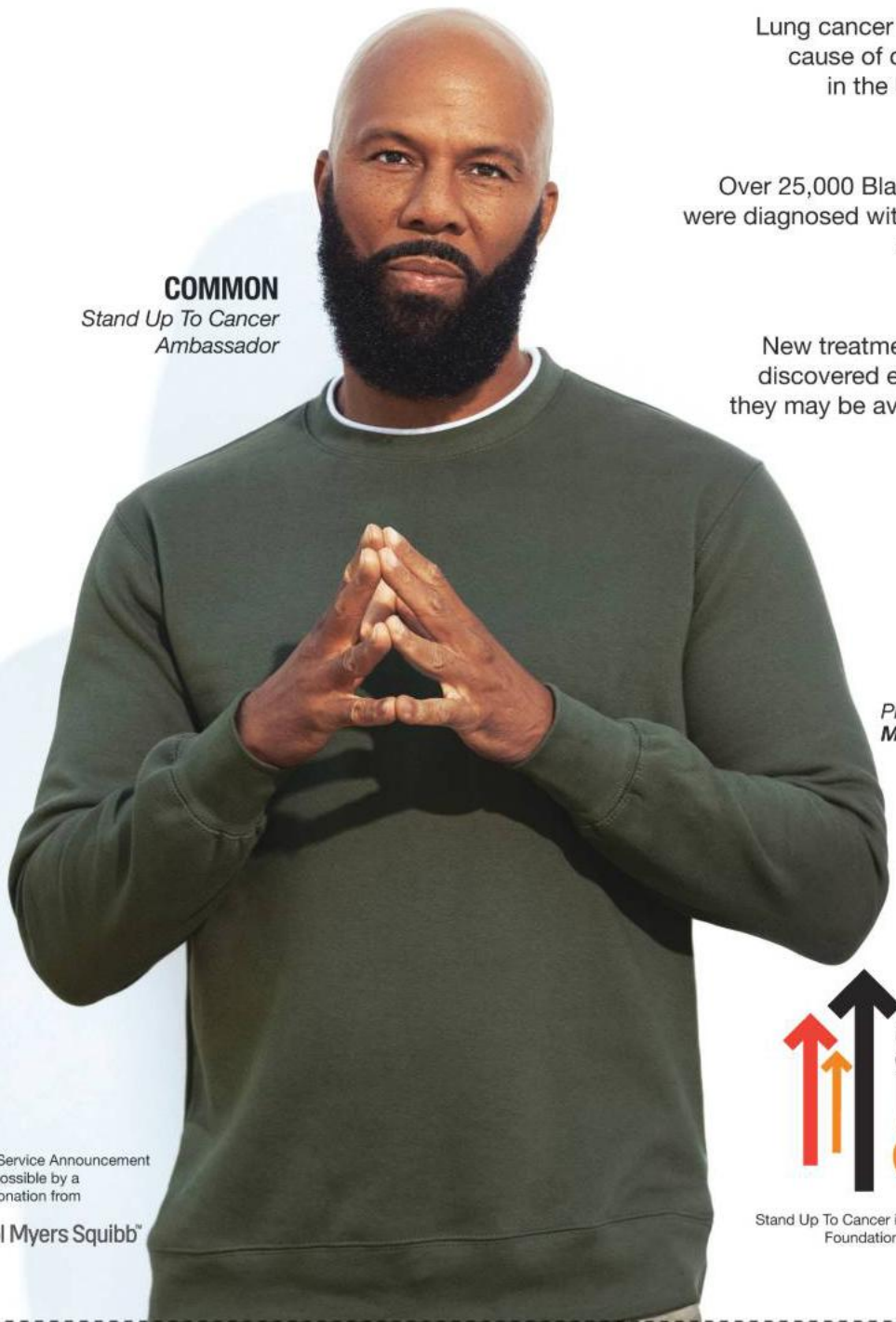
For more information on lung cancer and cancer clinical trials, visit StandUpToCancer.org/LungCancer

Fact:
Lung cancer is the leading cause of cancer deaths in the United States.

Fact:
Over 25,000 Black Americans were diagnosed with lung cancer in 2019 alone.

25k

Fact:
New treatments are being discovered every day, and they may be available to you.



COMMON
Stand Up To Cancer Ambassador

Photo By ***Matt Sayles***

STAND UP TO CANCER®

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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*.

A Faster Path to New Treatments

Medical trials that test many therapies at once are showing big benefits

By Claudia Wallis

A huge amount of money, skill and organizational complexity goes into testing a single new therapy in a randomized controlled trial—the "gold standard" type of study that forms the bedrock of modern medicine. Among the steps: devising a valid statistical design, determining dosages and measures of efficacy, passing ethical reviews, training collaborators in the study's protocol, and recruiting the required number and type of patients for both the novel treatment and a control group. It will often take years and an average of $20 million to learn whether the new intervention outperforms a placebo or the standard treatment. If the trial involves a brand-new drug, there is only a 14 percent chance that it will win approval from the U.S. Food and Drug Administration. Then, when the trial is over, its team disbands, and the organization shuts down. "It's like building a new football stadium each time we want to play just one game," says Scott Berry, president and senior statistical scientist at Berry Consultants, a Texas-based firm that advises on clinical trial design.

But suppose that stadium could be reused to test multiple treatments. And imagine that if one approach falls short, newly developed therapies could be added and tested against the same control group. This method, called an adaptive platform trial (APT), has been gaining ground in the past decade. Rather than focusing on a single new therapy, APTs aim more broadly at a disease. Drugs from multiple pharmaceutical firms can be tested at the same time and in various combinations. If data show that specific subsets of patients do better with certain therapies, new participants can be recruited into those treatment arms. In theory, APTs can run forever in search of ever better results.

Such trials are currently assessing therapies for Alzheimer's disease; influenza; cancers of the breast, brain and pancreas; severe COVID; and more. "My view is that these trials are revolutionary and transformative," says Steve Webb, a professor of critical care research at Monash University in Australia and a principal investigator in an APT directed at acute COVID.

The longest-running APT, begun in 2011, is I-SPY 2, which evaluates new drug therapies to shrink tumors in patients with breast cancer that has spread locally. I-SPY 2 has investigated about two dozen different compounds and regimens and shown which ones hold the most promise for patients with specific types of tumors. "One of the great advantages is that you can add an arm much faster than someone can design a separate trial," Berry says.

The time line for getting results is also greatly accelerated. Unlike traditional studies, APTs involve frequent analyses of the accumulating data so the trial can swiftly evolve in response to interim results. What makes this possible is sophisticated Bayesian statistical analysis—a method of comparing probabilities that can require intensive computing power. A study arm will be halted if the analysis shows a very strong probability that a given treatment is unsafe or futile—or if it is working so well that the treatment should be used more widely. "Real-time data reporting is something that's really novel," says oncologist Tufia Haddad of the Mayo Clinic, who works on traditional trials as well as on I-SPY 2. "The trial is continually learning from each patient. We answer research questions more quickly, and we bring drugs to market more quickly to help our patients."

Rapid answers make APTs popular with patient advocacy groups, several of which have funded such trials. The quickness also made them a natural choice for Operation Warp Speed, the federal effort to find COVID treatments and vaccines. In a fortuitous turn of events, a platform trial that could be adapted to study COVID was already underway when the pandemic struck. The study, called REMAP-CAP, sought better treatments for severe pneumonia, but it was also designed to test therapies when that illness was caused by a new, pandemic respiratory infection. The trial has completed evaluations of 10 different COVID interventions, Webb says. It has shown, for instance, that hydrocortisone and the immune system modulators tocilizumab and sarilumab are helpful for certain categories of patients but that convalescent plasma and hydroxychloroquine are not.

APTs are more complex to plan and manage than traditional trials, and their statistical methods may baffle the average physician, but the FDA has embraced the approach, and COVID has proved their utility. As for the old model of building a stadium for just one game, Berry says, "hopefully we will get to a day where people will laugh and say, 'There's no way that's how it was done.'" SA

Illustration by Fatinha Ramos

PHYSICS

The Origins of Space and

Spacetime may emerge from a more fundamental reality. Figuring out how could unlock the most urgent goal in physics—a quantum theory of gravity

By Adam Becker

Illustrations by Stephania Infante

Time

Adam Becker is a science writer at Lawrence Berkeley National Laboratory and author of *What Is Real?*, about the sordid untold history of quantum physics. His writing has appeared in the *New York Times*, the BBC, and elsewhere. He earned a Ph.D. in cosmology from the University of Michigan.

NATALIE PAQUETTE SPENDS HER TIME THINKING ABOUT HOW TO GROW AN EXTRA DIMENSION. Start with little circles, scattered across every point in space and time—a curlicue dimension, looped back onto itself. Then shrink those circles down, smaller and smaller, tightening the loop, until a curious transformation occurs: the dimension stops seeming tiny and instead becomes enormous, like when you realize something that looks small and nearby is actually huge and distant. "We're shrinking a spatial direction," Paquette says. "But when we try to shrink it past a certain point, a new, large spatial direction emerges instead."

Paquette, a theoretical physicist at the University of Washington, is not alone in thinking about this strange kind of dimensional transmutation. A growing number of physicists, working in different areas of the discipline with different approaches, are increasingly converging on a profound idea: space—and perhaps even time—is not fundamental. Instead space and time may be *emergent:* they could arise from the structure and behavior of more basic components of nature. At the deepest level of reality, questions like "Where?" and "When?" simply may not have answers at all. "We have a lot of hints from physics that spacetime as we understand it isn't the fundamental thing," Paquette says.

These radical notions come from the latest twists in the century-long hunt for a theory of quantum gravity. Physicists' best theory of gravity is general relativity, Albert Einstein's famous conception of how matter warps space and time. Their best theory of everything else is quantum physics, which is astonishingly accurate when it comes to the properties of matter, energy and subatomic particles. Both theories have easily passed all the tests physicists have been able to devise for the past century. Put them together, one might think, and you would have a "theory of everything."

But the two theories don't play nicely. Ask general relativity what happens in the context of quantum physics, and you'll get contradictory answers, with untamed infinities breaking loose across your calculations. Nature knows how to apply gravity in quantum contexts—it happened in the first moments of the big bang, and it still happens in the hearts of black holes—but we humans are still struggling to understand how the trick is done. Part of the problem lies in the ways the two theories deal with space and time. While quantum physics treats space and time as immutable, general relativity warps them for breakfast.

Somehow a theory of quantum gravity would need to reconcile these ideas about space and time. One way to do that would be to eliminate the problem at its source, spacetime itself, by making space and time emerge from something more fundamental. In recent years several different lines of inquiry have all suggested that, at the deepest level of reality, space and time do not exist in the same way that they do in our everyday world. Over the past decade these ideas have radically changed how physicists think about black holes. Now researchers are using these concepts to elucidate the workings of something even more exotic: wormholes—hypothetical tunnel-like connections between distant points in spacetime. These successes have kept alive the hope of an even deeper breakthrough. If spacetime is emergent, then figuring out where it comes from—and how it could arise from anything else—may just be the missing key that finally unlocks the door to a theory of everything.

THE WORLD IN A STRING DUET

TODAY THE MOST POPULAR candidate theory of quantum gravity among physicists is string theory. According to this idea, its eponymous strings are the fundamental constituents of matter and energy, giving rise to the myriad fundamental subatomic particles seen at particle accelerators around the world. They are even responsible for gravity—a hypothetical particle that carries the gravitational force, a "graviton," is an inevitable consequence of the theory.

But string theory is difficult to understand—it lives in mathematical territory that has taken physicists and mathematicians decades to explore. Much of the theo-

ry's structure is still uncharted, expeditions still planned and maps left to be made. Within this new realm, the main technique for navigation is through mathematical dualities—correspondences between one kind of system and another.

One example is the duality from the beginning of this article, between tiny dimensions and big ones. Try to cram a dimension down into a little space, and string theory tells you that you will end up with something mathematically identical to a world where that dimension is huge instead. The two situations are the same, according to string theory—you can go back and forth from one to the other freely and use techniques from one situation to understand how the other one works. "If you carefully keep track of the fundamental building blocks of the theory," Paquette says, "you can naturally find sometimes that … you might grow a new spatial dimension."

A similar duality suggests to many string theorists that space itself is emergent. The idea began in 1997, when Juan Maldacena, a physicist at the Institute for Advanced Study, uncovered a duality between a kind of well-understood quantum theory known as a conformal field theory (CFT) and a special kind of spacetime from general relativity known as anti–de Sitter space (AdS). The two seem to be wildly different theories—the CFT has no gravity in it whatsoever, and the AdS space has all of Einstein's theory of gravity thrown in. Yet the same mathematics can describe both worlds. When it was discovered, this AdS/CFT correspondence provided a tangible mathematical link between a quantum theory and a full universe with gravity in it.

Curiously, the AdS space in the AdS/CFT correspondence had one more dimension in it than the quantum CFT had. But physicists relished this mismatch because it was a fully worked-out example of another kind of correspondence conceived a few years earlier, from physicists Gerard 't Hooft of Utrecht University in the Netherlands and Leonard Susskind of Stanford University, known as the holographic principle. Based on some of the peculiar characteristics of black holes, 't Hooft and Susskind suspected that the properties of a region of space might be fully "encoded" by its boundary. In other words, the two-dimensional surface of a black hole would contain all the information needed to know what was in its three-dimensional interior—like a hologram. "I think a lot of people thought we were nuts," Susskind says. "Two good physicists gone bad."

Similarly, in the AdS/CFT correspondence, the four-dimensional CFT encodes everything about the five-dimensional AdS space it is associated with. In this system, the entire region of spacetime is built out of interactions between the components of the quantum system in the conformal field theory. Maldacena likens this process to reading a novel. "If you are telling a story in a book, there are the characters in the book that are doing something," he says. "But all there is is a line of text, right? What the characters are doing is inferred from this line of text. The characters in the book would be like the bulk [AdS] theory. And the line of text is the [CFT]."

But where does the space in the AdS space come from? If this space is emergent, what is it emerging from? The answer is a special and strangely quantum kind of interaction in the CFT: entanglement, a long-distance connection between objects, instantaneously correlating their behavior in statistically improbable ways. Entanglement famously troubled Einstein, who called it "spooky action at a distance."

Yet despite its spookiness, entanglement is a core feature of quantum physics. When any two objects interact in quantum mechanics, they generally become entangled and will stay entangled so long as they remain isolated from the rest of the world—no matter how far apart they may travel. In experiments, physicists have maintained entanglement between particles more than 1,000 kilometers apart and even between particles on the ground and others sent to orbiting satellites. In principle, two entangled particles could sustain their connection on opposite sides of the galaxy or the universe. Distance simply does not seem to matter for entanglement, a puzzle that has troubled many physicists for decades.

Will we ever know the real nature of space and time?

But if space is emergent, entanglement's ability to persist over large distances might not be terribly mysterious—after all, distance is a construct. According to studies of the AdS/CFT correspondence by physicists Shinsei Ryu of Princeton University and Tadashi Takayanagi of Kyoto University, entanglement is what produces distances in the AdS space in the first place. Any two nearby regions of space on the AdS side of the duality correspond to two highly entangled quantum components of the CFT. The more entangled they are, the closer together the regions of space are.

In recent years physicists have come to suspect that this relation might apply to our universe as well. "What is it that holds the space together and keeps it from falling apart into separate subregions? The answer is the entanglement between two parts of space," Susskind says. "The continuity and the connectivity of space owes its existence to quantum-mechanical entanglement." Entanglement, then, may undergird the structure of space itself, forming the warp and weft that give rise to the geometry of the world. "If you could somehow destroy the entanglement between two parts [of space], the space would fall apart," Susskind says. "It would do the opposite of emerging. It would dis-emerge."

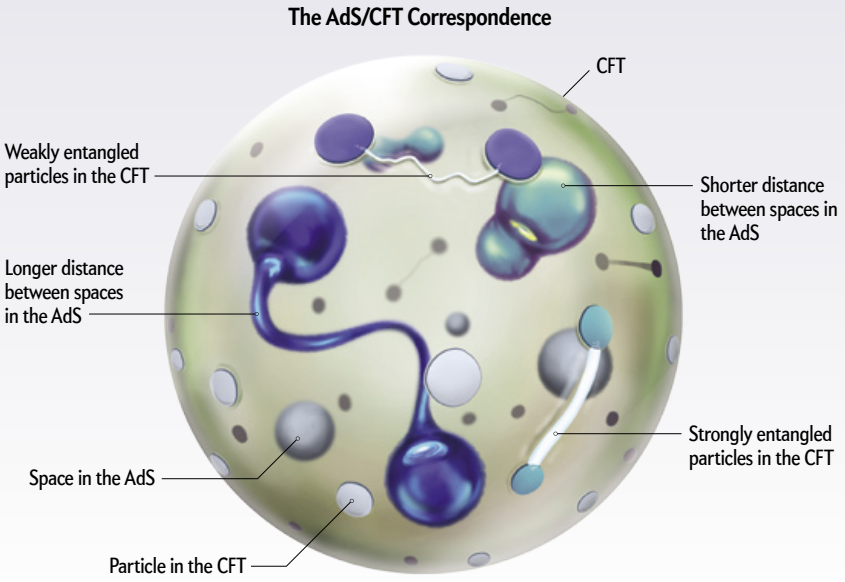
If space is made of entanglement, then the puzzle of quantum gravity seems much easier to solve: instead of trying to account for the warping of space in a quantum way, space itself emerges out of a fundamentally quantum phenomenon. Susskind suspects this is why a theory of quantum gravity has been so difficult to find in the first place. "I think the reason it never worked very

How Spacetime Emerges

Space and time are traditionally thought of as the backdrop to the universe. But new research suggests they might not be fundamental; instead spacetime could be an emergent property of a more basic reality, the true backdrop to the cosmos. This idea comes from two theories that attempt to bridge the divide between general relativity and quantum mechanics. The first, string theory, recasts subatomic particles as tiny loops of vibrating string. The second, loop quantum gravity, envisions spacetime being broken down into chunks—discrete bits that combine to create a seemingly smooth continuum.

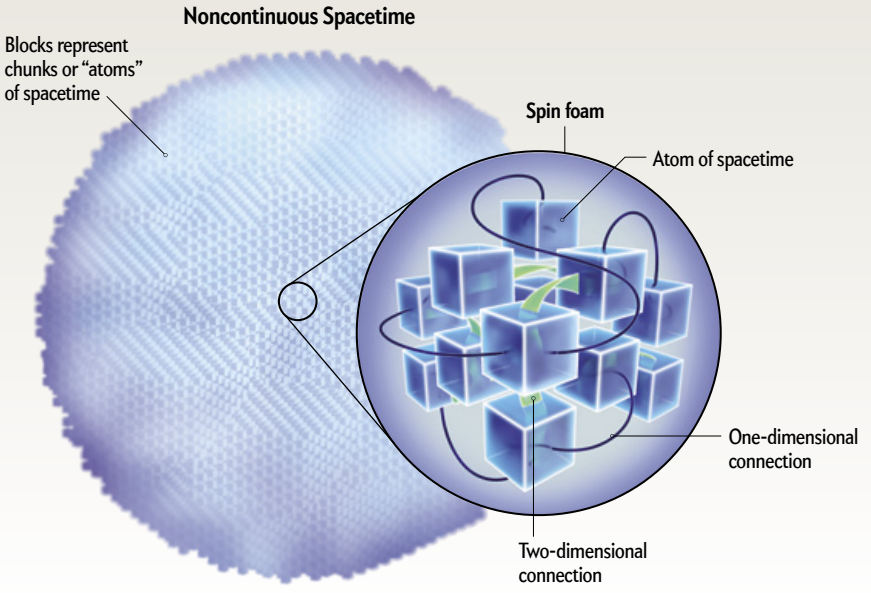
EMERGENT SPACETIME ACCORDING TO STRING THEORY

In the string theory scenario, spacetime emerges from a more fundamental reality because of an idea called the anti–de Sitter (AdS)/conformal field theory (CFT) correspondence. The CFT can be thought of as being like the two-dimensional surface of a three-dimensional sphere and the AdS as its interior. Connections between particles, through a quantum process called entanglement on the surface, give rise to regions of space inside that are located near one another. The stronger the entanglement, the closer the space regions are.



EMERGENT SPACETIME ACCORDING TO LOOP QUANTUM GRAVITY

Loop quantum gravity describes spacetime as noncontinuous: instead of being smooth, it is broken into chunks or "atoms" of spacetime if you zoom in close enough. These building blocks give rise to what we experience as continuous spacetime through one-dimensional strings and two-dimensional sheets that connect the blocks. These links create what physicists call a "spin foam."



Graphic by Elena Hartley

well is because it started with a picture of two different things, [general relativity] and quantum mechanics, and put them together," he says. "And I think the point is really that they're much too closely related to pull apart and then put back together again. There's no such thing as gravity without quantum mechanics."

Yet accounting for emergent space is only half the job. With space and time so intimately linked in relativity, any account of how space emerges must also explain time. "Time must also emerge somehow," says Mark van Raamsdonk, a physicist at the University of British Columbia and a pioneer in the connection between entanglement and spacetime. "But this is not well understood and is an active area of research."

Another active area, he says, is using models of emergent spacetime to understand wormholes. Previously many physicists had believed that sending objects through a wormhole was impossible, even in theory. But in the past few years physicists working on the AdS/CFT correspondence and similar models have found new ways to construct wormholes. "We don't know if we could do that in our universe," van Raamsdonk says. "But what we now know is that certain kinds of traversable wormholes are theoretically possible." Two papers—one in 2016 and one in 2018—led to an ongoing flurry of work in the area. But even if traversable wormholes could be built, they would not be much use for space travel. As Susskind points out, "you can't go through that wormhole faster than it would take for [light] to go the long way around."

SPACE TO THINK

IF THE STRING THEORISTS ARE CORRECT, then space is built from quantum entanglement, and time might be as well. But what would that really mean? How can space be "made of" entanglement between objects unless those objects are themselves somewhere? How can those objects become entangled unless they experience time and change? And what kind of existence could things have without inhabiting a true space and time?

These are questions verging on philosophy—and indeed, philosophers of physics are taking them seriously. "How the hell could spacetime be the kind of thing that could be emergent?" asks Eleanor Knox, a philosopher of physics at King's College London. Intuitively, she says, that seems impossible. But Knox doesn't think that is a problem. "Our intuitions are terrible sometimes," she says. They "evolved on the African savanna interacting with macro objects and macro fluids and biological animals" and tend not to transfer to the world of quantum mechanics. When it comes to quantum gravity, "'Where's the stuff?' and 'Where does it live?' aren't the right questions to be asking," Knox concludes.

It is certainly true that objects live in places in everyday life. But as Knox and many others point out, that does not mean that space and time have to be fundamental—just that they have to reliably emerge from whatever is fundamental. Consider a liquid, says Christian Wüthrich, a philosopher of physics at the University of Geneva. "Ultimately it's elementary particles, like electrons and protons and neutrons or, even more fundamental, quarks and leptons. Do quarks and leptons have liquid properties? That just doesn't make sense, right?… Nevertheless, when these fundamental particles come together in sufficient numbers and show a certain behavior together, collective behavior, then they will act in a way that is like a liquid."

Space and time, Wüthrich says, could work the same way in string theory and other theories of quantum gravity. Specifically, spacetime might emerge from the materials we usually think of as living in the universe—matter and energy itself. "It's not [that] we first have space and time and then we add in some matter," Wüthrich says. "Rather something material may be a necessary condition for there to be space and time. That's still a very close connection, but it's just the other way from what you might have thought originally."

But there are other ways to interpret the latest findings. The AdS/CFT correspondence is often seen as an example of how spacetime might emerge from a quantum system, but that might not actually be what it shows, according to Alyssa Ney, a philosopher of physics at the University of California, Davis. "AdS/CFT gives you this ability to provide a translation manual between facts about the spacetime and facts of the quantum theory," Ney says. "That's compatible with the claim that spacetime is emergent, and some quantum theory is fundamental." But the reverse is also true, she says. The correspondence could mean that quantum theory is emergent and spacetime is fundamental—or that neither is fundamental and that there is some even deeper fundamental theory out there. Emergence is a strong claim to make, Ney says, and she is open to the possibility that it is true. "But at least just looking at AdS/CFT, I'm still not seeing a clear argument for emergence."

An arguably bigger challenge to the string theory picture of emergent spacetime is hidden in plain sight, right in the name of the AdS/CFT correspondence itself. "We don't live in anti–de Sitter space," Susskind says. "We live in something much closer to de Sitter space." De Sitter space describes an accelerating and expanding universe much like our own. "We haven't got the vaguest idea how [holography] applies there," Susskind concludes. Figuring out how to set up this kind of correspondence for a space that more closely resembles the actual universe is one of the most pressing problems for string theorists. "I think we're going to be able to understand better how to get into a cosmological version of this," van Raamsdonk says.

Finally, there is the news—or lack thereof—from the latest particle accelerators, which have not found any evidence for the extra particles predicted by supersymmetry, an idea that string theory relies on. Supersymmetry dictates that all known particles would have their own "superpartners," doubling the number of fundamental particles. But CERN's Large Hadron Collider near Geneva, designed in part to search for superpartners, has seen no sign of them. "All of the really precise versions of [emergent spacetime] that we have are in supersymmetric theories," Susskind says. "Once you

don't have supersymmetry, the ability to mathematically follow the equations just evaporates out of your hands."

ATOMS OF SPACETIME

STRING THEORY IS NOT THE ONLY IDEA that suggests spacetime is emergent. String theory has "failed to live up to [its] promise as a way to unite gravity and quantum mechanics," says Abhay Ashtekar, a physicist at Pennsylvania State University. "The power of string theory now is in providing an extremely rich set of tools, which has been used widely across the whole spectrum of physics." Ashtekar is one of the original pioneers of the most popular alternative to string theory, known as loop quantum gravity. In loop quantum gravity, space and time are not smooth and continuous the way they are in general relativity—instead they are made of discrete components, what Ashtekar calls "chunks or atoms of spacetime."

These atoms of spacetime are connected in a network, with one- and two-dimensional surfaces joining them together into what practitioners of loop quantum gravity call a spin foam. And despite that foam being limited to two dimensions, it gives rise to our four-dimensional world, with three dimensions of space and one of time. Ashtekar likens it to a piece of clothing. "If you look at your shirt, it looks like a two-dimensional surface," he says. "If you just take a magnifying glass, you will immediately see that it's all one-dimensional threads. It's just that those threads are so densely packed that for all practical purposes, you can think of the shirt as being a two-dimensional surface. So, similarly, the space around us looks like a three-dimensional continuum. But there is really a crisscross by these [atoms of spacetime]."

Although string theory and loop quantum gravity both suggest that spacetime is emergent, the kind of emergence is different in the two theories. String theory suggests that spacetime (or at least space) emerges from the behavior of a seemingly unrelated system, in the form of entanglement. Think of how traffic jams emerge from the collective decisions of individual drivers. The cars are not made of traffic—the cars *make* the traffic. In loop quantum gravity, on the other hand, the emergence of spacetime is more like a sloping sand dune emerging from the collective motion of sand grains in wind. The smooth familiar spacetime comes from the collective behavior of tiny "grains" of spacetime; like the dunes, the grains are still sand, even though the chunky crystalline grains do not look or act like the undulating dunes.

Despite these differences, both loop quantum gravity and string theory suggest spacetime emerges from some underlying reality. Nor are they the only proposed theories of quantum gravity that point in this direction. Causal set theory, another contender for a theory of quantum gravity, posits that space and time are made of more fundamental components as well. "It's really striking that for most of the plausible theories of quantum gravity that we have, in some sense their message is, yeah, general relativistic spacetime isn't in there at the fundamental level," Knox says. "People get very excited when different theories of quantum gravity agree on at least something."

THE FUTURE OF SPACE AT THE EDGE OF TIME

MODERN PHYSICS IS A VICTIM of its own success. Because quantum physics and general relativity are both so phenomenally accurate, quantum gravity is needed only to describe extreme situations, when enormous masses are stuffed into unfathomably tiny spaces. Those conditions exist in only a few places in nature, such as the center of a black hole—and notably not in physics laboratories, not even the largest and most powerful ones. It would take a particle accelerator the size of a galaxy to directly test the behavior of nature under conditions where quantum gravity reigns. This lack of direct experimental data is a large part of the reason why scientists' search for a theory of quantum gravity has been so long.

Faced with the lack of evidence, most physicists have pinned their hopes on the sky. In the earliest moments of the big bang, the entire universe was phenomenally small and dense—a situation that calls for quantum gravity to describe it. And echoes of that era may remain in the sky today. "I think our best bet [for testing quantum gravity] is through cosmology," Maldacena says. "Maybe something in cosmology that we now think is unpredictable, that maybe can be predicted once we understand the full theory, or some new thing that we didn't even think about."

Laboratory experiments may come in handy, however, for testing string theory, at least indirectly. Scientists hope to study the AdS/CFT correspondence not by probing spacetime but by building highly entangled systems of atoms and seeing whether an analogue to spacetime and gravity shows up in their behavior. Such experiments might "have some features of gravity, though, perhaps not all the features," Maldacena says. "It also depends on exactly what you call gravity."

Will we ever know the real nature of space and time? The observational data from the skies may not be forthcoming any time soon. The lab experiments could be a bust. And as philosophers know well, questions about the true nature of space and time are very old indeed. What exists "is now all together, one, continuous," said the philosopher Parmenides 2,500 years ago. "All is full of what is." Parmenides insisted that time and change were illusions, that everything everywhere was one and the same. His pupil Zeno created famous paradoxes to prove his teacher's point, purporting to show that motion over any distance was impossible. Their work raised the question of whether time and space are somehow illusory, an unsettling prospect that has haunted Western philosophy for over two millennia.

"The fact that the ancient Greeks asked things like, 'What is space?' 'What is time?' 'What is change?' and that we still ask versions of these questions today means that they were the right questions to ask," Wüthrich says. "It's by thinking about these kinds of questions that we have learned a lot about physics." SA

FROM OUR ARCHIVES

Tangled Up in Spacetime. Clara Moskowitz; January 2017.

scientificamerican.com/magazine/sa

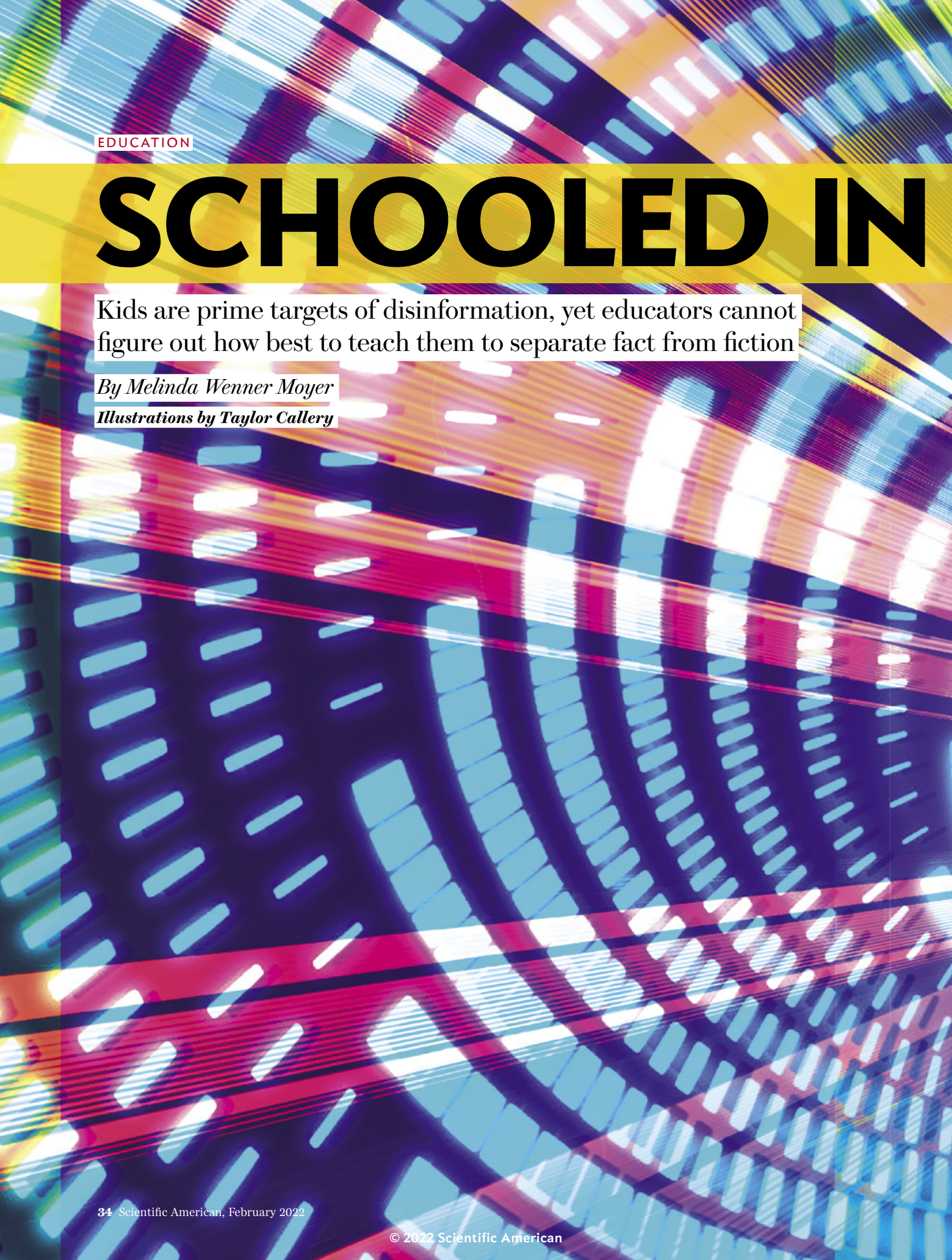
EDUCATION

SCHOOLED IN

Kids are prime targets of disinformation, yet educators cannot figure out how best to teach them to separate fact from fiction

By Melinda Wenner Moyer

Illustrations by Taylor Callery



LIES

Melinda Wenner Moyer, a contributing editor at *Scientific American*, is author of *How to Raise Kids Who Aren't Assholes: Science-Based Strategies for Better Parenting—from Tots to Teens* (G. P. Putnam's Sons, 2021). She wrote about the reasons that autoimmune diseases overwhelmingly affect women in the September 2021 issue.

WHEN AMANDA GARDNER, AN EDUCATOR WITH TWO DECADES OF EXPERIENCE, HELPED to start a new charter elementary and middle school outside of Seattle last year, she did not anticipate teaching students who denied that the Holocaust happened, argued that COVID is a hoax and told their teacher that the 2020 presidential election was rigged. Yet some children insisted that these conspiracy fantasies were true. Both misinformation, which includes honest mistakes, and disinformation, which involves an intention to mislead, have had "a growing impact on students over the past 10 to 20 years," Gardner says, yet many schools do not focus on the issue. "Most high schools probably do some teaching to prevent plagiarism, but I think that's about it."

Children, it turns out, are ripe targets for fake news. Age 14 is when kids often start believing in unproven conspiratorial ideas, according to a study published in September 2021 in the *British Journal of Developmental Psychology.* Many teens also have trouble assessing the credibility of online information. In a 2016 study involving nearly 8,000 U.S. students, Stanford University researchers found that more than 80 percent of middle schoolers believed that an advertisement labeled as sponsored content was actually a news story. The researchers also found that less than 20 percent of high schoolers seriously questioned spurious claims in social media, such as a Facebook post that said images of strange-looking flowers, supposedly near the site of a nuclear power plant accident in Japan, proved that dangerous radiation levels persisted in the area. When college students in the survey looked at a Twitter post touting a poll favoring gun control, more than two thirds failed to note that the liberal antigun groups behind the poll could have influenced the data.

Disinformation campaigns often directly go after young users, steering them toward misleading content. A 2018 *Wall Street Journal* investigation found that YouTube's recommendation algorithm, which offers personalized suggestions about what users should watch next, is skewed to recommend videos that are more extreme and far-fetched than what the viewer started with. For instance, when researchers searched for videos using the phrase "lunar eclipse," they were steered to a video suggesting that Earth is flat. YouTube is one of the most popular social media site among teens: After Zeynep Tufekci, an associate professor at the University of North Carolina, Chapel Hill, School of Information and Library Science, spent time searching for videos on YouTube and observed what the algorithm told her to watch next, she suggested that it was "one of the most powerful radicalizing instruments of the 21st century."

One tool that schools can use to deal with this problem is called media literacy education. The idea is to teach kids how to evaluate and think critically about the messages they receive and to recognize falsehoods masquerading as truth. For children whose parents might believe conspiracy fantasies or other lies fueled by disinformation, school is the one place where they can be taught skills to evaluate such claims objectively.

Yet few American kids are receiving this instruction. Last summer Illinois became the first U.S. state to require all high school students to take a media literacy class. Thirteen other states have laws that touch on media literacy, but requirements can be as general as putting a list of resources on an education department Web site. A growing number of students are being taught some form of media literacy in college,

but that is "way, way too late to begin this kind of instruction," says Howard Schneider, executive director of the Center for News Literacy at Stony Brook University. When he began teaching college students years ago, he found that "they came with tremendous deficits, and they were already falling into very bad habits."

Even if more students took such classes, there is profound disagreement about what those courses should teach. Certain curricula try to train students to give more weight to journalistic sources, but some researchers argue that this practice ignores the potential biases of publications and reporters. Other courses push students to identify where information comes from and ask how the content helps those disseminating it. Overall there are very few data showing the best way to teach children how to tell fact from fiction.

Most media literacy approaches "begin to look thin when you ask, 'Can you show me the evidence?'" says Sam Wineburg, a professor of education at Stanford University, who runs the Stanford History Education Group. There are factions of educational researchers behind each method, says Renee Hobbs, director of the Media Education Lab at the University of Rhode Island, and "each group goes out of its way to diss the other." These approaches have not been compared head-to-head, and some have only small studies supporting them. Like online media sources themselves, it is hard to know which ones to trust.

NEWS LITERACY IS A SUBSET of media literacy research that deals directly with the propagation of conspiracies and the ability to discern real news from fake stories. It entails a set of skills that help people judge the reliability and credibility of news and information. But as with media literacy, researchers have very different ideas about how this type of news analysis should be taught.

Some programs, such as Schneider's Stony Brook program and the nonprofit, Washington, D.C.–based News Literacy Project, teach students to discern the quality of the information in part by learning how responsible journalism works. They study how journalists pursue news, how to distinguish between different kinds of information and how to judge evidence behind reported stories. The goal, Schneider wrote in a 2007 article for *Nieman Reports,* is to shape students into "consumers who could differentiate between raw, unmediated information coursing through the Internet and independent, verified journalism."

Yet some media literacy scholars doubt the efficacy of these approaches. Hobbs, for instance, wrote a 2010 paper arguing that these methods glorify journalism, ignore its many problems and do little to instill critical thinking skills. "All that focus on the ideals of journalism is mere propaganda if it is blind to the realities of contemporary journalism, where partisan politics and smear fests are the surest way to build audiences," she stated.

Other approaches teach students methods for evaluating the credibility of news and information sources, in part by determining the goals and incentives of those sources. They teach students to ask: Who created the content and why? And what do other sources say? But these methods are relatively new and have not been widely studied.

The lack of rigorous studies of the different approaches is indeed a major roadblock, says Paul Mihailidis, a civic media and journalism expert at Emerson College. He is the principal investigator of the Mapping Impactful Media Literacy Practices initiative, a research project supported by the National Association for Media Literacy Education. "Most of the science done is very small scale, very exploratory. It's very qualitative," he says. That is not simply because of a lack of resources, he adds. "There's also a lack of clarity about what the goals are."

Children are ripe targets for fake news. Age 14 is when kids often start believing in unproven conspiratorial ideas, according to a recent study.

For instance, in a 2017 study researchers looked at how well students who had taken Stony Brook's undergraduate course could answer certain questions a year later compared with students who had not. Students who had taken the class were more likely to correctly answer questions about the news media, such as that PBS does not rely primarily on advertising for financial support. But the study did not test how well the students could discern fake from real news, so it is hard to know how well the program inoculates students against falsehoods.

Moreover, the small amount of research that does exist has largely been conducted with college students, not the middle school or high school students who are so vulnerable to disinformation. Indeed, the various approaches that are being used in K–12 classrooms have hardly been tested at all. As part of his current research initiative, Mihailidis and his team interviewed the heads of all major organizations that are part of the National Media Literacy Alliance, which works to promote media literacy education. "We are finding, repeatedly, that many of the ways in which they support schools and teachers—resources, guidelines, best practices, etcetera—are not studied in much of a rigorous fashion," he says.

Some researchers, including Wineburg, are trying to fill in the research gaps. In a study published in 2019, Wineburg and his team compared how 10 history professors, 10 journalism fact-checkers and 25 Stanford

undergraduates evaluated Web sites and information on social and political issues. They found that whereas historians and students were often fooled by manipulative Web sites, journalism fact-checkers were not. In addition, their methods of analysis differed significantly: historians and students tried to assess the validity of Web sites and information by reading vertically, navigating within a site to learn more about it, but fact-checkers read laterally, opening new browser tabs for different sources and running searches to judge the original Web site's credibility.

Working with the Poynter Institute and the Local Media Association and with support from Google.org (a charity founded by the technology giant), Wineburg and his team have created a civic online reasoning course that teaches students to evaluate information by reading laterally. The effects so far look promising. In a field experiment involving 40,000 high school students in urban public health districts, Wineburg and his group found that students who took the class became better able to evaluate Web sites and the credibility of online claims, such as Facebook posts, compared with students who did not take the class.

STILL, EVEN IF NEWS LITERACY EDUCATION teaches specific skills well, some researchers question its broader, longer-term impact. Once students learn how to evaluate Web sites and claims, how confident can we be that they will retain these skills and use them down the line? How sure can we be that these methods will inculcate students with skepticism about conspiracy theories and disinformation campaigns? And will these methods lead students to become civically engaged members of society? "There's always this kind of leap into 'that will make our democracy and news systems stronger.' And I don't know if that's necessarily the case," Mihailidis says.

Some research does hint that news literacy approaches could have these broader beneficial effects. In a 2017 study of 397 adults, researchers found that people who were more media-literate were less likely to endorse conspiracy theories compared with people who were less media-literate. "We can't definitely say news literacy causes you to reject conspiracy theories, but the fact that we see a positive relationship there tells us there's something to this that we need

to continue to explore," says co-author Seth Ashley, an associate professor of journalism and media studies at Boise State University.

While Ashley's results are encouraging, some experts worry that a focus only on evaluating Web sites and news articles is too narrow. "News literacy in a lot of ways focuses on credibility and whether we know something is true or not, and that's a really important question, but that is one question," says Michelle Ciulla Lipkin, executive director of the National Association for Media Literacy Education. "Once we figure out if it's false or true, what is the other assessment and the other analyzing we need to do?" Determining credibility of the information is just the first step, she argues. Students should also be thinking about why the news is being told in a particular way, whose stories are being told and whose are not, and how the information is getting to the news consumer.

Pressing students to be skeptical about all information also may have unexpected downsides. "We think that some approaches to media literacy not only don't work but might actually backfire by increasing students' cynicism or exacerbating misunderstandings about the way news media work," says Peter Adams, senior vice president of education at the News Literacy Project. Students may begin to "read all kinds of nefarious motives into everything." Adams's concern was amplified by danah boyd, a technology scholar at Microsoft Research and founder and president of the Data & Society research institute, in a 2018 talk at the South by Southwest media conference. Boyd argued that although it is good to ask students to challenge their assumptions, "the hole that opens up, that invites people to look for new explanations, that hole can be filled in deeply problematic ways." Jordan Russell, a high school social studies teacher in Bryan, Tex., agrees. "It's very easy for students to go from healthy critical thinking to unhealthy skepticism" and the idea that everyone is lying all the time, he says.

To avoid these potential problems, Ashley advocates for broad approaches that help students develop mindsets in which they become comfortable with uncertainty. According to educational psychologist William Perry of Harvard University, students go through various stages of learning. First children are black-and-white thinkers—they think there are right answers and wrong answers. Then they develop into relativists, realizing that knowledge can be contextual. This stage can be dangerous, however. It is the one where, as Russell notes, people can come to believe there is no truth. Ashley adds that when students think everything is a lie, they also think there is no point in engaging with difficult topics.

With news literacy education, the goal is to get students to the next level, "to that place where you can start to see and appreciate the fact that the world is messy, and that's okay," Ashley says. "You have these fundamental approaches to gathering knowledge that you can accept, but you still value uncertainty, and you value ongoing debates about how the world works." Instead of driving students to apathy, the goal is to steer them toward awareness and engagement.

SCHOOLS STILL HAVE a long way to go before they get there, though. One big challenge is how to expand these programs so they reach everyone, especially kids in lower-income school districts, who are much less likely to receive any news literacy instruction at all. And teachers already have so much material they have to impart—can they squeeze in more, especially if what they have to add is nuanced and complex? "[We] desperately need professional development and training and support for educators because they're not experts in the field," Adams says. "And it's the most complex and fraught and largest information landscape in human history."

"Some approaches to media literacy not only don't work but might actually backfire by increasing students' cynicism."
—Peter Adams *News Literacy Project*

In 2019 Senator Amy Klobuchar of Minnesota introduced the Digital Citizenship and Media Literacy Act into the U.S. Senate, which, if passed, would authorize $20 million to create a grant program at the Department of Education to help states develop and fund media literacy education initiatives in K–12 schools. More investment in this kind of education is critical if America's young people are going to learn how to navigate this new and constantly evolving media landscape with their wits about them. And more research is necessary to understand how to get them there. At the Center for News Literacy, Schneider plans to conduct a trial soon to determine how his course shapes the development of news literacy, civic engagement and critical thinking skills among students in middle school and high school.

But many more studies will be needed for researchers to reach a comprehensive understanding of what works and what doesn't over the long term. Education scholars need to take "an ambitious, big step forward," Schneider says. "What we're facing are transformational changes in the way we receive, process and share information. We're in the middle of the most profound revolution in 500 years." SA

FROM OUR ARCHIVES

Inside the Echo Chamber. Walter Quattrociocchi; April 2017.

scientificamerican.com/magazine/sa

NEUSE RIVER WATERDOG, clumsy on land, lives entirely underwater, feeding only when an insect happens to swim by.

BIOLOGY

GENETICALLY BLOATED BEASTS

The surprising persistence of salamanders is forcing us to rethink evolution

By Douglas Fox

Photographs by Andrew Hetherington

Douglas Fox writes about biology, geology and climate science from California. He wrote the July 2021 article "The Carbon Rocks of Oman," about efforts to turn carbon dioxide into solid minerals.

THE NEUSE RIVER WATERDOG LIVES A SLUGGISH EXISTENCE, AS IF BURDENED BY AN invisible weight. This mottled brown salamander, about as long as a human hand, rarely strays far from its concealed burrows beneath rocks or logs in the rivers of North Carolina. It "hunts" by sitting still in the riverbed, waiting for an insect to swim by, then lurches forward to swallow the object—a mindless reflex. It spends its entire life confined to water, an overgrown larva that never completes metamorphosis, with flaccid legs too small for its body, toes that haven't finished sprouting, a missing upper jawbone and puffy larval gills bulging from its neck.

View the animal up close, and another oddity becomes apparent: its cells are up to 300 times larger than those of a lizard, bird or mammal. You can see, with a simple magnifying glass, individual blood cells zipping through the capillaries in its transparent gills.

The Neuse River waterdog, *Necturus lewisi,* and other salamanders represent a long-standing conundrum scientists are only now starting to understand. The animal's strange traits stem from a hidden burden: Each of its cells is bloated with 38 times more DNA than a human cell. The waterdog has the largest genome of any four-footed beast on Earth. The only comparable animals of any kind are lungfish, which also have sluggardly tendencies.

Most mammal, bird, reptile and fish genomes fall within a narrow range of half a billion to six billion chemical building blocks, or base pairs, of DNA. The base pairs form genes—links in a long chain that constitute an animal's genome. But salamander genomes range wildly, from 10 billion to 120 billion base pairs (10 to 120 gigabases). Salamanders don't have more genes than other animals; instead their genomes are cluttered with segments of parasitic DNA that have multiplied out of control. Everything about their lives is dominated by their massive genome, which has pushed them into the extreme slow lane of existence. They slog through life with underdeveloped bodies, simplified brains and hearts as flimsy as paper bags, sometimes for 100 years.

In exchange for this burden, salamanders may have gained at least one amazing ability: regeneration. They can regrow not only limbs but also up to a quarter of their brain if it is cut out—handy for survival.

Salamanders owe their weird traits to their DNA, but not in the way you'd expect. DNA is often called the blueprint of life. It contains the precise information that determines the structure and function of every cell in every species. But the latest discoveries about salamanders upend this long-held notion of a fine-tuned genome. They reveal that DNA also shapes its owner in ways that have nothing to do with its informational content. DNA can distort bodies and organs like a funhouse mirror; a species can tolerate only so much DNA before experiencing those side effects. We humans, in fact, may be close to our limit: make our genome any larger, and it could compromise our species' greatest asset, our intelligence.

As for salamanders, one has to wonder why their burden hasn't dragged them down to extinction. Their very perseverance suggests that our idea of evolution, particularly "survival of the fittest," has a serious moralistic bias: *Work hard, young species, hone your body and brain for high performance, and someday you will succeed*. But salamanders owe their success to lying around. They have found a way to cheat the system.

INFLATED GENOMES

THE MYSTERY of gigantic genomes began during a pivotal moment decades ago, when biologists had just identified DNA as the hereditary molecule of life. A genome, unique to every species, contains thousands of genes, composed of DNA, that instruct cells to make proteins and other molecules that make an organism what it is. Researchers initially assumed that advanced species with complex bodies, such as primates and humans, would have more genes and therefore larger genomes.

But Alfred Mirsky and Hans Ris of the Rockefeller Institute for Medical Research overturned this notion in 1951. They measured the amount of DNA in individual

SALAMANDERS have giant genomes that encumber the critters with infantile bodies. But they can provide the power to regenerate limbs and even parts of the brain.

cells from several dozen animal species. To their surprise, the African lungfish and a giant salamander from the southeastern U.S., called amphiuma, had dozens of times more DNA per cell than humans, rats, birds or reptiles did. As scientists measured more species, it became clear that salamanders and lungfish were outliers.

Over the next two decades researchers got a closer view of gigantic genomes. Shigeki Mizuno and Herbert MacGregor of the University of Leicester in England studied a handful of North American salamander species called plethodontids. The species looked nearly identical, yet their genomes ranged from 18 to 55 gigabases—about five to 16 times the human genome, which has 3.06 gigabases.

In all the species, the DNA chain was wound into sausage-shaped structures called chromosomes. But in species with bigger genomes, the chromosome shape looked enlarged, like an overinflated sausage balloon. Extra DNA seemed to be sprinkled throughout the chromosomes' length.

Mizuno and MacGregor had no idea what that extra material was. But during the 1980s scientists found that cells in other species, from flies to humans, harbored "parasitic" DNA—short DNA segments, called transposons, which vaguely resemble viruses. Transposons contain several genes that allow the parasite to make copies of itself, which then insert themselves, sometimes randomly, into other parts of a cell's genome.

The exploration of gigantic genomes went slowly for several decades. Scientists labored to fully sequence the genomes of fruit flies, worms and humans, but most avoided salamanders, whose sheer volume of DNA would have been a nightmare to handle. Then in 2011 Rachel Mueller, an evolutionary biologist at Colorado State University, took a major step forward.

Mueller and her colleagues used high-throughput sequencing to analyze hundreds of thousands of random DNA snippets from six species of plethodontid salamanders, as well as another species called hellbender. The results confirmed what people had suspected: salamander genomes were overinflated with transposons. Many of the same transposons were present in both the plethodontids and hellbender, which suggested that the parasites had first multiplied out of control in the ancestor of all living salamanders, more than 200 million years ago.

The mystery of why that explosion happened has intrigued Mueller ever since. "It wasn't like one [transposon] went bananas," she says. "It was a global change in how those [transposon] sequences were permitted to inhabit the genome," allowing dozens of them to multiply simultaneously.

Although Mueller hasn't determined why, she has solved another puzzle: Even when transposons do proliferate in a host's genome, they are usually deleted over time through random mutations. This pruning happens

constantly in every species. But in two studies, Mueller estimated that salamanders clear out their inserted transposons several times more slowly than zebra fish or humans. This pace shifts the balance toward transposons accumulating rather than remaining constant, leaving the salamander genomes increasingly bloated over time.

That extra DNA has profoundly altered salamanders' bodies, brains and hearts. In species with the very largest genomes, the anatomic distortions are obvious at a glance.

EMBRYONIC BRAINS

GIGANTIC GENOMES often turn salamanders into overgrown babies. Of the 766 known species, more than 39 have lost the ability to metamorphose from aquatic larvae into landlubbing adults. (Another 39 metamorphose only occasionally.) These species tend to have larger genomes than others that do metamorphose. Like the Neuse River waterdog, they spend their entire lives confined to water with larval gills and weakling limbs.

Many of them are also missing toes because their limbs never finish developing. The waterdog has only four toes on its rear feet (most salamanders have five). Species of amphiuma have three, two or even just one toe per foot. And species in the siren family, which inhabit the southeastern U.S., have no rear legs at all.

Even land-dwelling salamanders with adult-looking bodies often have babylike traits, such as unfused skull bones or foot skeletons that haven't hardened into bone. A series of discoveries between 1988 and 1997 showed that many of these species even have larvalike brains.

The revelations began when David Wake, a prominent salamander biologist at the University of California, Berkeley, teamed up with Gerhard Roth, then a Ph.D. student at the University of Bremen in Germany. They decided to compare the brain structures of several dozen species of frogs and land-dwelling plethodontid salamanders.

Wake removed the critters' brains and soaked them in cedar wood oil, which turned them transparent for viewing under a microscope. As he and Roth examined the brains, they realized that most had simpler structures than those of frogs, which are also amphibians and therefore close relatives. The salamander nerve cells looked "embryonic," according to Wake: larger, rounder and less differentiated into specialized cell types.

This simplification was especially dramatic in the visual system. The salamanders had no more than 75,000 neural fibers in their optic nerves (which carry signals from the eyes to the brain); frogs had up to 470,000 fibers. In salamanders, far fewer of these nerve fibers were coated with myelin sheaths, which allow signals to reach the brain more quickly. And in the tectum, a brain region that processes images from the optic nerve, the neurons of salamanders were often strewn chaotically about—a trait seen in embryonic or larval brains—whereas in frogs, the neurons were nicely layered. Wake and Roth went on to show that salamanders with larger genomes generally have simpler visual systems.

In all of this, Roth was struck by one overarching pattern: the features missing in salamander brains were those that arise late in development. It seemed as if the critters' brains had run out of time to finish maturing. This stipulation made a lot of sense because another scientist had just demonstrated a link between salamanders' large genomes and their slow development.

Stanley Sessions, a former student of Wake's (like several of the experts in this story), was studying salamanders' special talent for regenerating severed limbs. Sessions, now a professor emeritus at Hartwick College, amputated the right rear legs from 27 species of plethodontid salamanders and measured how quickly they grew back. The animals' genomes varied from 13 to 74 gigabases (four to 24 times the human genome). Sure enough, Sessions found that animals with larger genomes regenerated more slowly. Their immature cells took longer to differentiate into specialized tissues such as muscle or bone.

The studies by Wake, Roth and Sessions also provided a rationale for understanding why salamanders with some of the largest genomes of all had lost toes, hind legs and even their ability to undergo metamorphosis. Their hefty genomes had slowed and truncated many aspects of development. People assumed that this depressed development stemmed from the simple fact that large genomes take longer to copy, so cells divide more slowly. But in 2018 a new milestone in genomics provided a critical insight.

Researchers published the first complete salamander genome, for the Mexican axolotl. This beast can grow almost as long as a person's forearm. It has pencil legs, fluffy gills and other larval traits but has a genome of "only" 32 gigabases, compared with the waterdog's 118 gigabases. This study showed that the animal's transposons aren't just scattered among its genes; they are also abundant *within* genes, in regions called introns.

This minor detail has enormous implications. When a gene is turned on, its entire length of DNA, including introns, must be copied into a chain of RNA. The introns must then be clipped out before the RNA chain can be used as a template to make proteins that will guide a cell's development. Axolotl introns are up to 13 times longer than human introns, because they are crowded with transposons. Therefore, the RNA chains take longer to build. The instructions for how cells should specialize take longer to exert their effects—so long, Sessions says, that salamanders "never quite grow up."

Slow development is only part of how giant genomes distort bodies. Massive genomes have another major impact. Scientists accidentally noticed it more than 150 years ago, but its importance is just now being recognized.

HEARTS LIKE PAPER BAGS

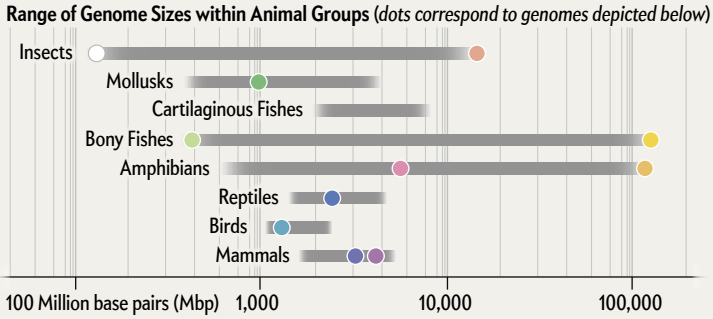
DURING THE EARLY 1800S a British army surgeon named George Gulliver pursued a pet interest as he traveled the world. At each destination he collected blood from local species, viewed the samples under a microscope and measured the red blood cells. He surveyed Mexican deer, American crocodiles, Indian pythons, spiny dogfish, electric eels, armadillos and hundreds of other animals.

A Kaleidoscope of Genomes

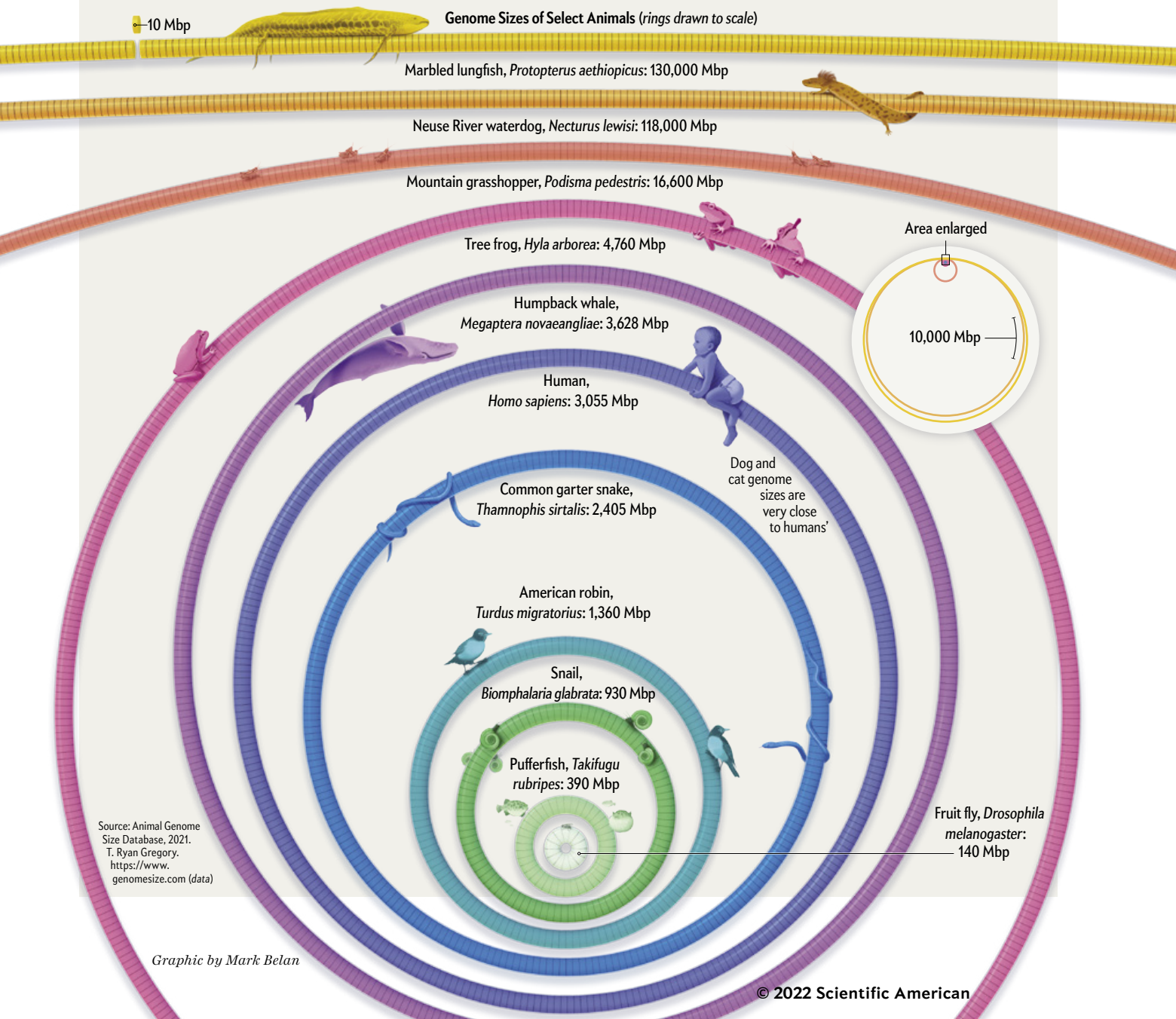
The marbled lungfish holds the record for the largest animal genome on Earth (*colored rings, below*). The Neuse River waterdog, a rare salamander, is not far behind. The human genome (*purple ring*) is just average size, about 43 times smaller than the lungfish's and 22 times larger than a fruit fly's. Bird genomes have the narrowest range; amphibian genomes vary wildly (*chart*).

The genomes of insects and mollusks vary considerably in size, yet the range for vertebrates is even broader—greatest for bony fishes and amphibians and least for reptiles, birds and mammals. Sizes are measured in base pairs—chemical building blocks of the DNA that forms genes. The complete set of an organism's genes constitutes its genome.

Range of Genome Sizes within Animal Groups (*dots correspond to genomes depicted below*)



Genome Sizes of Select Animals (*rings drawn to scale*)



Source: Animal Genome Size Database, 2021. T. Ryan Gregory. https://www.genomesize.com (*data*)

Graphic by Mark Belan

Gulliver found the largest cells by far in the three-toed amphiuma, whose vestigial legs are so tiny it resembles an eel. Its red blood cells occupied 300 times more volume than those of humans. Salamanders and a lungfish were close behind amphiuma, with the next-largest cells.

We now know that cell size and genome size go hand in hand: the more DNA, the larger the cell. Large cells have significant effects on an animal's structure. Some salamanders have responded by simply growing really big bodies. The Chinese giant salamander can be 1.8 meters long. Amphiuma species can reach 1.1 meters. The Neuse River waterdog can approach 28 centimeters, which is still twice as long as most other salamanders.

Large cellular building blocks also result in simpler bodies. Imagine that you're building two identical toy cars—one with small Lego blocks, the other with big Duplo blocks. If the cars are the same size, the one made with bigger blocks will have a simpler, more chunked-up design. That's how salamander bodies appear.

James Hanken, now at Harvard University, discovered the classic case of this in the 1980s. Hanken was studying wrist "bones" (actually made of cartilage that never finishes hardening) in the world's smallest salamanders. These species of the genus *Thorius* inhabit nooks in Mexico's montane forests. Some are small enough to sit on the face of a nickel. Dozens of related species have the same eight wrist bones, despite evolving separately for millions of years. But Hanken found that in *Thorius* species, some of the eight ancestral bones had merged. More surprisingly, the arrangement of bones varied within a single species. Some animals had as few as four wrist bones, others as many as seven. Some even had different bone patterns in their right and left wrists.

The perseverance of these salamanders demonstrates that our notion of "survival of the fittest" is incorrectly biased.

That kind of variability was "exceptional," Hanken says. He thinks that because *Thorius* has a small body and big cells, there literally aren't enough cells to go around when wrist bones form in the embryo.

Mueller and her Ph.D. student Michael Itgen were fascinated by Hanken's conclusion that larger cells lead to simplified bodies. But they wondered whether it actually mattered to these animals. In 2019 they started an ambitious project to understand how differences in cell size influence the structure of the heart; they looked at nine species of plethodontid salamanders with genomes ranging from 29 to 67 gigabases.

Plethodontids are lungless; they breathe through their skin. They have only one heart ventricle (rather than two, as mammals do). As Itgen examined the plethodontids' ventricles under a microscope, he was astonished at how different they were. Animals with the smallest genomes had muscular, thick-walled ventricles, with only a small space for blood in the center. As the animals' genomes escalated, their ventricles became increasingly hollowed out, with a larger blood cavity surrounded by ever thinner muscle walls. In the species with the largest genome, the ventricle resembled an empty bag made of a flimsy film of muscle, as little as one cell thick.

Seeing that hollow heart was a revelation. "I can't even imagine how that thing functionally works," says Itgen, who, along with Mueller, submitted his results to the journal *Evolution* in late 2021.

Itgen isn't sure why larger genomes lead to hollower hearts. He speculates that the ventricles of larger-genome species may need more space to accommodate larger blood cells, which can change blood's viscosity. Or, he says, the hollow hearts might have less muscle because the cells can't divide quickly enough during development.

Either way, this shoddy construction comes at a heavy price. Adam Chicco, who studies cardiac physiology at Colorado State University, sees parallels between these thin-bag ventricles and what he has observed in humans with severe heart failure: fewer muscle cells, stretched ever thinner, less and less able to pump blood.

The salamanders would be on death's door if they were human. "Everything about having a large genome is costly," Wake told me in 2020. Yet salamanders have survived for 200 million years. "So there must be some benefit," he said. The hunt for those benefits has led to some heretical surprises, potentially turning our understanding of evolution on its head.

PROFOUND DISTORTIONS

WAKE SPOKE WITH ME twice in 2020; he died in April 2021. But by then, he and Sessions had finally reached an insight that had eluded them for decades: a theory of how salamanders and lungfish might benefit from outsized genomes. The theory germinated from an audacious experiment.

Sessions and his undergraduate student, Yuri Mataev, had anesthetized several eastern newts, peeled back the thin flaps of their skulls and removed nearly a quarter of each animal's brain—a region involved in smelling. It's one thing for a salamander to regenerate a severed leg; Sessions wanted to test the limits of this ability. Sure enough, "within six weeks they were regenerating their brains," Sessions says.

The experiment showed that salamanders could regrow body parts they don't normally lose in nature. That concept was at odds with a basic evolutionary principle—that abilities arise in response to environmental stressors. Perhaps, Sessions suspected, regeneration had evolved only partly in response to such stressors, and a giant genome had enhanced the tendency as an ultimately beneficial side effect.

Sessions now thinks that slow development, caused by transposons located within introns, might leave adult salamanders full of immature cells that can still differ-

entiate into new tissues. "Salamanders are basically walking bags of stem cells," he says. This theory, which he put forth with Wake, was published in June 2021, shortly after Wake died.

The idea has "some plausibility," says Jeramiah Smith, who studies the axolotl genome at the University of Kentucky. He cautions that the picture may not be so simple; life has many ways of slowing down development when it is advantageous to do so. But with transposons so abundant in the salamander genome, it makes sense that they would play a role. "Evolution works with the material it has," Smith says.

The theory, if true, could have major repercussions. Scientists have spent decades studying salamander regeneration, in hopes of finding ways to regrow human tissues. But if regeneration requires having a multitude of genes with long introns, that could make the goal more challenging.

On a more profound level, Wake and Sessions's theory reflects the great depth to which genetic parasites have reprogrammed the very biology of salamanders. Many long-lived species such as humans keep their remaining stem cells muzzled once development is complete, an evolutionary trade-off that reduces the ever present risk of runaway cell division, which can cause cancer. Salamanders' stem cells are more numerous and far less constrained.

Wake and Sessions's theory may not fully explain why salamanders can tolerate huge genomes. Although it is handy to be able to regrow appendages that are lost on rare occasions, salamanders still have to survive day after day with those bizarre distortions of their hearts, brains and bodies. This paradox points to a surprising possibility, which emerged during a conversation between Mueller, Itgen and Hanken in mid-2021.

The trio were on a Zoom call, discussing how the hollowed-out hearts might affect the survival of salamanders. "I'll take the extreme position," Hanken said. Maybe the hollow hearts "are not having any impact" at all.

Strange as it might seem, that suggestion made sense to Mueller and Itgen. Salamanders grow and move slowly. They have by far the lowest metabolic rates and oxygen needs of any vertebrates. The plethodontids that Itgen and Mueller study don't even have lungs. Maybe salamanders tolerate hollow ventricles, Itgen said, "because the functional requirements on the heart are so low."

Indeed, when Sessions ran his regeneration experiments, he also removed up to half of the lone ventricle in a dozen eastern newts. The blood gushed out, and the hearts stopped beating, yet the animals survived and grew new ventricles—suggesting that they may not need their hearts as much as mammals do.

Salamanders don't seem to pay a price for their odd skeletons, either. Hanken thinks *Thorius* tolerates slipshod wrist bones because the animals' bodies are so small that the forces on their joints are minuscule. And *Thorius* doesn't need the fine-tuned limbs of a cheetah, because it doesn't chase its prey. It simply sits and waits for an insect to happen by.

Roth adds that if salamanders are just waiting for prey, they can simplify their entire vision system. The most extreme examples are the bolitoglossine salamanders of Europe and the Americas. These species include the largest genomes of any land-dwelling animals, up to 83 gigabases (24 times the human genome). They also happen to have the most stripped-down brains that Roth and Wake have ever seen in a salamander. They have lost 50 to 90 percent of their visual neurons to simplification, leaving them unable to distinguish between an insect crawling past them and a shiny metal pellet rolling by. What bolitoglossines do have, however, is one of the fastest tongues on Earth—"like walking around with a cocked gun," Wake said—able to zap an insect within a few milliseconds.

If you have that kind of tongue, if you don't need to see very well, if you can sit still for long periods, all that takes a lot of pressure off the body. You can have a simplified brain, a hollow heart and weird wrist bones, "and it doesn't matter," Mueller says. "It's pretty profound."

CRUEL IRONY

EVER SINCE IT BECAME CLEAR that salamanders and lungfish have far more DNA than humans, scientists have debated what purpose this extra DNA might serve. Initially some of them argued that DNA, in addition to its informational content, serves as a scaffold that determines the size of a cell's nucleus. That idea has fallen by the wayside. The latest view is more nuanced.

Transposons are indeed junk DNA, says Ting Wang, a genomic scientist who studies transposons at the Washington University School of Medicine in St. Louis. But this junk, scattered across the genome, becomes fodder for evolution. Sometimes it takes on legitimate functions. Transposons that land close to a gene can cause the gene to turn on more strongly, for example. In 2021 Wang discovered a transposon that activates a critical gene in mouse embryos; delete that single transposon, and many of the embryos die. Transposons also play structural roles, partitioning our genome into functional sections. "You can't separate them from us anymore," Wang says. "They're part of us."

And yet they can betray us. When Wang's team analyzed nearly 8,000 human tumors in 2019, the researchers found that in half, transposons were turning on key oncogenes that were driving the cancer's explosive growth.

All of this suggests that although transposons are sometimes coopted by the host, they have no inherent purpose. "Not everything is adaptive," says T. Ryan Gregory, a biologist who studies genome size at the University of Guelph in Ontario. DNA exists for its own sake. It doesn't just evolve to maximize the survival of its host; it also evolves to maximize itself—the host be damned.

As the host struggles to maintain its niche in the world, an equally dramatic struggle plays out in its cells. Transposons compete to populate the genomic landscape and evade predation by cell defenses. "We're starting to think about the genome as an ecological community and the transposable elements as species," Mueller says.

The propensity of transposons to multiply means that all genomes have a tendency to expand over time. Like stuff in a garage, DNA will accumulate to fill whatever space is available. It is the pressure of natural selection, penalizing the host when its genome gets too big, that maintains the genome at a certain size in most species. There are patterns to that size, Gregory says. The DNA load that a species can tolerate depends on its speed of development, its metabolic rate and the way it lives.

Birds, with their fast metabolism and energy-demanding flight, simply can't manage a lot of bulky DNA. Their genomes are smaller than those of most mammals, ranging from 0.89 to 2.11 gigabases—fewer than the 3.06 gigabases for humans. Among mammals, 19 of the 20 smallest genomes belong to bats, which face challenges similar to birds'.

We humans fall in the middle of the mammal pack, which probably reflects several competing factors. We develop slowly, taking almost 20 years to reach adulthood, which implies that we should have significant capacity for carting around extra DNA. But the size of our genome may sit on a razor's edge, kept in check by another critical factor: the brainpower that we depend on for survival. Suzana Herculano-Houzel, a brain scientist at Vanderbilt University, thinks humans and other primates owe their outsize intelligence to the fact that their nerve cells are relatively small, allowing us to cram more of them into our cerebral cortex. If her theory is

THE WATERDOG compensates for its frail heart and lungs by breathing through gills. Despite being riddled with junk DNA, the salamander has found ways to survive.

correct, then a larger human genome might leave us with fewer brain cells—and less smarts.

Frogs and toads, close relatives to salamanders, often have relatively large genomes, ranging up to 13.1 gigabases of DNA. But the ornate burrowing frog, whose genome was published in 2021, has only 1.06 gigabases, similar to a hummingbird's. It inhabits the Australian desert, laying eggs in puddles that form after infrequent rains. The tadpoles have only a few days to sprout legs before their aquatic nurseries evaporate. They simply can't afford to hoard genomic junk. Even among plants, the fast-spreading weeds that take over vacant lots—thistle, dandelions, and the like—often have smaller genomes than the slower-growing species that they smother.

In contrast to lean-and-mean species, the salamander probably evolved its bloated genome gradually. Gregory and Mueller think that 200 million years ago, the ancestor of all salamanders probably occupied the slow lane of life, with low energy needs and sluggish development. As a result, it suffered no immediate harm as transposons accumulated in its genome. As salamander genomes expanded, they pushed the critters further into niches where the slow-and-frugal strategy paid off.

In a 2020 paper, Gregory suggests that this process eventually hit a tipping point: transposons changed from being mere inhabitants of the genomic landscape to being full-blown ecosystem engineers. When a transposon inserts a new copy of itself, there is always a risk that it will disrupt a gene and harm the host—which is bad if you're a parasite because you depend on the host for survival. A newly inserted transposon won't be passed on to the next generation if it causes its host to be sterile, for example. But as transposons multiplied, their very presence provided more "habitat" in the genome where new transposons could insert themselves without hitting genes. "There is a feedback loop," Gregory says. "The more transposons you have, the more safe places you have to insert them."

And so it was that the Neuse River waterdog eventually found itself lugging around 118 gigabases of DNA. Its sister species, the dwarf waterdog (*Necturus punctatus*), is right behind, with 117 gigabases.

It's easy to look at the Neuse River waterdog and feel a pang of pity. Its slow development not only leaves it unable to metamorphose but may also prevent adult salamanders from regenerating limbs, a cruel irony. Unable to traverse dry land, the waterdog remains isolated in two small river systems in North Carolina. Agriculture and development have led to worsening water quality. In June 2021 the U.S. government listed the waterdog, whose population is falling, as "threatened." Although salamanders have survived as a group for 200 million years, it is tempting to think that this one species' ginormous genome has pushed it toward extinction.

Sessions isn't so sure. These bloated beasts have demonstrated, time and again, that when it comes to survival of the fittest, our notion of "fitness" is biased toward strength and agility. Genomic parasites have slowed the waterdog's development, swelled its cells and distorted its anatomy. This odd circumstance has pushed the animal onto a bizarre evolutionary side track that redefines fitness in such a way that hearts and complex brains are reduced to an afterthought. Yet somehow the animal's lineage persists, even as fires, floods and asteroids obliterate other species—furry, feathered and scaled—that seem more fit.

"Salamanders," Sessions says, "are tough survivors." SA

FROM OUR ARCHIVES

Hacking the Genome. Deborah Erickson; April 1992.

scientificamerican.com/magazine/sa

NEAND

EAGLE TALONS found in association with Neandertal remains at the site of Krapina in Croatia bear marks that suggest they were strung together to form an ornamental object such as a necklace.

EVOLUTION

ERTALS LIKE US

Remains from Croatia reveal that the much maligned Neandertals had more in common with modern humans than previously supposed

By David W. Frayer and Davorka Radovčić

David W. Frayer is an emeritus professor of biological anthropology at the University of Kansas. He has studied skeletal variation and behavior in Neandertals and other early human populations spanning more than a million years.

Davorka Radovčić is curator of the Krapina Neandertal Collection at the Croatian Natural History Museum. Her research focuses on Neandertals, early modern humans and *Homo naledi*.

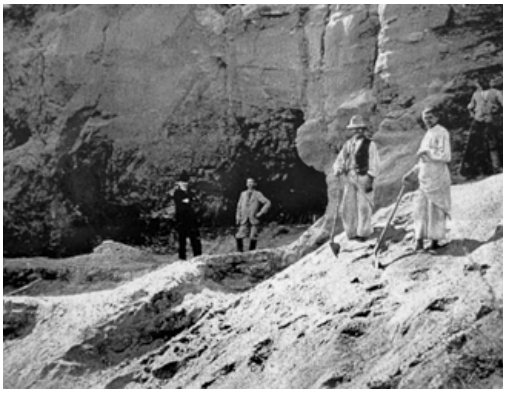
LAST MARCH, AS TEXAS AND MISSISSIPPI LIFTED THEIR CORONAVIRUS PANDEMIC MASK MANDATES against the advice of health officials, President Joe Biden accused the governors of those states of "Neandertal thinking." Biden was right to be concerned about rolling back coronavirus restrictions too soon, but he was wrong to use our evolutionary cousins as the basis for his reprimand.

Biden is hardly alone in wielding "Neandertal" as a pejorative term. In popular culture, it is common to make fun of Neandertals, pointing to their primitive physical features, their backward ways, their overall stupidity. Merriam-Webster suggests "clod," "lout" and "oaf" as suitable synonyms for "Neandertal." Even some of our paleoanthropologist colleagues consider Neandertals—who ruled Eurasia from 350,000 to 30,000 years ago—less than human, deficient in many of the cognitive and behavioral abilities typical of our kind.

Yet numerous studies underscore the similarities between Neandertals and us. Finds at Neandertal sites across Eurasia show that they had innovative technology, complex foraging strategies and nascent symbolic traditions.

Not everyone is convinced. Critics have argued that Neandertals learned advanced behaviors or acquired fancy goods from the modern humans they encountered rather than developing them independently.

Our research on Neandertal material from the site of Krapina in northwestern Croatia over the past 15 years provides evidence that the critics are wrong. The Neandertals there exhibited a range of behaviors traditionally assumed to be unique to modern humans, and they developed these behaviors independently, tens of thousands of years before modern humans arrived in this region. Much remains to be discovered about these enigmatic members of the human family, but it is now abundantly clear that they were behaving in cognitively sophisticated ways long before they ever met up with the likes of us.



KRAPINA ROCKSHELTER in northern Croatia, excavated at the start of the 20th century, was inhabited by Neandertals 130,000 years ago.

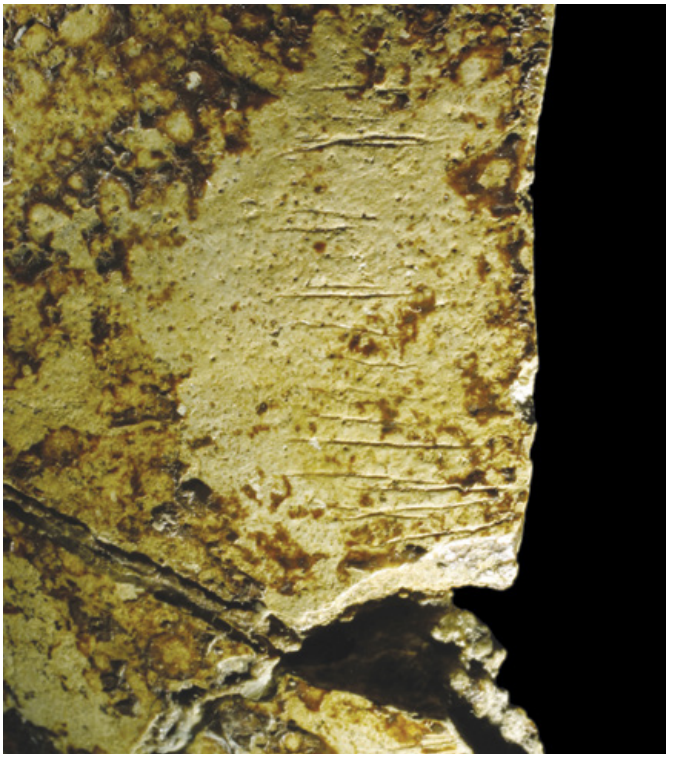
THE ORIGINAL OTHERS

THE NEANDERTALS' bad rap traces back to the mid-1800s, when British geologist William King wrote of the skull of the first Neandertal fossil from Germany: "the thoughts and desires which once dwelt within it never soared beyond those of the brute." This perception of Neandertals gained currency in the early 1900s, when French anatomist Marcellin Boule reconstructed a Neandertal skeleton from the site of La Chapelle-aux-Saints in France as a stooped, apelike creature—one that he saw as primitive in body and therefore mind. Ever since, paleoanthropologists have been debating just how much like us the Neandertals were in terms of anatomy as well as behavior.

For a long time it looked as though Neandertal behavior differed from that of early modern humans in several important respects. Researchers argued that Neandertals had the same tool kit for tens of thousands of years, whereas early modern humans eventually went on to make a variety of more complex tools that used a wider range of raw materials and took more steps to create. Similarly, moderns appeared to eat a far more varied diet of animal and plant foods compared with the Neandertals' apparent focus on large game. And moderns seemed to be unique in developing art and rituals.

In recent years, though, paleoanthropologists have recovered evidence of Neandertals behaving in ways no one would have pre-

Luka Mjeda (*preceding pages*); Croatian Natural History Museum (*this page*); all artifacts are housed at and shown courtesy of Croatian Natural History Museum



NEANDERTAL CRANIUM from Krapina (*left*) bears a series of parallel cut marks on the forehead that probably signify ritual behavior (*right*).

dicted just a couple of decades ago. Bruce Hardy and his colleagues have found bits of ancient twisted thread at the site of Abris du Maras in France that show Neandertals had fiber technology. Marie Soressi and her collaborators discovered specialized bone tools called lissoirs, which are used for leather-working, at Pech-de-l'Azé rockshelter in France. João Zilhão and his team have shown that Neandertals were eating mussels, crabs, sharks and seals, among other marine resources, at Figueira Brava in Portugal and other coastal sites. Elsewhere in Europe researchers have found indications that Neandertals exploited a wide variety of plant foods and even mushrooms.

It is not just previously unknown Neandertal technology and dietary strategies that have come to light. Other discoveries demonstrate that Neandertals engaged in symbolic behaviors, such as decorating their bodies and making art. Marco Peresani and his group have reported on cut marks on bird wings found in Fumane Cave in Italy that indicate Neandertals were collecting feathers. A team led by Clive Finlayson uncovered an abstract image resembling a hashtag etched into the floor of Gorham's Cave in Gibraltar. Dirk Leder and his colleagues found a toe bone from a giant deer engraved with a geometric pattern at the site of Einhornhöhle in Germany.

Researchers have unearthed many such examples of Neandertal creativity. But controversy has often accompanied their claims. Most evidence of Neandertal symbolism dates to the latter part of the Neandertals' reign, by which point anatomically modern humans were beginning to filter into Europe. Perhaps, critics have suggested, Neandertals merely copied what moderns were doing or obtained symbolic items from them through trade or even theft. Alternatively, at cave sites that were inhabited at different times by both groups, maybe natural disturbances—such as moving water or denning animals—mixed modern goods in with Neandertal remains. What investigators needed to find to bolster their case for Neandertal sophistication was evidence of advanced Neandertal behavior that was substantially older than the earliest-known modern humans in Europe. This is where our work at Krapina comes in.

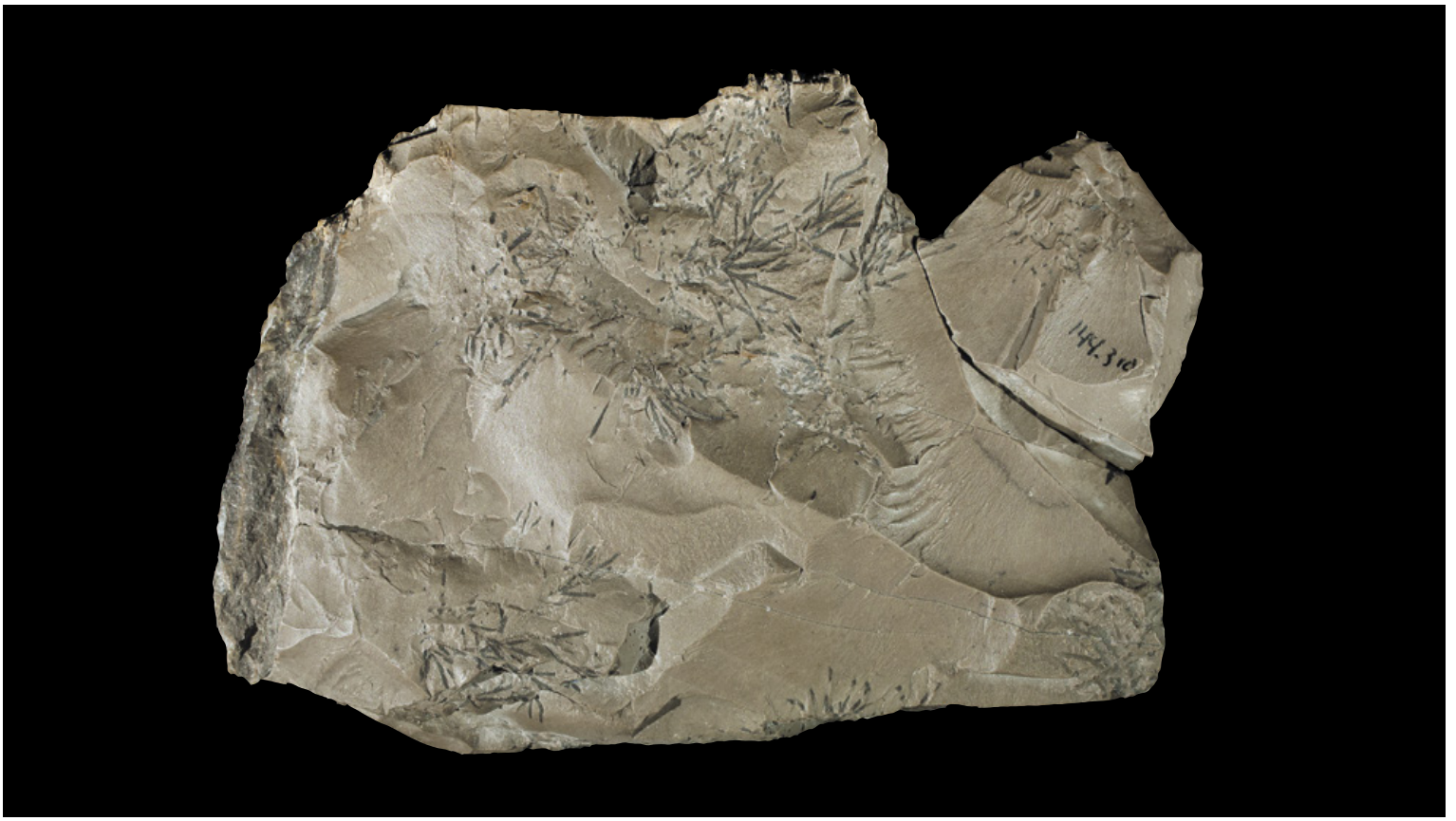
SYMBOLIC BEHAVIOR

FROM 1899 TO 1905 Croatian paleontologist Dragutin Gorjanović-Kramberger directed excavations at the Krapina rockshelter, collecting some 900 Neandertal bones, nearly 200 isolated Neandertal teeth, and thousands of animal bones and stone tools. He was a meticulous excavator. Uncommonly for his era, he dug in levels—removing one horizontal layer of sediment, bones and artifacts at a time—and saved much of what he excavated. In 1906 Gorjanović-Kramberger published a comprehensive monograph on the bones and tools from the site. To this day, Krapina remains one of Europe's richest Neandertal sites; thousands of publications about its inhabitants have appeared since 1899.

Our recent research provides unexpected new insights into the Neandertals who lived and died at Krapina some 130,000 years ago. In 2013 one of us (Radovčić) did a complete inventory of all the material from the site and "rediscovered" some unusual white-tailed eagle remains—eight talons and a foot bone—whose importance had previously gone unappreciated. Each bore multiple signs of having been intentionally modified. Discovered in the uppermost level at the site, the talons and foot bone were found in the same sedimentary layer as many cave bear bones, Neandertal tools, a fragmentary child's cranium and at least one hearth. No modern humans or modern tools are found at Krapina, so there is no doubt these white-tailed eagle bones are associated with Neandertals.

In life, eagle talons are covered with a thick carapace, which must have been stripped off, given the subsequent modifications on all the Krapina talons. One talon has cut marks on its upper surface and a preserved sinew fiber under a natural silicate coating, along with microscopic bits of red and yellow ochre in the pores on its surface. Three of the other Krapina talons and the phalanx show cut marks. The edges of many of these marks are

Luka Mjeda (*left*); David W. Frayer (*right*)



MUDSTONE ROCK found at Krapina appears to have been collected by a Neandertal for its aesthetic appeal.

Luka Mjeda

eroded, which we think may be the result of the talons having been tied together with a binding such as sinew. Other marks, including notches cut into some of the talons, support the hypothesis that these talons were strung into some kind of ornamental object—probably a necklace or bracelet or perhaps a rattle.

We know from the duplication of right second talons in this assemblage that the eight talons and foot bone came from at least three different white-tailed eagles. In the Paleolithic, as in modern times, eagles were the largest aerial predators around. Their rarity in the landscape would have made them difficult prey to catch. It therefore seems unlikely this was a random collection of eagle feet.

Instead these remains signal that the Krapina Neandertals had some kind of specialized hunting strategy. Although single talons have turned up at other Neandertal sites and probably served as pendants, no other Neandertal site has yielded eight talons from the same archaeological level.

The eagle talons are not the only sign of symbolic behavior among the Krapina Neandertals. The site has also yielded a unique rock with starburstlike inclusions that went undescribed until Radovčić noticed it while inventorying the collection. Formed of mudstone dating to the Middle Triassic epoch, the rock could not have originated in the Krapina rockshelter, which is composed of sandstone. Rather it seems that a Neandertal collected it from nearby outcrops of rock to the north of the site. Measuring 92 by 66 millimeters, with a maximum thickness of 17 millimeters, it easily fits in the hand. Because it shows no signs of surface modification or use wear, we can be fairly certain it was not used as a tool.

The rock is remarkable for its numerous dendritic structures, which are exposed in cross section and longitudinally. The structures have a three-dimensional appearance and are especially brilliant when the piece is wet, which increases the contrast between the striking black branching structures and the brown cortex. At the bottom of the rock a long, curved black feature traverses the entire lower face with a concentration of dendritic forms in the midpoint. It is apparently the impression of some kind of fossilized plant stem.

Any modern-day rockhound would collect a rock like this one. Did a Krapina Neandertal experience that same feeling of wonder about this uniquely patterned stone when she or he picked it up? In any case, the object generated enough interest that its discoverer brought it home. The collection and curation of this stone show that Neandertals had an eye for aesthetically pleasing objects and assigned significance to them.

A partial Neandertal cranium from the site, known as Krapina 3, provides a different kind of evidence for symbolic behavior. Assessed as a female based on its size and comparatively delicate build, the specimen bears 35 mostly parallel striations that run up the forehead. The marks show no signs of healing, so we know they were made after death. Other Neandertal bones from Krapina exhibit cut marks associated with defleshing related to cannibalism. But the cut marks on Krapina 3 are evenly spaced and differ from the closely packed criss-crossing butchering marks on these other specimens from the site. Nor do the cut marks appear to be the result of trampling of the bones by animals, which would have left more randomly scattered, overlapping marks.

Sometimes when anthropologists measure bones with calipers, the instrument can leave marks on the bone. But none of the standard measurements anthropologists take on skulls involve this part of the forehead. What is more, we know the cut marks are old be-

cause they are filled with cave sediment that buried the bone and are covered with lacquer, which paleontologists used to apply to fossils to preserve them. All these factors strongly suggest that a Neandertal made the marks.

Researchers have observed linear marks on bones at a few other Neandertal sites, but so far these cases involve only limb bones from animals found at these locales. The marks on the Krapina 3 Neandertal skull deviate from all the other examples of bone modification at the site and are unique in the fossil record. They probably signify some kind of ritual behavior, whether ceremonial modification of the remains of a loved one, numerical recording or doodling. Whatever the exact symbolic significance of these cut marks, the eagle talons or the starry stone, Neandertals were ascribing meaning to them 130,000 years ago—90,000 years before modern humans reached Croatia.

RIGHTIES AND LEFTIES

ANOTHER SYMBOLIC BEHAVIOR—one that scholars have often held up as a defining characteristic of modern humans and the secret of our success as a species—is language. Did Neandertals have language? Did they gossip about their neighbors, talk about their hopes and fears, tell their children bedtime stories? Without a time machine to transport us back to their era, we cannot know for certain. But there are hints in the archaeological and fossil records. A number of archaeologists consider body ornaments and other physical manifestations of symbolism to be proxies for language. Neandertal fossils themselves also contain clues.

We set out to determine whether Neandertals preferentially used one hand over the other in their daily tasks. Right-handedness is a common human trait; right-handers dominate left-handers in every living human population. Handedness reflects the fact that the two hemispheres of the brain are asymmetrical, with each side specialized for different tasks. This brain lateralization, as it is termed, is associated with language capacity. Other primates exhibit varying degrees of lateralization, but only humans show such a high frequency of right-handedness.

To assess the handedness of the Krapina Neandertals, we used optical and scanning electron microscopy to examine scratches in the enamel of their incisor and canine teeth. These striations, which occur exclusively on the lip side of the teeth, were produced when a stone tool accidentally etched the enamel. This kind of damage can occur when an individual uses his or her teeth as a third hand of sorts to grip an object—for instance, an animal hide. When a right-hander holds a tool and rakes it across material held between the front teeth, as one might do to clean an animal hide, any time the tool hits a tooth, it will leave a right-angled scratch on the tooth. A left-hander leaves an oppositely angled scratch. By studying the angles of the scratch marks evident in even a single fossil tooth, we can determine whether it belonged to a right-handed or left-handed individual.

Our analysis of the Krapina Neandertal teeth identified nine right-handers and two left-handers. If we expand our sample to include Neandertals from other European sites, the ratio of right-handers to left-handers replicates the typical 9:1 pattern of living humans. Interestingly, this pronounced dominance of right-handedness is not found first in Neandertals but extends back to their European predecessors and an even earlier member of our genus, *Homo,* from Africa. Apparently hemispheric brain asymmetry—and thus perhaps language—is an ancient human trait.

Neandertals had more than just behavior in common with modern humans. In-depth studies at Krapina and other sites show that many morphological characteristics once thought to be unique to Neandertals are found in moderns, and some modern features are found in Neandertals. One such trait is the form of an opening on the tongue side of the lower jaw (mandible) called the mandibular foramen. The mandibular nerve passes through this opening to innervate the teeth, gums and chin. In modern humans, the upper portion of the foramen is commonly V-shaped. In most Neandertals, the opening is covered by a bar of bone and is called a horizontal-oval (H-O) foramen. But at Krapina, only four of the nine Neandertal mandibles that preserve this part of the bone have the typical Neandertal H-O foramen; five show the modern V-shaped pattern.

Numerous other cranial and postcranial features in the Krapina Neandertals overlap with early modern humans, too. No doubt Neandertals had a distinctive morphology, but many of their traits are also found much later in the modern people who followed them. It is very unlikely moderns independently evolved these Neandertal-like traits. Rather there was probably a lot of variation in Neandertal morphology, and in later times some interbreeding occurred between them and our modern European ancestors. The "unique" traits were passed on as part of these interbreeding events. Given the apparent cognitive similarities between Neandertals and early modern humans, we should perhaps not be surprised that the two groups saw each other as humans and exchanged genes when they encountered each other.

Despite the fact that excavations at Krapina were concluded more than a century ago, the stones and bones from the site continue to provide new information about Neandertals and their place in human evolution. Undoubtedly more secrets remain to be revealed in the Krapina collection. We are endeavoring to tease out some of them. For example, with colleagues from England and Italy, we have been obtaining high-resolution, synchrotron images of baby teeth from the site to evaluate growth rates as measured by enamel formation. Modern humans are unique among living primates in having an extended period of childhood growth, which gives our large, powerful brains time to develop. Researchers have debated just how similar Neandertal childhood development was to that of moderns'. Our results show that Neandertal infants formed their enamel a little faster than moderns, indicating a more rapid growth rate on average. Yet it was still in the modern range.

Mounting evidence from sites across Europe is forcing scientists to rethink their conception of these long-disparaged members of the human family. The Krapina Neandertals are an important part of this shift. We suspect that future discoveries at Krapina and beyond will further narrow the list of behavioral and anatomical traits that supposedly set Neandertals apart from moderns. They were not the same as us. But we have far more in common with them than not. SA

This article is dedicated to the memory of Jakov Radovčić, who served as curator of the Krapina Neandertal Collection for 32 years.

FROM OUR ARCHIVES

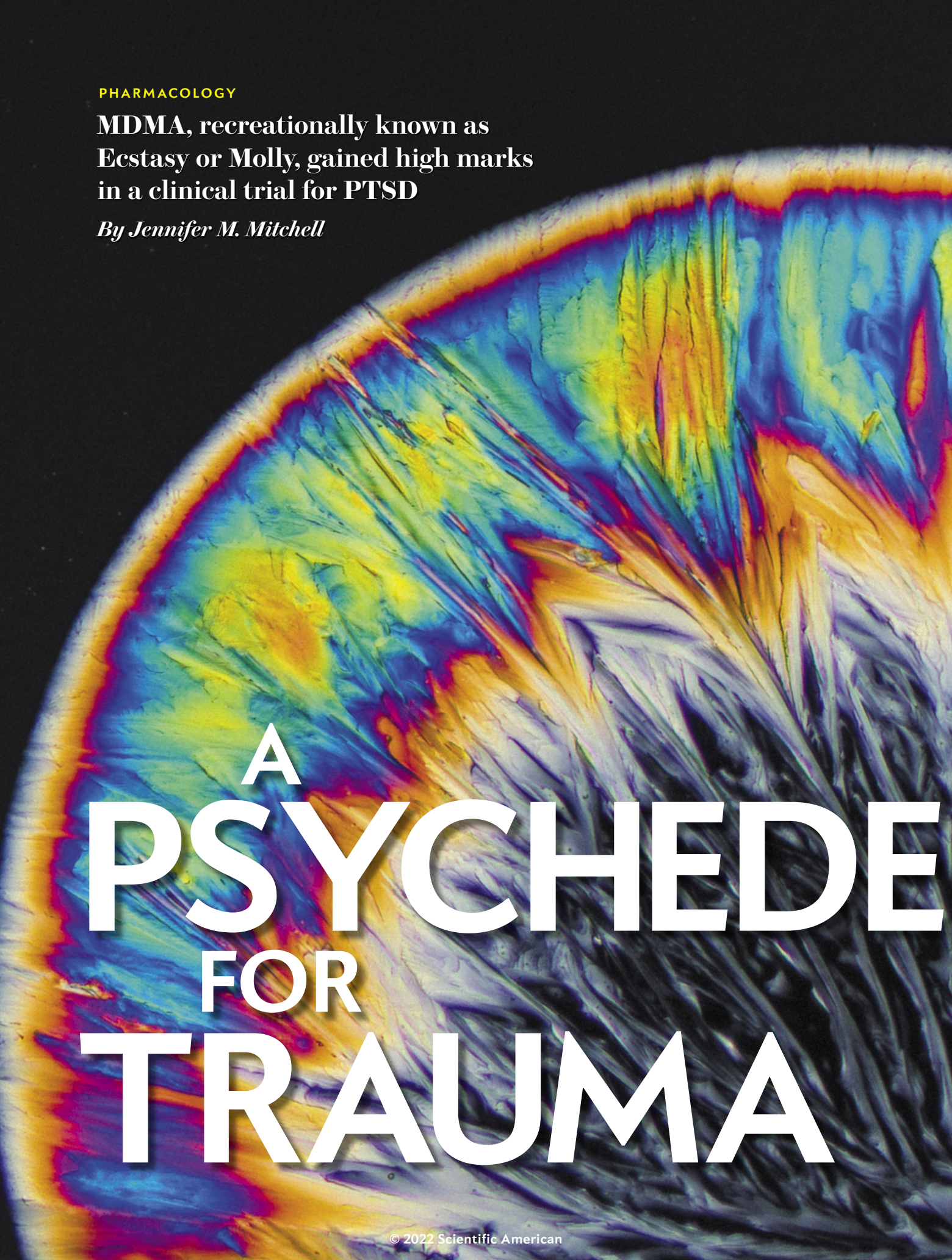
Neandertal Minds. Kate Wong; February 2015.

scientificamerican.com/magazine/sa

PHARMACOLOGY

MDMA, recreationally known as Ecstasy or Molly, gained high marks in a clinical trial for PTSD

By Jennifer M. Mitchell



A PSYCHEDE FOR TRAUMA

Maurice Mikkers

CRYSTALLIZED MDMA imaged through a polarized light microscope.

IN THE SPRING OF 2017 I WAS SERENDIPITOUSLY invited to what initially seemed to be the wrong scientific meeting. The invitation came thirdhand, and the details were murky but intriguing. I took a car to a train to a downtown hotel where I wound my way through a series of conference rooms before a sign on a door made it clear that something was terribly wrong. It said, "MAPS Phase 3 meeting."

Phase 3 is the final step in clinical drug testing before approval. It is conducted with a large group of study volunteers to make sure a drug is safe and effective. The endless meetings surrounding these trials typically involve months of vetting, confidentiality agreements and contracts; they are not to be crashed by wayward scientists with thirdhand invitations, and I immediately felt out of place.

Before I could retreat, someone emerged from the conference room and looked me over intensely. She asked me to explain myself, and then, to my surprise, she turned to staff at the check-in table and said, "Get her a name tag. We'll figure this out later." By the end of the day I had come to know this powerhouse by name: Berra Yazar-Klosinski, chief scientific officer at the Multidisciplinary Association for Psychedelic Studies (MAPS). My background in behavioral pharmacology and clinical trials seemed to pique her attention, and by the end of the meeting I had committed to working with her on the phase 3 program that would assess the efficacy and safety of MDMA—known recreationally as Molly or Ecstasy—for severe PTSD, or post-traumatic stress disorder. PTSD is characterized by the reliving of unwelcome traumatic memories, and according to the National Center for PTSD, upward of 15 million people in the U.S. suffer from this debilitating condition in any given year.

MDMA, short for 3,4-methylenedioxymethamphetamine, is an amphetaminelike compound that was first developed by European pharmaceutical giant Merck in 1912 as part of a research program on blood-clotting agents. Shelved for years, it was resynthesized by chemist Alexander Shulgin in the 1970s and immortalized in his book *PiHKAL,* which contains a recipe for MDMA. Not long after, Shulgin shared the compound with a friend, psychologist Leo Zeff in Oakland, Calif. Zeff and his colleagues began to use MDMA in conjunction with psychotherapy in private practice and noted that their patients were better able to confront emotionally evocative and distressing memories. Within an hour of ingesting the compound, patients could set aside their fears and face recollections of shame and trauma.

Right on the heels of this discovery, however, MDMA stepped out of the psychotherapist's office and barreled into general circulation, becoming one of the most used substances for recreational purposes of the 1980s. In 1985 the U.S. Drug Enforcement Agency (DEA) classified MDMA as a Schedule I substance, making its possession a crime punishable by up to 15 years in

prison. The National Institutes of Health subsequently spent two decades funding research that suggested MDMA is neurotoxic and often lethal.

Animal studies showed that MDMA induces a massive release of the neurotransmitter serotonin, a signaling molecule that is an important regulator of mood and affect. Once released into synapses (the small gaps between neurons across which chemical signals pass), serotonin acts on receptors on nearby neurons to improve one's emotional state. Not only does MDMA cause a serotonin surge, it also prevents the signaling molecule from being reabsorbed into the neurons that secreted it, allowing serotonin to sit in the synapse and signal for longer than usual. This serotonin surge also induces the release of the hormones oxytocin and vasopressin from a brain region called the hypothalamus. Both of these hormones are thought to foster interpersonal bonding and feelings of closeness.

These early studies indicated that MDMA can promote long-lasting restructuring of serotonin-containing nerve fibers, but they also suggested that such changes occurred only at high doses and were reversible over time. Then along came George Ricaurte, a neurologist at the Johns Hopkins University School of Medicine, who made a name for himself by touting the alleged neurotoxic and lethal effects of MDMA. Ricaurte claimed that "even one dose of MDMA can lead to permanent brain damage." His findings, proclaiming that MDMA could ravage the brain and leave nothing but damaged fibers in its wake, were published in the journal *Science* and used time and again by the National Institute on Drug Abuse to support the war on drugs.

These data were later retracted after it was revealed that amphetamine, not MDMA, had caused the reported neurotoxicity. But it has taken us years to get beyond sensationalistic antidrug propaganda posters in which phrases such as "This is your brain on Ecstasy" were splashed atop artificially colored brain scans, making it look as if MDMA, as one DEA official put it, "turns your brain into Swiss cheese."

More recent animal data indicate that MDMA helps to extinguish memories of fearful experiences and impairs the reactivation of traumatic memories in rodents. These studies have shown that even the notoriously solitary octopus develops a penchant for hugging under the influence of the compound. Perhaps most intriguing are animal data that demonstrate that MDMA, coupled with oxytocin release, may reinitiate a "critical period" similar to those that occur during the social and emotional learning of childhood. This reopening appears to create a fluid state in which the painfully negative feelings attached to deeply traumatic memories can be processed and attenuated.

Similarly, recent human data have shown that MDMA increases cooperative behavior when subjects play a game with someone trustworthy and may help emotional recovery when their trust is compromised. If MDMA can truly soften the grip of negative memories, how do we take the next step toward evaluating and developing it as a potential therapeutic drug for veterans, victims of physical and sexual assault, and survivors of natural disasters who experience PTSD?

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GETTING TO YES

AFTER THE MAPS MEETING, I sat in my car and contemplated the tremendous hurdles involved in a phase 3 clinical trial. I had explained to Yazar-Klosinski that although I had acquired a fair amount of experience with phase 2 testing, I had never conducted a phase 3 trial, and it seemed foolishly shortsighted to think that sheer determination alone would enable me to tackle the complications that would inevitably arise. She was undaunted, but I was terrified.

Schedule I status is a bane for drug developers. According to the U.S. Controlled Substances Act, Schedule I substances by definition have no medical use, no accepted safety data and a high potential for misuse, which means there is typically no federal funding to study such compounds as potential therapeutics.

Given the regulatory obstacles, creating a research program for a Schedule I substance is a difficult and time-consuming process. Such compounds are highly restricted, and permission must be obtained from the DEA to allow them to be stored at a research facility and dispensed to subjects. To make matters worse, the Controlled Substance Analogue Enforcement Act of 1986 states that all compounds that are "substantially similar" to Schedule I compounds are also illegal, so there is no way to even approximate the effects of a drug such as MDMA in the laboratory without risking criminal charges.

To work with a Schedule I substance, one first needs to apply for a DEA license that lists each compound involved, the amount that will be used for each experiment, where and how the compounds will be stored, who will have access to the space, what security measures will protect them, and what record-keeping procedure and audit trail will be used to track them. There are annual fees to be paid and amendments to file with every change. This arduous process discourages all but the most resolute of investigators. There is also no clearly delineated process for reclassifying scheduled drugs, so even if there were enough data to demonstrate that a compound such as MDMA has a true pharmaceutical effect and a low potential for abuse, there is no obvious path toward assigning them a new classification as Schedule II, III or IV substances.

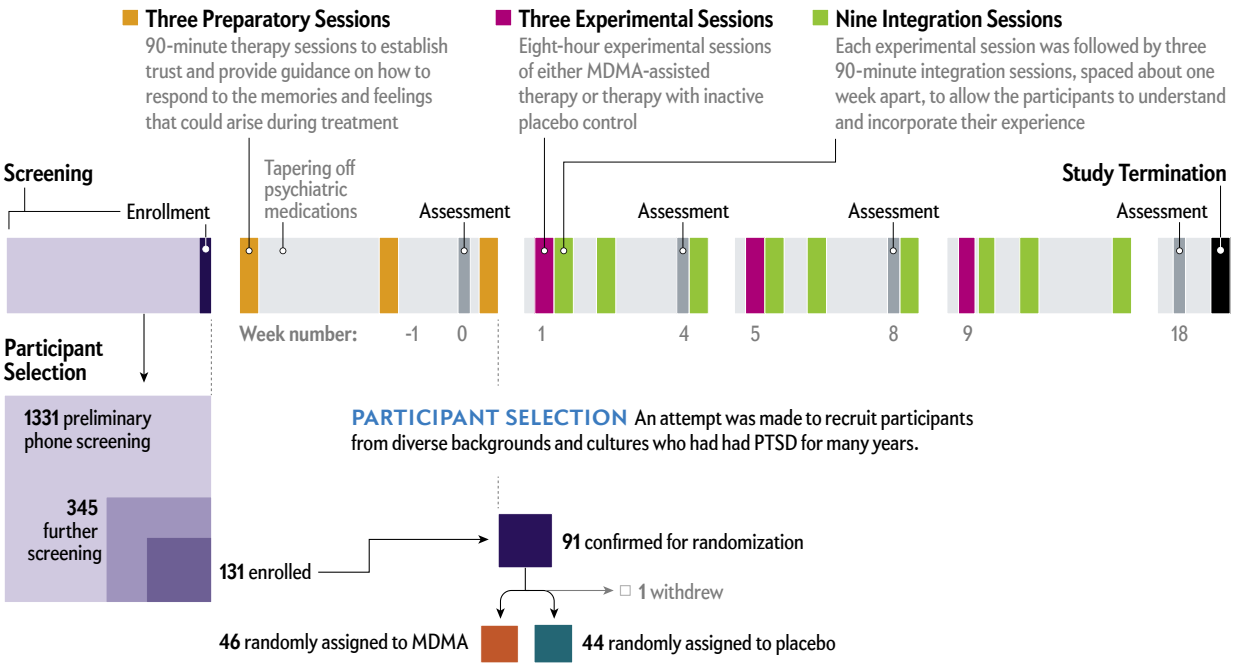
Once the DEA has signed off on Schedule I access, a similarly elaborate and time-consuming process is involved in getting approval from the Food and Drug Administration to give a Schedule I substance to humans. The first step is to submit an Investigational New Drug (IND) application to the appropriate division within the FDA Center for Drug Evaluation and Research. This application must contain virtually everything that is known about the drug to date, including data from animal pharmacology and toxicology studies, any results from human experiments, a manufacturing plan to assuage concerns about purity and supply, and other details about the clinical trial protocol and even the investigators involved. The FDA policy is to reply to IND applications within 30 days, but if for any reason the agency does not feel comfortable granting approval, a project can be placed on an indefinite clinical hold, which to clinical researchers is considered the kiss of death.

Our research team was able to take advantage of a Special Protocol Assessment (SPA), a new mecha-

A Daunting Trek toward FDA Approval

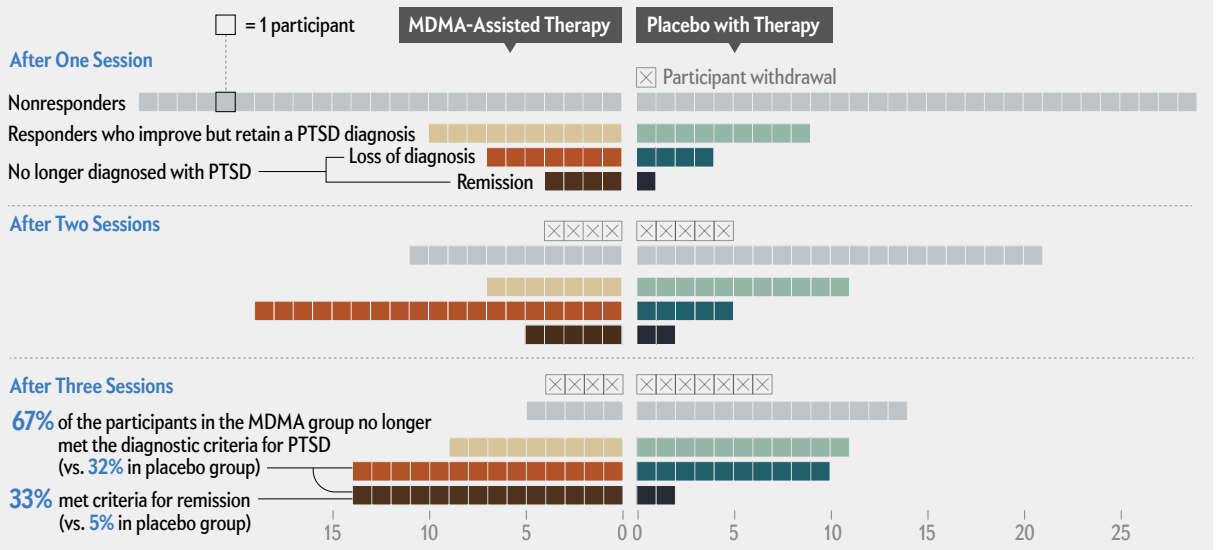
Revived interest in psychedelics for psychiatric disorders brought an immediate focus on MDMA as a possible treatment for intractable post-traumatic stress disorder (PTSD). A major challenge in conducting this type of research relates to the legal legacy of psychedelics, classified by regulators as recreational drugs of abuse with no medical use. To legitimize their use, the Multidisciplinary Association for Psychedelic Studies (MAPS) has undertaken a 20-year MDMA research program, some of it with crowdsourced funding. MAPS formulated an intricate study protocol involving 15 study sites across three countries with over 70 therapists. The researchers reported last May the results of the first-ever, late-stage clinical trial for a psychedelic. The phase 3 study showed a major benefit for PTSD patients and may be a model for future psychedelic studies. Here is a look at the study protocol devised by MAPS in preparation for a possible 2023 application for FDA approval.

TIME LINE The protocol for the phase 3 study administered three doses of MDMA in conjunction with therapy sessions over the course of 18 weeks.



PARTICIPANT SELECTION An attempt was made to recruit participants from diverse backgrounds and cultures who had had PTSD for many years.

RESULTS



Source: "MDMA-Assisted Therapy for Severe PTSD: A Randomized, Double-Blind, Placebo-Controlled Phase 3 Study," by Jennifer M. Mitchell et al., in *Nature Medicine*, Vol. 27; June 2021

Graphic by 5W Infographics

nism by which the FDA approval process can be made faster and more transparent. The SPA allows a sponsor—in this case, MAPS—to reach an agreement with the FDA on the study design, including a specific number of subjects, dosing, analysis plan and outcome measures. Because face time with the FDA is a rare and valuable commodity, it was quite a boon to receive a coveted SPA in 2017—and even better to be awarded Breakthrough Therapy Status the same year. The breakthrough designation grants expanded access to agency support and guidance and allows fast-tracking through the approval process if a drug is being developed to treat a serious or life-threatening condition.

Even once all the appropriate regulatory and compliance issues have been tackled, there is still the matter of manufacturing the compound. For clinical trials, this step must be performed in a "good manufacturing practices" (GMP)-certified laboratory. GMP ensures that production is consistent and conducted in a clean environment and meets FDA-prescribed quality standards. Although the process was seemingly straightforward, it took several tries to identify a GMP-certified lab able to reliably generate a pure compound. MDMA is also a painfully static molecule and tends to stick to everything it should not, meaning that it took practice for the GMP facility to successfully encapsulate the drug.

MDMA typically lets a person engage in active and open discussion about traumatic experiences without becoming emotionally overwhelmed.

CROWDFUNDING A CLINICAL TRIAL

BRINGING ANY NEW DRUG to market is difficult, but for psychedelics the process has been downright daunting. The first study of MDMA for PTSD, also funded by MAPS, obtained FDA approval in 2001, but recruitment of research participants for phase 3 did not begin until November 2018. Even an SPA and Breakthrough Therapy Status mean nothing without research funding. It costs an average of $985 million to bring a new drug to market. Because federal agencies typically do not support clinical research on Schedule I compounds, most funding for MDMA research to date has come through philanthropy and even some crowdfunding. (An aside: if someone had suggested to me 10 years ago that anyone, anywhere, would ever be conducting a phase 3 drug trial funded by crowdsourcing, I would have laughed them out of the room.)

The financial situation may soon improve, however. Just a few years ago, when psychedelics again started being tested in human trials, pharmaceutical companies were not exactly banging down the door to join the club. But in the past year enthusiasm has been dialed up, and psychedelic start-up companies now abound. With any luck, this funding and interest will help MAPS propel the first application for approval of MDMA for clinical use through the FDA within the next two years.

Although more than half a dozen phase 2 studies have demonstrated the effectiveness and safety of MDMA for PTSD, early trials often fail to accurately predict the outcome of the larger, multisite phase 3 trials that follow. In the case of MDMA, we have been lucky. At 15 study sites across three countries, working with more than 70 different therapists and with study participants with childhood trauma, depression and a treatment-resistant subtype of PTSD, we have obtained incredibly promising results.

Phase 3 study participants receiving MDMA-assisted therapy showed a greater reduction in PTSD symptoms and functional impairment than participants receiving placebo plus therapy. In addition, their symptoms of depression plummeted. By the end of the study more than 67 percent of the participants in the MDMA group no longer met criteria for PTSD. An additional 21 percent had a clinically meaningful response—in other words, a lessening of anxiety, depression, vigilant mental states, and emotional flatness.

And although there had been concern that administering any new medication to people with suicidal ideation could worsen their problems, MDMA-assisted therapy did not increase measures of suicidal thinking or behavior. MDMA also did not demonstrate any measurable misuse potential (which should compel us to reconsider the reasoning behind the war on drugs and scare tactics of the 1990s).

Yet despite these encouraging findings, it would be irresponsible to expect similarly impressive outcomes for MDMA in less clinically controlled situations and more heterogeneous populations. The success of psychedelic medications depends on tight control of variables such as the experience of the therapist team, the environment or setting in which the therapeutic is administered, and the amount of time participants spend integrating what they learn during the psychedelic session. Our work has no bearing, though, on recreational use of MDMA, which typically occurs in settings dramatically different from those of fastidiously planned clinical experiments and relies on street drugs that are often cut with all kinds of adulterants.

We are currently collecting long-term follow-up data from the phase 3 study. One important question is how long the therapeutic effects of MDMA and other psychedelics might last. Clearly, these compounds differ from drugs such as SSRIs (selective serotonin reuptake inhibitors), which must be administered daily, usually for years and sometimes indefinitely. We do not yet know whether our participants will have to return every couple of years for additional MDMA-assisted therapy. Although early clinical studies suggest that the therapeutic effects of psychedelics can be quite long-lasting, we also do not yet know whether there are subsets of our clinical population for whom the effects are particularly durable and others for whom additional dosing sessions or integration work will be needed.

MDMA is an experiential medicine, so its therapeutic effects are influenced by the setting in which it is administered. This is a key distinction from other medications. I would not expect a blood thinner to have certain effects if I took it in my parents' living room versus in my neighbor's kitchen. I would not expect it to work differently depending on my mood.

Psychedelics are undeniably different. They are dependent on frame of mind and environment. For this reason, it is essential to educate participants on the potential effects of the compound before consumption. The treatment setting must be thoughtfully constructed to provide the right amount of support and protection. It is even more critical that participants be guided through the expe-

rience by trained facilitators—often doctors or psychologists with special training—who know how to gently shift and shape the experience and to help them process the many facets of trauma that will arise. Additionally, if, as the animal data suggest, the MDMA-induced reopening of a critical period could last for several weeks, every effort should be made to use that time to heal, learn and grow.

Our study participants came from a multitude of backgrounds and cultures, but all had been diagnosed with severe PTSD and had been suffering from it for, on average, more than a decade. Many of them were considered treatment-resistant, having tried other PTSD therapies and therapeutics to no avail. More than 90 percent of them reported depression that accompanied their trauma, as well as suicidal thoughts.

Participants typically underwent three preparatory sessions with their therapy team before embarking on their three all-day experimental sessions. These prep sessions helped us set expectations for treatment and described what the subjects should anticipate if they were among those who received MDMA. Because this was a double-blind, placebo-controlled trial, these sessions also gave us a chance to explain what it might feel like to receive a placebo and how to manage disappointment about it. (Although it can be nearly impossible to fully mask the effects of a psychedelic, some of our participants guessed that they had received MDMA when in fact they had received placebo, and some guessed that they had received a placebo when they had received MDMA.)

Preparatory sessions were followed by an experimental session. Participants reclined on a sofa in a comfortable, dimly lit room and received a blister pack of study drug and a glass of water to begin their journey. Later came three integration sessions in which facilitators worked with participants to further untangle the trauma laid bare during the experimental session.

There is still much to learn about the neurobiological mechanisms of action of MDMA therapy, but it typically enables participants to engage in active, open discussions about their trauma without becoming emotionally overwhelmed—a major challenge to those suffering from PTSD. They frequently discuss their traumatic experiences with tremendous self-compassion, which some of our therapists speculate is the key to their eventual liberation from their burdens. By the end of the study participants are sometimes noticeably changed in physical appearance. They stand up straighter, they meet our eyes and they even smile.

WHICH IS IT?

ONE OF THE BIGGEST unanswered questions as we develop psychedelic medications is whether the subjective "psychedelic" experience is necessary for the therapeutic actions or is an irrelevant side effect that should be engineered away to make the treatment process faster and more marketable. Indeed, drug companies intent on developing "nonpsychedelic" psychedelics (those that have no psychoactive or hallucinogenic effects) have suddenly come out of the woodwork. Yet given the myriad data suggesting that the intensity of the mystical experience correlates with therapeutic improvement—and subjective reports espousing the beneficial impact of a psychedelic epiphany on years of negative thinking—it seems prudent to continue to focus on truly psychedelic compounds.

In addition to PTSD, data support the use of MDMA for depression, anxiety, eating disorders, and alcohol and drug use disorders. DEA rescheduling could reduce the barrier to clinical assessment of MDMA for these and other indications. Even after DEA and FDA approval of MDMA for PTSD has been obtained, however, a slew of tasks must be completed before the drug can reach the market. There should be a pipeline for training and credentialing psychedelic facilitators and for generating a system of clinics through which they can practice. Drug developers will need to develop a risk-evaluation and mitigation strategy and submit it to the FDA for approval—this step is to confirm that clinical use of MDMA carries no unchecked risks or side effects—and they will have to design a treatment cost structure to encourage HMOs and insurance providers to cover the expenses.

I first read about the potential therapeutic effects of psychedelics for anxiety and addiction in college, and by the time I entered graduate school I was convinced that understanding these compounds would lead to better treatments for a variety of mental health disorders. Because we were never able to obtain access to psychedelics for lab testing, we instead focused on separating out the various components of their biochemical activity (typically termed reverse engineering).

Most psychedelics have multiple pharmacological targets, and it is possible to tease them apart and test them one step at a time with more easily accessible drugs. For example, if a psychedelic induces the release of serotonin and oxytocin, we can try modifying behavior with an SSRI or oxytocin. If it acts as an NMDA receptor antagonist, which blocks the signaling molecule glutamate, we can use an NMDA receptor antagonist such as ketamine. Many of us have spent decades investigating the neural mechanisms and behavioral effects of potential therapeutics in this way based on our knowledge of the biochemistry of psychedelics. Although the fields of neuroscience and behavioral pharmacology have come quite a long way in terms of understanding behaviors such as anxiety, fear, substance craving and impulsivity, we have still fallen far short of generating a panacea for the suffering caused by these conditions. Perhaps it is time to take a different tack.

More than 50 years ago, after a decade of growing civil unrest and in response to the spreading recreational use of psychedelics, the pendulum of acceptance swung sharply. The turmoil and fear of the 1970s propelled a national agenda of regulation and criminalization. Half a century later the pendulum has swung again, and we find ourselves considering anew the medical value of psychedelic drugs. In addition to several dozen new studies on the effects of MDMA, there are now ongoing clinical trials for several other psychedelics, including psilocybin, LSD, ayahuasca and ibogaine.

As enlightened as this new direction might feel, we must take care to ensure that the zeal of the converted does not color our decision-making. We need to take the time to thoroughly investigate these powerful compounds—to understand both their benefits and their shortcomings. Without scientific rigor, the pendulum could swing again. "Nothing to excess" and "the dose makes the poison" are the adages I hear time and again. The road to MDMA approval as the first medical psychedelic may still be long and bumpy, but if the enthusiasm and drive I encountered in that hotel conference room nearly five years ago are any indication of things to come, then I believe we are steadily heading in the right direction. SA

FROM OUR ARCHIVES

Hallucinogens as Medicine. Roland R. Griffiths and Charles S. Grob; December 2010.

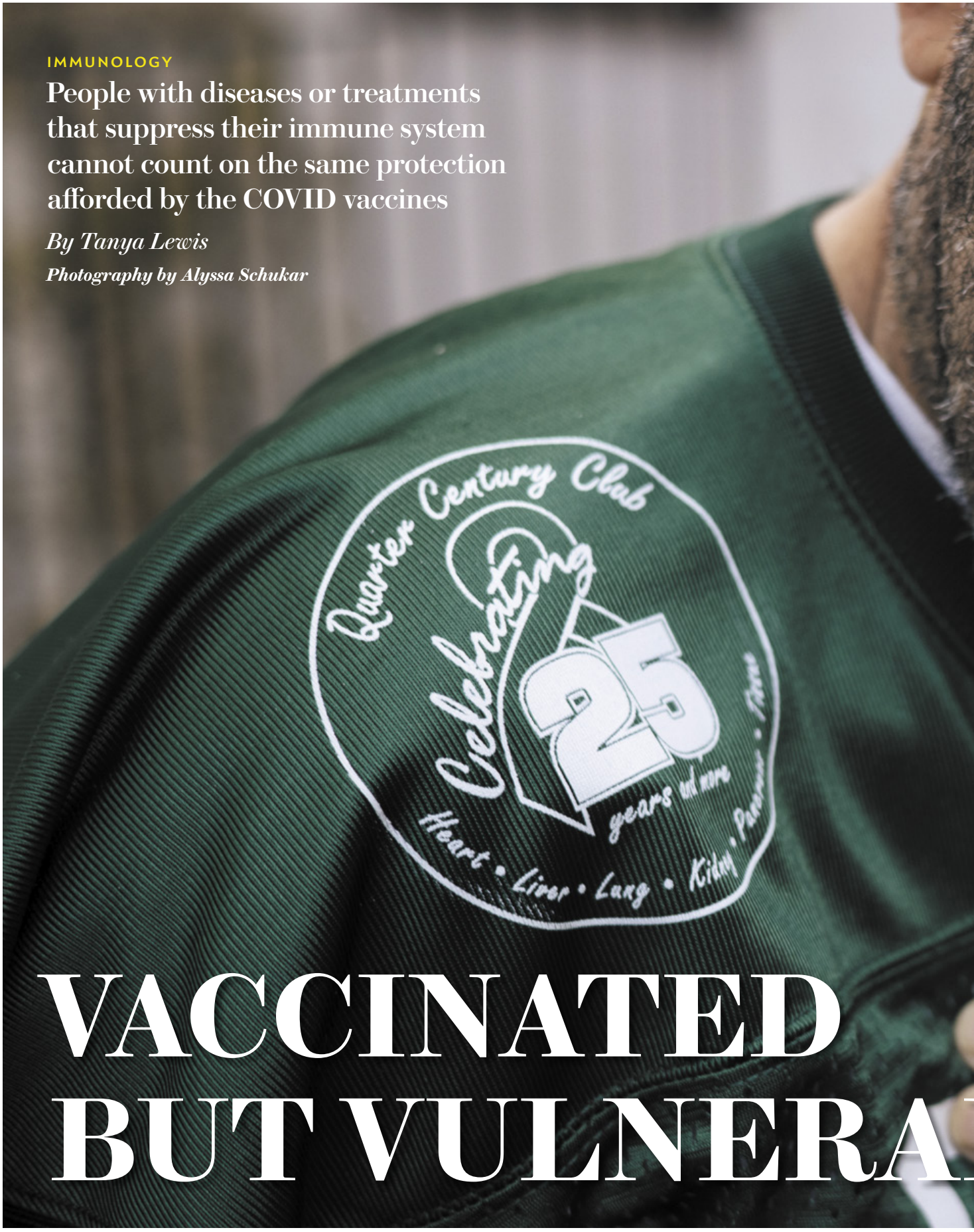
scientificamerican.com/magazine/sa

IMMUNOLOGY

People with diseases or treatments that suppress their immune system cannot count on the same protection afforded by the COVID vaccines

By Tanya Lewis

Photography by Alyssa Schukar



VACCINATED BUT VULNERA

BLE

GEORGE FRANKLIN III of Cumberland, Md., received a kidney transplant 46 years ago. He is one of many Americans who are immunocompromised and who remain highly susceptible to COVID despite vaccination.

Tanya Lewis is a senior editor covering health and medicine for *Scientific American*.

GEORGE FRANKLIN III IS ONE OF THE LONGEST-SURVIVING KIDNEY TRANSPLANT recipients in the U.S. Now 67, he received his lifesaving surgery 46 years ago, which has enabled him to lead a healthy and active life—swimming, bowling, visiting friends and even competing in a sporting tournament known as the International Transplant Games. But since the beginning of the COVID pandemic, he hasn't been able to do any of these things. Like most transplant recipients, Franklin, who lives in western Maryland, has to take medication to suppress his immune system and prevent his body from rejecting the donor organ. Last March he received the Johnson & Johnson COVID vaccine but did not develop detectable levels of antibodies. "Those of us that have no antibodies," he says, "it's as if we've never taken a shot." (Last November he got the Moderna vaccine and finally developed antibodies.)

Franklin is one of many people who belong to this vulnerable club. Former secretary of state Colin Powell, who died in October 2021 from COVID complications, was among them. He had been vaccinated but suffered from multiple myeloma, a blood cancer that attacks infection-fighting white blood cells and is often treated with drugs that suppress the immune system even further.

The pandemic has forced everyone to adjust to restrictions on normal life. But for those who belong to a broad category known as immunocompromised, even ordinary activities come with extraordinary risks. This umbrella term includes people whose immune systems have been weakened by diseases such as cancer, HIV infection or autoimmune disorders or by immunosuppressant treatments such as steroids, chemotherapy or drugs that prevent rejection of transplanted organs.

Studies have shown that immunocompromised people are more vulnerable to being hospitalized or dying from COVID and less likely to develop strong protection from vaccination. There have been hopeful signs. Additional doses of some COVID vaccines, strategic timing of immunosuppressant treatments and prophylactic COVID treatments may boost protection among a subset of these people and restore at least some of the freedoms they have lost during the pandemic.

But tempering that hope is the emergence of new variants—such as Omicron—that might erode some of the vaccines' immunity. As of press time, the Omicron variant appeared likely to evade at least some of that protection, although researchers were urgently working to determine just how much.

With Omicron, "I worry a lot for our immunocompromised folks," says Dawn Bodish, an immunologist at McMaster University and a Canada Research Chair in Aging and Immunity. "A few months ago I said confidently, 'Ah, fourth doses, nobody's thinking about that.' Now we all are—and mixing and matching the vaccine types and really optimizing the dosing regime, so these people can be protected as best as we're able."

INCOMPLETE PROTECTION

THERE IS STILL MUCH we don't know about how well the COVID vaccines work in people with immunosuppressing diseases or treatments, because the clinical trials that preceded their approval excluded this group for safety reasons. But scientists have begun to study this question. A recent report from the U.S. Centers for Disease Control and Prevention that examined immunocompromised people who received

TO PREVENT his body from rejecting the donor organ, Franklin takes immunosuppressive medication, but it also makes him vulnerable to COVID and other infections.

mRNA vaccines found that vaccination was 77 percent effective against hospitalization with COVID, compared with 90 percent for immunocompetent people. But the effectiveness ranged widely depending on the immune condition, from 59 percent for organ or stem cell transplant recipients to 81 percent for people with a rheumatological or inflammatory disorder.

Dorry Segev, a professor of surgery at Johns Hopkins University, and his colleagues have been studying how well transplant recipients and others with suppressed immune systems respond to the COVID vaccines. In June 2021 he and his team published a study in *JAMA* showing that out of more than 650 transplant recipients who received an mRNA COVID vaccine (either Pfizer's or Moderna's), 46 percent had no detectable response after one or two doses; 39 percent did not have a response to one dose but did after a second. In a separate study, they found that transplant recipients who received the Johnson & Johnson vaccine were much less likely to have a detectable response than those who had an mRNA vaccine. This lack of protection could be dangerous: Segev and his colleagues found that vaccinated recipients were 82 times more likely to have a breakthrough infection than the general population and 485 times more likely to be hospitalized and die from it.

Also in June, Segev and his colleagues published a study online in the *Annals of Internal Medicine* of 30 transplant recipients who received a third dose of a COVID vaccine. Six of the patients had low but detectable antibody levels after their initial two shots, and 24 had no detectable antibodies. Of those who had low antibody levels, all six had high levels after the third dose. But only six of those who had no antibodies had high antibody levels after a third dose.

These findings helped to form the basis of the CDC's decision last August to make a third dose available to immunocompromised people, before booster shots were authorized for all adults. In some people—mostly those with autoimmune diseases—"a third dose helps a lot and gets them over that hump to a more protected level of antibody," Segev says. Most transplant recipients, however, have not been as fortunate. "Only a fraction of transplant patients who got a third dose reach that kind of a milestone." For people who get vaccinated while waiting for a transplant, however, there is good news. "They will likely have a very, very good vaccine response—way better than they'll get once they're on immunosuppression," Segev says.

Another highly vulnerable group is patients with blood cancers, such as Powell. Nearly 35,000 people in the U.S. are diagnosed with multiple myeloma every year. The disease attacks bone marrow plasma cells, which make antibodies in response to the virus that causes COVID—and to the vaccines. Drugs prescribed to treat it kill off normal plasma cells, as well as cancerous ones, further compounding the problem.

BEFORE the pandemic, Franklin was physically active and competed in the International Transplant Games. But COVID has limited the activities he can safely do.

Diana M. Chavez of Los Angeles was diagnosed with multiple myeloma in 2020. "Nothing is more difficult than getting a cancer diagnosis during a pandemic," she says. "It's unknown territory." Chavez, age 66, had to attend doctor's appointments alone and was not able to have visitors in the hospital because of COVID restrictions. "There was no relative or friend who could be my advocate to remind me of all the questions I had and needed to ask, with all the decisions I had to quickly make," she says.

Chavez did not develop a protective antibody response after two doses of the Moderna vaccine, but she finally did after a third. She takes a steroid medication as part of her myeloma treatment, but she decided to briefly pause taking it around the time she got her third shot. (She informed her doctor of her intention. Patients should always consult their physicians before stopping or changing any treatment regimen.) "For the first time yesterday, I went out with a friend and had breakfast," Chavez says. But she is still being cautious. "Sometimes, even under the best of circumstances, when you're trying to be mindful, things still happen," she says, adding that the big question about cancer patients who are able to have a response to the vaccine is "How long will it hold? Are we going to have to keep getting vaccinated?"

Last July, James Berenson, medical and scientific director of the Institute for Myeloma & Bone Cancer Research in West Hollywood, Calif., and his colleagues published a study online in the journal *Leukemia* of the immune response to mRNA vaccination among multiple myeloma patients. They found that only 45 percent of those with active myeloma developed an adequate level of antibodies after two doses of the Pfizer or Moderna vaccine, and 22 percent had a partial response. Study participants who received the Moderna vaccine had higher antibody levels than those who received the Pfizer shot, Berenson found. "We discovered older folks like Colin Powell—those who are over about 70 and those people with lower lymphocyte [immune cell] counts, with lower antibody levels reflective of this impaired immune system, who are doing poorly with

their myeloma, those people who've [had] other treatments or were failing their treatment—were much less likely to respond" to COVID vaccination, Berenson says. He is now studying the effect of additional vaccine doses in multiple myeloma patients, and the results, he says, are "shockingly promising."

Antibody levels are only one part of immune protection, however. T cells and memory B cells also form a critical part of the body's immune arsenal after vaccination or infection, but Segev's and Berenson's studies did not evaluate them, because they are harder to measure. T cells may provide some protection even in people who lack detectable antibodies.

IMMUNE BOOST

REASSURINGLY, people with some types of autoimmune diseases have had fairly good responses to vaccination. Segev and his colleagues studied vaccinated people with rheumatic and musculoskeletal diseases—such as inflammatory arthritis or lupus—and found that the vast majority of them produced COVID antibodies after two doses of the mRNA vaccines.

Clinical neuroscientist Tjalf Ziemssen of University Hospital Carl Gustav Carus in Dresden, Germany, and his colleagues have been analyzing the response to COVID vaccination in patients with multiple sclerosis, a disease in which the immune system attacks the fatty sheath that protects nerves in the brain and spinal cord. It is often treated with immune-modulating drugs called S1P receptor modulators and anti-CD20 monoclonal antibodies. In patients taking the latter, Ziemssen and his team found that the response among B cells (which produce antibodies to COVID) was fairly low but that there was a good response involving T cells (which attack and kill viruses such as the COVID-causing SARS-CoV-2). Patients taking S1P receptor modulators had a weaker response, but about two thirds still developed a B or T cell response, or both.

Ziemssen does not recommend changing the dosing of multiple sclerosis treatment to improve the vaccine response. Rather he suggests that patients getting infusion treatments for the disease should wait a month after an infusion to get vaccinated. In patients who had a good B and T cell response, he recommends a booster shot at six months. For those who did not have a good response, he recommends a third dose given sooner.

Still, many people with other, rarer immune diseases are left wondering whether they are protected against COVID. Dinah S., who asked that her last name not be given to maintain her privacy, has a rare condition called mucous membrane pemphigoid, which causes blistering of the gums and other areas. She takes mycophenolate mofetil, an immunosuppressant drug often prescribed for organ transplant recipients, and has taken the steroid prednisone in the past.

Dinah was part of Segev and his colleagues' studies. She initially received two doses of the Pfizer vaccine, but an antibody test revealed she had no response. She then got the one-dose Johnson & Johnson shot and was still negative for antibodies. So Dinah next got three Moderna doses, after which she finally achieved a response similar to healthy people who have had two doses. The entire process lasted six months. "My ordeal has contributed to approval of boosters for everyone but especially for immunocompromised people," she says. "Boosters work and are needed!"

Since the pandemic began, Dinah has remained effectively locked down in a "bubble" of three people, taking strict precautions to limit her infection risk. Now that she has a measurable response to her vaccinations, she says she is finally able to relax a bit. "The big excitement that the vaccine brings me is that I might get to go into a grocery store for the first time since before lockdown," she says. "Fully masked, at a quiet time of day and in a big airy store but still. The bulk spice and tea aisle calls to me."

"The best thing we can do for immunocompromised people is for everybody else to get vaccinated."
—Dorry Segev *Johns Hopkins University*

Johns Hopkins's Segev recommends a three-pronged approach to improving the vaccine response among people with weakened immune systems. First, he recommends trying a third dose. If that does not work, some patients may be able to temporarily reduce the amount of immunosuppressive medication they are taking (although only if their doctor deems this safe) and get another dose. Finally, if vaccination fails, Segev recommends giving patients monoclonal antibodies as a form of passive immunity against COVID. Monoclonals are currently authorized for use after confirmed infection or exposure to COVID, but Segev hopes the Food and Drug Administration will consider allowing this option for prophylactic use.

Vaccination is not the only protective measure immunocompromised people can take. They can avoid crowds or being indoors with unvaccinated individuals or those with frequent exposure to other people. They can wear a high-quality mask such as an N95 around people they do not live with and increase ventilation by opening windows and using air purifiers. They can have others test themselves before interacting with them. These precautions, though more onerous than a shot in the arm, are effective when layered together. "The best thing we can do for immunocompromised people," Segev says, "is for everybody else to get vaccinated, so that we protect our vulnerable friends and neighbors." SA

FROM OUR ARCHIVES

The New Science of Autoimmune Disease. Special report; September 2021.

scientificamerican.com/magazine/sa

MIND

People who jump to conclusions tend to believe in conspiracy theories, are overconfident and make other mistakes in their thinking

By Carmen Sanchez and David Dunning

Illustration by Islenia Milien

Leaps of Confusion

Carmen Sanchez is an assistant professor at the University of Illinois at Urbana-Champaign's Gies College of Business. She studies the development of misbeliefs, decision-making and overconfidence.

David Dunning is a social psychologist and a professor of psychology at the University of Michigan. His research focuses on the psychology of human misbelief, particularly false beliefs people hold about themselves.

HOW MUCH TIME DO YOU SPEND DOING RESEARCH BEFORE YOU MAKE a big decision? The answer for many of us, it turns out, is hardly any. Before buying a car, for instance, most people make two or fewer trips to a dealership. And when picking a doctor, many individuals simply use recommendations from friends and family rather than consulting medical professionals or sources such as health-care Web sites or articles on good physicians, according to an analysis published in the journal *Health Services Research*.

We are not necessarily conserving our mental resources to spend them on even weightier decisions. One in five Americans spends more time planning their upcoming vacation than they do on their financial future. There are people who go over every detail exhaustively before making a choice, and it is certainly possible to overthink things. But a fair number of individuals are quick to jump to conclusions. Psychologists call this way of thinking a cognitive bias, a tendency toward a specific mental mistake. In this case, the error is making a call based on the sparsest of evidence.

In our own research, we have found that hasty judgments are often just one part of larger error-prone patterns in behavior and thinking. These patterns have costs. People who tend to make such jumps in their reasoning often choose a bet in which they have low chances of winning instead of one where their chances are much better.

To study jumping, we examined decision-making patterns among more than 600 people from the general population. Because much of the work on this type of bias comes from studies of schizophrenia (jumping to conclusions is common among people with the condition), we borrowed a thinking game used in that area of research.

In this game, players encountered someone who was fishing from one of two lakes: in one lake, most of the fish were red; in the other, most were gray. The fisher would catch one fish at a time and stop only when players thought they could say which lake was being fished. Some players had to see many fish before making a decision. Others—the jumpers—stopped after only one or two.

We also asked participants questions to learn more about their thought patterns. We found that the fewer fish a player waited to see, the more errors that individual made in other types of beliefs, reasoning and decisions.

For instance, the earlier people jumped, the more likely they were to endorse conspiracy theories, such as the idea that the Apollo moon landings had been faked. Such individuals were also more likely to believe in paranormal phenomena and medical myths, such as the idea that health officials are actively hiding a link between cell phones and cancer.

Jumpers made more errors than nonjumpers on problems that require thoughtful analysis. Consider this brainteaser: "A baseball bat and ball cost $1.10 together. The bat costs $1 more than the ball. How much does the ball cost?" Many respondents leaped to the conclusion of 10 cents, but a little thought

reveals the right answer to be five cents. (It's true; think the problem through.)

In a gambling task, people with a tendency to jump were more often lured into choosing inferior bets over those in which they had a better chance of winning. Specifically, jumpers fell into the trap of focusing on the number of times a winning outcome could happen rather than the full range of possible outcomes.

Jumpers also had problems with overconfidence: on a quiz about U.S. civics, they overestimated the chance that their answers were right significantly more than other participants did—even when their answers were wrong.

The distinctions in decision quality between those who jumped and those who did not remained even after we took intelligence—based on a test of verbal intellect—and personality differences into account. Our data also suggested the difference was not merely the result of jumpers rushing through our tasks.

So what *is* behind jumping? Psychological researchers commonly distinguish between two pathways of thought: automatic, known as system 1, which reflects ideas that come to the mind easily, spontaneously and without effort; and controlled, or system 2, comprising conscious and effortful reasoning that is analytic, mindful and deliberate.

We used several assessments that teased apart how automatic our participants' responses were and how much they engaged in deliberate analysis. We found that jumpers and nonjumpers were equally swayed by automatic (system 1) thoughts. The jumpers, however, did not engage in controlled (system 2) reasoning to the same degree as nonjumpers.

It is system 2 thinking that helps people counterbalance mental contaminants and other biases introduced by the more knee-jerk system 1. Put another way, jumpers were more likely to accept the conclusions they made at first blush without deliberative examination or questioning. A lack of system 2 thinking was also more broadly connected to their problematic beliefs and faulty reasoning.

Happily, there may be some hope for jumpers: Our work suggests that using training to target their biases can help people think more deliberatively. Specifically, we adapted a method called metacognitive training from schizophrenia research and created a self-paced online version of the intervention. In this training, participants are confronted with their own biases. For example, as part of our approach, we ask people to tackle puzzles, and after they make mistakes related to specific biases, these errors are called out so the participants can learn about the missteps and other ways of thinking through the problem at hand. This intervention helps to chip away at participants' overconfidence.

We plan to continue this work to trace other problems introduced by jumping. Also, we wonder whether this cognitive bias offers any potential benefits that could account for how common it is. In the process, we aim to give back to schizophrenia research. In some studies, as many as two thirds of people with schizophrenia who express delusions also exhibit a jumping bias when solving simple, abstract probability problems, in comparison with up to one fifth of the general population.

Schizophrenia is a relatively rare condition, and much about the connection between jumping and judgment issues is not well understood. Our work with general populations could potentially fill this gap in ways that help people with schizophrenia.

In everyday life, the question of whether we should think things through or instead go with our gut is a frequent and important one. Recent studies show that even gathering just a little bit more evidence may help us avoid a major mistake. Sometimes the most important decision we make can be to take some more time before making a choice. SA

A baseball bat and ball cost $1.10 together. The bat costs $1 more than the ball. How much does the ball cost?

Hint: It is not 10 cents, although many people jump to that answer.

FROM OUR ARCHIVES

The Psychology of Preferences. Daniel Kahneman and Amos Tversky; January 1982.

scientificamerican.com/magazine/sa

NONFICTION

Life, Linked

A reverse journey through geologic time shows the interconnectedness of Earth's species

Review by Steve Brusatte

As a teenager, I was obsessed with dinosaurs, but I had little aptitude for what came before them. I couldn't make sense of what John McPhee, in that most glorious line of geopoetry, called "deep time." Planet Earth is 4.5 billion years old, and life has been around for about 90 percent of it. When *T. rex* stalked its prey, every trilobite that ever fossilized was already in the ground. Every *Brontosaurus*, too. The time spans seem inconceivable, yesterday's worlds far too distant from our own. Then, a book made it click: this was Richard Fortey's 1997 *Life*, which I devoured around the time I started studying geology in college. It was hard science, but it read like a novel, and it made the murky depths of prehistory into a riotous story.

Fortey wrote from his perch at the Natural History Museum in London, as one of the world's most respected and experienced paleontologists, the letters F.R.S. (Fellow of the Royal Society) trailing his name. A quarter of a century later Fortey's *Life* has a worthy successor in Thomas Halliday's *Otherlands*. Writing with gusto and bravado, Halliday is part of our generation of 30-something paleontologists, not long out of grad school, putting a millennial spin on popular science writing.

In a genre that can tend toward cookie-cutter sameness (*another* dinosaur encyclopedia?), Halliday has honed a unique voice. His approach is novel as well. *Otherlands* is a Benjamin Button tale, which begins in the present day and runs in reverse, the evolution of life in rewind. He structures the narrative through an ecological lens: Each major division of geologic time is given a single chapter, which is focused on a single lost ecosystem. As you read along, Earth gets weirder and weirder, the creatures more alien, more removed from the norms and comforts of today. Soon enough, you find yourself underwater 550 million years ago, in what is now Australia, where fish and whales and corals are nothing but a future fantasy, as blobs of primitive cells leave ghostly impressions on the seafloor.

Otherlands:
Journeys in Earth's Extinct Ecosystems
by Thomas Halliday.
Random House, 2022 ($28.99)

Otherlands is a verbal feast. You feel like you are there on the Mammoth Steppe, some 20,000 years ago, as frigid winds blow off the glacial front. You sense fear in a band of human ancestors as they clamber up a tree, fleeing a python. You can taste the salty air over a Jurassic lagoon and commiserate with a gorgonopsian—a ghastly mammal predecessor—as a tumor presses down on its jaw.

Along the way, we learn astounding facts. Some trees that are alive today emerged from seeds while mammoths trudged through snow; reefs of sponges once stretched from Poland to Oklahoma. And we meet some sublime creatures. There's *Haikouichthys*, one of the oldest fishes, "only a few centimeters long, shaped like a fallen leaf." Even more ancient is *Eoandromeda*, probably one of the oldest animals (or maybe not), a "coiling helter-skelter, floating hypnotically" in the Precambrian oceans. My favorite, the official fossil of my home state of Illinois, is the mystifying Tully Monster, with its "segmented torpedo of a body" and a "hose of a vacuum cleaner" as a nose.

During this backwards journey across time, Halliday centers his tale on how species work together as ecosystems and food webs. Yes, dinosaurs and megafaunal mammals pop up throughout, but plants, bugs, mushrooms and deep-sea bacteria all get their due. The great calamities and transformations of prehistory are treated more like background; the end-Permian mass extinction—the closest complex life has ever come to annihilation—garners a single paragraph, and the origin of limbed tetrapods from finned fish takes all of four sentences. This keeps attention on the bigger picture, as Halliday shows that the same rules of energy flow have governed all ecosystems over time, linking that dream world of 550 million years ago to dinosaurs to our fragile Earth of today.

Otherlands is a book for people who like books. Chapters begin with verses and proverbs in many languages (original and translated), poetry and mythology are liberally quoted throughout, and fossils are described with comparisons to Gaudí's architecture and L. S. Lowry's paintings. In many ways, it is more literature than traditional popular science, which makes me wonder how it will connect with people who haven't studied science (or poetry) since school.

Another new book on evolutionary history is more tailor-made for a general audience. *A (Very) Short History of Life on Earth*, written by *Nature* editor Henry Gee and published in late 2021, does what it promises. Punchy and breezy, his book reads like a bedtime story, the triumphs and cataclysms of life waltzing by at breakneck speed. Gee's book is more appetizer, Halliday's is more main course, and together they weave an evocative tapestry of what Earth and life have endured—which helps us understand where we are going next.

Steve Brusatte is a professor of paleontology at the University of Edinburgh.

Illustration by London Ladd

FICTION

Interspecies Epic

Saving rare horses from calamities past and future

Review by Robin Marie MacArthur

imageBROKER/Erdenebulgan Battsengel/Getty Images

The Last Wild Horses: A Novel
by Maja Lunde. Translated by Diane Oatley. HarperVia, 2022 ($27.99)

Norwegian author Maja Lunde became an international sensation with *The History of Bees*, the first novel in what she is calling her "Climate Quartet." The much anticipated third book in that series, *The Last Wild Horses*, is further evidence that some writers know how to spin a tale. The novel braids three time periods and places, all linked by the takhi, a rare wild horse species, and the humans devoted to saving them.

We start in 2064 in postapocalyptic Norway. Weather has become unpredictable, society has collapsed, and migrants move north by foot in search of food, infrastructure and clean water. But Eva and her 14-year-old daughter, Isa, have stayed put on their family's farm, trying to stay alive with their cows and chickens, as well as to protect the takhi that Eva's sister began sheltering years ago.

We then leap back to St. Petersburg in 1882, where a zoologist discovers that the long-presumed extinct takhi might still be living in the far reaches of Mongolia. He becomes consumed with how to capture some for the garden where he works.

Soon we are spinning forward in time again to meet Karin in Mongolia in 1992. Karin has been obsessed with the takhi since she first saw them as a child during the war in Germany. She has built a stable herd in a small village in France and is transporting them back to their native habitat in Mongolia with the hope that they can once again breed and survive in the wild.

In quixotic and propulsive interweaving chapters, Lunde captures the depth and range of human love in all forms—our capacity to care for species other than our own, our desire to connect with others, and how both these are so often thwarted by the external circumstances of trauma and war. Filled with haunting notions of interspecies kinship, the reverberations of kindness and care, and the innate drive to love and survive despite the odds, this book is one to savor.

IN BRIEF

This Way to the Universe: A Theoretical Physicist's Journey to the Edge of Reality

by Michael Dine. Dutton, 2022 ($28)

Renowned physicist Michael Dine takes us from the innards of the atom to the depths of black holes in this readable, though occasionally vexing, celebration of science's most mind-bending discipline. The text is conversational and full of delightful asides, but a reader with only one high school physics course under her belt might lose her way in some of the thornier explanations of quantum mechanics, for example. Dine's enthusiastic storytelling makes the read worth it for those who want to finally wrap their mind around string theory or the Higgs boson and are up for an intellectual challenge. *—Tess Joosse*

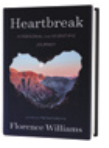
Origin: A Genetic History of the Americas

by Jennifer Raff. Twelve, 2022 ($30)

Jennifer Raff, who wrote our May 2021 cover story, "Journey into the Americas," applies her experience as an anthropologist and geneticist to a sizable task: righting the wrongs of both fields' treatment of Native peoples while addressing how modern methodologies are now closer to understanding the origins of Native Americans. *Origin* presents how centuries of racist thinking informed theories that were widely accepted. Interstitial case studies could merit entire chapters, from a Monacan burial mound in Thomas Jefferson's backyard to a digression on whether gender or occupation can be inferred from remains. And Raff makes ample space for Native voices through original interviews. *—Maddie Bender*

Heartbreak: A Personal and Scientific Journey

by Florence Williams. W. W. Norton, 2022 ($30)



When journalist and author Florence Williams's 25-year marriage falls apart, her health starts to, too. Desperate to avoid more of the dangerous physical damage that heartbreak can inflict, she pursues information on the "comingled destinies of our cells and our passions." The result is an engrossing survey of the latest research on the cardiology, neurology and genomics of lost love punctuated by the author's many experiments with healing, from EMDR therapy to a solo canoeing trip to magic mushrooms. Williams's journey through her pain is by turns wrenching, fascinating, funny and, for so many of us, deeply relatable. *—Dana Dunham*

Breaking the Techno-Promise

We do not have enough time for nuclear power to save us from the climate crisis

By Naomi Oreskes

Last fall my Harvard University class and I went through an exercise to help the students understand how the world might address the climate crisis and keep the average global temperature increase below two degrees Celsius. Guided by John Sterman, a management professor at the Massachusetts Institute of Technology, the students pretended to be climate negotiators, offering or blocking climate policies. Then, using En-ROADS, a computer simulation of the effects of climate policies that Sterman co-developed, they were able to see the consequences of their proposals on the 2100 average global temperature.

The exercise offered both bad news and good. The bad news is that keeping the rise in temperature below 2° C is going to be very hard and holding it under 1.5° probably impossible. The good news is that the challenge can be met—if we implement a large portfolio of solutions, the most important of which are eliminating fossil-fuel subsidies and putting a stiff price on carbon.

None of this will come as a shock to climate experts: our results were consistent with numerous reports that have argued against the silver bullet approach and in favor of "silver buckshot." But several things surprised the students. One was that planting a trillion trees doesn't help much, because it takes too long for them to grow. Another was that nuclear power doesn't help either, for essentially the same reason: nuclear plants take too long to build and bring online. Globally, the average construction time is about 10 years, and you need to add many years on to that period for site selection, regulatory approval and licensing. Some notorious examples have taken much longer. The most recent nuclear power reactors built in the U.S., at Georgia Power's Vogtle plant, were started in 2013 and are still not finished. That's the problem with imagined "breakthrough" technologies, too. Breakthroughs can be sudden, but implementation is slow.

I left the class thinking about nuclear power. Many people think nuclear energy is going to be the climate solution (or at least a big part of it). President Barack Obama included federal loan guarantees for nuclear power in his energy plan, in the hopes of jump-starting construction and garnering Republican support. (It did neither, but some Republicans are now pushing nuclear power as the key to cleaner U.S. energy.) If I want to rile up my Twitter feed, all I need do is post something even faintly skeptical about nuclear power, and its advocates come out in force, accusing me of being a Luddite, or a troglodyte, or worse.

What is it about nuclear energy that makes its advocates so determined in the face of what should be discouraging facts? After all, unlike futuristic, untried technologies, we have plenty of facts about this one, and most of them are discouraging.

The first American civilian nuclear power plant broke ground in Pennsylvania in 1954, around the same time that physicist John von Neumann predicted that, within a few decades, nuclear power would be so efficient as to make energy "free —just like the unmetered air—with coal and oil used mainly as raw materials for organic chemical synthesis." That didn't happen. Today nuclear power remains the most expensive form of electricity generation in the U.S.—typically costing twice as much to operate as a fossil-fuel-based plant. While the price of renewables has dropped dramatically, the cost of nuclear has remained stubbornly high. Nuclear fission is a technology with a track record of overpromising and underdelivering.

Why then do so many people keep coming back to it? I've come to think it's the same reason people turn to geoengineering and nuclear fusion (which has been "just around the corner" since 1943): the promise of technological progress. For the past century or more, humans have been accustomed to technological breakthroughs that made life easier, more comfortable and more entertaining. But climate change throws future advancement into doubt. It breaks the promise of progress. No matter what we do, we are going to be paying for the costs of our historical and current use of fossil fuels for decades to come.

So we turn to technofideism—the faith that technology will save us. Perhaps it will. But perhaps it won't, and our long-standing patterns of behavior will have to change along with our technology. And that's a hard pill to swallow.

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).

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Illustration by Jianan Liu

50, 100 & 150 YEARS AGO

INNOVATION AND DISCOVERY AS CHRONICLED IN *SCIENTIFIC AMERICAN*

Compiled by Mark Fischetti

FEBRUARY

1972 Tectonic Dump

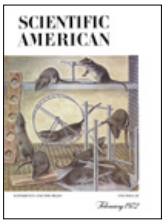
"A speculative but intriguing scheme for disposing of man-made solid wastes has been put forward by two investigators at the University of Washington. The plan would take advantage of regions called subduction sinks, where sedimentary material is being drawn downward into the earth's mantle as a consequence of seafloor spreading. A hypothetical disposal system would consist of three stages: collection, compaction of waste into blocks and its sea transportation to tectonic sinks. The one-way system would take care of quantities larger than we can produce."

Fiber-Optic Television

"The use of a laser beam as a high-capacity channel for carrying voice, video, digital and other signals has seemed an attractive possibility. A single coherent beam of laser light can in principle carry the equivalent of several thousand television channels. Until recently it seemed that if a laser beam was to be useful in communications, it would have to travel in a carefully designed pipe complete with lenses and other features enabling the light to bend around corners. A much more attractive possibility is to use thin glass fibers to carry the laser beam. At the Bell Telephone Laboratories, experimental fibers have been made that exhibit an absorption loss of about 60 decibels per kilometer, and fibers with a loss as low as 18 decibels per kilometer have been made by the Corning Glass Works. With repeaters spaced every mile or two, glass-fiber systems could be a strong contender for future long-haul transmission applications."

1922 Nuclear Power from Coal?

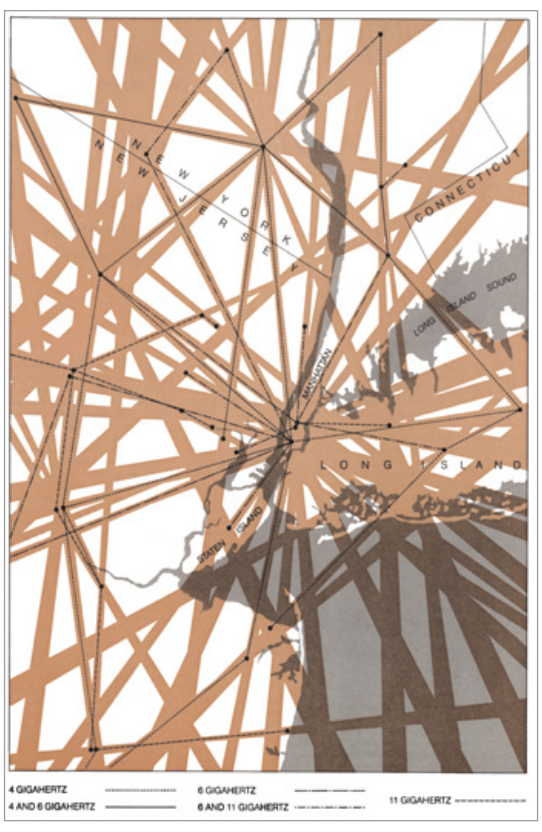
"Atoms, those smallest bricks of nature, are the seat of unbounded energy. Scientists are today of the opinion that radioactivity is not only a property of radium, uranium or thorium atoms, but that it is common to all atoms, only that in other atoms this power is latent. If it were possible to start the decomposition of the atoms, the radioactivity must appear. The quantity that could be won by such means is infinitely greater than that attained by chemical reaction or combustion. We have produced energy from coal [through combustion]. If it were possible to break up the atoms and cause them to spend their latent energy, an ocean liner of 50,000 horsepower could travel across the oceans uninterruptedly for ten years using only a single kilogram of coal. Perhaps there will come a time when we shall use the energy in the atoms to drive our machines, cook our food and heat our rooms."



1972

1922

1872



1972: "Near saturation in microwave communication is indicated by the colored beams on this map of the New York metropolitan area. The routes are radio channels that carry a variety of traffic."

1872 Mastodons in New York

"A farmer in the town of Mount Hope, Orange County, N.Y., digging recently in a swamp on his premises, exhumed from the muck, about eight feet below the surface, a number of bones which, from their size and formation, are supposed to be those of a mastodon. There are two ribs nearly five feet long, and two sections of vertebrae six inches wide. Several discoveries of mastodon remains have been made in this county during the past thirty or forty years."

The Channel Tunnel

"The successful completion and operation of the Mont Cenis railway tunnel through the Alps has given new impetus to establishing railway communication between England and France, by means of a tunnel under the British Channel. The distance is 22 miles. The Channel Tunnel Company has been formed in London to solve the problem. The tunnel is to extend from Dover, England, to Calais, France. The tunnel will be made through the lower or gray chalk, chiefly, if not entirely, and by the adoption of machinery. Any [cost] estimate must at present be purely conjectural, but it is reckoned that the work, if practicable at all, could be completed within five years and for $25,000,000."

No channel tunnel was built until Eurotunnel opened the "Chunnel" in 1994, between Folkestone, England, and Coquelles, France. Price tag: about £9 billion.

Scientific American, Vol. 226, No. 2; February 1972

Text by Andrea Thompson | Graphic by Amanda Montañez

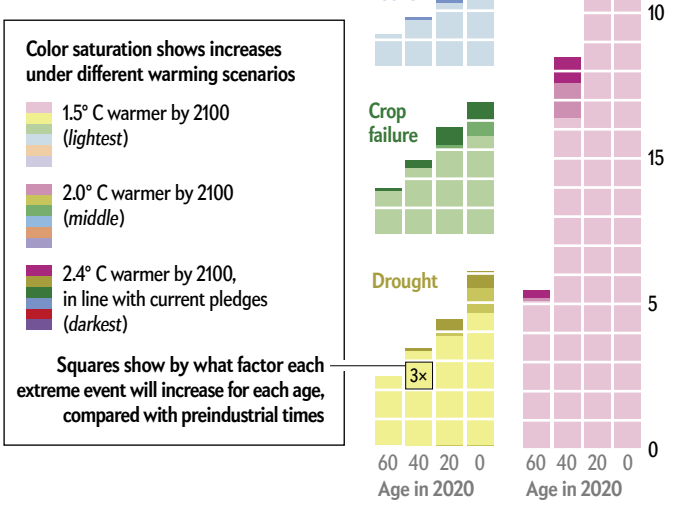
Generational Climate Change

Young people will suffer the most from warming temperatures

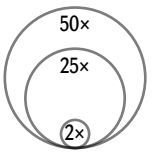
Babies born today will experience far more disruptions fueled by climate change than their parents or grandparents. In a study published recently in *Science,* Wim Thiery of Vrije Universiteit Brussel in Belgium and his colleagues combined climate model projections under three global warming scenarios with demography data to calculate the lifetime exposure to six types of extreme weather for every generation born between 1960 and 2020. Even as a climate scientist acutely aware of the dangers of rising temperatures, "seeing the numbers as a person, as a parent, is a punch in the stomach," he says. Young people in the Middle East and sub-Saharan Africa and those in low-income countries will see the largest increases in exposure. These estimates examine only changes in the frequency of extreme events—they do not represent how those events may become more intense and longer-lived. Although "young generations have the most to lose if global warming reaches higher levels," Thiery says, they also have the most to gain if greenhouse gas emissions can be reined in. "That is a key message of hope."

EXPOSURE TO EXTREME EVENTS BY AGE

It seems intuitive that younger generations will feel the effects of climate change more than older ones. But quantifying this phenomenon reveals just how stark the disparities are, particularly in terms of exposure to heat waves.

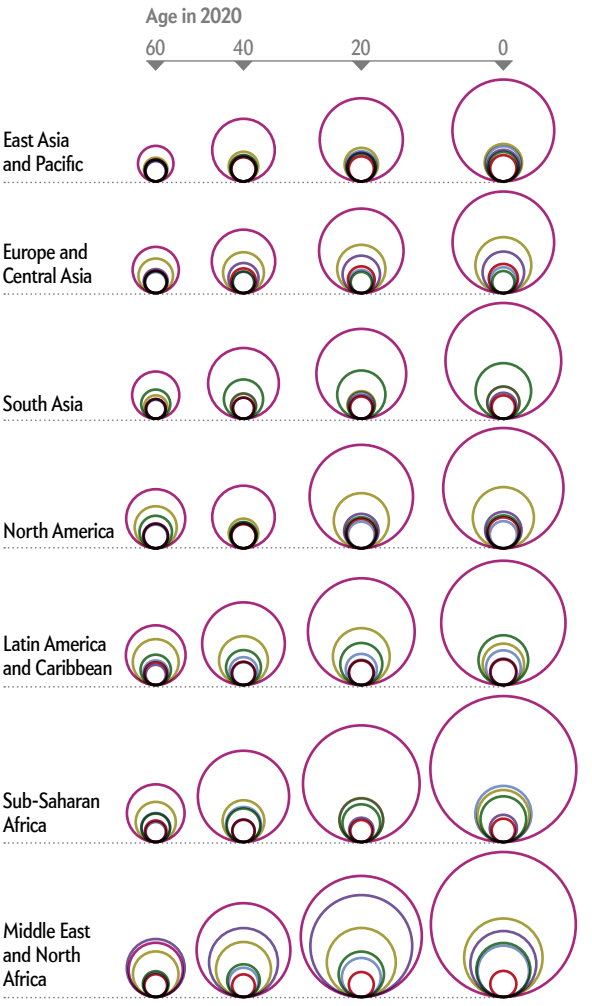


Circle sizes show by what factor each type of extreme event will increase for each age under the 2.4° C warming scenario

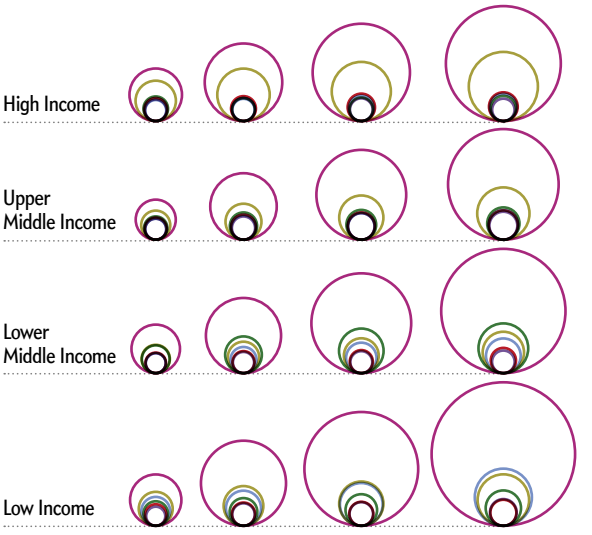


Heat waves
Drought
Crop failure
River floods
Wildfires
Tropical cyclones

VARIATION BY WORLD REGION



VARIATION BY COUNTRY INCOME



Source: "Intergenerational Inequities in Exposure to Climate Extremes," by Wim Thiery et al., in *Science*, Vol. 374; September 26, 2021 (*data*)

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