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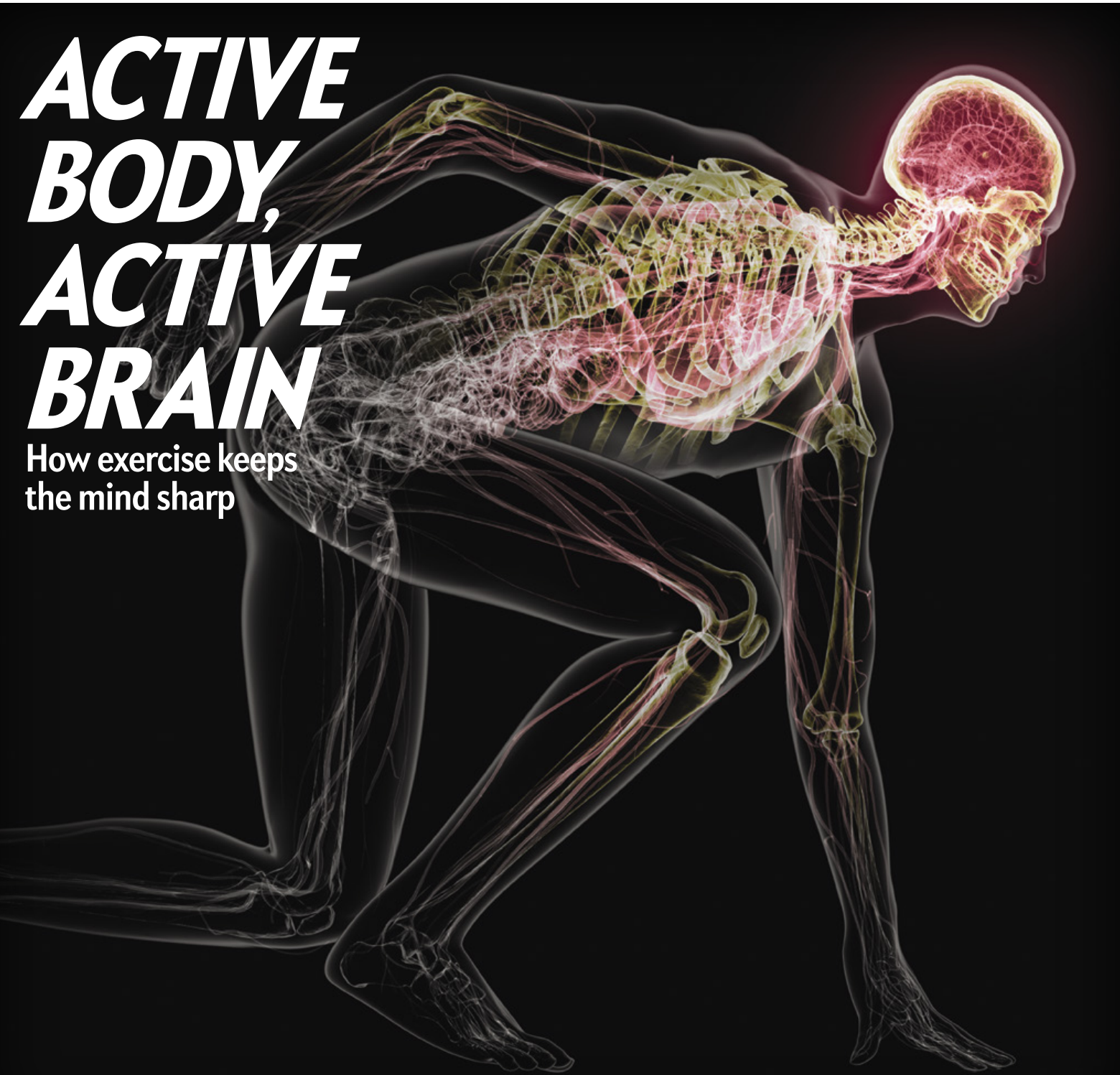

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SCIENTIFIC AMERICAN

ON THE COVER

Exercise is well known to have positive effects on the aging brain. New research hints at why this is the case and suggests that combining cognitive tasks with physical activity can enhance those benefits. Illustration by Bryan Christie Design.

Photograph by Tim Flach

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10


12


64

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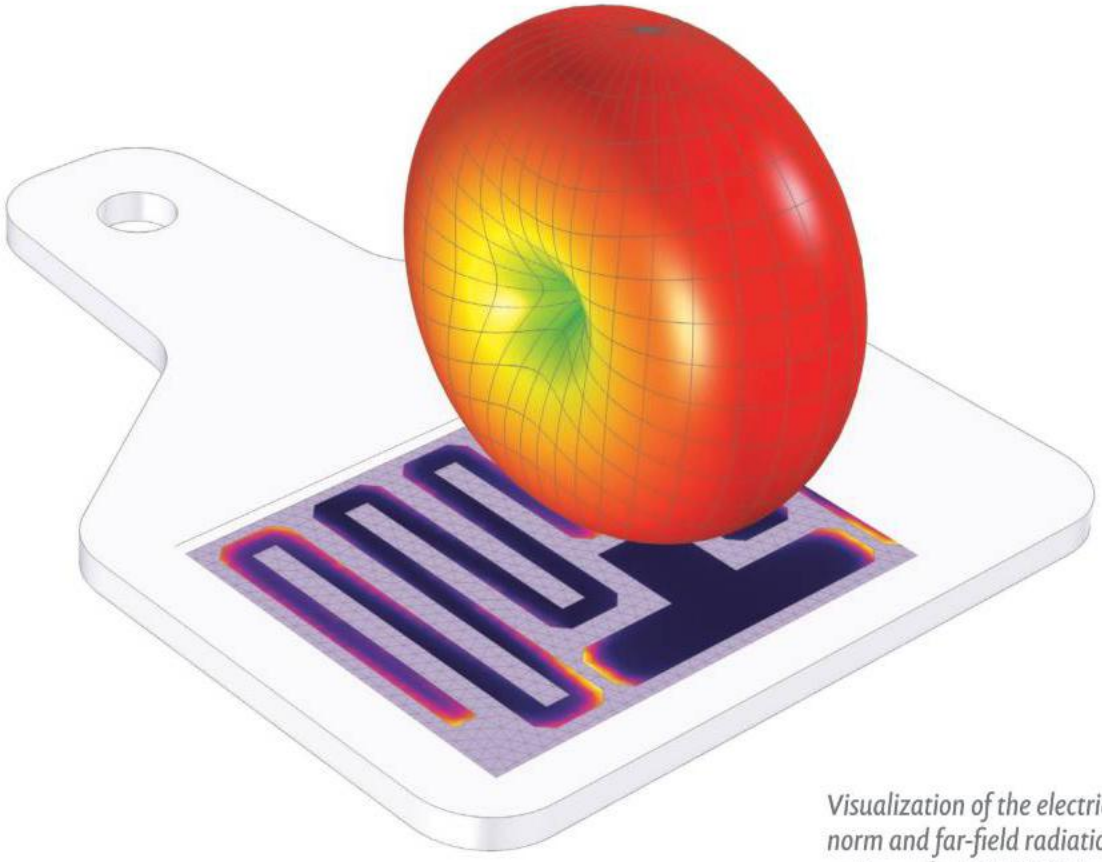
Smartphones, smart homes, smart...healthcare?



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

175th Anniversary Year Jamboree

The first issue of *Scientific American* was published on August 28, 1845, so it's another eight months until our 175th birthday. But we're kicking off our anniversary year right away with some exciting changes to your monthly issue, most conspicuously a redesigned cover that harks back to the white space and square images used in the 1940s and the latter half of the 20th century.

We're also reintroducing poetry in a new column, Meter, edited by Dava Sobel. The magazine's founder Rufus Porter ran two poems on the cover of the first issue, and that tradition continued beyond his relatively brief tenure until September 15, 1849. Thereafter, such stanzas seem to have mostly disappeared except for a short flourishing in 1969, when we published no less than W. H. Auden and John Updike, in addition to a reader's lovely ode to a quasar, which ran in the Letters section. Now we begin anew with a panegyric to the late 17th-century naturalist and scientific illustrator Maria Sibylla Merian by Diane Ackerman (*page 22*).

Naomi Oreskes, a historian of science at Harvard, is also joining the lineup with a new column, Observatory, where she'll cast a critical eye on the ways science helps us ascertain what is true and false in our lives and in the world. She starts by warning journalists not to fact-check scientific judgments (*page 64*).

Elsewhere *Scientific American*'s resident historian Dan Schlenoff is adding a pithy Epic Tales commentary to 50, 100 & 150 Years Ago about big stories' evolution in our pages over the decades. On page 67, he looks at entertainment technology from the late 19th to the early 21st century. If you'd like more snackable tales along these lines, look for the Artifacts from the Archive series, which will be appearing weekdays on ScientificAmerican.com and our Facebook, Twitter and Instagram channels throughout 2020.

Other anniversary-themed content over the coming year will appear in commemorative issues and online reports. In this month's Graphic Science (*page 70*), Jen Christiansen, our senior graphics editor, and data designer Nicholas Rougeux showcase the color scheme of all 5,148 covers of the magazine since 1845. (Visit www.sciam.com/175-covers for the interactive visualization.)

Meanwhile we will keep publishing the usual mix of in-depth articles about the most important advances in research and discovery. January's cover story by David A. Raichlen, an evolutionary biologist, and Gene E. Alexander, an expert in brain imaging and neuroscience, reveals why the surprising connection between exercise and brain health may trace back to traits that developed at the dawn of humankind (*page 26*). Contributing editor Claudia Wallis examines progressive techniques for weaning chronic pain sufferers off debilitating opioids without agony (*page 40*). Astrobiologist Caleb Scharf revisits the famous question about alien life that physicist Enrico Fermi posed over a lunch in 1950, "Don't you ever wonder where everybody is?" (*page 32*). And we wrap up with a special report, "The DNA Drug Revolution," produced independently with the support of UPMC, about treating genetic diseases with genetic material itself (*page S1*).

As events unfold in 2020, we look forward to celebrating the history and the future of science with you. SA

Illustration by Nick Higgins


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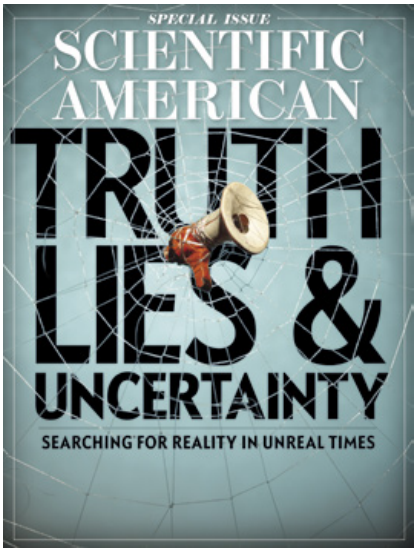

September 2019

"I hope *Scientific American* chooses a successor who has the intelligence and vision that Mariette DiChristina has exhibited."

JON DEAK *NEW YORK PHILHARMONIC*

A LEGEND DEPARTS

I was taken aback by Mariette DiChristina's announcement in "Science Communication 101" [From the Editor] that she was stepping down as editor in chief and moving on to a position at Boston University.

I have been a consistent reader of *Scientific American* since 1963. About 10 years ago I began to notice a positive difference in the magazine: coverage of both science and world events! Finally, you were encouraging scientists to take their rightful place in the world, with coverage of topics such as women's health and the reality of industrially caused global warming.

Most media publications have succumbed to glitzy marketing. The opposite has happened in your case. I credit much of this welcome orientation to DiChristina. I'll probably never meet her, but I hope she continues to exercise her incredible vision in her new position and that the editors of *Scientific American* choose a successor who has the intelligence and vision that she has exhibited.

JON DEAK *Artistic Director, Very Young Composers, New York Philharmonic*

PERSONAL DISINFORMATION

"When 'Like' Is a Weapon" [Science Agenda], the editors' opinion article on the growing use of disinformation campaigns, says that journalists "must be trained in how to cover deception" and governments "should strengthen their information agencies to fight back." What it overlooks is that, in many cases, politicians and journalists not only do not want to stop deception, they benefit from it. In this current political cycle, Donald Trump and the GOP have become masters of disinformation. Likewise, some journalists are already trained to cover deception.

FRANK GREGORIO *Manassas, Va.*

The editors say, "Little is known ... about the effects of long-term exposure to disinformation." But the American colonies and the U.S. have a 400-year history of it, including lies supporting the African slave trade, the deliberate genocide of Native Americans and the Jim Crow era of racism—as well as those about the "imminent threat" of Russia and China during the cold war and Iraq having weapons of mass destruction.

There is no need for further research. What is required is a clear-cut exposure of the liars that is just as nasty as they are.

JOHN JAROS *Philadelphia*

After reading the editors' assessment, I was disappointed to go to your Web site and see articles identified as "Most Popular." You cannot know which articles are most visited in the print magazine, so this seems to be another clickbait system where those that get the highest number of "views" are promoted. It doesn't mean they are better written or convey better science.

JOHN DOHRMANN *via e-mail*

WORLDS OF DIFFERENCE

In "Virtually Reality," George Musser refers to both the multiverse seemingly implicit in some cosmological models, which appears straightforward, and the many-worlds interpretation of quantum theory, which seems to engender difficulties.

He presents a scenario in which a photon may pass through or be reflected from a half-silvered mirror. It seems there should be a 50–50 chance of each result and two equally real worlds where each has occurred. Yet what if we prepare the mirror so that there is a two-thirds probability of the photon passing through? Are there now "A" and "B" worlds where it did so and a "C" world where it was reflected? Or are there still just two worlds, but one is somehow twice as "real" or probable?

ROBERT SMITH *Waretown, N.J.*

MUSSER REPLIES: Smith has put his finger on the main conceptual problem with the many-worlds interpretation: probability. For the very reasons he gives, you can't just count worlds; you need a more sophisticated analysis of how observers should weigh the possibilities, given that they don't know which world they live in. California Institute of Technology cosmologist Sean Carroll has an easy-to-follow discussion regarding the quantum multiverse in his new book Something Deeply Hidden.

FRACTURED LINK

"Too Much of a Good Thing," by Claudia Wallis [The Science of Health], reports on a study that links vitamin B consumption with hip fractures. This kind of correlation does not imply causation. Older people who consume large amounts of vitamin B may just be more active, which could also lead to more hip fractures.

WILLIAM QUARLES *Berkeley, Calif.*

WALLIS REPLIES: Good point. Epidemiological studies such as the ones I described indeed cannot prove causality. These were, however, two large, high-quality studies, and there are some plausible mechanisms to link the vitamins and fractures, which makes a connection harder to dismiss.

"REAL" NUMBERS

I am amazed there is a debate on the reality of mathematical objects, as described in "Numbers Game," by Kelsey Houston-Edwards. At least since the days of Immanuel Kant, it has been clear we live in a reality of ideas that reside in our individual and collective mind. These ideas represent an

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external reality but are not that reality itself. Furthermore, most of our conscious thoughts build on our understanding of external reality and affect it through our actions. Mathematics is only as fictional as law, love, economics and government.

CLYDE OAKLEY *Centennial, Colo.*

Why are mathematical constructs singled out when the question of existence is applicable to every word, symbol and concept? To suggest the number one or the verb "run" are real rather than models of real things is to espouse a dualism similar to Plato's worlds of being and becoming. The instantiations of mathematics and every field of study are discovered; the models are invented. Otherwise the current theory of physics is foundationally flawed.

CHARLES H. JONES *Eugene, Ore.*

WEAPONIZED INFORMATION

In "A New World Disorder," Claire Wardle refers to Russians hacking into e-mails from the Hillary Clinton campaign as an example of "genuine information that is shared with an intent to cause harm."

I don't understand the fuss about Russians' efforts to discredit Clinton. If they didn't falsify anything, I would have considered it a public service. Aren't voters entitled to get as much information about the character of a candidate as possible?

FRED BUSHNELL *Pfalzgrafenweiler, Germany*

WARDLE REPLIES: There are a number of reasons certain information should be leaked or shared, which is why we have protections for whistle-blowers. But illegally hacking into an e-mail service to "reveal" information that should have been secured is not a characteristic of a functioning society. We have freedom-of-information laws in many countries to allow the investigation of communications and actions by people in authority. I wrote the article partly to get people to think about the complexities of this space. Sometimes it's in our interest to have access to genuine information, but that's why we have laws and ethical guidelines around secret recordings, hacking and whistle-blowing: the same techniques that can be used for the public good can be used by bad actors who are trying to publicize information that does not benefit the public interest.

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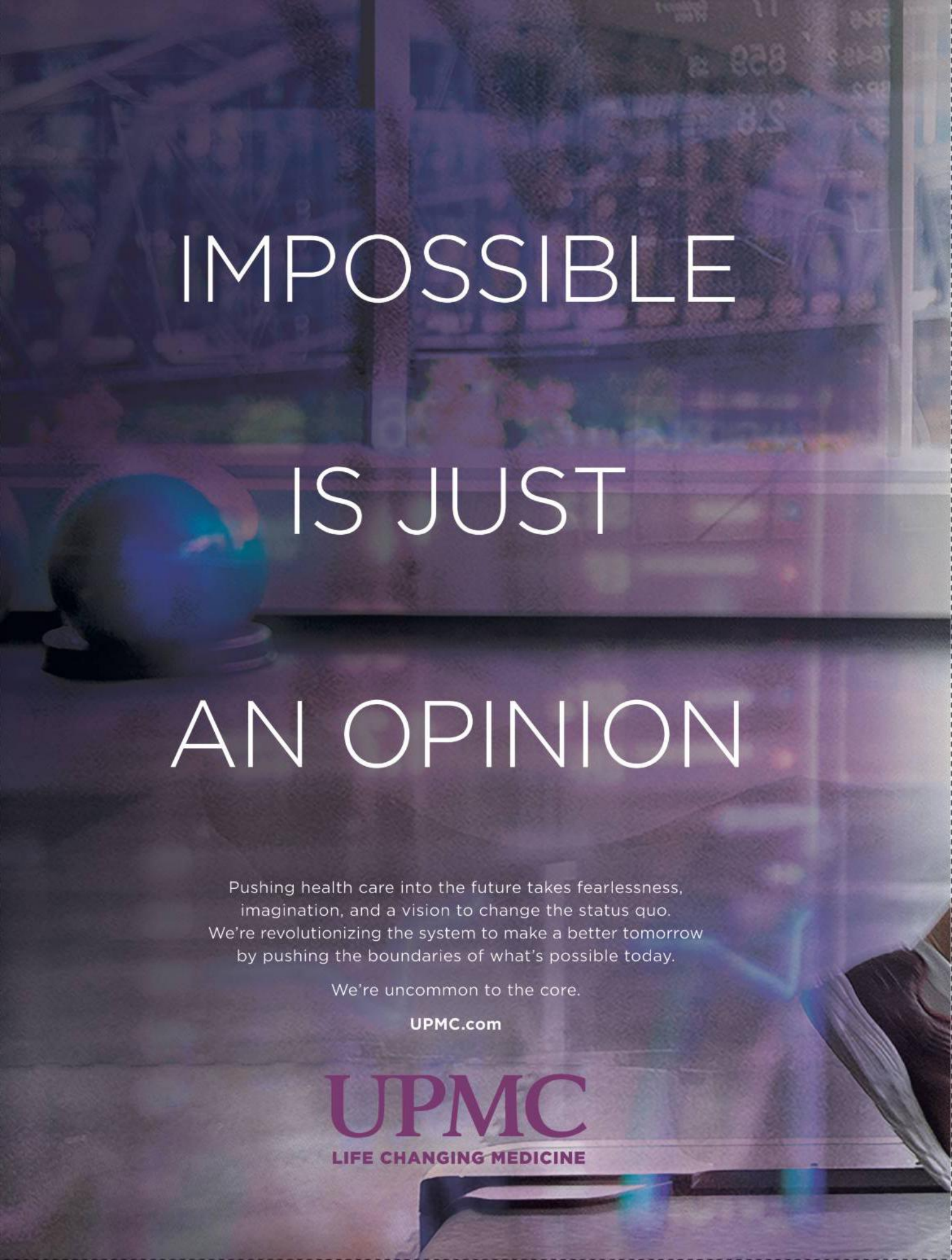
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Time's Up for "Anti-Gay Therapy"

Most states still allow this damaging practice targeting young teens

By the Editors

Last summer a South Carolina man named McKrae Game, who founded a network to promote "conversion therapy" for gay people, disavowed his own work. The Hope for Wholeness group Game established tries to help individuals follow his entreaty to attain "freedom from homosexuality through Jesus Christ." But Game, who revealed that he was gay last year, pleaded on Facebook: "I WAS WRONG! Please forgive me!"

It might be assumed from this refutation that any attempts to forcibly change a young person's sexual orientation are about to go the way of bloodletting, frontal lobotomy and trepanation. But that supposition would be wrong: if past trends hold, 16,000 LGBTQ—lesbian, gay, bisexual, transgender and queer—teenagers in the U.S. will go through conversion therapy before they turn 18, according to the Williams Institute at the U.C.L.A. School of Law, and only 18 states have banned this harmful practice for minors.

Some conservative religious organizations still back "anti-gay therapy" and on occasion end up in court to defend it. Their chances of prevailing have been bolstered by an increasingly right-leaning judiciary fostered by the nation's red/blue divide.

The reason no minor should be subjected to this practice has nothing to do with partisan politics or religious beliefs. The putative therapy should be discarded because it is rooted in bad science. Its origins are tied to both rejected concepts about sexuality and therapies based on those discredited notions.

Homosexuality—once explained erroneously as the result of an overbearing mother—was classified as a form of mental illness in psychiatry's first diagnostic manual, published in 1952. In the past, treatments to "cure" it included electroshock, chemical therapies such as the forced hormone treatments infamously inflicted on British mathematician Alan M. Turing, and the hiring of prostitutes for "behavioral" interventions. But milder versions persist today in the form of aggressive counseling and, at times, the administration of measures that induce nausea or vomiting.

Trying to alter an individual's sexual identity should be banned simply because of the irreparable harm it causes. In a 2019 survey of almost 35,000 young people, the Trevor Project, which provides crisis intervention for LGBTQ youths, found that 42 percent of a subgroup who had received conversion therapy attempted suicide.

The medical establishment, thankfully, has become a solid critic of anti-gay conversion. The American Medical Association, the American Psychological Association and other organizations characterize it as useless and injurious. The public is also opposed: a 2019 Reuters/Ipsos national poll found that 56 percent of U.S. adults think conversion therapy should be illegal.

Although medical and psychological associations have asked explicitly that Congress and state governments ban anti-gay conversion, there has been a backlash from groups such as the Liberty Counsel, which promotes "evangelical values." Listed by the Southern Poverty Law Center (SPLC) as an anti-LGBTQ hate group, the Liberty Counsel noted in a press release that it is fighting several existing bans on conversion therapy. Luckily, verdicts can go both ways: in a 2015 case brought by the SPLC, a New Jersey state court ruled that Jews Offering New Alternatives for Healing—tellingly abbreviated as JONAH—had engaged in consumer fraud by offering conversion therapy because homosexuality is not a mental illness.

The best way to stop this practice is through a federal resolution or through additional bans by the other 32 states—or even by local jurisdictions. Bills have been introduced to put a ban in place at the federal level, but these are still languishing in the House of Representatives.

Time may be running out. New York City had a ban but voted to undo it in September 2019: the City Council feared that a lawsuit to quash the ban, filed by another Christian advocacy group, might make its way up to an ever more conservative Supreme Court that could rule against the injunction. Whether this detestable practice continues may depend on the 2020 presidential and congressional elections—which, depending on the outcome, might provide an opening for legislation to finally put an end to a pseudoscientific technique masquerading as therapy. SA

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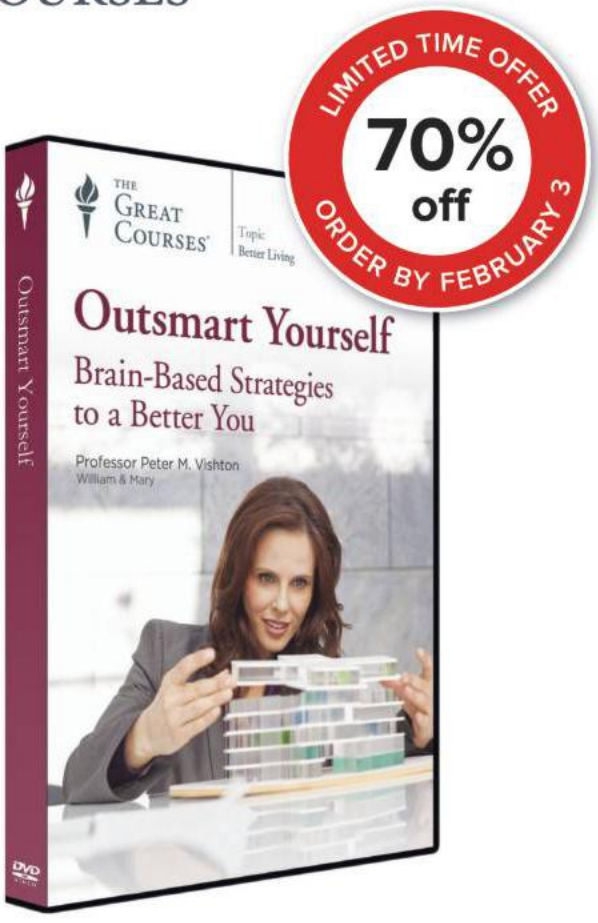

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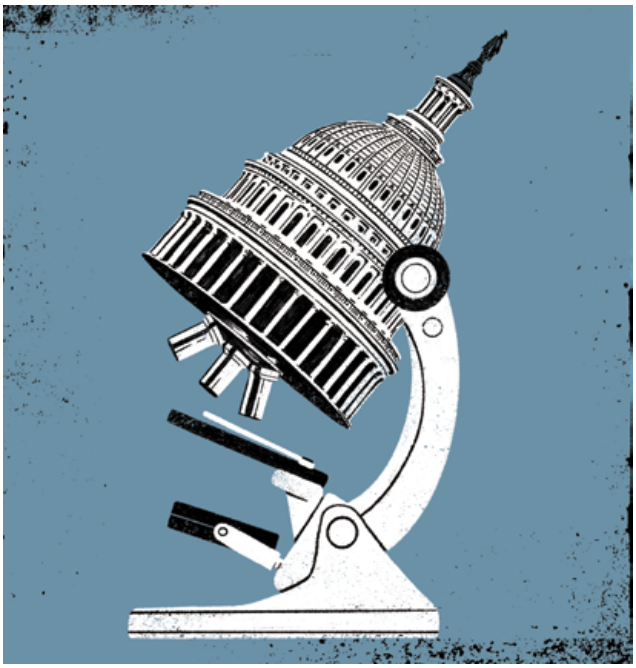
Stop Suppressing Science

Congress can and must protect scientific integrity with legislation

By Chuck Hagel



For much of my time in public service, there were some things government officials did just because they were the right things to do—which included respecting the research done by government scientists. That respect has faded over recent presidencies; "Sharpie-gate" may have been its death knell. Our ability to keep the public safe and move the country forward economically rests, in large part, on federal research. But that work is being endangered by manipulation for political ends, and the ramifications are vast and should concern all Americans. Congress can protect scientific integrity with legislation, and it must do so.

To help rebuild ethics, integrity and trust in government, I joined a nonpartisan task force of former government officials concerned about the executive branch's growing disregard for norms and unwritten rules that had formerly kept its power in check. Recently our National Task Force on Rule of Law & Democracy—a project of the Brennan Center for Justice—published a report proposing legislation that would effectively respond to the threat. We identified at least 60 instances over the terms of the past three presidential administrations in which officials took actions that threatened scientific integrity—among them an episode during the Obama presidency when the National Institutes of Health allowed alcohol-industry representatives to give input on a study investigating the benefits of moderate drinking.

The distortion or downplaying of climate science is perhaps the most egregious category of examples. In 2017, for instance, the ranking policy expert on climate change in the Department of the Interior was reassigned to an accounting job days after he addressed the United Nations about the dangers that climate-induced global disruption poses to Alaska's Native communities. And this year the U.S. Department of Agriculture failed to publicize a groundbreaking study showing that rice loses vitamins when it is grown in an atmosphere with high levels of carbon dioxide—a potentially serious health concern for the 600 million people worldwide whose diets consist mostly of that staple.

Downplaying climate science also affects the military, which depends on reliable data to keep our defenses at the ready. Altered weather patterns and increased storm severity have caused major damage to our military bases and installations, in some cases devastating them and leading to lost training and diminished combat readiness. This is a real and present threat to our national security that will most likely get worse.

Congress should respond to these abuses. Our task force urges representatives to prohibit politically motivated manipulation and suppression of research by the executive branch, as well as discrimination and retaliation against government researchers when their scientific conclusions are politically inconvenient. Further, we propose requiring federal agencies to create and implement scientific integrity policies, which would codify an executive branch policy created during the Obama presidency. These policies would establish standards and procedures to uphold the principle that the scientific process at federal agencies should be free from politics, ideology and financial conflicts of interest.

We also recommend that Congress require agencies to articulate clear standards for how political officials may interact with career researchers during the preparation of scientific reports and the technical stages of regulatory development. Congress should require agencies to log these contacts and to make the records available to the legislature and independent agency watchdogs to ensure accountability. It should pass legislation to ensure the proper functioning of science advisory committees, guaranteeing that such panels are created in good faith and consider the weight of scientific evidence. It should also demand that the public have timely access to taxpayer-funded research, so political officials cannot hide the facts they find inconvenient.

With these and other reforms we lay out, Congress has a road map for bipartisan action. In fact, it has begun to act: in October the House Science, Space, and Technology Committee approved the Scientific Integrity Act, already under consideration before our report came out, on a bipartisan basis. It would mandate some of the reforms we call for. We hope the House and Senate will vote it into law. Just about everything we do depends in some way on research and data coming out of the federal government. A failure to protect this information puts us all at risk. SA

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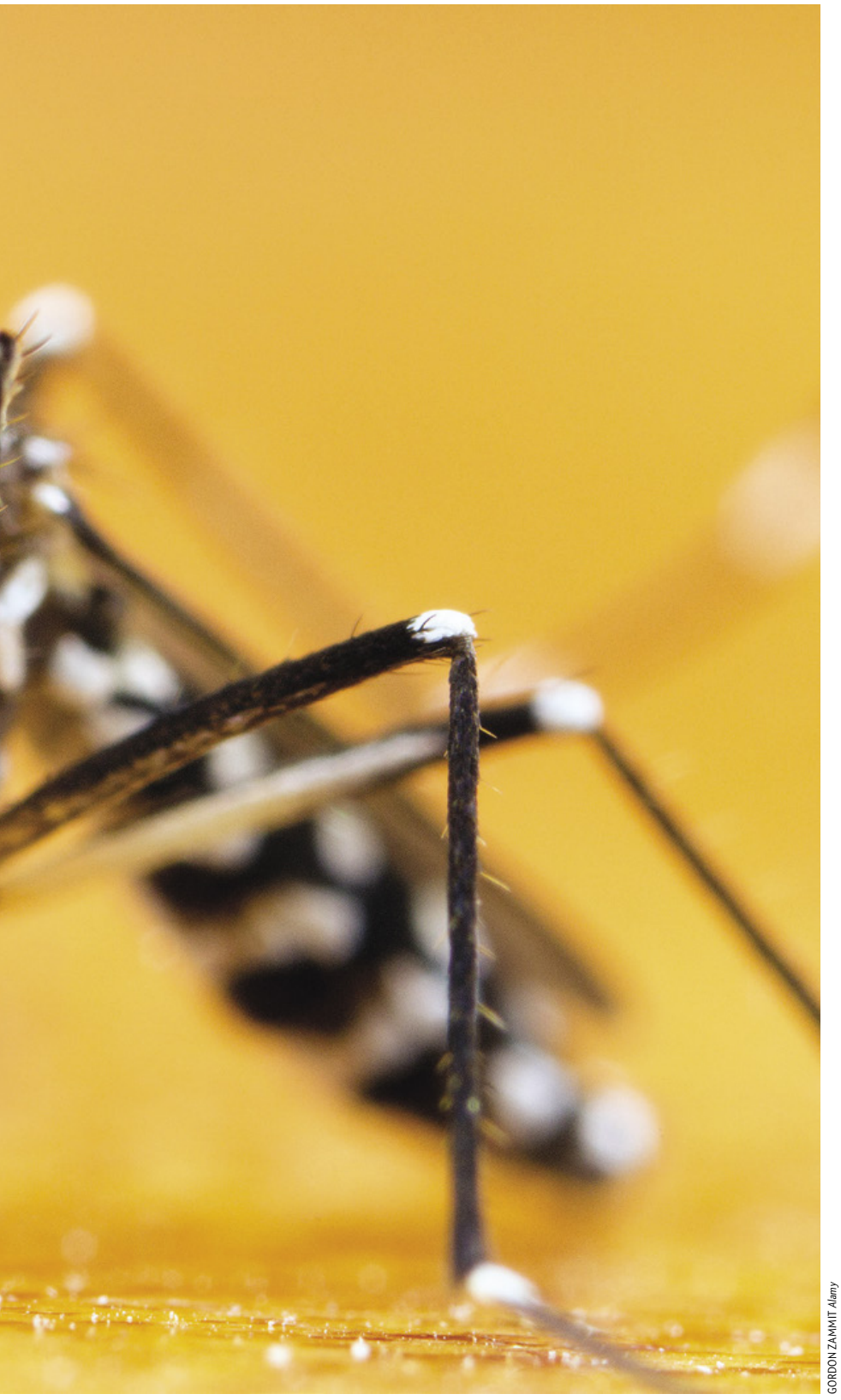
Illustration by Adria Fruitos

ADVANCES

Larger, more dangerous Asian tiger mosquitoes grow in Baltimore zones with more vacant buildings.



GORDON ZAMMIT *Alamy*

INSIDE

ENVIRONMENT

Neighborhood Threats

Tiger mosquitoes thrive in abandoned urban buildings

Over the past five decades mosquito populations in parts of the U.S. have skyrocketed by a factor of 10—a situation with worrying implications for the spread of diseases such as West Nile virus, dengue and chikungunya. And some places are apparently more vulnerable than others. A new study published last October in the *Journal of Medical Entomology* found that in Baltimore, low-income neighborhoods bear the biggest burden: they have not only more mosquitoes but also larger ones, which often survive longer. The problem most likely is rooted in the fact that Baltimore has nearly 17,000 abandoned buildings, which are concentrated in economically disadvantaged areas and serve as convenient mosquito-breeding zones. To effectively combat mosquitoes and the diseases they carry, the study suggests, cities will need to account for urban infrastructure.

Researchers at the Cary Institute of Ecosystem Studies in Millbrook, N.Y., and the University of Maryland trapped adult *Aedes albopictus* (better known as Asian tiger mosquitoes) in five Baltimore residential neighborhoods over three years. This species, introduced to the U.S. in 1987, is now the most common in many American cities. When the researchers measured the mosquitoes' wing lengths, a proxy for body size, they found that the insects grew larger in lower-income blocks. Bigger mosquitoes are not just a bigger annoyance: the larger they are, the longer they tend to live—and the more times each one can bite. Because mosquitoes have to bite at least once to become infected with disease-causing microorganisms and again to pass them on

to people, bigger mosquitoes could pose higher disease risks. Larger mosquitoes also lay more eggs, setting the stage for higher numbers later on. Senior study author Shannon LaDeau, a Cary Institute disease ecologist, and her colleagues found in a 2013 study that low-income blocks in Baltimore were 72 percent more likely to have Asian tiger mosquitoes than high-income blocks were and showed higher mosquito densities.

The researchers say low-income blocks produce more and larger mosquitoes because they have more abandoned buildings than affluent blocks do and are more heavily littered with discarded containers that collect standing water. And water that pools in degraded buildings is protected by shade—which helps mosquitoes grow larger. Some cities' well-intentioned efforts to plant trees in low-income blocks may worsen the problem: trees and shrubs not only shade outdoor breeding pools but also shed leaves into the water and feed the mosquito larvae, helping them grow bigger.

"There appears to be a complex pathway between low-income neighborhoods, the types of habitats in which mosquito juveniles develop in those neighborhoods, and the resulting size of adult mosquitoes potentially capable of transmitting disease to humans," says Brian Allan, an integrative biologist at the University of Illinois at Urbana-Champaign, who was not involved in the study.

Fortunately, mosquito-borne diseases are not a massive problem in the U.S. for now. From January through October 2019, the Centers for Disease Control and Prevention reported 777 cases of West Nile virus and 614 cases of dengue (and most of the latter occurred in people infected outside the U.S.). But climate change could worsen the country's disease landscape by broadening habitats and lengthening the time every summer that mosquitoes can breed and survive.

"The longer you have each season for [a disease] to be introduced and take off, the more likely it is to happen," LaDeau says. If mosquito-borne diseases start to spread more widely in U.S. cities, the new study indicates low-income neighborhoods could be hit especially hard.

These findings have implications that stretch across the country. A 2018 report by the Massachusetts-based nonprofit Lincoln Institute of Land Policy says the number of unoccupied homes in the U.S. rose from 9.5 million to 12 million between 2005 and 2010, possibly because of the lingering effects from the 2008 housing crisis. The number has since declined a bit, but it is still far higher than it was in 2005. Vacant land areas are another problem: Philadelphia alone has approximately 40,000 such parcels concentrated in poor neighborhoods. And low-income areas affected by natural disasters such as hurricanes can also become mosquito-breeding grounds. Research has shown that disasters disproportionately damage low-income housing, which also tends to be rebuilt slowly, if at all.

Cities may, then, need to focus more mosquito-control efforts on these areas. Urban health departments typically educate homeowners about the importance of emptying water out of outdoor containers such as pet bowls, as well as trash and recycling bins. But nobody empties such receptacles in or around abandoned buildings, and so far most municipalities have not been willing to take on the job. "It is something that is fairly difficult for a city to address because it's really expensive to go into private properties and clean them up," says Dina Fonseca, a molecular ecologist at Rutgers University, who was not involved in the study. Yet if these properties become breeding grounds not only for annoying mosquitoes but also for dangerous vector-borne diseases, officials' calculus may need to shift.

—Melinda Wenner Moyer

OPTICS

Undercover Wings

A nocturnal moth species has a flashy secret

The forewings have a shifting pattern.

K. JAYARAM *Science Source*

The nocturnal dot-underwing moth may use shape-shifting patterns on its wings as a stealthy way to attract mates in the dark. In a study published last September in *Current Biology,* scientists report the discovery on males' forewings of three patches that change darkness and size when viewed from particular angles. In females, the entire forewing darkens.

Although butterfly and moth species that are active during the day are known to employ dynamic visual effects to communicate, researchers had thought their nocturnal cousins relied almost exclusively on chemical signals because of the lack of light. But these changing wing patterns, now found for the first time in a nocturnal moth, suggest the insects may also incorporate visual signals. Because only the males have this pattern, researchers say it is likely a sexually selected mechanism.

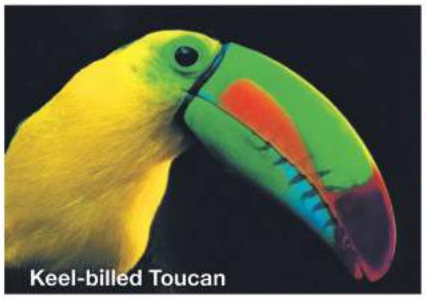
Jennifer Kelley, an ecologist based at the University of Western Australia, and her colleagues first noticed the visual phenomenon while looking at museum moth specimens for another project. "As soon as we figured the effect was angle-dependent, we knew that to understand how it works, we had to understand the underlying optical physics," Kelley says. The group contacted Gerd Schröder-Turk, who studies materials geometry at Murdoch University in Perth, and Bodo Wilts, a nanophotonics expert at the Adolphe Merkle Institute in Switzerland.

Together the researchers traced the optical effects to nano-sized scales in the moths' wings. When the wings are viewed from above, the scales reflect available light directly, like a dull mirror. When viewed from an angle, however, they let some of the light through to reveal a deeper layer of darker scales, which appear as patches on the male's wings. If the insects were to beat their wings vigorously—a common behavior among males approaching potential mates—the patches would flash on and off, creating a striking signal even in very dim light.

"These moths have a great solution to the problem of eavesdropping," says Elizabeth Tibbetts, a behavioral ecologist at the University of Michigan, who was not part of the study. "Their signal is very obvious from one direction but invisible from others, allowing males to advertise their sexiness to females without predators noticing."

—Harini Barath


Manuel Antonio National Park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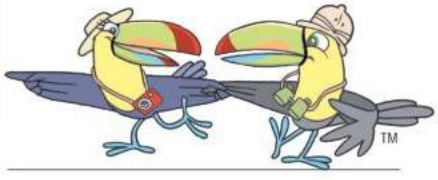

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SYNTHETIC BIOLOGY

E. coli High

Scientists have engineered bacteria to produce psilocybin

Psilocybe cubensis mushrooms

FORD McCANN *Science Source*

Studying psychedelics was taboo for decades, but in recent years drugs such as psilocybin—the active ingredient in "magic mushrooms"—have shown promise in clinical trials for treating conditions from depression to nicotine addiction. Growing the mushrooms can take months and is not practical for pharmaceutical production, however, and chemically synthesizing psilocybin is a costly and intensive process. Now scientists have successfully engineered *Escherichia coli* bacteria to produce the mind-bending drug.

The modified microbes generated up to 1.16 grams of psilocybin per liter of culture medium—the highest yield to date from any engineered organism and a 10-fold increase over the next best attempt. Scaled up, the new method could produce psilocybin for potential therapeutic use.

"The number-one advantage is it's simply cheaper" than—or at least cost-competitive with—other methods, says lead study author Alexandra Adams, an undergraduate student in chemical engineering at Miami University in Ohio. Furthermore, "it's easier to manipulate *E. coli* than other organisms," she says.

Adams and her colleagues engineered *E. coli* that incorporated three genes from the *Psilocybe cubensis* mushroom, enabling the bacteria to synthesize psilocybin from the cheap and easily obtainable precursor molecule 4-hydroxyindole, and then they optimized the process to produce the drug on a larger scale. They reported their results last December in *Metabolic Engineering*.

Dirk Hoffmeister, a pharmaceutical microbiologist at Friedrich Schiller University in Germany, who led a team that previously produced psilocybin via an engineered fungus, called the study "an intriguing alternative and proof of principle" that shows "the power and possibilities of synthetic biology." Nevertheless,

NEUROBIOLOGY

The Craving Circuit

Rats change "compulsive" behavior when a brain connection is adjusted

For many people battling addictions, seeing drug paraphernalia—or even places associated with past use—can ignite cravings that make relapse more likely. Associating environmental cues with pleasurable experiences is a basic form of learning, but some researchers think such associations can "hijack" behavior, contributing to problems such as addiction and eating disorders.

Researchers led by neuroscientist Shelly Flagel of the University of Michigan have found a brain circuit that may control this hijacking; rats that exhibit a type of compulsive behavior show different brain connectivity and activity than those that do not, and manipulation of the circuit altered their behavior. These findings may help researchers understand why some individuals are more susceptible to impulse-control disorders. "This is technically a really excellent study," says neuroscientist Jeff Dalley of the University of Cambridge, who was not involved in the work.

In the study, published last September in *eLife*, researchers showed rats an inert lever shortly before delivering a tasty treat via a chute, then sorted them into groups based on their responses. All rats learned to associate the lever with the treat, but some—dubbed "goal trackers"—began to approach the food chute directly after seeing the lever, whereas inherent "sign trackers" kept compulsively returning to the lever itself.

The team suspected that two brain regions were involved: the paraventricular nucleus of the thalamus (PVT), which drives behavior, and the prelimbic cortex, which is involved in reward learning. The researchers used a technique called chemogenetics to alter neurons in the circuit connecting these regions, which let them turn on or inhibit signals from the prelimbic

KTSDESIGN *Getty Images*

cortex using drugs. Activating the circuit reduced sign trackers' tendency to approach the lever but did not affect goal trackers. Deactivating it drew goal trackers to the lever (sign-tracking behavior), without affecting preexisting sign trackers. The

the engineered bacteria could potentially produce toxic or allergenic microbial material that would need to be removed by purification, says Hoffmeister, who was not involved in the new study. According to Adams, manufacturers could avoid this risk by using industrial techniques already proved for bacterially produced drugs such as antibiotics or insulin.

Medicinal chemist David Nichols of Purdue University, who was also not involved in the work, says the technique's yield is impressive. But he notes that the approach requires a particular precursor chemical, rather than making psilocybin from even simpler starting materials. Senior study author Andrew Jones, a chemical and biological engineer at Miami University, aims to eventually synthesize psilocybin from glucose. He and his colleagues are talking with several companies about licensing the team's method for commercial use.

Psilocybin can be therapeutically effective after just one dose. But given how many people have depression and other mental health disorders, the potential market for such treatments is substantial. "If it were approved for everything it's being tested for," Jones says, "that's a significant proportion of the population." —*Tanya Lewis*

team also found increased dopamine, a chemical messenger involved in reward processing, in the newly sign-tracking brains.

The prelimbic cortex appears to exert top-down control, whereas the PVT processes the motivational signal triggered by the cue. "Individuals seem to be wired differently regarding this balance between top-down cortical control versus bottom-up subcortical processes that are more emotional," Flagel says. Those "who are highly reactive to cues in the environment may suffer from deficits in top-down control." She suggests that cognitive-training therapies might combat such deficits in humans.

The circuit itself could also represent a new treatment target, but the exact human anatomy is unclear, Dalley notes—and addiction is more complex than a single mechanism.

Next, the researchers will try to examine these traits in people. "Once we've established the sign- and goal-tracker paradigm in humans, we can test whether these traits are predictive of psychopathology," Flagel says. "We hope this will help identify individuals who are more susceptible to certain mental illnesses or facets such as relapse." —*Simon Makin*

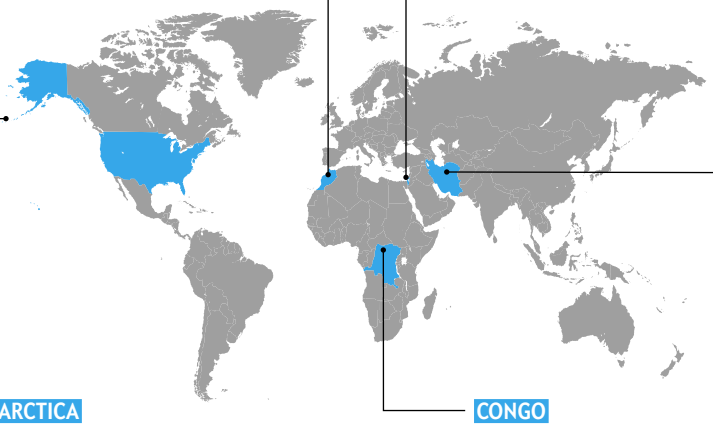
IN THE NEWS

Quick Hits

By Sarah Lewin Frasier

MOROCCO
A single-file line of traveling trilobites, all facing the same direction, were caught in a sediment avalanche 480 million years ago. Scientists uncovered the ancient arthropods in a formation they described as similar to modern-day migrating spiny lobsters.

ISRAEL
Researchers found that inhabitants of central Israel's Qesem Cave more than 200,000 years ago likely saved deer leg bones for up to nine weeks to eat bone marrow. This could be the earliest known instance of prehistoric humans storing food for later.



U.S.
Alaska's northern fur seals are gathering in large numbers on Bogoslof Island, the tip of an active volcano that last erupted in 2017. More than 36,000 pups may have been born on the island in 2019, amid mud-spewing geysers.

IRAN
After lingering for months in areas with no cell service, an eagle electronically tracked by Russian scientists flew over Iran, suddenly sending a long backlog of texts with coordinate information—and incurring overwhelming phone bills for the research project.

ANTARCTICA
An iceberg larger than the Hawaiian island of Oahu split from Antarctica's Amery Ice Shelf, an event that happens every 60 to 70 years, scientists say. This time, satellite images provided real-time views of the breakup.

CONGO
The Congolese giant toad's shape and color scheme imitate the Gaboon viper's head, researchers found, in the first known case of a toad mimicking a dangerous snake. Its alter ego has the longest fangs and most venom of any known snake species.

For more details, visit www.ScientificAmerican.com/jan2020/advances

CONDENSED MATTER PHYSICS

Quantum Loop

A new material's strange properties could be useful in future quantum computers

Superconductors are materials that shepherd electrons seamlessly from one place to another with zero resistance. Most have just one "lane"—but a newly discovered material can carry current racing in both directions at once.

The material, β-Bi_2Pd, is a thin film of crystalline bismuth and palladium. When shaped into a ring, it displays an unconventional ability to cycle current clockwise and counterclockwise simultaneously. Its developers say it could potentially play a role in building the next generation of quantum computers, machines that rely on quantum physics to perform vastly more calculations than contemporary computers can.

The "superposition of clockwise and counterclockwise currents" may let the material act as a qubit, the basic building block of a quantum computer, says Yufan Li, a physicist at Johns Hopkins University and the study's lead author. Whereas a classical computer bit exists in one of two states, 1 or 0, a qubit can exist in a superposition of both states (not unlike Schrodinger's famous dead-and-alive cat). Qubits can thus hold far more information than classical bits, giving them the potential to achieve superior computing power.

Superconducting qubits designed so far require a highly precise magnetic field to work. But the β-Bi_2Pd ring that Li and his team designed, called a superconducting flux qubit, does not need external magnets to circulate current in both directions. The researchers say this attribute could be an "immediate improvement" to existing qubit technology. "In our case, the qubit works without a magnetic field," Li says. "This implies substantial simplification to the circuit design and calibration."

It is also possible that the particular qualities of β-Bi_2Pd mean it can give rise to particlelike phenomena called quasiparticles—specifically, a theoretical object called a Majorana fermion that is also its own antiparticle. (An antiparticle has the same mass as, but opposite physical charges to, its corresponding particle.) If the superconducting material has this property, it could potentially work in a highly theoretical kind of qubit that withstands environmental noise by separating its components across greater distances, Li says.

Building functional qubits of either kind with β-Bi_2Pd rings may still be a long way off, however. Javad Shabani, a physicist at New York University, who was not involved in the study, says that among other things, the rings would have to be more controllable to be feasible as qubits. "We need more knobs," Shabani says. "If we can't control [them], then we can't really use them."

—Jim Daley

Illustrations by Thomas Fuchs

Wild tigers have disappeared from Nam Et-Phou Louey.

CONSERVATION

Lost Tigers of Laos

Even bountiful habitat will not save species if poaching cannot be stopped

A decade ago carnivore biologists identified a remote protected area in northern Laos, called Nam Et-Phou Louey, as the country's probable last haven for wild tigers. To formally test this supposition, researchers set up camera traps in 2013 and quickly confirmed two tigers' presence. But the success was short-lived: over their study's four-year course, they never saw those or any other tigers again.

This result, reported last October in *Global Ecology and Conservation,* confirms that tigers are now functionally extinct in Laos. The researchers also found that leopards, formerly presumed to still live in the park, have vanished as well. "For the constellation of remaining protected areas in Southeast Asia for tigers, this was an important one—maybe even a potential jewel in the crown," says senior author David Macdonald, a wildlife conservationist at the University of Oxford. "To find that that jewel has blinked out is devastating."

Laos's tiger loss is part of an alarming trend across Southeast Asia; the animals have already disappeared from Vietnam and Cambodia. In almost every study site Macdonald and his colleagues have surveyed, wild tigers—which number fewer than 4,000 worldwide—are in steep decline or completely absent. So are once common leopards. Habitat loss is partly to blame, but Macdonald says that the main driver is "the astonishing, corrosive tide of poaching."

Akchousanh Rasphone, the study's lead author and the first Laotian woman to earn a doctoral degree from Oxford, and her colleagues installed and monitored 300 camera stations across Nam Et-Phou Louey's nearly 6,000 square kilometers of rugged, steep mountain ridges and dense forest. Over four years they observed 43 mammal and bird species—but no leopards and, after 2013, no tigers. Leading international nonprofit groups support antipoaching efforts in Laos's main protected areas, but as in many other countries, poachers still find ways to kill wildlife.

"These findings are not at all surprising," says Ullas Karanth, a carnivore biologist at the Center for Wildlife Studies in Bengaluru, India, who was not involved in the research. "There's so much forest and so much habitat at this study site and throughout Southeast Asia, but without ground-level protections against local people doing industrial-scale hunting, the wildlife will go."

Tigers can thrive in human-dominated landscapes: India has the world's second-highest human population, but it has prioritized tiger conservation and now hosts two thirds of the planet's remaining wild tigers. Macdonald says the respective examples of India and Laos offer lessons for countries such as Thailand, which still has about 200 wild tigers; conserving habitat is critical but so is weeding out corruption, cracking down on poaching and reducing demand for big cat parts. "One way or another," he adds, "people have to change."

—*Rachel Nuwer*

OZBALCI Getty Images

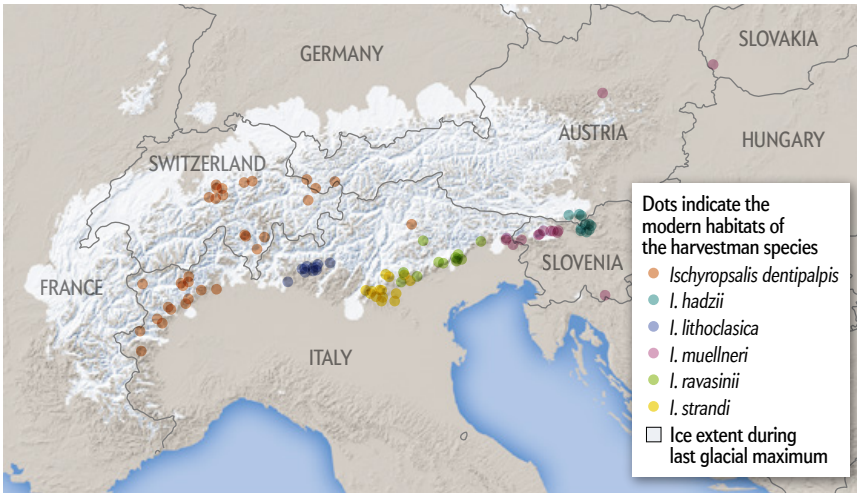
PALEOGEOGRAPHY

An Ancient Outline

Spiderlike cave creatures help to map the last ice age

The modern-day homes of cave-dwelling arachnids called harvestmen trace the long-gone southern limits of glaciers at the peak of the last major ice age, about 22,000 years ago, recent research suggests. "We can now potentially look at the distribution of this species just to reconstruct this glacial maximum," says Stefano Mammola, an ecologist at the Italian National Research Council's Water Research Institute. Mammola is lead author on the new work, published last August in the *Journal of Zoological Systematics and Evolutionary Research*.

Harvestmen, sometimes called daddy longlegs, are often mistaken for spiders. Some large-pincer harvestman species live in cold, humid caves in the Pyrenees, the Alps and the Balkan Peninsula, forming a narrow band across Europe. Mammola and his collaborators compared this range with geologists' models of glacier cover during the last ice age and found the band almost exactly matched the maximum southern edges of the glaciers, with only slight variations.



Map by Mapping Specialists

Mammola says the creatures would likely not have survived if ice had covered their caves, but they also probably could not have withstood the warmer temperatures farther from the glaciers' edge. (The cave temperatures have since warmed, but Mammola says this happened slowly enough for the arachnids to adapt.) "There

SOURCE: "TRACKING THE ICE: SUBTERRANEAN HARVESTMEN DISTRIBUTION MATCHES ANCIENT GLACIER MARGINS," BY STEFANO MAMMOLA ET AL., IN *JOURNAL OF ZOOLOGICAL SYSTEMATICS AND EVOLUTIONARY RESEARCH*, VOL. 57; JANUARY 17, 2019

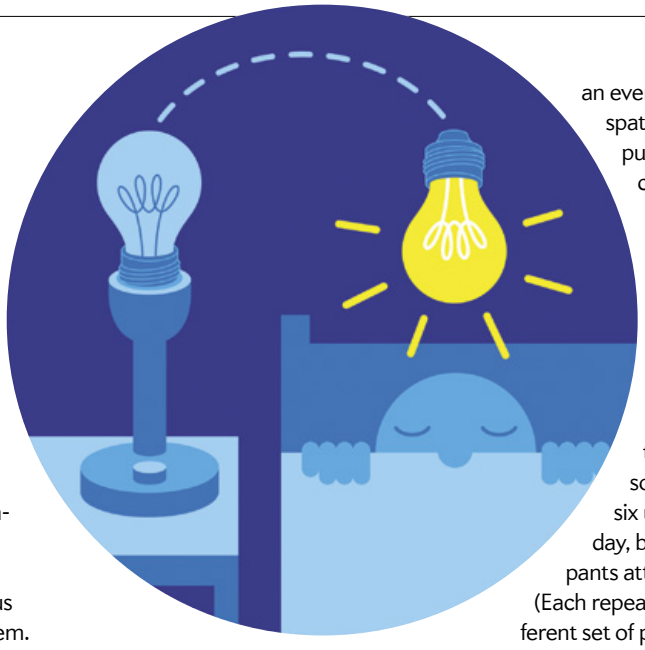
PSYCHOLOGY

From Zzz to Aha!

Reactivating remembered problems during sleep can trigger solutions

When you are stuck on a problem, sometimes it is best to stop thinking about it—consciously, anyway. Research has shown that taking a break or a nap can help the brain create pathways to a solution. Now a new study expands on the effect of this so-called incubation by using sound cues to focus the sleeping mind on a targeted problem.

When humans sleep, parts of the brain replay certain memories, strengthening and transforming them. About a decade ago researchers developed a technique, called targeted memory reactivation (TMR), aimed at further reinforcing selected memories: when a sound becomes associated with a memory and is later played during sleep, that memory gets reactivated. In a study published last November in *Psychological Science*, scientists tested whether revisiting the memory of a puzzle during sleep might also improve problem-solving.



About 60 participants visited the laboratory before and after a night of sleep. In an evening session, they attempted spatial, verbal and conceptual puzzles, with a distinct music clip repeating in the background for each, until they had worked on six puzzles they could not solve. Overnight they wore electrodes to detect slow-wave sleep—slumber's deepest phase, which may be important for memory consolidation—and a device played the sounds assigned to three of the six unsolved puzzles. The next day, back at the lab, the participants attempted the six puzzles again. (Each repeated the experiment with a different set of puzzles the following night.) All told, the subjects solved 32 percent of the sound-prompted puzzles versus 21 percent of the untargeted puzzles—a boost of more than 50 percent.

The researchers "very bravely went for quite complex tasks that involved a lot of complex processing, and remarkably they found these really strong effects in all of

was a balance between cool conditions and a cave that wasn't totally covered," he notes. "What you see now is just the shadow of a larger ancestral distribution."

Mercedes Burns, a biologist at the University of Maryland, Baltimore County, who studies harvestmen but was not involved in the study, says it makes sense the arachnids' range still matches that ancient outline. "Their idea of using presence of these species to track long-term changes in geography is a good one," Burns says. "These species are indicators of geographic change since they don't move much over a lifetime or over a generation." She adds that researchers have shown some plant species to similarly reflect ancient geography.

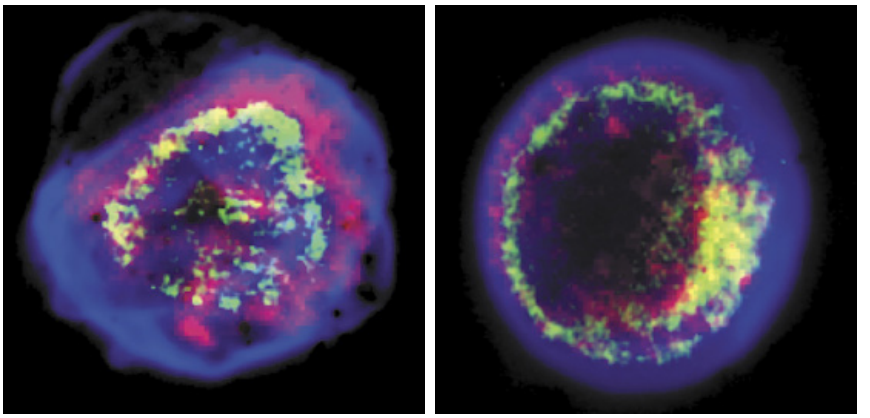
Mapping the distribution of cave species such as harvestmen or other arthropods, Mammola says, could act as additional evidence for researchers investigating past climate conditions.

—Joshua Rapp Learn

their tasks," says Penny Lewis, a psychologist at Cardiff University, who was not involved in the research. "These are supercool results. Now we need to go out and try to understand them by firstly replicating them and secondly trying to work out the component processes that are actually being influenced."

Beyond providing new evidence that humans restructure memories while sleeping, the research may have practical implications. "In a futuristic world, maybe TMR could help us use sleep to work on our problems," says lead author Kristin Sanders, who was a graduate student at Northwestern University during the study. Sleep-monitoring technology is increasingly accessible—and even without gadgets, prospective solvers can focus on important problems before bed.

Still, sleep is not magic; people need to do their homework and load their heads with the puzzle pieces involved. "I'm not going to solve cancer with this technique," Sanders says, "because I don't know anything about cancer research." *—Matthew Hutson*



I. R. SEITENZAHL ET AL.

Light emitted by two supernova remnants. Green indicates charged iron.

ASTRONOMY

A Supernova Map

New tool provides a dynamic chemical view of exploded star systems

When a dense stellar core called a white dwarf acquires enough material from a companion star orbiting nearby, it burns up in the nuclear fusion blast of a Type Ia supernova. This ejects freshly synthesized elements that mix with interstellar gas and eventually form stars and galaxies. But astrophysicists still don't know the specific conditions that ignite these explosions.

Ivo Seitenzahl, an astrophysicist at University of New South Wales Canberra, and his colleagues used the upgraded Very Large Telescope (VLT) in Chile to build unprecedented 3-D chemical maps of the debris left behind by these supernovae. These maps can help scientists work backward to "constrain the fundamental properties of these explosions, including the amount of kinetic energy and the mass of the exploding star," says Carles Badenes, an astrophysicist at the University of Pittsburgh, who was not involved in the study.

During a supernova event, heavy elements shoot from the white dwarf's core at supersonic speeds. This drives a shock wave outward through the surrounding interstellar gas and dust, and another shock wave bounces backward into the explosion debris, eventually heating the ejected matter to x-ray-emitting temperatures. Scientists can learn about a supernova remnant's composition from these x-rays—but current x-ray instruments lack the resolution to measure the movement of ejected material.

Seitenzahl's group used visible-light data from the VLT to analyze supernova remnants in a new way, described in July in *Physical Review Letters.* Basic models suggest that Type Ia supernovae produce most of the universe's iron. That iron should hold a stronger electrical charge the farther it is behind the supernova's shock wave and emit distinctive visible wavelengths of light; however, those emissions were too faint to detect before the VLT's recent instrument upgrade.

With the upgrade, the researchers detected concentric layers of charged iron within supernova remnants in the Large Magellanic Cloud, a nearby satellite galaxy of our Milky Way. From distortion patterns in light released by the charged iron, they determined the inward shock wave's velocity in Type Ia supernova remnants for the first time. "This is exciting science that's been enabled by new technology, used on precisely the type of [supernova] that needs it," says Dan Milisavljevic, an astronomer at Purdue University, who was also not involved in the work.

Seitenzahl's group also found that one particular supernova originated from a white dwarf whose mass was thought to be too small to trigger such an explosion, suggesting there is still more to learn about this process. Further work could reveal more details about the chemicals produced in Type Ia supernovae, whether an explosion initiates on the surface or interior of the star and what conditions trigger the blast. *—Rachel Berkowitz*

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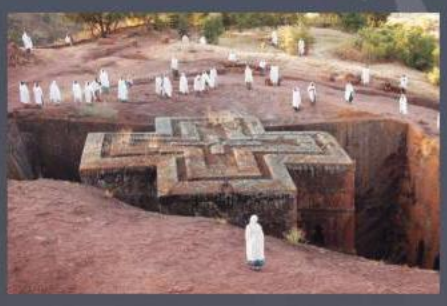

Catalog N°.	AL 288-1
Common name	Lucy
Species	*Australopithecus afarensis*
Age	3.2 million years
Place discovered	Afar Depression, Ethiopia
Date discovered	November 24, 1974
Discovered by	Donald Johanson

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Diane Ackerman is author of 25 works of nonfiction and poetry, including *The Zookeeper's Wife, The Human Age: The World Shaped by Us,* and *Jaguar of Sweet Laughter: New and Selected Poems.* She is currently at work on a novel about Maria Sibylla Merian.

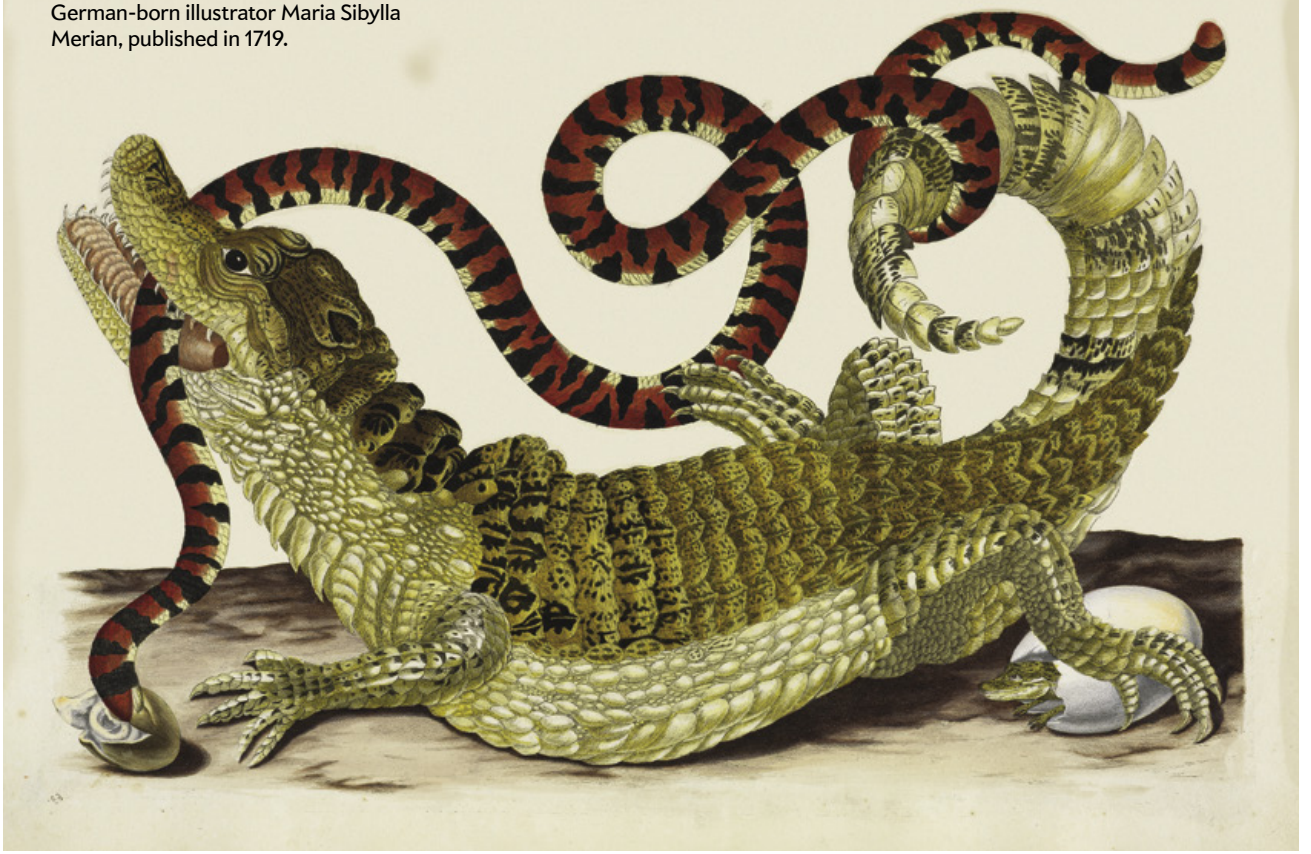
Maria Sibylla Merian, January 1670

There was a way of beholding nature
that was like a form of prayer.
When she painted a caterpillar,
she limned the whole bracing saga of its life
from birth, instars, and metamorphosis
to the plants it gorged on
and the predators who stalked,
ambushed and gobbled it.

Balancing the mingled dramas
on one toothy page of vellum,
she by the bye bore witness
to feats of nature both outlandish
and ordinary, such as maggots
hatching freely from eggs
like many living things,
not from dead flesh or dust,
without cause or coupling,
in a mysterious brew
of spontaneous generation.

She chose to reveal the smallest,
most despised creatures on earth
as divine works of nature,
and without cant or vanity tag them
not in Latin, the scholar's language
and *lingua franca* of elite circles,
but colloquially, in the colorful cant
of street talk, inviting men, women,
experts and workaday people alike
to join her in putting aside the mask of habit,
the hostile omens of superstition,
any disgust they might harbor about vermin,
or fable that bugs toil as Satan's minions,
and peer in wonder at the visible
but unseen life all around them,
dining, sparring, molting, mating,
in a mad frenzy of war and survival—
worlds unseen because unnoticed,
not because, as piety taught,
God purposely hid them from view.
Here is a caterpillar's eye, her paintings said,
look how cleverly it's designed!
Here is a spider's toe with tiny hairs.
Can you imagine how they tread?
Here is time elapsing inside a chrysalis,
where caterpillar becomes butterfly,
shape-shifting with infinite gradualness
from one unlikely form to another,
its behavior and purpose radically changed.
Come closer, I will show you.

CAIMAN defends her young against a false coral snake in this engraving by German-born illustrator Maria Sibylla Merian, published in 1719.



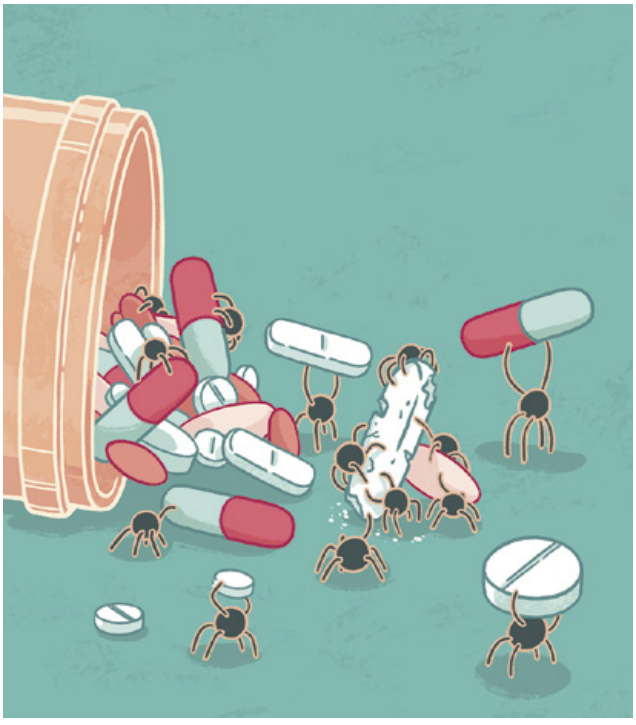
GETTY IMAGES

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*.

Our Tiny Inner Pharmacists

Gut microbes play a surprising role in activating and thwarting medicines and causing side effects

By Claudia Wallis



Next time you swallow a pill, think about this: you may not be the only one digesting it. You might not even be the first. By now most people are aware that our gastrointestinal tract is teeming with microbes that live mostly in harmony with us, helping us break down food, synthesize vitamins, resist germs, and relay chemical signals to our brain and immune system. But an emerging field of research with a mouthful of a name—pharmacomicrobiomics—is demonstrating that our tiny inner denizens can process our drugs in ways that both help and harm us.

Consider the case of levodopa (L-dopa), a mainstay of treating Parkinson's disease. When it enters the brain, L-dopa is converted into dopamine, a neurotransmitter that is in short supply in Parkinson's patients. It is typically given with carbidopa, a compound that prevents enzymes in the body from breaking it down before it gets to the brain. Even so, the amount of L-dopa that actually reaches its destination varies widely from patient to patient for reasons that only recently became clear. Turns out that certain intestinal microbes can also digest the drug, and, surprisingly, carbidopa does not stop them. It is, in fact, "completely ineffective" against these microbes, according to a 2019 study published in *Science*. The quantity of these subversive bugs varies from person to person and may explain why some patients get less bang from L-dopa than others do, says Emily Balskus, senior author of the paper and a professor of chemistry at Harvard University.

Microbes can also sabotage the classic cardiac drug digoxin, which is used to treat arrhythmias and heart failure. Doctors have long known that about 10 percent of patients who take it do not benefit, because so much of the drug—more than 50 percent in some cases—is inactivated by a gut bacterium called *Eggerthella lenta*. Newer research by microbiologist Peter Turnbaugh of the University of California, San Francisco, shows that only a few specific strains of *E. lenta* have this talent.

Our inner microbes can work in our favor, too. The drug sulfasalazine, widely used for rheumatoid arthritis, Crohn's disease and ulcerative colitis, does nothing *unless* gut bacteria metabolize it into an active form by breaking a chemical bond. This is also true of multiple oral antibiotics in the class known as sulfa drugs.

Another drug that gets a microbial helping hand is metformin, the first-line medication for type 2 diabetes. In this case, it's more of a two-way interaction. Recent studies show the drug somehow alters the mix of gut microbes in ways that make metformin more effective. How it does so, Balskus says, "has remained a mystery."

Perhaps the most exciting work in this nascent field concerns irinotecan, used as part of a cocktail of drugs to fight advanced colon and pancreatic cancers. Irinotecan is a powerful killer of tumor cells but provokes such severe diarrhea and intestinal damage that many patients cannot tolerate enough of it to treat their disease—a phenomenon known as dose-limiting toxicity. Chemist Matthew Redinbo of the University of North Carolina at Chapel Hill has traced the issue to a family of bugs called Enterobacteriaceae (members include *Salmonella* and *Escherichia coli*). The drug, given intravenously, circulates to the tumor and gets tagged for excretion in the liver, where it is rendered harmless by the addition of a simple sugar. Unfortunately, Redinbo explains, "microbes love sugar," so when the neutralized drug hits the GI tract on its way out of the body, the bugs pick off the sugar, reactivating the toxic drug, which then proceeds to "rip the GI tract apart."

Motivated in part by a young colleague's battle with colon cancer and with irinotecan's side effects, Redinbo has developed a small molecule that stops the microbes from eating the sugar so that the drug passes harmlessly through the gut. It prevents GI toxicity in animal studies, and Redinbo hopes to begin testing it in chemotherapy patients. He and a company he co-founded, Symberix, are also working on a drug that would prevent the intestinal distress and ulceration caused by popular painkillers called nonsteroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen and naproxen. Those side effects, which can be dire in chronic NSAID users, are caused by the same sugar-loving bacteria.

If Redinbo and his colleagues succeed, they will have opened the door to a class of drugs that can modify microbes with great precision. Balskus and her team, meanwhile, are testing a molecule that would stop bacteria from breaking down L-dopa. It is "a whole new area of drug development waiting to be explored," she says. SA

Illustration by Celia Krampien

BIG QUESTIONS FROM... JENNIFER DOUDNA

A pioneer in genome editing, Jennifer Doudna started a revolution in genetic engineering by developing the CRISPR-Cas9 system. Here, Doudna discusses how to fine-tune this molecular tool, which stands to change the way we treat and even think about human disease.

It began as an effort to understand how microbes fight viral infections. Within their chromosomes bacteria store snippets of DNA taken from the viruses they encounter. These fragments, which are tagged by a set of DNA segments called CRISPRs (clustered regulatory interspaced short palindromic repeats), serve as a record of past infections, and allow bacteria to become immune to future infections.

For Jennifer Doudna, an HHMI investigator and professor of chemistry as well as biochemistry and molecular biology at the University of California, Berkeley, the big question was, how did the system work? The answer lay with an enzyme named Cas9. Doudna and her team found that when armed with an RNA copy of one of the viral mug shots, the Cas9 enzyme could recognize and disable viruses that carried a matching sequence.

Once she understood this system, Doudna set out to harness it. By feeding the Cas9 enzyme a guide RNA of her choosing, Doudna found that she could edit target DNA much more easily and accurately than with existing methods. A Cas9-directed incision could inactivate a target gene. It could also provide an insertion site for new DNA, such as an altered version of the target gene.

The description of this CRISPR-Cas9 system—published in *Science* in 2012—launched a revolution in biology and biotechnology. In just seven years, CRISPR has become an essential research tool and the inspiration for scores of new start-ups. The technology has the potential to transform basic science, improve agricultural crops and cure genetic diseases. At the same time, it raises ethical questions about how to handle a technology that has the power to alter human evolution.

In 2018, Doudna and two of her colleagues, Professors Emmanuelle Charpentier at the Max Planck Institute for Infection Biology and Virginijus Siksnys at Vilnius University, were awarded the Kavli Prize in Nanoscience for their work on CRISPR-Cas9.

Now, Doudna outlines the next big questions that need to be addressed before CRISPR can reach its full potential.

What is CRISPR 2.0, and how do we develop it?

One big issue with CRISPR technology is how we can ensure the accuracy and the efficiency of genome editing, meaning the exact changes that are introduced into DNA. Right now, scientists can trigger targeted changes to DNA at a particular place in the genome, but we have a harder time ensuring the

exact kind of change that gets introduced. A couple of things that are in the pipeline right now, not just in my own lab, but generally in the field: One is to develop what are called base-editing versions of CRISPR-Cas proteins. This means developing ways of using these programmable enzymes, not to cut DNA, but actually to trigger a chemical change to a particular DNA base in a sequence. With these base-editing molecules, we could reduce opportunities for the cell to make an undesired change. This is the kind of very specific manipulation of a DNA sequence that could, in principle, cure a disease-causing mutation in a cell.

Can we turn CRISPR-Cas9 against infectious disease?

There's been a lot of interest in asking the question, at least in a research setting. Could you harness the adaptive immune functions of CRISPR-Cas systems for protecting other kinds of cells from viruses? I think that is not too likely, at least in its present form, because viruses have a remarkable ability to adapt and evolve resistance to targeting mechanisms, such as the one used by CRISPR-Cas. On the other hand, do I think that there may be ways to target bacteria that are infectious agents in people? Absolutely. One of the forefronts of the field is to explore how we could use CRISPR-Cas systems to target some of the bacteria that are harmful to people.

Can we turn to microbes to find alternative gene-editing tools?

One of the amazing questions in biology is, what are all of the microbes that populate our planet? Many scientists, including my colleague, Jillian Banfield here at University of California, Berkeley, are studying microbes in the environment by sequencing their DNA and piecing together information about their lifestyles, community partners and environmental niches. That's something where I think a biochemist and structural biologist like myself can engage with experts in DNA metagenomics to try to understand the molecular pathways in these organisms. Some of these pathways provide a defense against viruses, like CRISPR systems do. CasX is a newer iteration of CRISPR-Cas that can be programmed to find and cut DNA just like Cas9. But it's a lot smaller, and it has a completely different molecular shape, so it may be easier to deliver it into cells and ensure that it does the accurate editing necessary for clinical use.

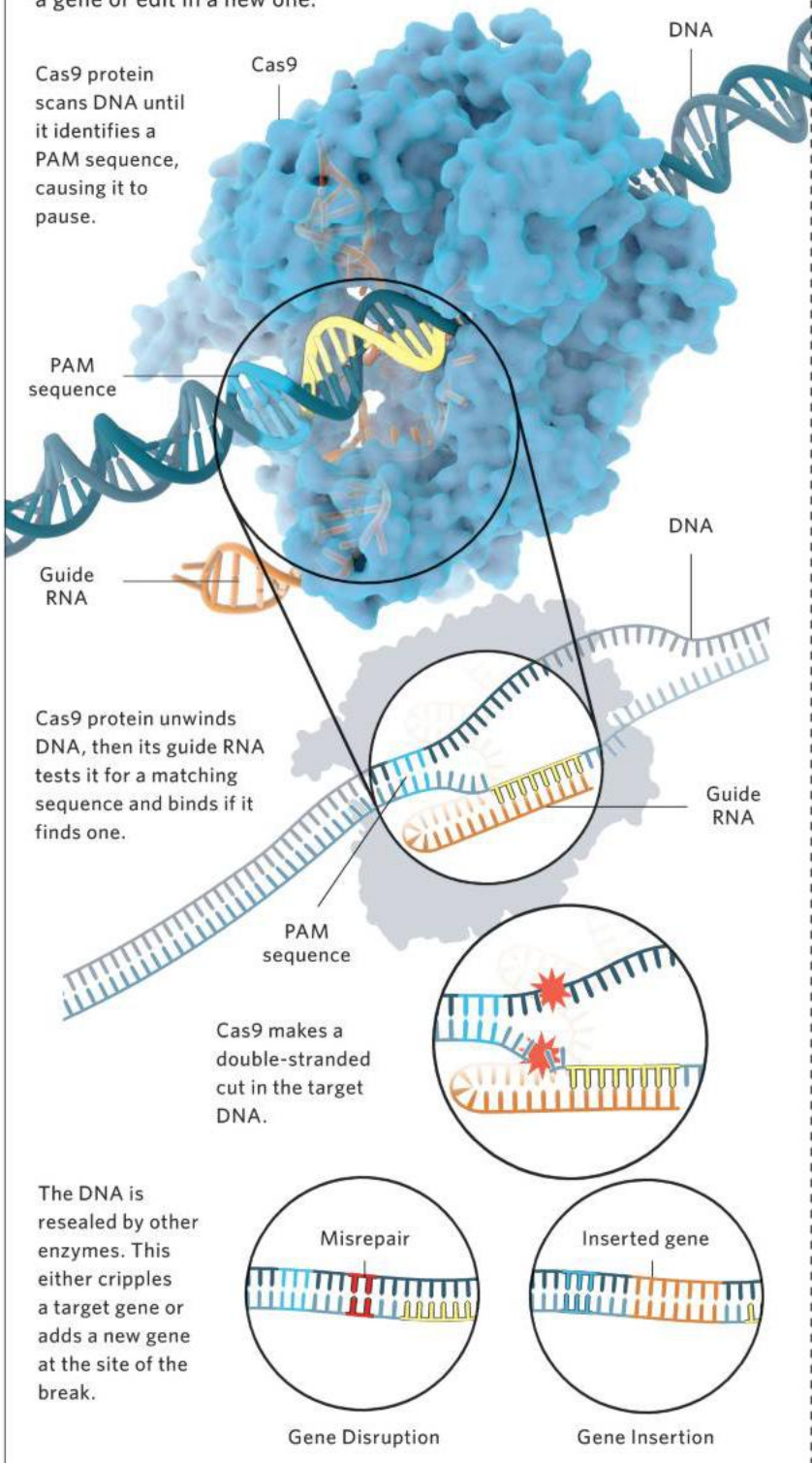
How can we ensure gene editing benefits everyone?

Very soon, we will be faced with many opportunities for manipulating DNA—not only in individuals but also in the cells that can transmit changes to future generations. Given that, I'd like to see a lot more opportunities for public interaction with scientists and more opportunities to explore the broader implications of gene editing. How does it affect the inequalities that we see across society? How does it affect people's decisions about reproduction and genetic disease? How do we even define genetic disease? What do we consider to be health versus disease? Those kinds of questions need to be openly debated.

To learn more, listen to a podcast with Jennifer Doudna on ScientificAmerican.com. Also, stay tuned for the announcement of the next Kavli Prize laureates on May 27, 2020.

EDITING THE GENOME

The CRISPR gene-editing system uses an enzyme called Cas9 and a customized guide RNA to help target, cut, alter and stitch up particular stretches of the genome. It can disrupt a gene or edit in a new one.



THE KAVLI PRIZE

One Phone, One Vote

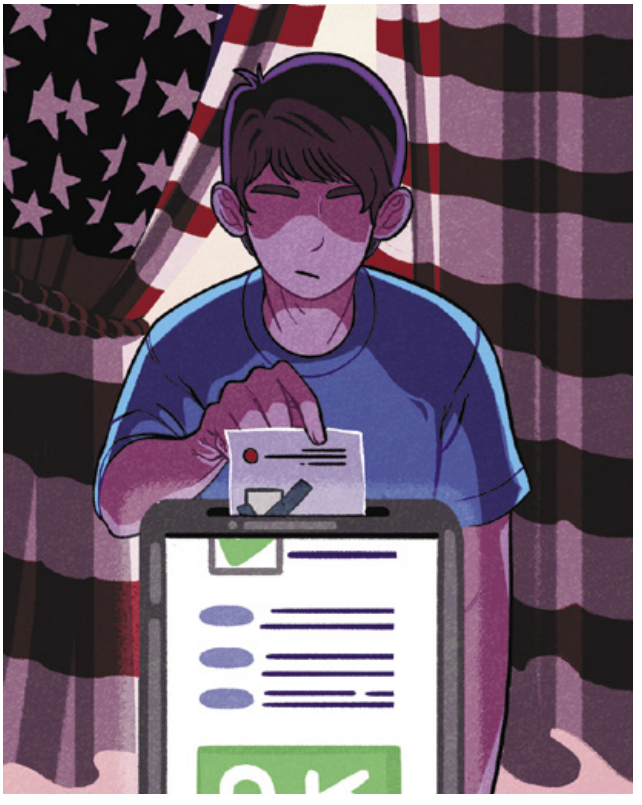
Technology will make elections more secure—but not soon

By Wade Roush

In the run-up to the 2016 U.S. elections, Russian hackers penetrated state voter-registration databases, and Russia's Internet Research Agency targeted millions of social media users with pro-Trump propaganda posts and ads. On Election Day, voting machines malfunctioned in at least nine states. Even now, nearly a whole election cycle later, about a quarter of the states do not insist on voting equipment that generates the paper trails needed for rigorous postelection audits. How can we be sure, then, that the 2020 elections will be fair and tamper-free?

We can't. But one piece of good news is that in September 2019, Senate majority leader Mitch McConnell of Kentucky dropped his opposition to an amendment providing $250 million in new federal spending on election security. The money will go to help state election offices replace outdated voting equipment and improve cybersecurity.

Another positive development is that technologists in the private and nonprofit sectors are tackling the election security challenge at multiple levels. Microsoft, for example, is partnering with Galois, a Portland, Ore.–based firm focused on trustworthy computing, to build a free, open-source software kit for election officials called ElectionGuard. It uses a technique called homomorphic encryption to maintain voter anonymity while allowing anyone to verify that votes have been correctly counted. Similarly, the San Francisco nonprofit VotingWorks is creating free, open-source software that helps jurisdictions run "risk-limiting audits," which have emerged as the gold standard for efficiently determining whether the outcome of an election was correct.



Soon it may even be possible for everyone to vote easily and securely on their smartphones. I visited a Boston start-up called Voatz whose iOS and Android apps have already been used in three states to allow remote voting by military personnel stationed abroad and people with disabilities. It uses video selfies to verify voters' identities and sends blockchain-encrypted votes to a digital lockbox. On Election Day, officials in the voters' jurisdiction open the lockbox, print corresponding paper ballots (creating an auditable paper trail) and run them through standard optical scanners. "We felt like that was a good step, to show that even a very modern system can integrate with a legacy infrastructure," says Voatz co-founder and CEO Nimit Sawhney.

The bad news is that none of this technology will be ready for wide deployment in the 2020 election. ElectionGuard is only in the pilot-testing phase, and Voatz's most significant remote-voting project, during West Virginia's 2018 midterm elections, involved only 144 ballots in 24 counties.

And none of these fixes addresses voters' vulnerability to social media–based influence operations. "If I were the Russians, how do I win, if I want Trump to win? I suppress 20,000 African-American votes in Michigan," says Juliette Kayyem, a counterterrorism scholar at Harvard University, who was an Obama-era assistant secretary in the Department of Homeland Security. "I don't do it the same way I did it before. I'm going to do fake news that there is an active shooter" at a polling place.

Don't expect much help on the disinformation front from the social media giants, which are already dodging responsibility for the ways their platforms could amplify division in 2020. Last September, Facebook said that it won't try to fact-check political speech or ban political ads that make false claims. "How the players play the game is up to them, not us," said Nick Clegg, Facebook's vice president of global affairs and communications.

In the end, an election is a complex sociotechnical machine, which means all citizens—not just election officials—will need to be on guard in 2020 and beyond. "While we can be very sure that it's really, really hard to alter a vote, it's a lot easier to convince people that something bad happened by just spreading bad information," Sawhney says. "I think that is the hardest problem to solve." SA

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

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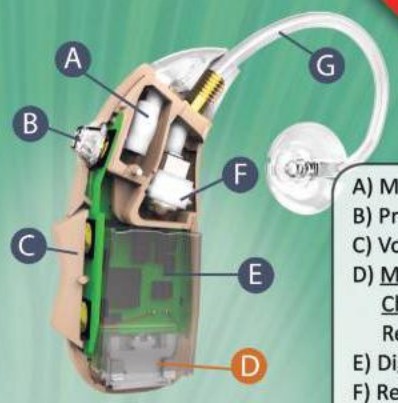

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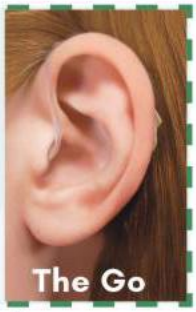

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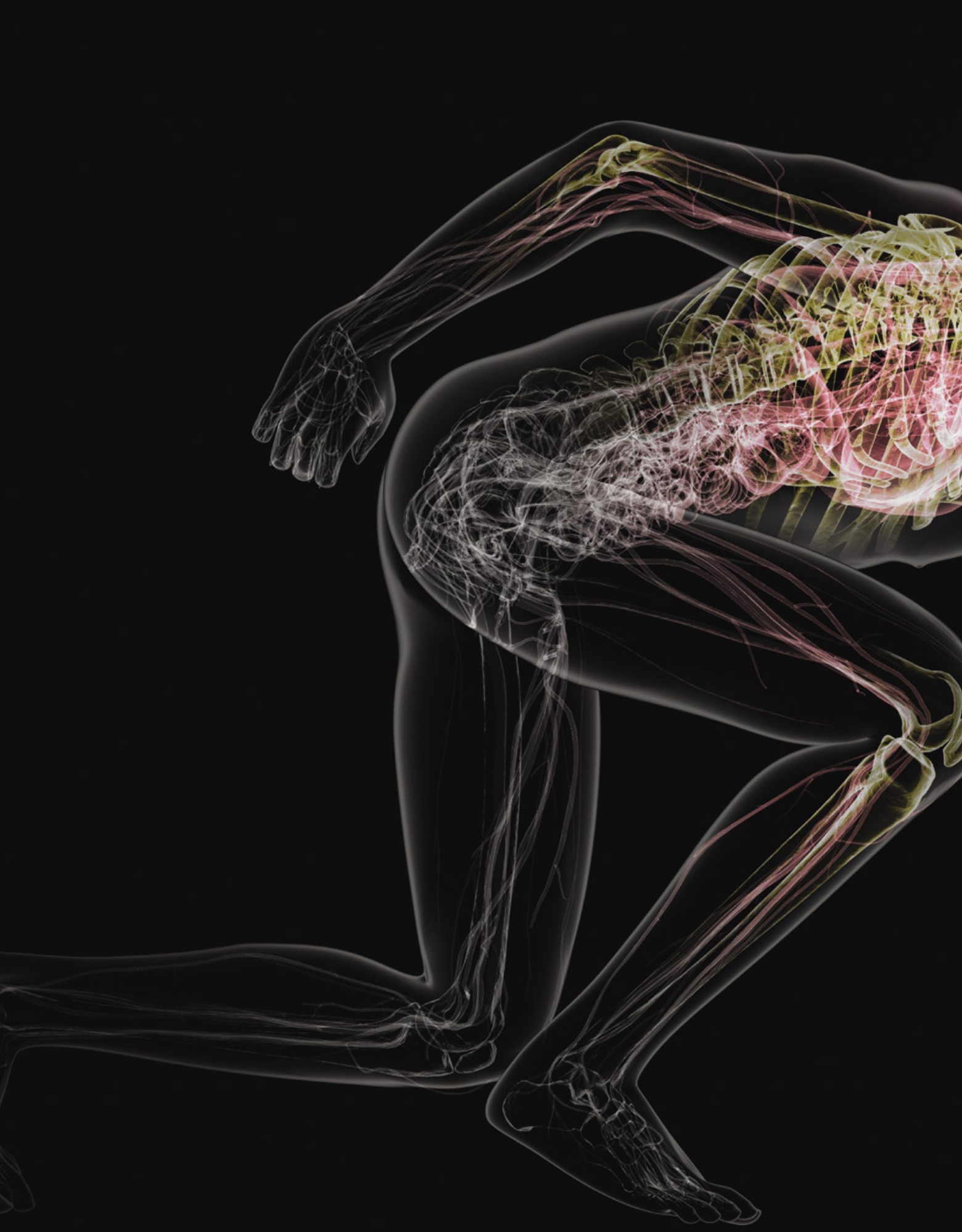


EVOLUTION

WHY YOUR BRAIN NEEDS EXERCISE

Key transitions in the evolutionary history of humans may have linked body and mind in ways that we can exploit to slow brain aging

By David A. Raichlen and Gene E. Alexander

Illustration by Bryan Christie Design

David A. Raichlen is a professor of biological sciences and director of the evolutionary biology of exercise laboratory at the University of Southern California. His research focuses on the biomechanics and physiology of exercise from an evolutionary perspective.

Gene E. Alexander is a professor of psychology and psychiatry and director of the brain imaging, behavior and aging laboratory at the University of Arizona. He studies the aging brain in both healthy adults and those suffering from neurodegenerative disease.

IN THE 1990s RESEARCHERS ANNOUNCED A SERIES OF DISCOVERIES THAT WOULD UPEND a bedrock tenet of neuroscience. For decades the mature brain was understood to be incapable of growing new neurons. Once an individual reached adulthood, the thinking went, the brain began losing neurons rather than gaining them. But evidence was building that the adult brain could, in fact, generate new neurons. In one particularly striking experiment with mice, scientists found that simply running on a wheel led to the birth of new neurons in the hippocampus, a brain structure that is associated with memory. Since then, other studies have established that exercise also has positive effects on the brains of humans, especially as we age, and that it may even help reduce the risk of Alzheimer's disease and other neurodegenerative conditions. But the research raised a key question: Why does exercise affect the brain at all?

IN BRIEF

It is by now well established that exercise has positive effects on the brain, especially as we age. **Less clear has been** why physical activity affects the brain in the first place. **Key events** in the evolutionary history of humans may have forged the link between exercise and brain function. **Cognitively challenging** exercise may benefit the brain more than physical activity that makes fewer cognitive demands.

Physical activity improves the function of many organ systems in the body, but the effects are usually linked to better athletic performance. For example, when you walk or run, your muscles demand more oxygen, and over time your cardiovascular system responds by increasing the size of the heart and building new blood vessels. The cardiovascular changes are primarily a response to the physical challenges of exercise, which can enhance endurance. But what challenge elicits a response from the brain?

Answering this question requires that we rethink our views of exercise. People often consider walking and running to be activities that the body is able to perform on autopilot. But research carried out over the past decade by us and others would indicate that this folk wisdom is wrong. Instead exercise seems to be as much a cognitive activity as a physical one. In fact, this link between physical activity and brain health may trace back millions of years to the origin of hallmark traits of humankind. If we can better understand why and how exercise engages the brain, perhaps we can leverage the relevant physiological pathways to design novel exercise routines that will boost people's cognition as they age—work that we have begun to undertake.

FLEXING THE BRAIN

TO EXPLORE WHY exercise benefits the brain, we need to first consider which aspects of brain structure and cognition seem most responsive to it. When researchers at the Salk Institute for Biological Studies in La Jolla, Calif., led by Fred Gage and Henriette Van Praag, showed in the 1990s that running increased the birth of new hippocampal neurons in mice, they noted that this process appeared to be tied to the production of a protein called brain-derived neurotrophic factor (BDNF). BDNF is produced throughout the body and in the brain, and it promotes both the growth and the survival of nascent neurons. The Salk group and others went on to demonstrate that exercise-induced neurogenesis is associated with improved performance on memory-related tasks in rodents. The results of these studies were striking because atrophy of the hippocampus is widely linked to memory difficulties during healthy human aging and occurs to a greater extent in individuals with neurodegenerative diseases such as Alzheimer's. The findings in rodents provided an initial glimpse of how exercise could counter this decline.

Following up on this work in animals, researchers carried out a series of investigations that determined

that in humans, just like in rodents, aerobic exercise leads to the production of BDNF and augments the structure—that is, the size and connectivity—of key areas of the brain, including the hippocampus. In a randomized trial conducted at the University of Illinois at Urbana-Champaign by Kirk Erickson and Arthur Kramer, 12 months of aerobic exercise led to an increase in BDNF levels, an increase in the size of the hippocampus and improvements in memory in older adults.

Other investigators have found associations between exercise and the hippocampus in a variety of observational studies. In our own study of more than 7,000 middle-aged to older adults in the U.K., published in 2019 in *Brain Imaging and Behavior,* we demonstrated that people who spent more time engaged in moderate to vigorous physical activity had larger hippocampal volumes. Although it is not yet possible to say whether these effects in humans are related to neurogenesis or other forms of brain plasticity, such as increasing connections among existing neurons, together the results clearly indicate that exercise can benefit the brain's hippocampus and its cognitive functions.

Researchers have also documented clear links between aerobic exercise and benefits to other parts of the brain, including expansion of the prefrontal cortex, which sits just behind the forehead. Such augmentation of this region has been tied to sharper executive cognitive functions, which involve aspects of planning, decision-making and multitasking—abilities that, like memory, tend to decline with healthy aging and are further degraded in the presence of Alzheimer's. Scientists suspect that increased connections between existing neurons, rather than the birth of new neurons, are responsible for the beneficial effects of exercise on the prefrontal cortex and other brain regions outside the hippocampus.

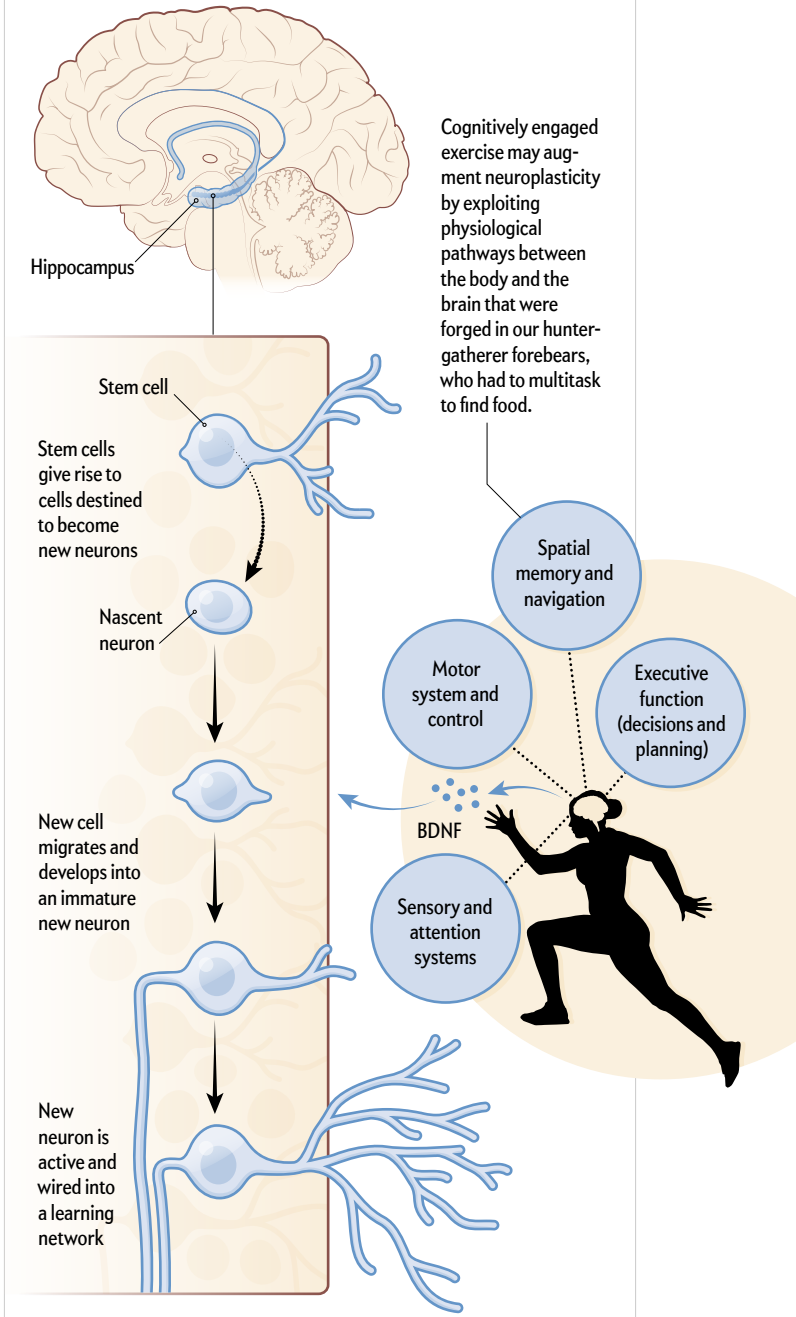
UPRIGHT AND ACTIVE

WITH MOUNTING EVIDENCE that aerobic exercise can boost brain health, especially in older adults, the next step was to figure out exactly what cognitive challenges physical activity poses that trigger this adaptive response. We began to think that examining the evolutionary relation between the brain and the body might be a good place to start. Hominins (the group that includes modern humans and our close extinct relatives) split from the lineage leading to our closest living relatives, chimpanzees and bonobos, between six million and seven million years ago. In that time, hominins evolved a number of anatomical and behavioral adaptations that distinguish us from other primates. We think two of these evolutionary changes in particular bound exercise to brain function in ways that people can make use of today.

First, our ancestors shifted from walking on all fours to walking upright on just their hind legs. This bipedal posture means that there are times when our bodies are precariously balanced over one foot rather than two or more limbs like in other apes. To accomplish this task, our brains must coordinate a great deal of information and, in the process, make adjustments to muscle activity throughout the body to maintain our balance. While coordinating these actions, we must also watch out for any environmental obstacles. In other words, simply because we are bipedal, our brains may be more cognitively challenged than those of our quadrupedal ancestors.

New Neurons in Aging Brains

Exercise leads to beneficial changes in the adult brain, including the birth of new neurons and increased connections among existing neurons. One of the ways in which physical activity seems to induce this neuroplasticity is by increasing production of a protein called brain-derived neurotrophic factor (BDNF), which promotes neuron growth and survival. Recent research suggests that cognitively engaging the brain during physical activity enhances this process.



Illustrations by Tami Tolpa

Up and at 'Em

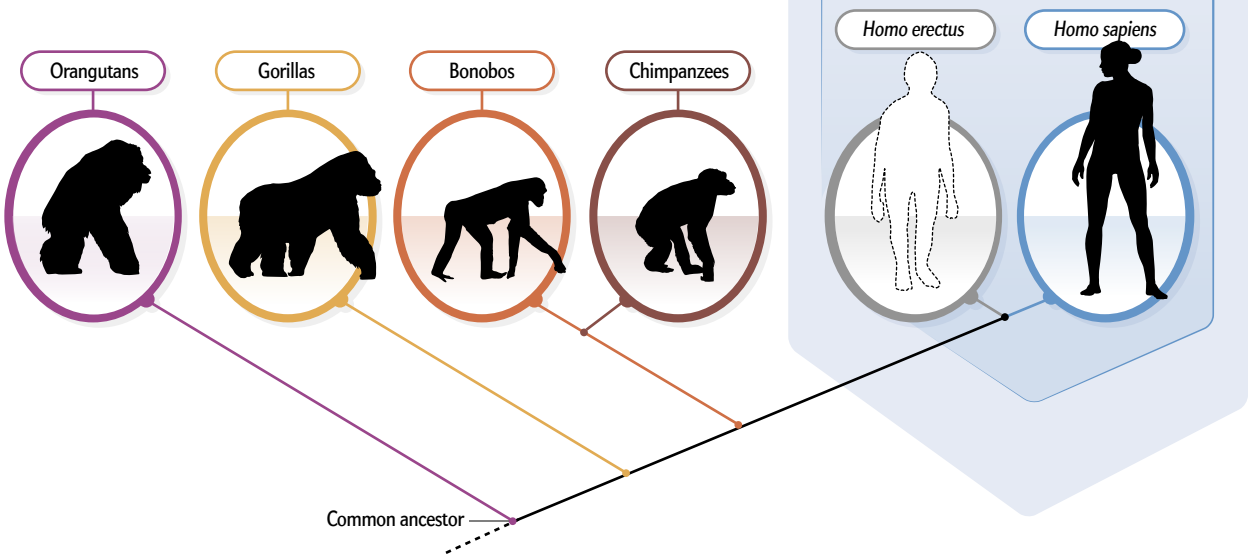
In the six million to seven million years since the human lineage diverged from that of the chimpanzees and bonobos, our kind has evolved a host of characteristics that set us apart from other apes. The beneficial effects of cognitively engaged exercise on the brain may stem from two evolutionary changes in particular that made humans more physically active than our ape cousins and supercharged our ability to multitask: the shift to upright walking and the adoption of hunting and gathering as a subsistence strategy.

Bipedalism

By around six million to seven million years ago human ancestors had abandoned walking on all fours for striding upright on their hind limbs like us. The shift from quadrupedal to bipedal locomotion introduced balance challenges that may have placed new demands on the brain.

Hunting and Gathering

Some two million years ago our ancestors began to forage in a new way, hunting animals and gathering plant foods. This strategy involves far more aerobic activity than is seen in other apes, which subsist mainly on plants. And it requires that the brain carry out an array of cognitive tasks while on the move.



Second, the hominin way of life changed to incorporate higher levels of aerobic activity. Fossil evidence indicates that in the early stages of human evolution, our ancestors were probably relatively sedentary bipedal apes who ate mainly plants. By some two million years ago, however, as habitats dried out under a cooling climate, at least one group of ancestral humans began to forage in a new way, hunting animals and gathering plant foods. Hunting and gathering dominated human subsistence strategies for nearly two million years until the advent of farming and herding around 10,000 years ago. With Herman Pontzer of Duke University and Brian Wood of the University of California, Los Angeles, we have shown that because of the long distances traversed in search of food, hunting and gathering involves much more aerobic activity than seen in other apes.

Increased demands on the brain accompanied this shift toward a more physically active routine. When out foraging afar, hunter-gatherers must survey their surroundings to make sure they know where they are. This kind of spatial navigation relies on the hippocampus, the same brain region that benefits from exercise and that tends to atrophy as we get older. In addition, they have to scan the landscape for signs of food, using sensory information from their visual and auditory systems. They must remember where they have been before and when certain kinds of food were available. The brain uses this information from both short- and long-term memory, allowing people to make decisions and plan their routes—cognitive tasks that are supported by the hippocampus and the prefrontal cortex, among other regions. Hunter-gatherers also often forage in groups, in which case they may have conversations while their brains are maintaining their balance and keeping them spatially located in their environment. All of this multitasking is controlled, in part, by the prefrontal cortex, which also tends to diminish with age.

Although any foraging animal must navigate and figure out where to find food, hunter-gatherers have to perform these functions during fast-paced treks that can extend over more than 20 kilometers. At high speeds, multitasking becomes even more difficult and requires faster information processing. From an evolutionary perspective, it would make sense to have a brain ready to respond to an array of challenges during and after foraging to maximize the chances of success in finding food. But the physiological resources required to build and maintain such a brain—including those that support the birth and survival of new neurons—cost the body energy, meaning that if we do not regularly make use of this system, we are likely to lose these benefits.

This evolutionary neuroscience perspective on exercise and the brain, which we detailed in an article published in 2017 in *Trends in Neurosciences,* has profound implications for humans today. In our modern society, we do not need to engage in aerobic physical activity to find food for survival. The brain atrophy and attendant cognitive declines that commonly occur during aging may be partly related to our sedentary habits.

But simply exercising more may not realize the full potential of physical activity for keeping brain decline at bay. Indeed, our model suggests that even people who already get a lot of aerobic activity may want to rethink their routines. It is possible that we might not always exercise in ways that take full advantage of our evolved mechanisms for sustaining brain performance.

Think about the ways in which many of us get our aerobic exercise. Often we go to gyms and use a stationary exercise machine; the most cognitively demanding task in such a workout might be deciding what channel to watch on the built-in television. What is more, these machines remove some of the demands of maintaining balance and adjusting speed, among many other intrinsic cognitive challenges of movement through a changing environment.

What if this form of exercise is shortchanging us? Our ancestors evolved in an unpredictable world. What if we could modify our exercise routines to include cognitive challenges like those faced by our hunter-gatherer forebears? If we can augment the effects of exercise by including a cognitively demanding activity, then perhaps we can increase the efficacy of exercise regimens aimed at boosting cognition during aging and potentially even alter the course of neurodegenerative diseases such as Alzheimer's.

MOVE AND THINK

IN FACT, a growing body of research suggests that exercise that is cognitively stimulating may indeed benefit the brain more than exercise that does not make such cognitive demands. For example, Gerd Kempermann and his colleagues at the Center for Regenerative Therapies Dresden in Germany explored this possibility by comparing the growth and survival of new neurons in the mouse hippocampus after exercise alone or after exercise combined with access to a cognitively enriched environment. They found an additive effect: exercise alone was good for the hippocampus, but combining physical activity with cognitive demands in a stimulating environment was even better, leading to even more new neurons. Using the brain during and after exercise seemed to trigger enhanced neuron survival.

We and others have recently begun to extend these studies from animals to humans—with encouraging results. For example, researchers have been exploring combining exercise and cognitive challenges in individuals experiencing notable cognitive decline. Cay Anderson-Hanley of Union College in Schenectady, N.Y., has tested simultaneous exercise and cognitive interventions in people with mild cognitive impairment, a condition associated with increased risk for Alzheimer's. More work certainly needs to be done in populations such as this one before we can draw any firm conclusions, but the results so far suggest that people who are already experiencing some cognitive decline may benefit from exercising while playing a mentally demanding video game. In studies of healthy adults, Anderson-Hanley and her colleagues have also shown that simultaneously exercising and playing a cognitive challenging video game may elicit a greater increase in circulating BDNF than exercise alone. These findings further bolster the idea that BDNF is instrumental in bringing about exercise-induced brain benefits.

In our own work, we have developed a game designed to specifically challenge aspects of cognition that tend to decline with age and that are probably needed during foraging. In the game, players spatially navigate and complete attention and memory tasks while cycling at a moderate aerobic intensity level. To evaluate the potential of this approach to boost cognitive performance in healthy older adults, we are comparing a group exercising while playing the game with a group exercising without the game, a group playing the game without exercising, and a control group that only watches nature videos. The results to date are promising.

Many other research groups are testing combinations of exercise and cognitive tasks. In the near future, we will probably have a better idea of how best to deploy them to support and enhance cognition in both healthy individuals and those experiencing disease-related cognitive decline.

In addition to specially designed interventions similar to the ones described here, it is possible that participation in sports that require combinations of cognitive and aerobic tasks may be a way to activate these brain benefits. For example, we recently showed that collegiate cross-country runners who train extensively on outdoor trails have increased connectivity among brain regions associated with executive cognitive functions compared with healthy but more sedentary young adults. Future work will help us understand whether these benefits are also greater than those seen in runners who train in less complex settings—on a treadmill, for instance.

Much remains to be discovered. Although it is still too early to make specific prescriptions for combining exercise and cognitive tasks, we can say with certainty that exercise is a key player in preserving brain function as we age. The U.S. Department of Health and Human Services guidelines suggest that people should engage in aerobic exercise for at least 150 minutes a week at a moderate intensity or at least 75 minutes a week at a vigorous intensity (or an equivalent combination of the two). Meeting or exceeding these exercise recommendations is good for the body and may improve brain health.

Clinical trials will tell us much more about the efficacy of cognitively engaged exercise—what kinds of mental and physical activities are most impactful, for example, and the optimal intensity and duration of exercise for augmenting cognition. But in light of the evidence we have so far, we believe that with continued careful research we can target physiological pathways linking the brain and the body and exploit our brain's evolved adaptive capacity for exercise-induced plasticity during aging. In the end, working out both the body and the brain during exercise may help keep the mind sharp for life. SA

MORE TO EXPLORE

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FROM OUR ARCHIVES

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SPACE

Even if the Milky Way is teeming with spacefaring aliens, we should not be surprised that Earth remains unvisited

The Galactic Archipelago

By Caleb Scharf

Illustration by María Corte

Caleb Scharf is director of the Columbia Astrobiology Center and author of several books, including *The Copernicus Complex* (2014) and *The Zoomable Universe* (2017). He writes the Life, Unbounded blog for *Scientific American* and has written for many other publications. He lives in New York City with his wife and two daughters.

ON THE 15TH OF JANUARY IN 1790, NINE MUTINEERS FROM HMS *Bounty,* 18 people from Tahiti and one baby arrived on Pitcairn Island—one of the most isolated habitable places on the planet. Surrounded by the southern Pacific Ocean and with hundreds of miles of open water between it and the nearest other islands, Pitcairn is the epitome of solitude.

IN BRIEF

Basic extrapolations suggest that if there are other spacefaring civilizations in the Milky Way, they could spread across the entire galaxy with surprising speed. Why, then, have we found no irrefutable evidence of aliens visiting Earth?

Popular answers to this puzzle—that we are alone, that interstellar travel is impossible, that aliens are hiding from us—all rest on assumptions that verge on implausibility.

The most likely explanation for Earth's apparent solitude may be that galactic settlement occurs in waves and that our species has arisen on an out-of-the-way planet during a local lull in interstellar exploration.

Before the *Bounty* escapees showed up, the island may not have seen human occupation of any kind since the 1400s, when it was still inhabited by Polynesians. That community perhaps existed for centuries—centuries that seem to have culminated with a depletion of natural resources, as well as conflicts on other, distant islands that cut off lines of trade and supply, leading to the effective extinction of Pitcairn's human occupants. What was, at least superficially, a habitable place had become unsustainable, until the arrival of the *Bounty* on that fateful day in 1790. Remarkably, it took another 18 years for any other ship to drop anchor at Pitcairn, even though the settlers recorded sightings of vessels passing in the distance.

The story of Pitcairn is just one extreme example of the unusual dynamics of human occupation across the southern Pacific. Within the regions of Polynesia, Micronesia and Melanesia, there are tens of thousands of islands scattered across millions of square miles of ocean. Many are barely more than a protuberance of rock and coral, and even the habitable spots are not all inhabited at any given time. But taken together, they represent a vast landscape of potential settlement and civilization for people motivated to navigate across Earth's watery depths.

The parallels between this unmistakably terrestrial environment and our cosmic surroundings are striking. In the Milky Way galaxy, there are perhaps as many as 300 billion stars. The best estimates from exoplanet-hunting efforts, such as those undertaken with NASA's Kepler space telescope, suggest that within this ocean of stellar bodies there may be more than 10 billion small, rocky worlds in orbital configurations conducive to temperate surface conditions. Like the islands of Earth, these exoplanetary specks might both generate and support living systems and could provide a network of waypoints for any species determined to migrate across interstellar space. And that is where things get really interesting.

JUST AS WESTERN EUROPEANS EVENTUALLY REALIZED THAT the peoples of the southern Pacific had spread across its thousands of miles of ocean on simple vessels gliding along at just a few knots, we can now see that spreading across our galaxy need not require much more than persistence and a modest amount of cosmic time.

Most famously, over a lunch in 1950 with fellow scientists, physicist Enrico Fermi first recognized this fact and—as the story goes—blurted out, "Don't you ever wonder where everybody is?" The "everybody" in this case was any spacefaring species, and the question developed over time into the equally famous, albeit somewhat mislabeled, Fermi paradox: unless technologically proficient species are vanishingly rare, they should have spread practically everywhere across the galaxy by now, yet we see no evidence for them. Fermi, renowned for his ability to carry out so-called back-of-the-envelope calculations in his head, had figured out in approximate terms that the Milky Way could be settled in the blink of a cosmic eye when each tick of the galactic clock accounts for millions of years.

In 1975 astrophysicist Michael Hart produced the first properly quantitative and nuanced study of this idea, in which he put forward what has become known as Hart's "fact A." This refers to the absence of aliens on Earth today. That unassailable fact (for most level-headed people) led Hart to the conclusion that no other technological civilizations currently exist—or have

ever existed—in our galaxy. The key to this assertion, much as with Fermi's original insight, lies in the relatively short amount of time it would apparently take for a species to spread across the Milky Way's 100,000-light-year girth even using modest, far-slower-than-light propulsion systems.

Physicist Frank Tipler also studied the problem, and he reported on his work in 1980, demonstrating, much like Hart, that in a few million years suitably motivated aliens could indeed visit everywhere. Given that our solar system has been around for 4.5 billion years and that the Milky Way assembled at least 10 billion years ago, there has been more than enough time for species to wind up on all inhabitable worlds.

Critically, though, these investigations considered the spread of life somewhat differently. Hart assumed a process of settlement "in the flesh" by a biological species, whereas Tipler imagined star-hopping swarms of self-replicating machine probes that would spread without restraint. In most settlement scenarios, the stellar systems and their planets become inhabited, if they were not already, and then serve as the next base of operations for launching onward to new systems. For Tipler's self-replicating machines, the primary limits to their expansion would be the availability of sufficient energy and raw materials for making each subsequent generation.

These radically different approaches highlight the challenges of making meaningful statements about interstellar migration. There are always a lot of big assumptions in any study like these. Some are reasonable and easily justifiable, but others are trickier. For example, all scenarios involve guesses about the scope of the technology used for interstellar travel. Furthermore, when the species is "along for the ride" rather than sending out sophisticated robotic emissaries, the most fundamental assumption is that living things can survive any kind of interstellar travel at all.

We know that traveling at even a paltry 10 percent of the speed of light requires some pretty wild technology—for example, fusion-bomb propulsion or colossal laser-driven light sails. There also has to be shielding from the hull-eroding impacts of interstellar gas atoms, as well as from starship-destroying crumbs of rock, each of which carries the punch of a bomb for a spacecraft at any decent fraction of light speed. Traveling at more modest speeds is potentially much safer but results in transit times between stars of centuries or millennia—and it is far from obvious how to keep a crew alive and well for time spans that may greatly exceed individual lifetimes.

The most contentious assumptions, though, revolve around questions of motivation and the projections we make about the longevity of entire civilizations and their settlements. For example, if an alien species is simply not interested in reaching other stars, the whole idea of galactic settlement literally stalls. This was one argument put forward by Carl Sagan and William Newman in 1983 as a rebuttal to what they called the "solipsist approach" to extraterrestrial intelligence. But as my colleague astronomer Jason Wright points out, this kind of proposition is itself arguably a "monocultural fallacy." To put this another way: it seems impossible to speculate with any accuracy about the behavior of an entire species as if it were thinking with one unified mind. We humans certainly do not fit in that box. And even if the vast majority of the Milky Way's putative spacefaring civilizations do not attempt galactic diasporas, all it may take is one culture going against the grain to spread signs of life and technology across hundreds of billions of star systems.

In fact, the history of Fermi's paradox is awash with diverse debates on its underlying suppositions, as well as with a huge variety of posited "solutions." Few, if any, of these solutions are readily testable. Although some include ideas that are pretty straightforward, others are strictly science fiction. For example, it could be that the cost in resources of attaining the ability to rapidly traverse interstellar space is too high even for a superbly technological species. That could certainly trim the number of explorers and explain Hart's fact A. Or perhaps population growth is not, as many researchers have supposed, a strong motivation for voyaging to the stars, especially for a species that restrains any rapacious impulses and develops a truly sustainable existence in its home system. The ultimate green revolution would remove the impetus to go farther afield for anything other than scientific exploration.

Spreading across our galaxy need not require much more than persistence and a modest amount of cosmic time.

Sounding a more ominous note are concepts such as the "great filter"—the idea that there is something that always limits a species, perhaps an inevitable failure to achieve that green revolution, leading to an implosive extinction of all potentially technological life. Alternatively, maybe natural cataclysms, from supernovae explosions to outbursts from the Milky Way's central black hole, simply prune galactic life regularly enough to keep it from becoming widespread.

More outrageous proposals include the zoo hypothesis. In this scenario, we are being kept deliberately isolated and in the dark by alien powers that be. There is also what I like to call the paranoia scenario: other civilizations are out there but are hiding from one another and refusing to communicate because of some kind of cosmic xenophobia.

Perhaps, though, there are simpler ways to explain our current ignorance about aliens. Those answers could share characteristics with the example right

Alone in a Crowd

Of all possible answers to the question of why we have not seen other cosmic cultures in the Milky Way, perhaps the most plausible is that they exist but that they are not in our neighborhood. This situation could arise if interstellar exploration and migration are patchy and occur in waves, with spacefaring civilizations periodically expanding to settle the closest, choicest planetary systems. Accounting for stellar motions and a finite lifetime for each civilization, simulations of this process produce clusters of continuously occupied systems—as well as isolated, sparsely settled regions, one of which could harbor our own lonely world.

GALACTIC DIASPORAS

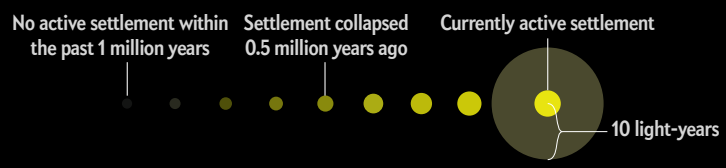
A snapshot from a simulation depicts 10 million years of interstellar exploration for 10,000 settleable systems within a box roughly 464 light-years on a side. (Systems unfit for settlement outnumber inviting systems by a factor of 22 but are not rendered here.) At this scale, stars move like particles in a gas, impeding or aiding interstellar travel via their trajectories with respect to one another. Probes originating from cultures scattered across this virtual space move at 3,000 kilometers per second—100 times faster than the average speed of surrounding stars, which follow a density distribution similar to that of our region of the galaxy.

● Each dot represents the current position of a settled or settleable planetary system.

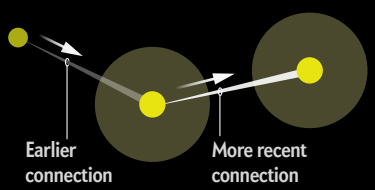
At the simulation's conclusion (*represented here*), 6,948 of the considered systems had been visited by a probe, but only 403 harbored active settlements; 3,052 settleable systems remained unvisited. This generated 11 distinct interstellar "empires" consisting of at least 10 settled systems, each denoted by a different color indicating common ancestry.

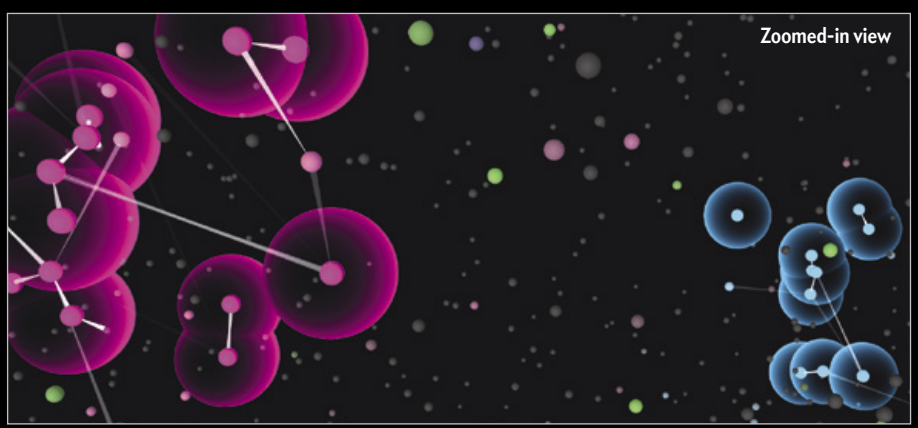
Additional settlement waves that settled fewer systems are depicted in gray.

Fading colors indicate systems that no longer harbor active settlements: currently active settlements are surrounded by semitransparent bubbles with radii of 10 light-years, demarcating the notional sphere of influence for any single system.



Agents only targeted systems within 10 light-years that could be settled, were not currently settled and were not targeted by another agent. Lines denote successful interstellar voyages and connect recently settled systems with their parents: lines do not show the actual path traveled—the relative positions of systems are in constant flux, frozen here at the end of the simulation.



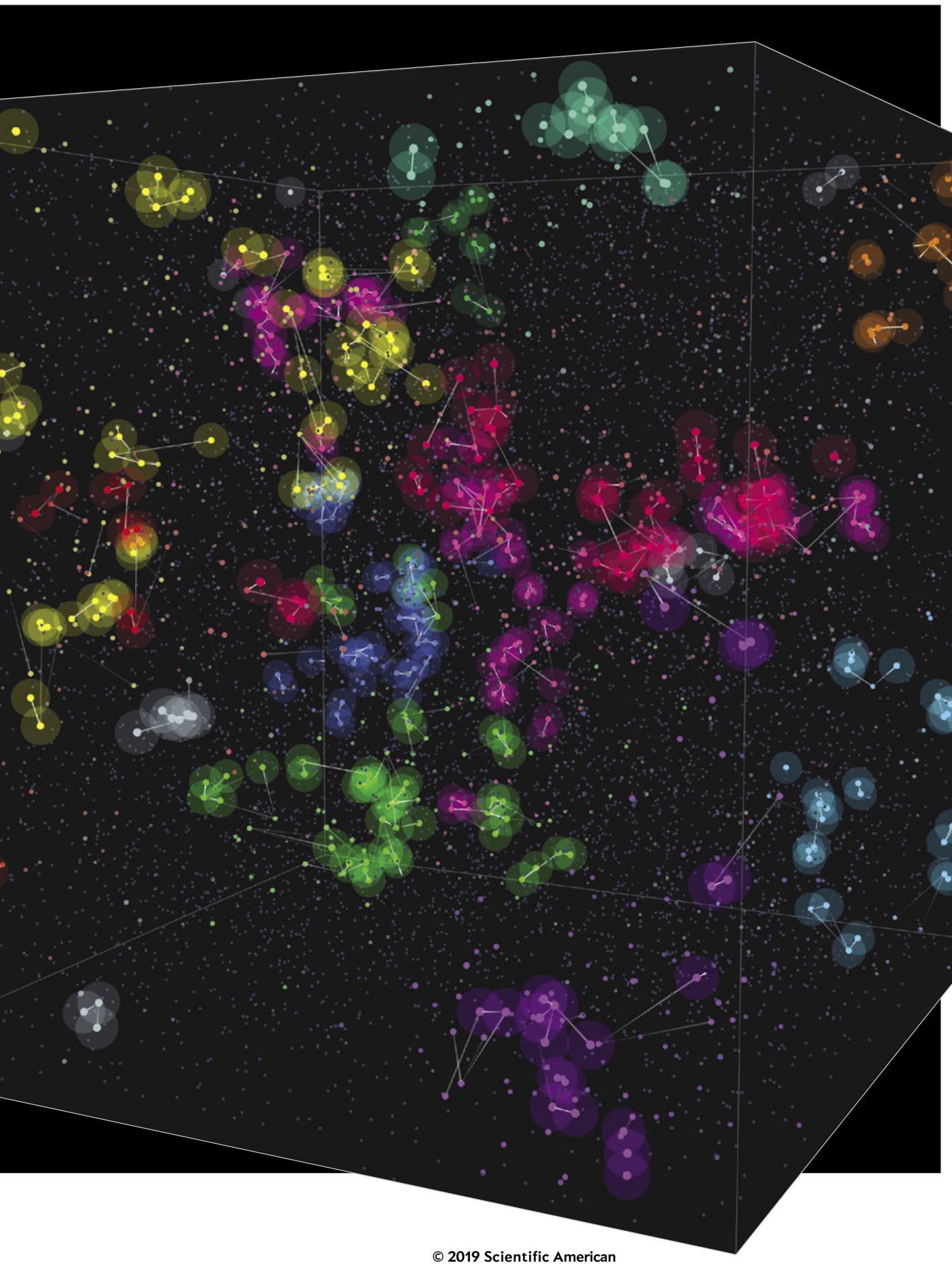


WHERE IS EARTH?

This simulation is a crude approximation of our galactic neighborhood. The solar system could reside within any unsettled portion of this box. Produced by statistical fluctuations in the trajectories and planetary architectures of surrounding stars, these transient "voids" are regions in which habitable worlds would lie beyond the reach of surrounding civilizations.

SOURCE: JONATHAN CARROLL-NELLENBACK *University of Rochester*

Graphic by Nadieh Bremer



under our noses—the time-varying and patchy nature of human occupation in the islands of the South Pacific. In both terrestrial and extraterrestrial cases, there are basic, universal factors at play, from the scarcity of good places to drop anchor to the time it might take for a population to ready itself to push farther across the void.

BACK IN 2015 MY COLLEAGUE ADAM FRANK OF THE UNIVERSITY of Rochester and I were having lunch near Columbia University's campus in New York City. As at Fermi's lunch 65 years earlier, the conversation was about the nature of spacefaring species. And inspired by Fermi's spur-of-the-moment mental calculation, we were trying to craft an investigative strategy that made the fewest possible unsubstantiated assumptions and that could be somehow tested or constrained with real data. At the center of this exercise was the simple thought that, just as with Pitcairn Island's transitory occupants, waves of exploration or settlement could come and go across the galaxy, with humans happening to emerge in one of the lonely periods.

Elsewhere in the galaxy there may be archipelagos of interstellar species for whom cosmic visitors are the norm.

This idea relates to Hart's original fact A: that there is no evidence here on Earth today of extraterrestrial explorers. But it goes further by asking whether we can obtain meaningful limits on galactic life by constraining the exact length of time over which Earth might have gone unvisited. Perhaps long, long ago aliens came and went. A number of scientists have, over the years, discussed the possibility of looking for artifacts that might have been left behind after such visitations of our solar system. The necessary scope of a complete search is hard to predict, but the situation on Earth alone turns out to be a bit more manageable. In 2018 another of my colleagues, Gavin Schmidt of NASA's Goddard Institute for Space Studies, together with Adam Frank, produced a critical assessment of whether we could even tell if there had been an earlier industrial civilization on our planet.

As fantastic as it may seem, Schmidt and Frank argue—as do most planetary scientists—that it is actually very easy for time to erase essentially all signs of technological life on Earth. The only real evidence after a million or more years would boil down to isotopic or chemical stratigraphic anomalies—odd features such as synthetic molecules, plastics or radioactive fallout. Fossil remains and other paleontological markers are so rare and so contingent on special conditions of formation that they might not tell us anything in this case.

Indeed, modern human urbanization covers only on order of about 1 percent of the planetary surface, providing a very small target area for any paleontologists in the distant future. Schmidt and Frank also conclude that nobody has yet performed the necessary experiments to look exhaustively for such nonnatural signatures on Earth. The bottom line is, if an industrial civilization on the scale of our own had existed a few million years ago, we might not know about it. That absolutely does not mean one existed; it indicates only that the possibility cannot be rigorously eliminated.

Over the past few years we have pursued the grander, galaxy-wide implications of these ideas in an investigation led by Jonathan Carroll-Nellenback of the University of Rochester and with Jason Wright of the Pennsylvania State University. A key advance has been the development of a series of agent-based computer simulations, backed up by old-fashioned paper-and-pencil mathematics, enabling us to build a more realistic picture of how species might move around in a galaxy that is itself full of motion.

If you take a snapshot of stars within a couple of hundred light-years of the sun, you will find that they are moving like the particles in a gas. Relative to any fixed point in this space, a star may be moving rapidly or slowly and in what is effectively a random direction. Zoom out farther, to scales of thousands of light-years, and you will begin to register the grand, shared orbital motion that carries a star such as our sun around the Milky Way once every 230 million years or so. Stars much closer to the galactic center take much less time to complete a circuit, and there are fast-moving "halo" stars diving in and out of the plane of the galactic disk as part of a distinct, rather spherically shaped swarm surrounding that disk.

What this means is that for a civilization looking around itself for target stars to explore, what is closest and what will be closest in the future vary significantly over time. A good illustration of this is our own solar system. Right now our nearest star, Proxima Centauri, is 4.24 light-years away, but in about 10,000 years it will be only 3.5 light-years distant—a significant savings in interstellar travel time. If we were to wait until about 37,000 years from today, our nearest neighbor would for a time be a small red dwarf star called Ross 248, which would then be a mere three light-years from us.

To model this shifting stellar map, our simulation uses a three-dimensional box of stars, with movements akin to those in a small part of a real galaxy. It then initiates a "front" of settlement by assigning a selection of those stars as hosts to spacefaring civilizations. Those civilizations have finite life spans, so a system can also become unoccupied. And a civilization has a waiting period before it is capable of launching a probe or settlement effort to its nearest neighboring star. All these factors can be altered, tweaked and explored to see how they affect the outcome. For a wide range of possibilities, a somewhat

raggedy-looking settlement front self-propagates through interstellar space. The speed of this propagating front is the key to cross-checking and confirming possible solutions to Fermi's original puzzle.

What we find is both simple and subtle. First, the natural, gaslike motion of stars in the galaxy means that even the slowest interstellar probes, moving at some 30 kilometers per second (nearly twice as fast as Voyager 1's current speed of 17 kilometers per second in its outbound motion from our sun), would ensure that a settlement front would cross the galaxy in much less than a billion years. If we factor in other stellar motions, from galactic rotation or halo stars, this time span only shrinks. In other words, just as Fermi saw, it is not hard to fill the galaxy with life. But it is also the case that exactly how "filled" the galaxy becomes depends on both the number of genuinely settleable worlds out there—what we have dubbed the Aurora effect in homage to Kim Stanley Robinson's epic 2015 science-fiction novel *Aurora*—and the length of the period civilizations are able to endure on a world.

At one extreme, it is easy to make the galaxy empty by simply shrinking the number of usable planets and having civilizations last for only, say, 100,000 years or so. At the other extreme, it is easy to tweak these factors to fill space with active spacefaring settlements. In fact, if suitable worlds are numerous enough, it almost does not matter how long settled civilizations last on average. If they retain the technology that allowed them to travel in the first place, then enough of them could carry on exploring and eventually fill the galaxy.

But it is between these extremes that the most compelling and potentially realistic situations arise. When the frequency of occurrence of settleable worlds in a galaxy is intermediate between high and very low, fascinating things can happen. Specifically, ordinary statistical fluctuations in the number and location of suitable worlds in patches of galactic space can create clusters of systems that are continually visited or resettled by wave after wave of interstellar explorers. Think of it as an archipelago, a group or chain of islands. The flip side to the existence of these clusters is that they are typically surrounded by large unsettled regions of space, places just too far and too sparsely distributed to bother setting out for.

CAN THIS "GALACTIC ARCHIPELAGO" SCENARIO EXPLAIN OUR situation on Earth? Remarkably, it may. For example, if typical planetary civilizations can last for a million years and if only 3 percent of star systems are actually settleable, there is a roughly 10 percent probability that a planet like Earth has not been visited in at least the past million years. In other words, it is not terribly unlikely that we would find ourselves on the lonely side of the equation.

Conversely, this scenario implies that elsewhere in the galaxy there are clusters, archipelagos, of interstellar species for whom cosmic neighbors or visitors are the norm. No extreme hypotheses are needed for any of this to take place; it would require just a rather ordinary accounting of planetary numbers and the nature of stellar movements amid the swirling stars of the Milky Way. And although it is true that assumptions linger about the feasibility of any kind of interstellar travel and about the likelihood that a species will actually undertake it, other factors are just parameters to be tuned. Some, such as the number of inhabitable worlds, are in astronomers' sights already as we seek greater knowledge of exoplanets. Others, such as the longevity of civilizations, are the subject of intense scrutiny as we attempt to deal with our own issues of planetary sustainability.

The possibility also exists for us to discover evidence of settled stellar archipelagos or the ongoing propagation of a settlement front. Targeting our searches for extraterrestrial intelligence and technology not on individual, known exoplanets but rather on galactic regions where the topography of stars might lend itself to interstellar expansion or clustering could be an interesting new strategy. Until recently, our three-dimensional map of galactic space was woefully limited, but with instruments such as the European Space Agency's Gaia observatory mapping a billion astronomical objects and stellar motions, we might be able to chart these hotspots.

In the end, though, the true paradox of Fermi's paradox may be that there is no paradox at all. What my colleagues' work shows is that it is an entirely natural state for a habitable, inhabited world such as Earth to exhibit no discernible evidence of having ever been visited or settled by an extraterrestrial species. This is true whether the galaxy is devoid of other technologically advanced life or is as teeming as it can be with interstellar explorers. Just as Pitcairn may have sat unoccupied for as much as three centuries in the Pacific Ocean, Earth might simply be passing through a period of isolation before the cosmic ripple of pan-galactic life washes over it once again.

The real question, as it was for Polynesian settlers across the centuries, is whether our planetary civilization will still be here when that happens. SA

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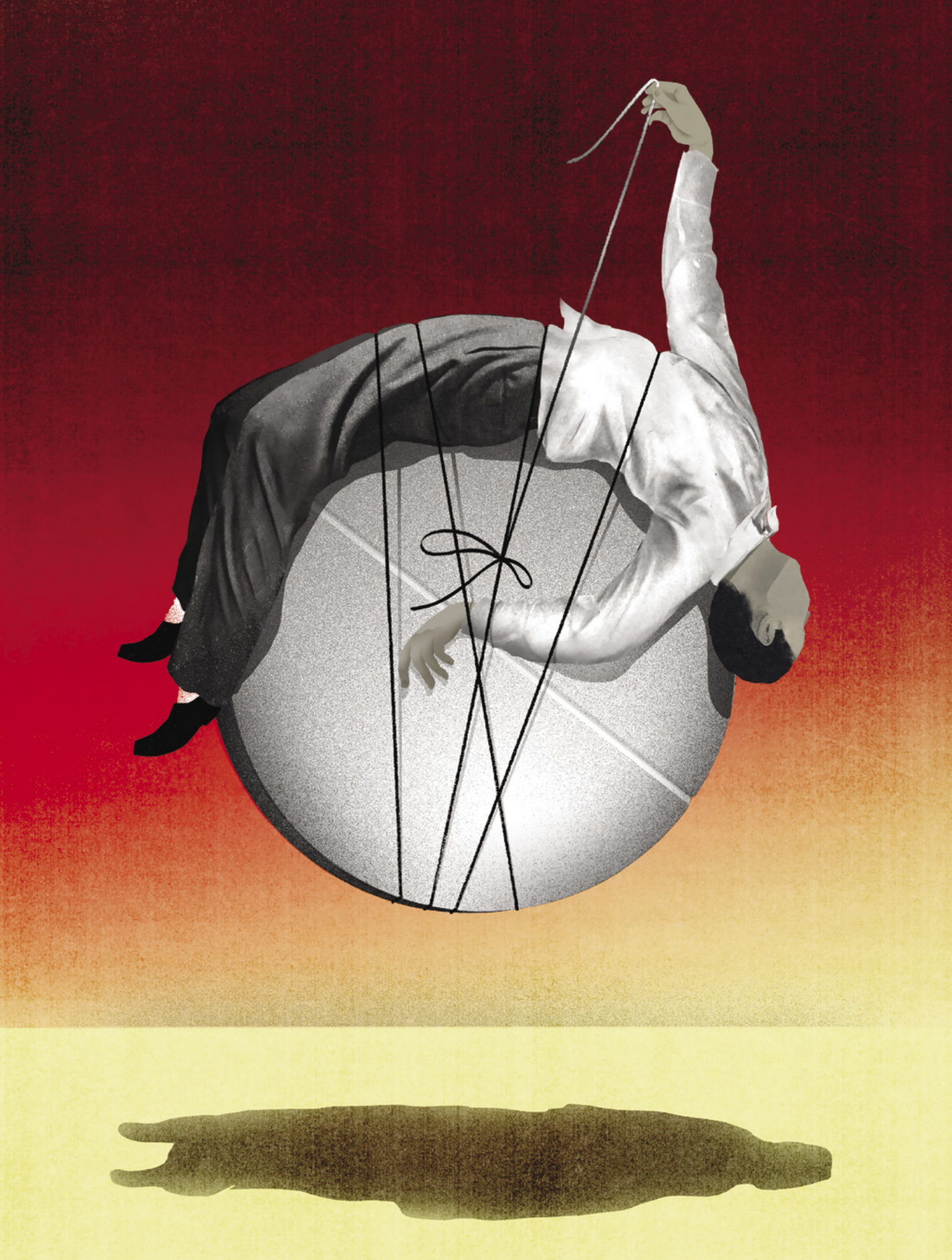

HEALTH

UNBOUND FROM OPIOIDS

More than seven million chronic pain patients take the risky painkillers. Researchers are finding better ways to help them quit or cut back without igniting agony

By Claudia Wallis

Illustration by Brian Stauffer

Photographs by Grant Delin

Science journalist and contributor **Claudia Wallis** writes the Science of Health column for *Scientific American*.

AT 6 FEET, 3 INCHES TALL, BRETT MUCCINO IS A BIG MAN WITH a powerful frame, so he finds it hard to imagine how he could have flown through the narrow windshield of his old Ford Ranger. "It was a little, tiny thing," he recalls. The devastating 1986 car crash crunched vertebrae in his neck and lower back. It also launched a 34-year battle with chronic pain and a love-hate relationship with the opioids he relied on to manage it.

IN BRIEF

A severe crackdown on opioid prescriptions has been a disaster for millions of patients who use the medicine to blunt chronic pain.
Pain researchers are developing ways to help people taper the drugs safely, without misery.
Methods include a variety of psychosocial supports, coupled with very slow dose reductions.

On a sunny fall day Muccino was decked out in a hat and jacket emblazoned with the words "Vietnam Veteran" while visiting the West Haven VA Medical Center in Connecticut. He moved haltingly through the long corridors of polished linoleum, slightly bent over a walker. A bad back is not the only source of misery for this retired nursing home operations director. Diabetic nerve damage—the VA attributes his diabetes to wartime Agent Orange exposure—has rendered his feet and his hands painful, tingly and unreliable. He also suffers from chronic infections around an artificial knee.

Muccino, now 68, had come to West Haven's Opioid Reassessment Clinic after a long and perilous journey that included seven spinal surgeries and escalating doses of opioids when the operations, and physical therapy, failed to bring relief. In the 1990s doctors switched him from short-acting Percocet to 40 milligrams a day of a hot new drug: long-acting OxyContin. Within a few months he needed twice the dose, but "at least it allowed me to work," he says. No one told him it was addictive. He found out when a surgeon cut him off shortly before a back procedure. "It was cold turkey with no discussion of what I was going to go through," he recalls. Within 48 hours he was in an emergency room wracked by the agony of withdrawal—screaming in pain, shaking and unable to hold down food. Back on opioids, he began supplementing his prescription by buying drugs on the street and later from an unscrupulous doctor, taking upward of 320 milligrams of Oxy a day. He would try to get clean periodically, but pain always brought him back.

By the summer of 2016 Muccino was sick to death of the whole vicious cycle. After his final back surgery brought him some relief, he told his doctors, "I want off of everything." His timing was good: a few years earlier the VA had opened this specialized clinic less than an hour from his home. Its team helped him learn a variety of pain-management techniques and gave him a medication that both reduces pain and controls withdrawal symptoms. Thus began a slow, many-months taper of Oxy that ended up at his goal: zero.

Muccino's struggles are common, but the help he has received is rare. As U.S. deaths from both legal and illegal opioids exploded from 9,489 in 2001 to 47,600 in 2017, the country began a widespread crackdown on the prescription painkillers. Health authorities, insurance companies, medical groups and even pharmacies began cutting off patients and sharply limiting dosages. The restrictions have caused anguish among the seven million to 10 million people who take these medications for chronic pain that stems from conditions ranging from fibromyalgia to spinal cord injuries to tissue damage left by war wounds or surgery. Even though illegal drugs (especially illicit fentanyl) cause the majority of overdoses, policy makers were alarmed that more than a third of opioid deaths involved prescription pills. In 2016 the Centers for Disease Control and Prevention issued a guideline, reminding doctors that the drugs should be used only as a last resort for chronic pain. It cautioned against prescribing daily doses above 50-milligram morphine equivalents (MMEs are a way to equate the doses of various opioids). States also jumped into action. At least 36 issued policies or guidelines that in some way limited the amount of opioids that doctors could prescribe. In addition, many doctors miscon-

Brett Muccino

strued the CDC guideline as a hard limit on dosage—even for long-term users. By 2017 almost 70 percent of family medicine physicians had cut back on prescribing the drugs, and nearly 10 percent stopped offering them altogether, according to a *Boston Globe* survey.

Abruptly cutting off patients, however, is a dangerous practice that can cause their pain to spike and lead them to turn to street drugs or suicide, experts warn. "It creates intense destabilization, both medically and psychologically," says pain psychologist Beth Darnall of the Stanford University School of Medicine. She was among 92 experts and advocates who wrote an open letter in September 2018 to the federal Pain Management Task Force warning of "an alarming increase in reports of patient suffering and suicides." Last April both the cdc and the Food and Drug Administration took action to warn doctors about these risks.

There is no question that cold-turkey cutoffs are bad, but sadly, there is a lot less clarity about how best to reduce opioid dependence among chronic pain patients. There never was much science to justify using these powerful drugs for months and years at a time and precious little to show how to reverse course. Fortunately, research, fueled by an influx of federal dollars, is beginning to point the way. Among the early findings: tapering long-term users appears to work best when done very slowly, with close individualized attention and instruction in alternative ways to handle pain—much the way Muccino has been helped. Surprisingly, some studies suggest that many patients wind up feeling better on lower doses or none at all, as side effects such as lethargy, mental fog and extreme constipation fade away. A new guide to dose reduction, issued last October by the U.S. Department of Health and Human Services (hhs), endorses these go-slow, collaborative, "patient-centered" techniques.

Many key questions remain the subject of ongoing studies, including such basic issues as when these drugs remain appropriate for chronic pain and at what doses, who truly needs to be tapered from opioids, and how best to go about it when patients are reluctant and fearful. "The pain research question that probably has the biggest impact on society right now is: What is the long-term safety and effectiveness of opioids?" says Sean Mackey, chief of the division of pain medicine at Stanford. "The reality is, we don't know." But slowly and surely, answers are arriving to safely unwind the great American love affair with opioids.

THE OPIOID ATTRACTION

THE IDEA that opioids are an appropriate choice for pain that is chronic—lasting more than three months—took off in the mid-1990s. It was a period when the medical community had begun to take pain more seriously in general, labeling it "the fifth vital sign" (after blood pressure, pulse, respiratory rate and temperature). It was also when OxyContin, an extended-release version of the opioid oxycodone, was introduced with much

When to Stick with Opioids

While researchers are determining how best to wean pain patients from high-dose opioids, it is quite clear that not everyone can or should cut back. The CDC has explicitly exempted people in pain from cancer or sickle-cell anemia from its cautions about prescribing the drugs. In addition, experts will often hesitate to mess with patients who are living with such profound pain that their lives are balanced on a knife's edge. Andrea Anderson, a patient advocate who was executive director of the Alliance for the Treatment of Intractable Pain, tells story after story of people in extremis—a man who survived 20 minutes of electrocution, a patient who had been engulfed in flames—who depend on large quantities of opioids but who do not dare to taper. No one should be forced to, experts agree.

Clinicians also have seen patients who remain stable and functional on a steady dose, holding down jobs, taking care of their families, not escalating their dosage. "We've got guys who stay on 15- to 20-milligram morphine equivalents [MMEs] for years and do well," says Will Becker, who directs the Opioid Reassessment Clinic at the VA Medical Center in West Haven, Conn., although he concedes that "I've seen a whole lot more who have not stayed on low doses and do poorly."

The thorniest questions arise for patients who are on high doses, continue to struggle with pain and an overall poor quality of life, but do not wish to taper. Often these patients are medically complex, with a variety of physical or psychological conditions that make it difficult to tease apart what portion of their pain is caused by an underlying biological issue, what is the result of drug side effects, and what stems from other ailments that afflict them. "This is where we get into the gray zone," says Sean Mackey, who heads the division of pain medicine at Stanford University. "We need to personalize the approach to each patient and work collaboratively. There is not a one-size-fits-all here."

Not all patients do well with tapering, even if it is done slowly and carefully. Take Nadine Hagl, a 53-year-old army veteran who was referred to Becker's clinic after many years on high-dose Percocet (an oxycodone-acetaminophen combo). Hagl is medically complex in several ways. In addition to painful arthritis that leaves her reliant on a cane, she suffers from PTSD and used to carry 240 pounds on her 5-foot, 1-inch frame before undergoing gastric bypass surgery in 2014 and losing 130 lbs. Her rerouted gut cannot tolerate nonsteroidal anti-inflammatory painkillers, which might otherwise be an alternative to opioids, nor does she respond well to buprenorphine, a medication used to mitigate opioid withdrawal. Hagl is psychosocially complex,

Nadine Hagl

too, given her PTSD diagnosis and the fact that she is the single mom of a son who is on the autism spectrum. Working with Becker's team, Hagl made a good faith effort to try a number of alternatives to opioids, but her pain flared up. They agreed to return her to Percocet, along with an array of nondrug therapies, but specified a lower dose than before and close monitoring.

Pain and addiction specialists agree that patients who remain on long-term opioids should be monitored carefully for side effects and for signs of abuse. All 50 states have prescription-monitoring programs that enable clinicians to detect if a patient is double-dipping with another prescriber and putting themselves at risk.

Given all the pressures to reduce opioid use, it is likely that the number of people taking these drugs long term will continue to dwindle. Mark Sullivan, a pain psychiatrist at the University of Washington, remembers the sparing use of these narcotics that prevailed when he entered the field 30 years ago. "I think we will get to the point where, as it was when I started, opioids are very useful and should be used short term and long term only in exceptional circumstances." —*C.W.*

fanfare, along with some seriously misleading claims about its long-term safety and nonaddictive nature—claims that later became the subject of multimillion-dollar lawsuits. Prior to that, natural opiates such as morphine and synthetic opioids such as oxycodone were mainly used for acute short-term pain, cancer and palliative care. According to a cdc analysis, prescriptions for opioids quadrupled between 1999 and 2010.

The drugs were seen as a cheap alternative to the gold-standard treatment for intractable chronic pain: interdisciplinary pain-management and rehabilitation programs that involve a team of psychologists, doctors, physical and occupational therapists, and other specialists working with a patient over several weeks at specialized clinics. That approach is far more labor-intensive than taking a pill, but it addresses the "biopsychosocial" nature of chronic pain—the fact that what an individual feels is not wholly determined by the firing of pain nerve fibers but can be affected by mood, personality, social context and even the meaning a person attaches to pain. "If your pain means your cancer is getting worse, it's much less tolerable than if it means you've trained hard for the marathon or you're having a nice baby," observes Mark Sullivan, a psychiatrist at the University of Washington's Center for Pain Relief in Seattle.

Even though opioids were suddenly being prescribed en masse for people with bad back pain and all manner of long-term conditions, most studies had looked only at their effects over six weeks or less. That clearly was not enough time to observe the physical and psychological dependences that develop over months and years or how, as the body habituates to the drugs, people often require higher amounts that raise the risk of respiratory problems, dizziness and life-threatening overdoses.

A few doctors, at the time, were bothered by the knowledge gap. Opioid researcher Erin Krebs was in medical school in the mid-1990s. She remembers being surprised and skeptical that drugs that had never been studied over the long term were being prescribed for months and years at a time. Krebs, now chief of general internal medicine at the Minneapolis VA Health Care System, is researching ways to help the so-called legacy patients of the opioid era manage pain with safer doses. But she is also investigating the more basic question of whether opioids are ever a valid choice for long-term pain. Last year she published the first randomized trial to directly compare opioids with nonopioid painkillers—ranging from popular anti-inflammatories such as ibuprofen to nerve pain drugs such as gabapentin—during a full year. Her team followed 240 patients with moderate to severe back or joint pain and found that, on average, the nonopioid group reported less intense pain and fewer side effects. When she proposed the study in 2010, Krebs says, "the assumption was so strong that opioids were better, some people felt it would be unethical to say some patients couldn't get opioids!"

Krebs has since found further evidence that opioids can be a poor choice for chronic pain. At a 2018 pain conference she presented some shocking preliminary

data from a long-term study of 9,245 veterans taking opioids for six months or more. Only a quarter of participants rated the effectiveness of their pain treatment as very good or excellent, and 80.9 percent said that their pain was throughout their body—a symptom that might reflect a suspected drug side effect: a pain syndrome called opioid-induced hyperalgesia. "My initial impression was just wow," Krebs told me. "These people are really sick. We have not fixed these folks."

HOW TO CUT BACK

WHEN THE RISK OF opioids seems greater than the benefits—if patients are misusing the drugs or show overdose-related symptoms, for example—the new HHS guidelines urge doctors to consider tapering. The central questions then become how to do that without triggering more agony and desperation and what to offer for pain relief instead. In an ideal world, patients with intractable suffering would go to the interdisciplinary pain and rehabilitation clinics, which have a good track record of switching patients from opioids to other ways of managing pain. But many of these clinics closed when the medical community embraced opioids, and treatment at those that remain is costly. So the search is on for cheaper, practical approaches. In 2018 Darnall published one of the first papers to provide an answer: a very slow, personalized dose reduction.

> "If we do these microdose reductions, it allows patients to relax into the process, to gain a sense of trust with their doctor and also with themselves."
> —*Beth Darnall, Stanford University School of Medicine*

In a pilot study with 68 patients published in *JAMA Internal Medicine,* Darnall showed that over the course of four months, the 51 individuals who completed the trial were able to cut their opioid dosages nearly in half, on average, without worsening pain. They received careful guidance from a community doctor and a self-help book. A slow reduction was especially critical during the first four weeks, she says, when the dosage was cut by no more than two 5 percent increments. That is considerably less than the 10 percent a week originally suggested in the cdc's 2016 "pocket guide" to tapering opioids and in line with the hhs's updated version.

"If we do these microdose reductions, it allows patients to relax into the process, to gain a sense of trust with their doctor and also with themselves," Darnall explains. "Their number-one concern is increased pain." The goal, she emphasizes, was not to get to zero but to "the lowest comfortable dose." Four participants did manage to taper off completely, she says, "but four people didn't budge or actually increased their dose," and 17 dropped out of the trial. Notably, there was no correlation between a patient's dose at the start of the trial or how long the person had been taking opioids and his or her ability to cut back.

Darnall is eager to determine if additional tools might help more patients succeed in tapering. With funding from the Patient-Centered Outcomes Research Institute (PCORI), an agency created by the 2010 Affordable Care Act, she is now overseeing a one-year trial with 1,365 chronic pain patients called EMPOWER (for Effective Management of Pain and Opioid-Free Ways to Enhance Relief). Five hundred of the patients do not wish to taper and will stick with their current opioid treatment, serving as a control group. The others will be randomly assigned to one of three treatments. One group will simply repeat the methods of Darnall's pilot study. Another will do that regimen plus get eight weekly sessions of group cognitive-behavioral therapy (CBT) for pain, a type of short-term psychological counseling that focuses on changing patterns of thoughts and beliefs to affect behaviors and feelings. The third group will also follow the pilot protocol and add six weekly group workshops on pain "self-management."

Pain self-management is a low-cost intervention led by trained peers rather than health professionals, but it has never been studied in the context of opioid tapering. The method, developed by Stanford health educator Kate Lorig, takes participants through a highly structured series of activities, lessons and discussions that offer tools for managing pain and reclaiming a more active life. At a typical session, patients make weekly "action plans" to do something they have been avoiding because of pain, such as taking a daily walk or cleaning out a closet, and report back on their progress. They learn exercises to warm up achy joints and brainstorm better ways to communicate with doctors. Participants say that being with others who understand chronic pain—including the group leaders—provides inspiration, support and accountability. "You realize that everyone is in a similar boat, and that helps," says Sylvia Nomikos, a retired teacher with severe spinal stenosis, who attended a self-management workshop in Pleasantville, N.Y. Two studies of this type of intervention have found that participants report lasting reductions in pain, disability, depression and health-related anxiety.

Darnall's team will assess how the pain self-management method stacks up against costlier CBT in her EMPOWER study and whether either improves on the basic, slow-tapering protocol. Along the way, they will also collect data on participants' use of marijuana and cannabis products to see what impact they have on opioid reduction, and vice versa. The need for such research is pressing, Darnall says. No matter which interventions come out on top, if the outcomes for any group match or exceed those of her pilot study, she will have demonstrated a safe, practical and economical way to taper opioids that could be carried out in communities everywhere.

EASING WITHDRAWAL

OTHER RESEARCHERS, including Sullivan and Krebs, are also testing practical, low-cost ways to help pain patients reduce their reliance on opioids that, if successful, could be scaled up to meet the country's huge need. Krebs is leading a large trial, also funded by PCORI, in which 500 U.S. veterans will work by phone with a pharmacist to optimize the safety and efficacy of their drug regimen. Another 500 will be assigned to a multidisciplinary team (a physician, psychologist and pharmacist or physical therapist) that will put less emphasis on meds as the solution and focus more on achieving personal goals and a better quality of life even if their pain cannot be cured. The study will also look at the usefulness of a medication designed to ease withdrawal.

"No one is required to taper in this study," Krebs points out, but participants who are on high doses of opioids will be educated about their risks. Those who opt to taper will be randomly assigned to do so with or without the help of buprenorphine-naloxone (the generic version of Suboxone), a medication that combines an opioid painkiller with an opioid blocker and provides pain relief, reduces symptoms of withdrawal and has a relatively low risk of overdose. "We know this medication works in the opioid-addiction setting," Krebs explains, "so we're wondering if it could also help people in a pain-treatment context."

The Opioid Reassessment Clinic in West Haven, where Muccino gets treatment, is a site in Krebs's study. Its director, Will Becker, routinely offers buprenorphine-naloxone to patients to help trim their opioid use. About two thirds say yes, Muccino among them. Becker believes the drug provides "a soft landing" to people who have been opioid-dependent for years and years. He also thinks that just presenting patients with choices makes a big difference in their ability to taper: "Having an option empowers them."

Opioid tapering at Becker's clinic emphasizes achieving functional goals defined by patients. These could be returning to work or just getting out of bed earlier. "We try to target SMART goals: specific, measurable, action-oriented, realistic and time-bound," Becker explains. "These are discrete, real things that they can reengage with—things that pain has taken away."

For Muccino, a major goal was to enjoy time with his seven grandkids or, as he put it, "being able to see my grandchildren grow as long as I can—through clean eyes." He regrets missing much of his own kids' childhood: "I was working 60 to 70 hours a week, and I was high on drugs. I'd come home and pass out on the couch." Using buprenorphine-naloxone under Becker's supervision helped him stop taking the OxyContin entirely.

A handful of studies and clinical experience suggest that once patients get past their initial fears, many feel better on lower doses or leaving opiates behind. The underlying pain will not necessarily change, says Stanford's Mackey, but on low doses "what I see is they feel more alive, alert and aware." This is presumably because opiate compounds—including those made in our own bodies—work on several systems in the brain, including those that regulate emotions and attention. "When you flood those systems [with drugs], you get blunted over time." Still, there is a minority of patients who do worse, and pain specialists worry about this group, especially at a time when patients are being pressured to cut back. They point out that not everyone can be weaned or even tapered from opioids, and not everyone should be [*see box on page 44*].

BEYOND OPIOIDS

THE PATH AWAY from opioids is going to mean starting fewer patients on them to begin with and making other treatments more accessible—including physical and behavioral therapies and scores of nonopioid medications that are used to fight pain. The first part is easier and already happening: a large study published last year found that first-time opioid prescriptions fell 54 percent between July 2012 and December 2017. What's harder is changing medical practice and patient expectations about what chronic pain treatment looks like. As Sullivan observes, "There's no better way to make your patient happier than to give him some OxyContin, because he feels better in the car on the way home from the pharmacy." Other therapies, he notes, tend to take effect more slowly: "they can make you feel worse before they make you feel better. They can be a lot of work," as is the case with physical or behavioral therapy.

It would help if doctors, especially those in primary care, got better training in how to assess and treat pain, an issue noted by the federal National Pain Strategy released in 2018. (U.S. medical students get only four to 12 hours of instruction on pain, according to a 2011 survey. Veterinarians, by comparison, get 28 hours, Darnall says.) The strategy also points out that "the public at large" would benefit from a better grasp of pain's complexity and how to manage it.

Muccino has gained that understanding. These days, in addition to a low dose of buprenorphine-naloxone, he manages his pain with relaxation, distraction and methods he learned in CBT. At home, he pipes some James Taylor songs through his earbuds, stretches and strengthens with physical therapy exercises. He counts himself lucky to have a supportive family so when the going gets rough, he says, "I play with my grandkids. I go for a ride. Anything but take a pill." SA

MORE TO EXPLORE

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ANIMAL COGNITION

The Surprising Power of the Avian Mind

Some bird species use tools and can recognize themselves in the mirror. How do tiny brains pull off such big feats?

By Onur Güntürkün

Photographs by Tim Flach

Onur Güntürkün is a professor of biopsychology at Ruhr University Bochum in Germany. He studies cognition and neuroscience in pigeons, humans, and other animals.

IN MY LABORATORY AT RUHR UNIVERSITY BOCHUM IN GERMANY, MY COLLEAGUES and I took Gerti, a Eurasian magpie, out of her home cage, covered her head with a cloth, and placed a small yellow paper sticker on the black plumage of her throat, which she could not see. Then we placed her into a test cage with a large mirror, left her alone and went to the neighboring room to observe her through a monitor. Gerti first looked into the mirror and immediately tried to vigorously remove the sticker by scratching her throat or rubbing it on the floor. Once she did, she took a final look into the mirror to calm herself down. In apes, such behavior is taken as evidence for self-recognition. Never before had this been observed in a bird.

We were all excited that day in 2006, but we also had to ask the obvious question: What if we were wrong? Couldn't it be that Gerti removed the mark simply because she had felt something on her throat? Our team at Bochum, including Helmut Prior, Ariane Schwarz and me, further tested Gerti under identical conditions, except that the magpie had a black sticker that was hardly visible on her black plumage. In still other control conditions, we marked her with a yellow sticker but did not provide a mirror. In all these instances, Gerti did not attempt to remove the marks. The sticker-extracting behavior occurred only when the bird could see a salient mark on her plumage in the mirror. Because several other magpies we tested behaved in a similar fashion, we concluded that Eurasian magpies seemed to understand that they were seeing their own reflection in the mirror.

Other than humans, only a few mammals with large brains such as chimpanzees, orangutans, Indian elephants and bottlenose dolphins had at the time demonstrated similar evidence for self-recognition. The ability of magpies to recognize themselves in the mirror is just one of many aspects of complex cognition that have recently been demonstrated in corvids and parrots. These new discoveries shake the dominant, century-old theory that such skills require the presence of a large cortex, the forebrain's outer layer. Because birds have no cortex, they should not excel in self-recognition or other cognitive tests. Investigations of avian cognition in the past two decades have indicated how vastly different brain physiology in birds and humans can, over the course of hundreds of millions of years, result in astonishingly similar cognitive faculties that form the basis for high-level learning, self-awareness and decision-making.

VARIETIES OF COGNITIVE EVOLUTION

TO UNDERSTAND WHY biologists thought birds lacked these skills, we have to go back to the neuroanatomical lab of Ludwig Edinger of Goethe University Frankfurt in Germany at the end of the 19th century. Edinger, who lived from 1855 to 1918, devoted his scientific life to revealing how brains and minds of vertebrates evolved. He was confident that evolution unfolds in a step-by-step path from primitive to complex—advancing from fish on to amphibians, reptiles, birds and mammals. He discovered that the most basic brain components had always existed in vertebrates.

But a large region of the brain called the cerebrum seemed to

IN BRIEF

Corvids, parrots and other bird groups demonstrate complex cognition, including causal reasoning, mental flexibility, planning, social cognition and imagination.

These cognitive abilities were a surprise to many scientists. They were not expected to be found in birds because of their small brains and the absence of a cerebral cortex.

Birds compensate for their small brains with a much higher density of neurons. Independently, both birds and mammals have evolved similar neural networks and brain areas that serve cognitive functions.

EURASIAN MAGPIE inspects its own image in a mock-up of a self-recognition experiment.

have undergone major evolutionary changes that were possibly the reason for the expansion of cognitive abilities. The cerebrum consists of two main parts: the uppermost pallium (Latin for "mantle") and the underlying subpallium. The mammalian pallium is mostly made up of the six-layered cortex—the main seat of mammalian cognition—but also contains smaller parts such as the amygdala and the hippocampus. In contrast, the subpallium looks like a homogeneous lump of neurons that stores and later activates learned movement patterns. The situation in birds is radically different. When working within the anatomical scheme set out by Edinger, an observer finds the pallium strongly resembles the subpallium. As a result, Edinger mistook most of it for the subpallium. Consequently, he concluded that birds have a huge subpallium but only a small pallium, and so their cognitive abilities should be very limited.

What a mistake! Edinger was a towering scientist of his time, and his theory appeared to explain convincingly why we mammals excel in cognition. For that reason, his fallacious theory persisted for more than a century and deeply influenced neuroscientific thinking up to the dawn of the 21st century.

There was another reason that birds' brains were considered to be inferior. Avian and mammalian brains differ also in terms of size. Ostriches have the largest brain among birds, weighing in at 25 grams. In contrast, a chimpanzee brain is about 400 grams, that of a human is 1,300 grams, and a sperm whale brain weighs a whopping 9,000 grams. At least among primates, brain size correlates with cognitive abilities. Thus, because of both the lack of a large cortical pallium and the presence of their small brains, birds were thought to have severely limited cognition. But how then is it possible that Gerti the magpie was able to pass the mark-and-mirror test, leaving most large-brained mammals behind? Either birds are not that smart, or something is wrong with our century-old view on the need for a large cortex for cognition.

THE CROWS OF NEW CALEDONIA

SOME PERSPECTIVE can be found by considering New Caledonian crows from the South Pacific, which mostly live on grubs that they retrieve from crevices in the barks of trees. In 1996 Gavin Hunt, then at Massey University in New Zealand, reported that New Caledonian crows manufacture two different tool types with which they capture their prey. The process of making these tools is so complex that Hunt compared it with stone-tool production of Middle Paleolithic humans, who lived from 300,000 to 40,000 years ago.

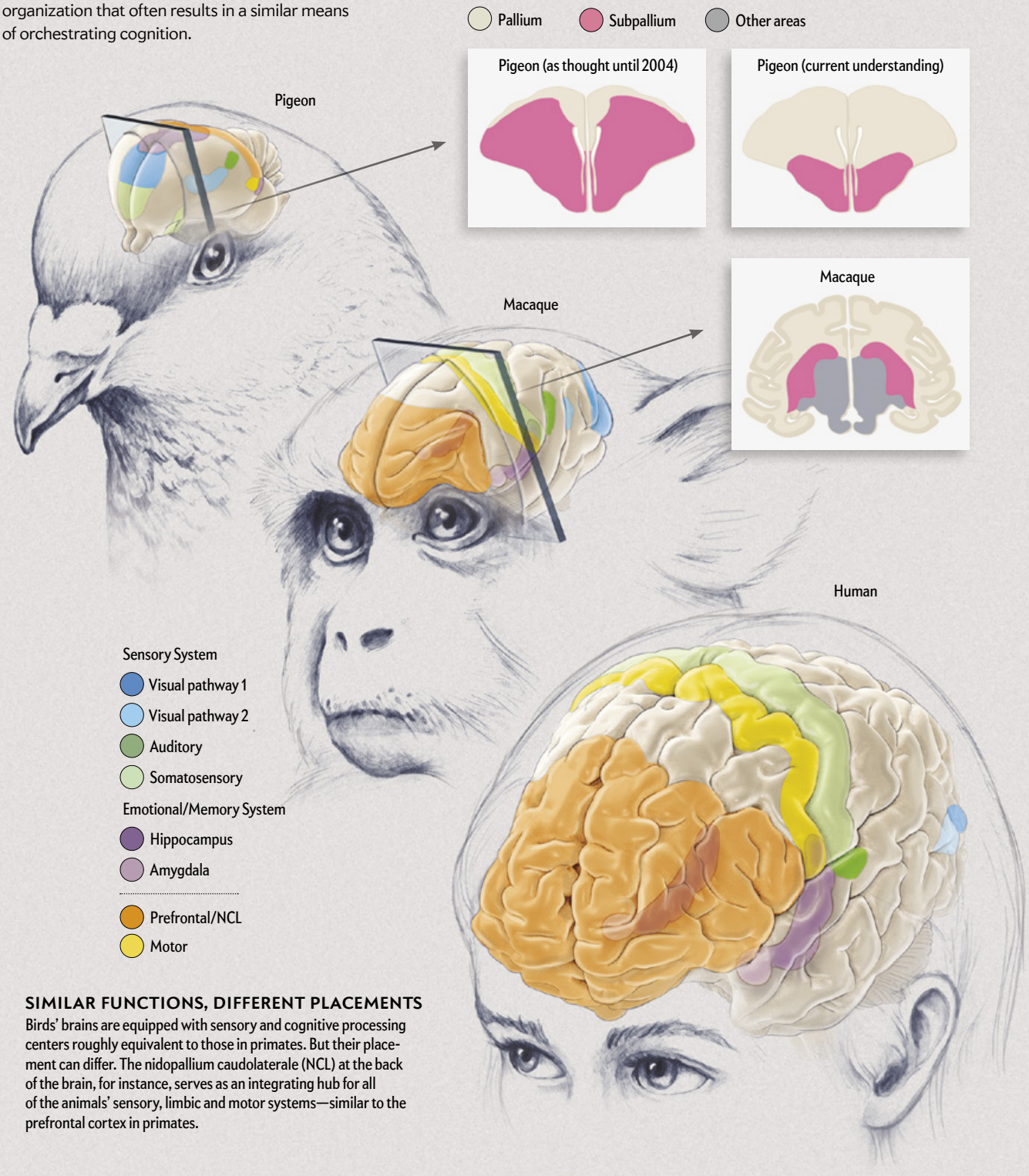
Several animal species seem to engage in tool use, but when properly tested, much of this behavior turns out to be based on innate programmed sequences of responses, not on cognitive evaluation of a problem. Alex H. Taylor of the University of Auckland in New Zealand and Russell Gray of the Max Planck Institute for the Science of Human History in Jena, Germany, embarked on studies to properly understand the mental basis of tool use in New Caledonian crows. These experiments demon-

Bird Braininess

The tiny size of birds' brains initially made neuroanatomists think that they simply could not be that smart. But the phrase "birdbrain" has lost its meaning. Evolution in birds has produced a differing neural organization that often results in a similar means of orchestrating cognition.

SHIFTING UNDERSTANDING

Until 2004, it was thought that the front of a bird's brain, the cerebrum, apportioned a small area to the pallium, which is involved with complex cognition. In the revised view, it occupies an area equivalent in relative size to the pallium in the macaque brain.



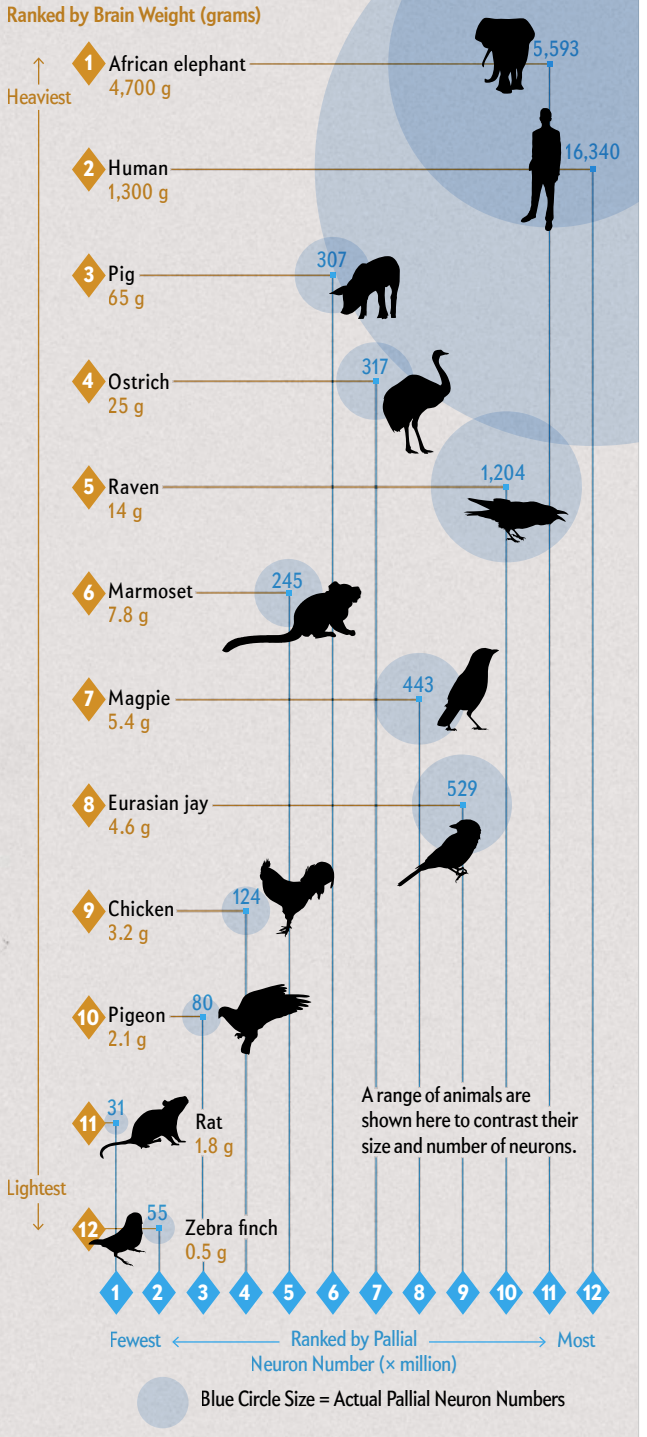
SIMILAR FUNCTIONS, DIFFERENT PLACEMENTS

Birds' brains are equipped with sensory and cognitive processing centers roughly equivalent to those in primates. But their placement can differ. The nidopallium caudolaterale (NCL) at the back of the brain, for instance, serves as an integrating hub for all of the animals' sensory, limbic and motor systems—similar to the prefrontal cortex in primates.

Illustration by Mesa Schumacher

A COMPARISON OF ANIMAL BRAINS

How do birds pull off their cognitive feats? One advantage is they have more neurons than expected for animals of their size. But there is still a gap in neuron number between birds and mammals. It turns out, though, that signals traveling between densely packed neurons in a bird's brain travel a shorter distance. So faster transmission speeds may compensate for the lesser numbers of neurons.



Graphic by MSJONESNYC

strated that the crows can solve diverse problems by reasoning about underlying causal relationships. They plan ahead using mental representations of unseen objects and make inferences about cause-and-effect relationships of observed events.

The crows' understanding of the physics of their actions, however, does have certain limits. Although they infer the weight of objects from the way they sway in the wind, they sometimes fail to understand that heavy objects have more impact on the surface on which they fall. Overall, New Caledonian crows show outstanding prowess in most but not all aspects of physical cognition.

How about social cognition? The crows can work within a team but do not understand that their partners can collaborate on a task to become, in effect, a "social tool" that assists in better accomplishing a goal. They look at objects that others manipulate but miss critical details of the other birds' behavior in comprehending the relevant action sequences. Instead they seem to visualize how a tool works and then reverse engineer it from memory rather than learning directly from others. Although the crows evolved extraordinary physical cognition, the same did not occur for mental activities involving their social interactions. Is such a limitation specific for New Caledonian crows, or does it also apply to other birds? An answer comes from examining ravens.

RAVEN POLITICS

YOUNG RAVENS that do not have a bonding partner or territory form temporary flocks that congregate at major food resources, such as an animal carcass. When large predators defend their food caches, ravens call in other flock members to engage in diversionary tactics for gaining access to the food. To prevent pilfering, they also implement devious strategies to stop other birds from observing their food stores. Likewise, ravens observe other birds to steal any unattended caches. Breeding pairs also defend a territory against other ravens. During such fights, mates as well as nonbreeders with developed social networks have considerably higher chances to win competitions and save their food caches. Thomas Bugnyar of the University of Vienna in Austria, Bernd Heinrich of the University of Vermont and their collaborators have been leaders in studies showing that ravens demonstrate these highly developed social strategies.

A prerequisite for all such activities is an ability to intuit the networks to which other birds belong—and the intentions of any individual that might be encountered in their daily wanderings. Ravens stay alert for calls that indicate when a dominance rank reversal might have occurred. They also use their knowledge about social networks when under attack from a dominant raven. When their own kin are nearby, they try to alert them by issuing repeated distress calls, but they stay more silent when the bonding partner of the attacking bird is close. Because rank in a dominance hierarchy increases after bonding, birds track the bonding of others and intervene aggressively to disrupt their pairings. By doing this, they are likely to prevent others from forming new bonds and to keep competing birds from increasing in rank.

Social competence is also needed in other settings. A raven will track when it is being observed and another bird could have spied its cache. Ravens seem to understand what others can or cannot see and even assess another bird's level of knowledge—an attribute of what is called theory of mind. If necessary, ravens deceive potential cache thieves by leading them to an empty place where they pretend to have food stockpiled.

These social skills are complemented by a high degree of self-control and a solid understanding of when to use force in their dealings with other animals and alternatively when to back off. Can Kabadayi and Mathias Osvath, both at Lund University in Sweden, showed that ravens are able to plan for different kinds of future events. The birds opt to choose a tool, such as a stone, over an immediately available small reward. With these implements, they can obtain a larger reward the next day by either bartering or using the tool to directly obtain some benefit. Ravens, in sum, combine all aspects of complex cognition in a brain of just 14 grams.

OF PARROTS AND PIGEONS

RAVENS AND New Caledonian crows are just two examples of cognitively capable corvid species. Nicola Clayton of the University of Cambridge has shown in two decades of research that scrub jays excel in all aspects of complex cognition. Most important, these birds were the first nonhuman animals in which episodic memory could be demonstrated. Episodic memory allows an animal to recall past life events and to imagine future undertakings.

Some parrot species, in fact, can attain feats equal to those of nonhuman primates. Recall Alex, the legendary grey parrot. Irene Pepperberg of Harvard University, who along with Clayton pioneered studies on cognition in parrots and corvids, demonstrated Alex's skills in categorizing various objects, actions and numerical quantities up to eight. The researchers also confirmed Alex's understanding of concepts of relative size, his discerning of when an object was absent, and his ability to detect similarities and differences in an object's individual attributes. Alex could even engage in simple addition by applying a zerolike concept in numerical tasks.

As impressive as these studies are, primatologists have raised the question of whether these birds might be clever in only a few highly circumscribed cognitive domains compared with the broader reach of primate cognition. If that were true, corvids and parrots should fail when tested with a wide diversity of tasks. To explore this question, Bugnyar and I looked for studies on assorted types of cognition in nonhuman primates and for similar research on corvids and parrots. After having collected all such available publications in eight areas of complex cognition, we concluded that corvid and parrot cognition is on par, both in magnitude and in breadth, with that of nonhuman primates.

Corvids and parrots are known to be smart birds. But what about other birds such as pigeons? While European magpies, ravens and New Caledonian crows have brain weights of about 5.5, eight and 14 grams, respectively, pigeons' brains weigh in at about two grams—comparable to the weight of a rat's brain. But even pigeons are brainier than assumed. Lorenzo von Fersen and Juan Delius, then both at Bochum, demonstrated that pigeons can memorize 725 abstract patterns and use transitive inference logic. (An example: You can deduce that Jennifer is taller than Sarah if it is known that Jennifer is taller than Sonia and Sonia is taller than Sarah.)

Recently Damian Scarf and Mike Colombo, both at the University of Otago in New Zealand, and I, with other colleagues, showed that pigeons learned to distinguish between four-letter English words and nonwords, which were composed of combinations of one vowel and three consonants. Pigeons mastered that task and transferred their knowledge to new sets of words and nonwords by using spelling strategies akin to those practiced by primary school pupils. Overall, pigeons can achieve cognitive performances on these tasks similar to those of corvids and parrots in some but not all tasks. Even when successful, they need much longer to learn a task and require more training to grasp an abstract rule. Not all birds are as clever as a crow or a parrot. But they are brainier than once thought.

When birds succeed in managing such diverse cognitive tasks using a small brain without a cortex, they find a way to compensate for these limitations. In fact, beginning in the 1960s, Harvey Karten, now at the University of California, San Diego, used new methods to begin a series of studies that demonstrated that most of what Edinger coined the subpallium in birds must instead be the pallium. He went on to show that the sensory and motor pathways that connect the avian pallium to other brain areas were identical to those of the mammalian cortex. In 2002 an international consortium of neuroscientists reviewed all accumulated evidence and concluded that birds indeed have a much larger pallium than previously assumed. In addition, the avian pallium is similar to that of mammals and shares common ancestry with the mammalian one.

The mammalian pallium is not all cortex and includes other areas such as the hippocampus or parts of the amygdala. How much of the bird pallium is like the cortex is still subject to debate. Whereas some researchers are confident that most of the bird pallium is similar to some cortical layers or cell types, others contend that most of it is only analogous to the amygdala and other noncortical pallial areas. It is important to emphasize that dissimilar brain structures of two groups of animals

BIRD SMARTS: A grey parrot succumbs to an illusion (*1*), a raven wields a tool (*2*) and a scrub jay shows off its memory skills (*3*).

ARLENE LEVIN-ROWE AND THE ALEX FOUNDATION (1); HELENA OSVATH (2); NICOLA CLAYTON (3)

can perform identical functions through an evolutionary process called convergent evolution. The prefrontal area is a perfect example. The mammalian prefrontal cortex (PFC) plays a key role in all aspects of complex cognition.

In the beginning of the 1980s Jesper Mogensen and Ivan Divac of the University of Copenhagen in Denmark reported that an area of the posterior pigeon pallium resembled the mammalian PFC. Because this was a first clue to the neural basis of bird cognition, I started a still ongoing series of studies in which we could indeed show that this area—the nidopallium caudolaterale (NCL)—is, like the PFC, a zone of encounter between incoming sensory inputs and outgoing commands to the motor system to initiate an action. As in the PFC, the NCL also plays a critical part in all cognitive tasks, and its neurons encode cognitive functions such as decision-making, adherence to rules devised for the experiments, and the assigning of values to various options before a choice is made.

Although the NCL and PFC are highly similar, genetic evidence and their locations in the most posterior and most anterior parts of the pallium, respectively, make it unlikely that these two areas stem from a common precursor of birds and mammals. Instead they possibly once had quite different functions in early precursors of mammals and birds but converged over the course of 300 million years into areas dedicated to cognitive integration of sensory inputs with motor outputs. During our research, I often thought of the famous phrase of Dr. Ian Malcolm in *Jurassic Park:* "Life finds a way." If two unlike animal groups both desperately need a brain area that orchestrates cognition, they both independently evolve a prefrontal area.

To explore how distinctive physiology can end up furnishing the same cognitive function, Murray Shanahan of Imperial College London and I, along with other colleagues, looked at how the connectome, or brain wiring diagram, of the pigeon pallium is organized. Because the bird pallium seems to be so different from the cortex, we also expected a different connectivity pattern. After reconstructing the pigeons' connectome, we had our aha moment: the avian pallial networks—with different areas dedicated to distinctive functions—were astonishingly similar to that of mammals. Our take-home message was simple: if two groups of animals develop similar mental functions during evolution, they also develop the same blueprints of connectivity because similar mental functions seem to require similar networks.

A major puzzle still remained. How do birds manage to come up with all their cognitive power given the small size of their brains? To find an answer to this question, Seweryn Olkowicz and Pavel Němec, both at Charles University in Prague, Czech Republic, and Suzana Herculano-Houzel, now at Vanderbilt University, along with other colleagues, estimated the neuron numbers of 28 avian species. They were amazed to discover that corvid and parrot brains contain twice as many neurons as expected for their brain size. Because these "surplus" neurons are mostly located in the pallium, corvids and parrots have more computing power than some monkeys with larger brains.

Even if birds have more neurons than expected, the extremely small size of their brains means there still remains a gap between the neuron numbers of birds and mammals that are cognitively on a par. For example, keas (a type of parrot found in New Zealand) have 1.28 billion pallial neurons, ravens possess 1.2 billion and chimpanzees have 7.4 billion neurons, although research could not evince systematic cognitive differences among them.

How do birds compensate for the numerical gap? It turns out that a greater concentration of neurons results in the distances between avian neurons being shorter. In tasks in which information is repeatedly sent back and forth among groups of neurons in the densely packed cerebrum, a time gain may result as signals take less time to travel from one point to the next. Indeed, Sara Letzner and Christian Beste, both at TU Dresden in Germany, and I showed that pigeons can react faster than humans when working on a particular cognitive task. The density of neurons in the bird pallium compensates for some of the smaller neuron numbers by affording faster conduction speeds.

A NEW LOOK AT AVIAN COGNITION

WHEN SCIENTISTS across the globe started to discover the extraordinary cognitive abilities of birds, the derogative "birdbrain" lost its scientific rationale. Indeed, we now know that brains of birds and mammals are much more similar than previously thought.

Behind these discoveries, a deeper insight becomes visible. To comprehend it, we first have to realize that independent from each other, both birds and mammals spread throughout the globe by conquering nearly every ecological niche that can sustain a vertebrate. Both branches of the animal kingdom also became "generalist species" that are not bound to a narrow ecosystem but survive nearly everywhere. High cognitive capacities were needed to quickly find solutions to novel problems and to outsmart competitors. Thus, the strong selection pressure in both vertebrate classes produced very sophisticated cognitive abilities.

It is less of interest that both groups succeeded in growing smart. Rather this accomplishment came about through development of mostly identical neural mechanisms despite differently organized pallia. Birds and mammals cognitively thrived by increasing neuron numbers. Mammals did so by expanding brain size and birds by amplifying neuron density. They both developed substantially similar networks of pallial connections and evolved "prefrontal" areas with identical physiological, neurochemical and functional features. The same can be said for cognition itself. The way birds and mammals learn, remember, forget, err, generalize and make decisions follows identical principles. This astonishing degree of similarity is only possible when nature offers severely limited degrees of freedom in generating neural structures for complex cognition. Birds and mammals evolved similar neural mechanisms and ways of thinking—taking different paths that ended in the same place. SA

MORE TO EXPLORE

New Caledonian Crows Reason about Hidden Causal Agents. Alex H. Taylor et al. in *Proceedings of the National Academy of Sciences USA,* Vol. 109, No. 40, pages 16,389–16,391; October 2, 2012.

Cognition without Cortex. Onur Güntürkün and Thomas Bugnyar in *Trends in Cognitive Sciences,* Vol. 20, No. 4, pages 291–303; April 1, 2016.

Orthographic Processing in Pigeons (*Columba livia*). Damian Scarf et al. in *Proceedings of the National Academy of Sciences USA,* Vol. 113, No. 40, pages 11,272–11276; October 4, 2016.

Ravens Parallel Great Apes in Flexible Planning for Tool-Use and Bartering. Can Kabadayi and Mathias Osvath in *Science,* Vol. 357, pages 202–204; July 14, 2017.

FROM OUR ARCHIVES

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

scientificamerican.com/magazine/sa

PHYSICS

An update to a classic experiment establishes new quantum-mechanical truths and paves the way toward a novel strategy for quantum computing

THE TRIPLE-SLIT EXPERIMENT

By Urbasi Sinha

Illustration by Andrea Ucini

"ALL OF THE MYSTERY OF QUANTUM MECHANICS" IS CONTAINED within the double-slit experiment, Nobel laureate Richard Feynman famously said. In the experiment, first proposed in 1801 by British polymath Thomas Young, a beam of photons—particles of light—flies toward a wall with two slits

IN BRIEF

The "double-slit" experiment revealed that light and matter are both particles and waves and demonstrated the superposition principle: that particles can be in multiple states and locations simultaneously.

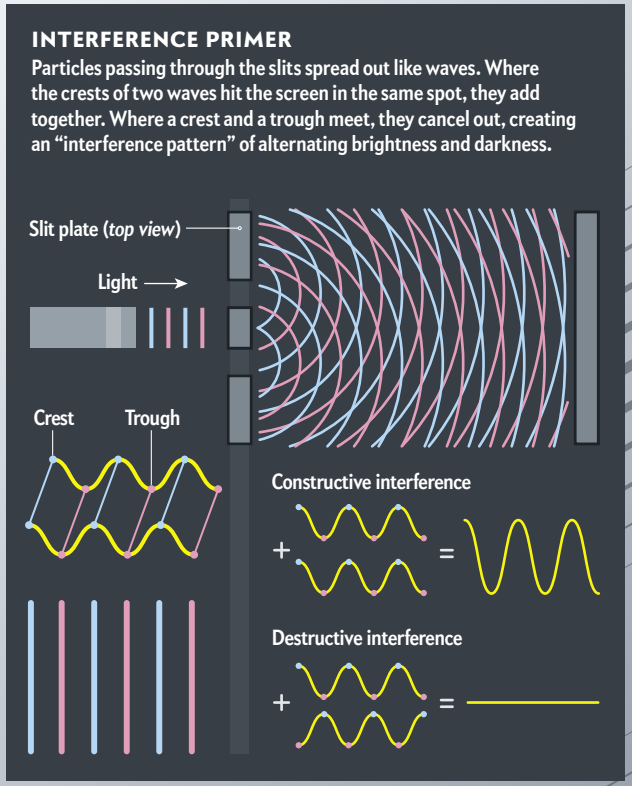
Recently scientists have run versions of the experiment with three slits instead of two. The change has revealed new details about how the superposition must be calculated in slit-experiment boundary conditions.

The triple-slit experiment is also helpful in quantum computing. It offers the chance to create three-dimensional quantum bits (instead of the usual two), which may help scale up quantum computers to useful size.

Urbasi Sinha is a physicist at the Raman Research Institute in Bangalore, India, as well as an affiliate member of the Institute for Quantum Computing at the University of Waterloo in Ontario and the Center for Quantum Information and Quantum Control at the University of Toronto. Her research focuses on experimental quantum information and quantum computing.

Slit Experiments

The famous double-slit experiment established two of the bedrock principles of quantum theory: wave-particle duality—the concept that matter and light are both particles and waves—and superposition, the notion that particles can be in multiple states and locations simultaneously. More recently, scientists have performed versions of the experiment with three slits rather than two, opening the door to new theoretical and technological possibilities.



cut in it. When the light reaches a screen behind the wall, it produces a telltale "interference pattern": stripes of light interspersed with darkness. This pattern results only if the photons act like waves rather than like point particles, and the peaks and troughs of the waves coming through the two slits interfere with one another, sometimes adding light and sometimes canceling it out. When Young performed the experiment, using a modified setup, it seemed to establish that light was a wave and not a particle.

Or was it? Weirdly, in experiments centuries later in which researchers took care to shine only one photon at a time toward the wall, the interference pattern remained, as if a single particle were interfering with itself. Even stranger, if you place a detector by the slits to record which slit each particle passes through, the interference pattern disappears. Instead you get two lines of light on the screen, just what you would expect if point particles and not waves were passing through—as if the act of measurement changed the nature of the particles.

To this day, the double-slit experiment, with its inherent simplicity of concept, remains one of the most intriguing tests ever performed. It has been repeated many times, with particles of both light and matter. It clearly demonstrates the fundamental strangeness of quantum mechanics: that light, and matter as well, is in fact both a particle and a wave—a concept known as wave-particle duality. It also establishes the superposition principle: particles can exist in multiple states and even simultaneously in multiple places. In the double-slit experiment, particles must not be traveling through one slit or the other—for interference to occur, each particle must be traveling through *both*.

As celebrated as this experiment is, we have not yet plumbed its depths. Recently my team at the Quantum Information and Computing laboratory at the Raman Research Institute in Bangalore, India, has set up "triple-slit" experiments in the microwave-wavelength range—instead of two slits, we use three. It is a seemingly simple adjustment, but it has profound consequences. On the theory side, our triple-slit trials have clarified how the superposition principle applies in these circumstances and have revealed new subtleties in our fundamental understanding of this phenomenon.

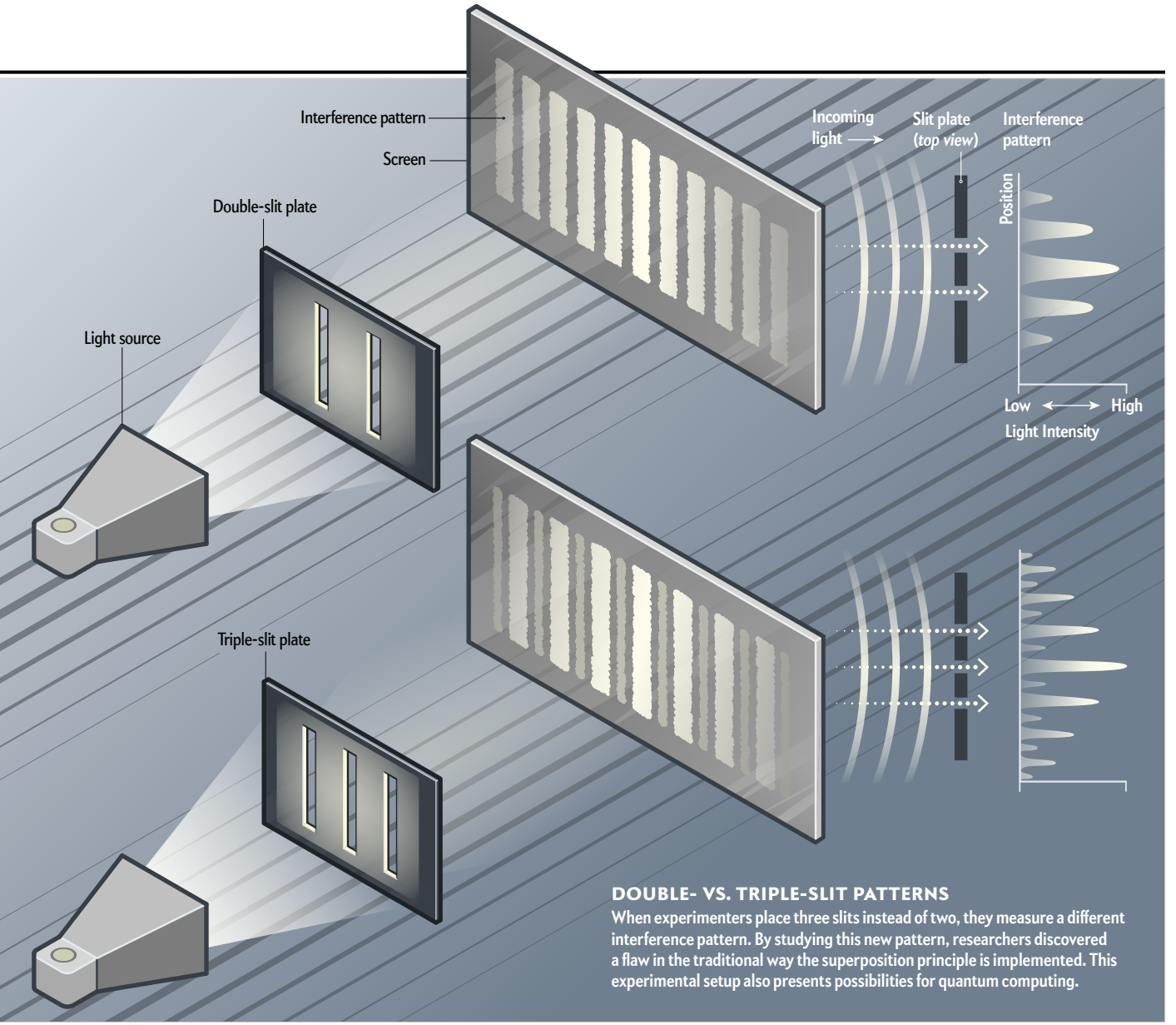
Our triple-slit experiment architecture also offers intriguing opportunities in the emerging field of quantum computing. Quantum computers promise to enable calculations that were previously intractable—if we can harness the power of quantum physics to build them. One of the central challenges in quantum computing is finding a way to increase the number of bits a quantum computer contains, called qubits, without destroying the superposition that allows qubits to be in two states at once—the key to achieving huge gains in computing speed. Whereas most of the community is working on increasing the number of qubits in a system, my lab is trying an alternative, less explored approach by using higher-dimensional "qudits" instead of two-dimensional qubits. Using the triple-slit system, we can create three-dimensional qudits called qutrits.

THE SUPERPOSITION PRINCIPLE

QUANTUM THEORY describes fundamental particles not just as physical waves but also as being determined by the so-called wave equation, whose solutions may be designated by the Greek letter psi, ψ. These solutions express the probability amplitude of the particle being in any particular state.

Our research, however, has revealed a flaw in the way physicists have traditionally dealt with wave-equation calculations when they are applied to the double-slit experiment. Imagine the classic experiment and let the two slits be named A and B, respectively. The solutions to the wave equation describing a

Illustrations by Nick Bockelman



DOUBLE- VS. TRIPLE-SLIT PATTERNS
When experimenters place three slits instead of two, they measure a different interference pattern. By studying this new pattern, researchers discovered a flaw in the traditional way the superposition principle is implemented. This experimental setup also presents possibilities for quantum computing.

particle in this system can be labeled ψ_A when slit A is open and ψ_B when slit B is open. What happens when both slits are open? It is common practice in textbooks to call the solution $\psi_A + \psi_B$ to represent the fact that the particle is in a superposition state in which it is passing through both slits. This is indeed an application of the superposition principle, though an incomplete one. The reason is simple: The situation with two slits open at once is not the same as the combination of having the slits open separately. We know that when they are open at the same time, a particle in some ways passes through both and interacts with itself, and we cannot represent these interactions by simply adding the two solutions.

Scientists have suggested before that some correction term might be needed to make our equations accurate. This quantity is called the Sorkin parameter because it was predicted in 1994 by physicist Rafael Sorkin, then at Syracuse University. Most researchers, however, have assumed that this term would be so small as to be negligible. And indeed, we know it cannot be too large, or it would have been observed much earlier. But our triple-slit experiment proved that this term does exist and that it is not always small enough to be ignored. The use of three or more slits provides us with a natural test bed for this correction term because we can measure a quantity (the Sorkin parameter) that will be zero if the correction term does not exist and nonzero if it does exist. (In the two-slit case, the correction term gets added to something that is already nonzero, so it does not show up in a noticeable way.)

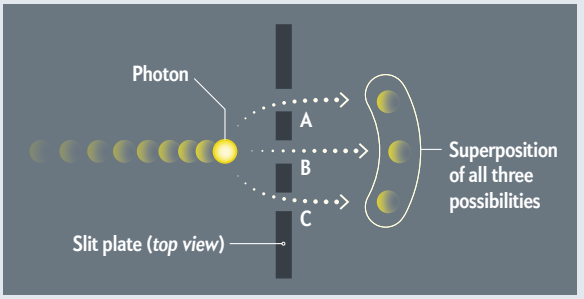
I have been working on triple-slit experiments for more than a decade. In 2010 my colleagues and I published our first results in a paper in *Science*. In 2014 my team and I began to run new trials of our triple-slit experiment using microwaves at the Gauribidanur astronomical observatory in Karnataka, India. We carried out the project in an open field in a tent next to corn crops. Although the setting might sound odd for a precision physics experiment, the corn provided a good source of absorption for stray microwaves that might have interfered with our measurements. It also helped that we were not working with walls or lots of equipment in the space that could reflect waves.

From Slits to Qutrits to Quantum Computing

Quantum computers promise faster computing than classical machines. Most quantum bits, called qubits, have two possible states (basis states), just as traditional bits do. But quantum bits with three or more basis states offer advantages.

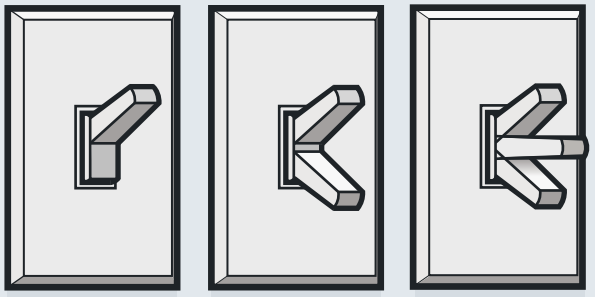
GENERATING A QUTRIT USING A SINGLE PHOTON

When a photon (a particle of light) travels toward the slits, it has an equal probability of going through each. A classical particle would pass through just one, but a quantum particle may actually go through all three, taking on a superposition state of being in three places at once. The photon can now be used as a "qutrit" with three basis states.



QUANTUM COMPUTING WITH QUTRITS

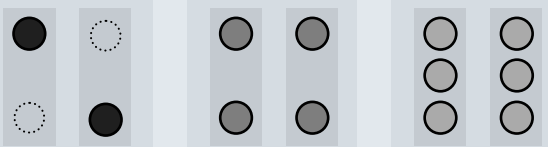
If scientists want to create a quantum computer with some total number of possible states, they would need fewer qutrits than two-dimensional qubits. This property is an advantage because the more bits in a quantum computer, the more likely it is to lose its quantum properties.



BIT
A classical computer bit has two basis states, like a light switch. It can be in only one or the other. With two bits, we can have four possible states.

QUBIT
A quantum bit also has two basis states, but it can be in both at once. The total number of states = 2^n, where n is the number of qubits. Two qubits gives $2^2 = 4$ states.

QUTRIT
A qutrit has three basis states and gives a total number of possible states = 3^n. For example, two qutrits gives $3^2 = 9$.



Furthermore, our isolated location had poor cell service—another benefit in avoiding contamination—and we were able to run our experiment on a very large scale.

Our setup used two horn antennas—one to release microwave photons and one to detect them. Between them was a plate with three slots, each 10 centimers wide, spaced 13 centimeters apart. Staying true to the style of the first slit-based experiments, we housed the detector on a rail that we could move to measure the different interference patterns as a function of detector position. We found that the interference pattern we measured did not match the approximate solution to the wave equation given by $\psi_A + \psi_B$, but it did match the solution that included the nonzero Sorkin parameter. We also used a blocking material to obstruct the space between the slits, essentially stopping the photons from traveling between the slits and interacting with the neighboring slits. When we did this, we saw that the value of the Sorkin parameter changed with the size of the block—showing that the parameter indeed measures interactions between the slits and that it varies depending on the level of interactions. This finding established that the correction term we measured was not some systematic error from our experiment that we had failed to understand but was indeed the thing we were looking for.

Ours was the first definitive validation of the Sorkin parameter as a correction term to the superposition principle in the classical microwave domain. The results, published in June 2018 in the *New Journal of Physics,* have already led to some textbook edits, and they affect our basic understanding of fundamental physics. They might also have implications for work being done in astronomy and astrophysics to study signals from the early universe. This research often involves arrays of radio antennas spread over the ground. Commonly, the data received by the different antennas are added together. But now that we know the wave-equation solution is not just the sum of the individual solutions, some calculations may need to be updated with the correct Sorkin parameter. Our findings might eventually help scientists develop better error models for these observations.

QUANTUM QUTRITS

OUR EXPERIMENT IS INTERESTING not just theoretically but potentially practically as well. We hope to use our triple-slit process to help design new tools for quantum computing.

Quantum computers take advantage of quantum laws such as superposition to enable computations much quicker than those of classical machines. Consider a traditional computer bit as if it were a light switch: it can be either "on" or "off" (corresponding to a value of 1 or 0, respectively, in binary code). In the quantum world, though, a switch need not be either on or off—it can be both. In a qubit, we define a state with a finite probability of being in the on state and in the off state at the same time. This combination of both states with some probability of each is the essence of superposition.

The two states that contribute to the superposition state are called the basis states. A regular qubit has two basis states, and for n qubits one has access to 2^n possible states. Thus, with two qubits, there are $2^2 = 4$ possible states. Whereas for n classical bits the state occurs in only one of the 2^n possibilities, for n quantum bits all 2^n possibilities can coexist. The power of quantum computing comes from cleverly designed quantum algo-

rithms that can make use of the superposition state during execution and perform a certain class of operations at exponentially higher speeds than a classical computer.

Yet to reach this goal, we need a reasonably high number of qubits—certainly more than just two. One number many in the community are working toward right now is $n = 50$, which offers many interesting possibilities for quantum algorithms. With 50 qubits, we have 2^{50} possible states available for quantum operations. Recently Google claimed it had achieved this milestone by successfully implementing a random sampling calculation on a 54-qubit quantum processor. Getting to large numbers of qubits, however, is easier said than done. The more qubits we put together, the greater the chance they will lose their special quantum ability for superposition and collapse back into normal, classical bits. This happens when a qubit interacts with the outside environment and loses "coherence." As we try to get more qubits into a coherent superposition, it becomes more and more difficult to maintain this state for long. It is much like putting people into a room for a party. If you have 10 people in a 100-square-foot room, there is enough area for them to coexist without getting into one another's space. If we increase the number of people to 30, some crowding starts, which leads to a general loss of peaceful coexistence. The same thing happens with qubits.

One alternative to the usual strategy is to increase the dimension of each quantum bit rather than trying to fit more qubits into the same space. To see why this helps, let us go back to an elementary mathematics problem:

What is 2^3? The answer is, of course, 8 ($2 \times 2 \times 2 = 8$).

Now, what is 3^2? The answer here is 9 ($3 \times 3 = 9$).

These results are of the same order of magnitude—quite close. Thus, instead of three qubits, if we were to use two qutrits—that is, three-dimensional quantum bits—we would have access to a similar number of possible states. So, instead of trying to increase the exponent, why not try to change the base? If we increase the number of basis states, we will need a smaller number of bits to achieve the same goal. This realization is what defines research in higher-dimensional quantum systems.

And our strategy has another benefit: we are no longer bound by binary code. Consider the outcome of a game of football. Usually we think of two outcomes, "win" and "loss," which can be specified using two states, so in a quantum world a qubit is sufficient. But if we add two more possible outcomes, say, "abandoned" and "draw," one qubit is not enough to declare the results. We need two qubits. But if we had a four-state system, one would be enough. Such a system would be a "ququad."

Higher-dimensional quantum systems, or qudit systems, can thus pack more information in a smaller number of systems. This benefit has been theoretically proved to offer an advantage with respect to a certain goal for quantum computers—namely, creating hack-proof communication using so-called quantum key distribution. In this method, two parties create a shared secret "key" that only they can use to decode messages. If you can increase the dimension of your quantum bits by increasing the number of basis states, the result is a key that is more resistant to certain kinds of attacks. In addition to the possibility of higher security in key distribution, qudits also promise a greater amount of randomness in true random number generation—another hoped-for application of quantum computers.

Despite these benefits, qudit-based systems have some drawbacks. It is hard to actually come up with stable physical systems in which all the basis states are equally easy to reach. For instance, sometimes a system may be biased toward its lowest-energy, or ground, state, and resulting calculations could carry this bias. A second hurdle is simply that this line of research is newer than qubits, so fewer algorithms and tools have been developed for qudits. Although there is a lot to be done, the number of open problems makes this research exciting and rich in potential.

TOWARD A QUANTUM COMPUTER

SO HOW DO WE GET from our basic triple-slit experiment to a working qutrit system? The first step is to generate single photons.

We start with a very strong laser beam, which we shine toward a special crystal material. Under certain conditions, one in about 10^8 to 10^{10} photons splits into two photons of lower energy in a process called down conversion. The daughter photons always appear as a pair. We measure one of the photons using a single-photon detector, and this measurement heralds the presence of the other photon because we know they were produced simultaneously. We can then use the second photon for experiments.

In our team's work, we have played with the characteristics of the "mother" photon to ensure that the daughter photons share its characteristics. The mother photon is directed at three slits, and its spatial profile then mimics the triple-slit profile. The daughter photons in turn carry this profile through. The photon enters a superposition that gives us a "spatial-bin" qutrit whose three basis states are the three slit positions.

Still, this qutrit we have created is a far cry from what is needed for a functional quantum computer. We would need to use our slit system to generate numerous qutrits and then feed them into an architecture with so-called gate operations capable of using the qutrits to perform calculations. This area is the focus of my team's current efforts. We must design the specific optical elements needed to accomplish this manipulation and then miniaturize everything so it can define a working computer system.

Triple slits therefore represent the yin and the yang of physics research—both fundamental and functional. Our research on the superposition principle and its first measured correction term explores the very basic concepts of physics. Meanwhile triple-slit-based qudits represent a technological feat in the advancement toward higher-dimensional quantum computing and quantum communications. This most famous of physics experiments, it turns out, is still offering new insights and possibilities. SA

MORE TO EXPLORE

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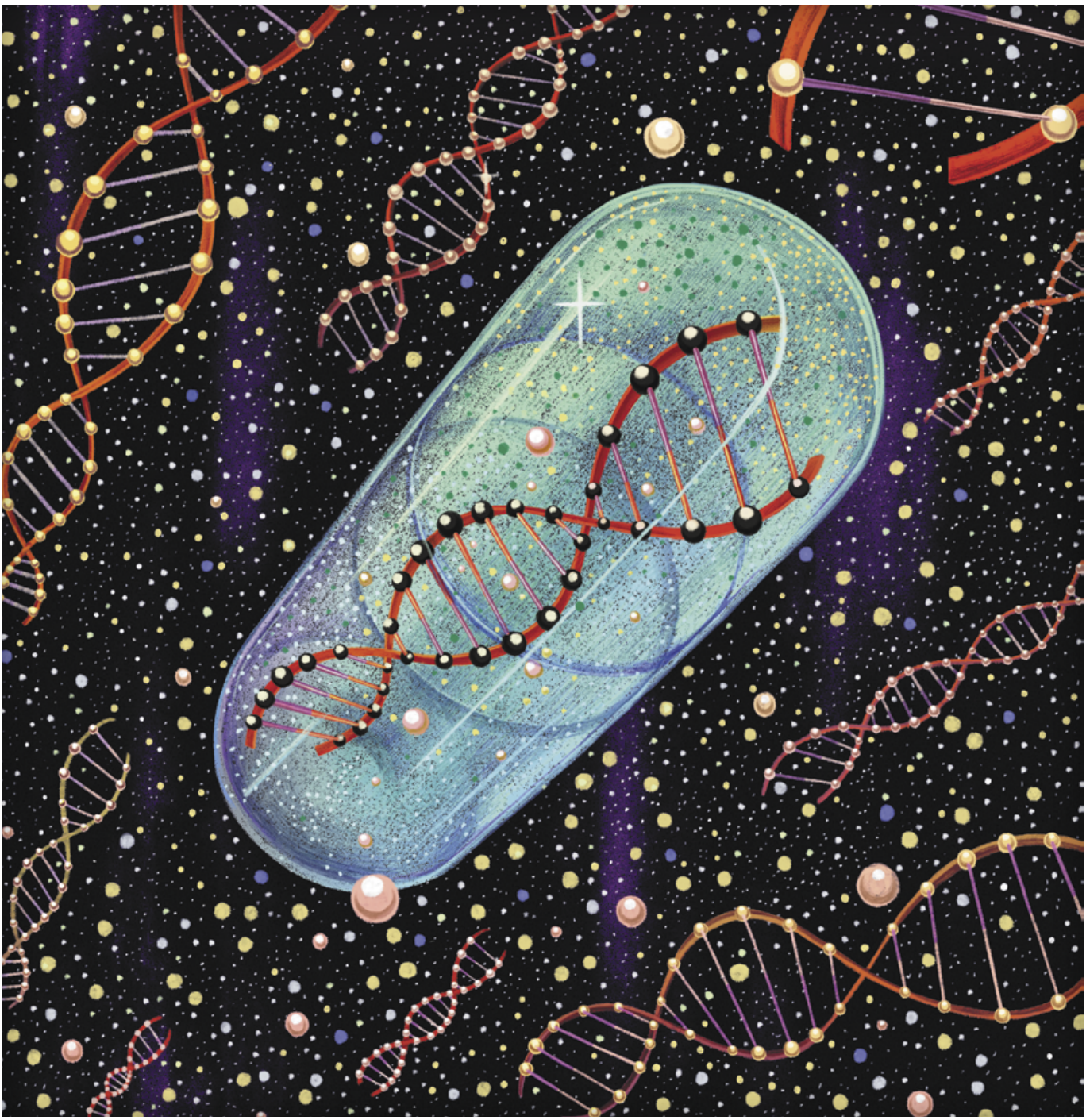

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Curing What Ails Us

DOCTORS HAVE BEEN TREATING THE SYMPTOMS of most diseases, and not the source, for centuries. They have cut out tumors, unclogged arteries, injected insulin and soothed fevers—and have been unable to touch the biological code within cells that tells them to grow malignantly, pass along abnormal nerve signals, take in too much or too little energy, and swell with inflammation. The code is the DNA molecule in each cell that tells it what to do and when, and it triggers dreaded diseases when it goes wrong. The molecule, and its messengers, had remained tucked away, beyond the reach of almost all drugs, unfixable when broken. But as this special report explains, that is no longer the case.

Things began to change after the DNA sequence for the entire human genome was laid out early in this century, and within the past several years the ability to synthesize and custom-design shorter sequences has shown scientists that the best substance for reaching DNA is, well, DNA. Fabricating new genes to replace badly working versions, or to "silence" them, has produced 14 approved DNA-related drugs (*page S12*). And the latest research indicates that such therapies can be even more effective if scientists depart from the basic linear strands and instead make DNA spheres, which have enhanced abilities to enter cells (*page S3*). DNA analysis has also yielded new targets, showing that although newborn babies in the U.S. are typically screened for between 30 and 60 genetic conditions right now, it is possible to find nearly 1,000 genes linked to childhood diseases that could be new treatment points (*page S8*).

But that same science has also created troubling issues: some of the gene tests for infants can raise false alarms, for instance, and not every child with a disease-associated gene ends up getting that disease. Research has also revealed unfair bias in DNA targets. Most of the data about those sequences comes from studies of white people and has missed gene variants that cause disease in nonwhites—inequality in research that will produce inequality in health if it isn't fixed (*page S14*). Geneticists are starting projects designed to improve this diversity level. DNA in medicine has great power, and that power should be used for the many, not the few.

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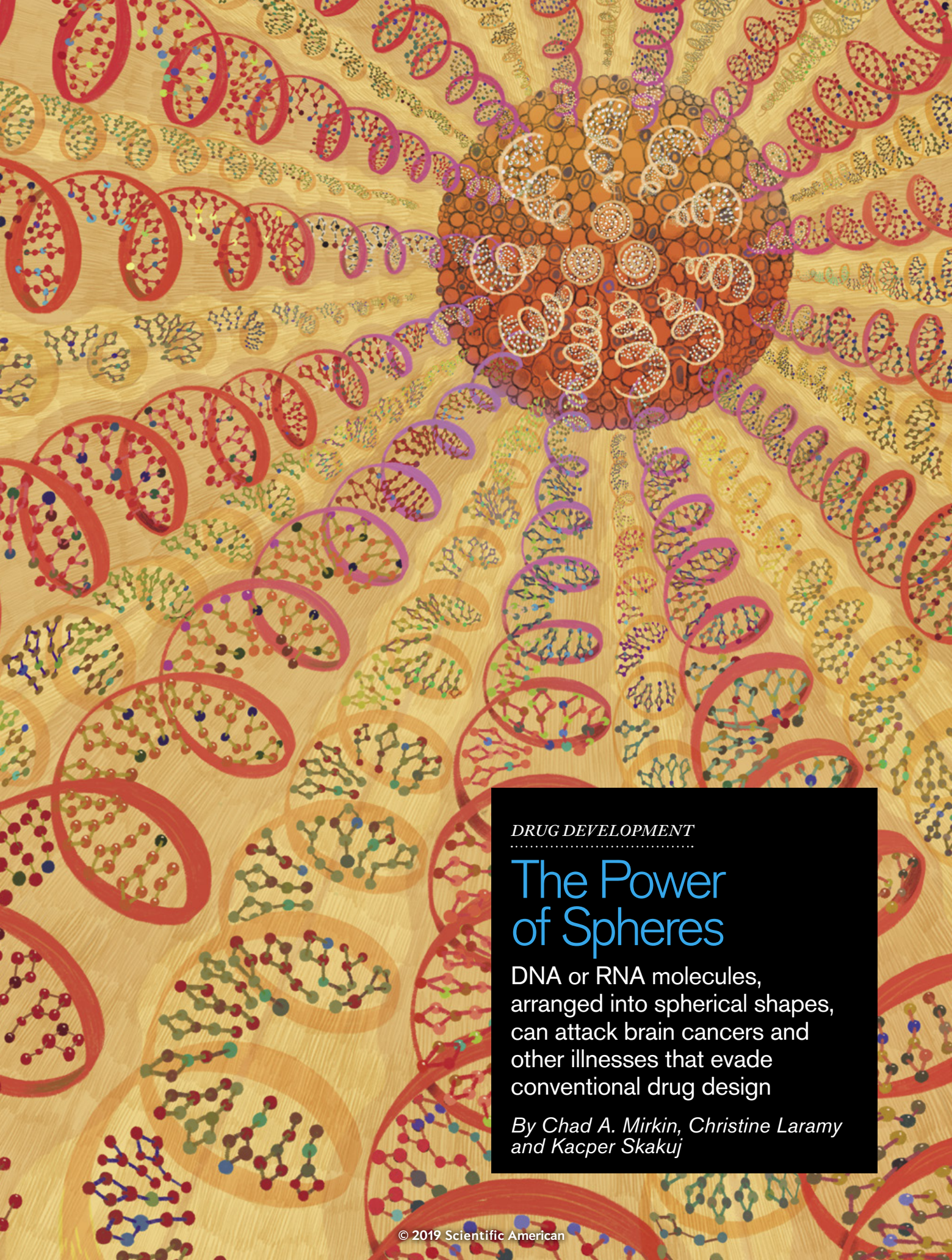


DRUG DEVELOPMENT

The Power of Spheres

DNA or RNA molecules, arranged into spherical shapes, can attack brain cancers and other illnesses that evade conventional drug design

By Chad A. Mirkin, Christine Laramy and Kacper Skakuj

BRAIN CANCER IS TERRIFYING. It attacks an organ we see as the core of our personality, our mind, our very humanity. And because the disease grows inside the brain, it is notoriously difficult to treat. The organ has evolved many defenses to keep foreign substances out as a method of self-protection, but those substances include many anticancer drugs. Using knives or radiation on this citadel of consciousness carries tremendous risks. For these reasons, the five-year relative survival rate for people aged 55 to 64 who get glioblastoma, the most common type of primary brain tumor, is a grim 5 percent. The disease killed John McCain, Edward Kennedy and Beau Biden, and it takes the lives of about 15,000 less famous Americans every year.

Now we have developed a nano-sized drug that travels through the body and into the brain, where it can kill off cancerous cells. These drug particles are composed of oligonucleotides—strands of DNA or RNA, the molecules that make up the master code that tells every cell what to do—and they stick out from a central core like the many spines of a sea urchin. The spiny round particles are called spherical nucleic acids. In an early trial with eight patients, these spheres went into glioblastoma cells and bound up other "code" molecules that are key to the cancer's incessant growth.

Such spherical drugs appear to work against a variety of diseases. Another terrible affliction, this one affecting infants, is spinal muscular atrophy, or SMA. It robs children of muscle control until swallowing and breathing become first difficult and ultimately impossible. Most youngsters with the disorder succumb before they enter kindergarten, and until recently there was no help doctors could offer. In 2016 the U.S. Food and Drug Administration approved one remedy: a drug called Spinraza that is injected directly into the spinal cord several times every year and, at a list price of $125,000 per shot, is one of the most expensive drugs in the world. We recently compared our spheres, studded with nucleic acids that get inside cells and interfere with messenger molecules that lead to SMA's symptoms, with the Spinraza approach in studies of rodents. The spheres improved survival by four times—115 days versus 28 days—and the rate of toxic side effects was much lower.

Spherical nucleic acids, or SNAs, avoid problems that have plagued the pharmaceutical industry's attempts to develop new drugs. Conventional drugs are nonspecific: they can affect many cells and organs, not just diseased ones; hence, they have numerous side effects. Nucleic acids, however, can be designed to interfere with only disease-causing genes or their related instruction molecules sent to control a cell's behavior. Biologists have tried to use nucleic acids in the past but primarily as linear molecules and with little ability to direct where they go. And because the body has robust defenses against foreign genetic material—the immune system, for one—in most cases, these defenses damaged the drugs immediately or sent them to organs such as the liver and kidneys for waste removal.

But SNAs, at only billionths of a meter across, seem able to travel anywhere in the body and get inside cells before immune defenses can waylay them. The spherical shape lets us pack a high density of nucleic acid "spines" into a small space, and that density creates a strong interaction with receptors on cell surfaces that admit the particles inside. There the sequence of the components—the same nucleotides, abbreviated as A, T, C and G, that constitute the DNA code of life—ensures that they affect only complementary sequences of DNA or RNA. (The latter molecule uses U—uracil—instead of T, and we design for that.) We construct our strands to match only sequences in the cells that are crucial to the disease. SNAs are not magic bullets and will have to pass many more tests before they can be used on lots of patients. But the potential is there: because the nucleic components can be reordered to interfere with many different disease-causing molecules within cells, the spheres have the ability to tackle some of the world's most debilitating conditions.

PROGRAMMABLE DRUGS

TRADITIONALLY, SCIENTISTS have found disease treatments by screening hundreds of thousands of small synthetic or natural molecules, going through a long trial-and-error process to see if any of them have therapeutic benefits. Although this pipeline has led to a number of amazing medicines, such as antibiotics, even the most promising ones can cause unwanted side effects. Many other diseases are unaffected by these molecules and therefore still lack a cure or treatment. Even biologics, a newer class of drugs that are often based on proteins made by immune cells of mice, rabbits and other animals, typically rely on an abbreviated trial-and-error discovery process.

An ideal drug-design process would allow scientists to rapidly and rationally design specific drugs that use the same language as our cells, instead of looking for a needle-in-a-haystack molecule. Cells communicate many complex messages through DNA and RNA to make millions of proteins. The number of steps that cells must execute correctly to make these proteins is staggering: they must select a specific sequence of DNA made of A, T, C and G nucleotides, transcribe that sequence into a form called messenger RNA (mRNA), and then accurately read that mRNA to arrange molecules called amino acids into a chain—as long as 35,000 units—that forms a single protein.

Errors where one nucleotide such as a T or a G is added, deleted or placed in an incorrect order can halt protein production or generate an irregular protein that causes disease. Too many copies of an mRNA, and therefore of its related protein, can also lead to disease. (So can the introduction of foreign nucleic acids from a virus, which leads the infected cell to make harmful viral protein.)

But we can synthesize our own stretches of DNA or RNA components, called oligonucleotides. Because the genetic alphabet has very specific rules—A can bind only to T, and C binds only to G—we can make our oligonucleotides with sequences that selectively bind to and inactivate one disease-driving sequence. When they do so, the synthetic oligonucleotides gum up the cellular works, pre-

venting the affected cells from producing a disease-causing protein.

Yet despite automated equipment that can rapidly make synthetic oligonucleotides with any desired sequence one could imagine, fewer than a dozen oligonucleotide-based drugs have been approved for patients. This is because these strands of oligonucleotides face a significant hurdle once they are injected into the bloodstream: because they are foreign—that is, not native to the patient—they get treated as hazardous material or waste. The body's immune system either destroys these oligonucleotides, or the body's waste-filtration stations, the liver and kidneys, remove them. They do not reach their intended target. Even if oligonucleotide strands could make it to a cell that contained the target mRNA, that cell has an outer membrane that acts as a barrier to prevent the oligonucleotides from getting inside. As a result, drug companies working with oligonucleotides have often settled for treating diseases that can be targeted in the liver. The liver is an important organ. But sequestering these drugs in this one place really limits their use. (An alternative approach—injecting oligonucleotides directly into the disease site, such as into the spinal column with Spinraza—is technically difficult and still does not ensure entry of the medicine into all the appropriate cells.)

A SURPRISING RESULT

ADVANCES IN NANOTECHNOLOGY made by our group at Northwestern University, along with several other researchers, have led us to the SNAs, which may be a way around this problem. Prior to 2006, our group had been interested in using the highly specific binding ability of SNAs in probes for ultrasensitive diagnostics—to fish out stretches of cancer DNA from blood samples, for instance. We could do this by chemically decorating a gold nanoparticle with many strands of DNA designed to anchor one end to the particle, producing the sea urchin spine pattern. The outer end of the DNA was designed to be a complementary sequence to the cancer DNA sequence, so it worked nicely as a probe. We also used the spheres as artificial atoms with programmable bonds to fashion new types of materials. Drug design, however, was not really on our radar. After all, according to the dominant paradigm of drug biology and chemistry, RNA and DNA would not naturally cross cell membranes.

We were curious, though, about how nucleic acids in this new geometry would interact with living systems. Drug developers had already been experimenting with single strands of oligonucleotides, with, as we noted, limited success. From our research with SNAs as a diagnostic platform, we knew that target DNA and RNA would bind to our clusters of spines much more strongly than they would attach to free oligonucleotide strands. The reason is that our spines are packed densely on the nanoparticle's surface. That makes them more rigid, which helps the As, Ts, Gs and Cs on each strand align and bind when they encounter a target strand. This characteristic made us suspect that with the right nucleic acid sequences, SNAs could be a very potent oligonucleotide drug.

To test this idea, we carried out an experiment that, at the time, we thought had only a slim chance of working. We took strands of free oligonucleotides and put them into a test tube with mouse cells. In a different tube we added a bunch of SNAs to the same type of mouse cells. We attached red fluorescent molecules to both the spheres and the strands to help us track them. When we looked at the cells under a microscope, the ones mixed with free strands appeared transparent, as expected. Free oligonucleotides did not cross the cell membrane. But the cells mixed with SNAs lit up the screen with bright red fluorescence. The spheres had made it inside!

How could this happen? In general, cell membranes closely regulate which molecules may enter, and oligonucleotides are not typically among the approved guests. Furthermore, oligonucleotides carry a negative electrical charge, as do cell surfaces. Like two magnets, the two biological objects should repel each other. Yet when we repeated this experiment over and over again using more than 50 other human and animal cell types, all but one glowed red, a signal of success.

Today we think we know what the gateway is: a type of doorway molecule called a scavenger receptor that dots the cell surface. These receptors play a major role when a cell engages with its environment; for example, they admit nano-sized biomolecules the cell needs. Some of the structural features at the ends of SNA spines happen to mimic the natural substrates of these scavenger receptors. As noted earlier, the strands on the spheres are densely packed, and like with Velcro, the more hooks, the stronger the bond. With free strands, even if scavenger receptors recognized them as molecules to take in, they have only one hook and float away.

The ability of SNAs to reach the brain and their lack of toxicity generate hope for treating a dangerous cancer, as well as other neurological disorders, and set the stage for the next set of clinical trials.

With the aid of an electron microscope, we could see that once an SNA binds to these receptors, the surrounding cell membrane folds inward to create a pocket, ushering the SNA into the cell.

SPHERES AS MEDICINE

BUT GETTING IN was only half the battle. To work as a drug, the SNA needed to find, bind to and inactivate a particular stretch of mRNA that instructed the cell to make a disease-associated protein.

The first stretch of mRNA in a cell that we targeted did not cause disease but did instruct the cell to make a protein that glowed bright green under a microscope. Our goal was to stop this mRNA. When

we exposed mouse cells to an SNA designed to match that green-causing mRNA and compared them with similar cells that did not get the spheres, the color difference was clear. Sphere-free cells were bright green, showing the mRNA had encoded proteins. But cells exposed to our SNAs were transparent, meaning we had blocked the mRNA before it could pass along instructions to make anything green, as we reported in *Science* in 2006.

Next we pitted SNAs against the major challenge plaguing linear oligonucleotide drugs: destruction by the body's natural defense system. We found that our spheres have a strong electrical charge—again because of the dense packing—that helped them evade immune interference. This high charge inhibits defense molecules called nucleases, proteins that degrade foreign DNA and RNA, from getting close.

REALITY TEST

WE WERE ON TO SOMETHING, at least in the laboratory. Other scientists replicated and independently advanced some of our work, including dermatologist Amy Paller, Arthur Burghes, an expert on SMA, immunotherapy specialist Bin Zhang, cancer biologist Alex Stegh, transplant surgeon Jason Wertheim, and oncologist Priya Kumthekar. But the path from benchtop breakthroughs to healthier patients is long and hard, so nearly 10 years ago researchers from our group founded a company called Exicure to advance SNA-based drugs to the clinic.

We initially explored whether these potent drugs could be delivered to diseased tissues in skin creams and eye drops, which is feasible because SNAs are easily taken up by cells and a big improvement over invasive strategies such as direct injections. Two of our first targets were psoriasis and poorly healing wounds, and there are several promising SNA candidates already in early-stage clinical trials for some of these ailments.

Skin, of course, is relatively easy to get to. The brain is not. Defended by a vigilant immune system and a web of blood vessels—the blood-brain barrier—designed to keep foreign molecules out, the brain makes cancers such as glioblastoma particularly difficult to treat. We thought, however, that SNAs might move across these defenses via the same doorway molecules that ease their path through cell membranes. Once in the brain the spheres could home in on cancer cells by targeting genes and proteins responsible for keeping the cells alive, which malignancies produce in excessive amounts.

To start this project, we created an SNA drug with many short pieces of RNA specifically designed to knock down the production of a protein in glioblastoma cells called Bcl2L12. That protein acts as a biochemical defender that helps to keep the cancer cells functioning. We thought that by intercepting the mRNA that tells the cells to make this protein, the SNAs could make the cancer vulnerable to conventional medicines. Indeed, in our animal studies, reported in 2013 in *Science Translational Medicine,* that is what happened: SNAs injected into the bloodstream of mice reached the brain, crossed the blood-brain barrier and prevented the production of Bcl2L12 protein inside of glioblastoma cells. Last year early clinical results showed that these SNAs also reach glioblastoma cells in human patients. We did not cure people, and we have yet to test whether the SNAs make the cancer cells more vulnerable. Still, the ability of SNAs to reach the brain and their lack of toxicity generate hope for treating this cancer, as well as other neurological disorders, and set the stage for the next set of clinical trials. And tests in other diseases, such as spinal muscular atrophy, show promise in animals.

Another exciting direction for SNAs is their use as immunotherapies against cancer. Cancer cells often have proteins in their membrane that are different from the proteins found in healthy cells. Therefore, a cancer cell protein can act as a red flag, and if our immune system can be trained to go after it the way it goes after a flu virus, our own bodies can do a better job of protecting us from the disease.

To make an SNA cancer vaccine, we exchanged the gold-nanoparticle core for a hollow nanoparticle called a liposome, filled it with one of these red-flag proteins and injected it into animals with the corresponding cancer. Some of our most recent experiments, published in 2019 in the *Proceedings of the National Academy of Sciences USA,* showed that such SNAs elicit an immediate immune response to the tumor, apparently teaching the immune system to go after cells showing that red flag. The effects appear long-lasting, too: the immune system keeps going after cells with that protein after the SNAs have vanished. SNAs are already showing potency and safety in phase I clinical trials in humans, and other spheres targeting a deadly skin cancer are being tested in a separate set of safety trials.

SNAs are, however, not yet approved drugs. There are a number of challenges that they have to overcome first. Because the spheres do get to a wide set of cells, we need to carefully study whether or not they produce any negative "off target" effects even though their design should limit them to only problem DNA and RNA. Larger patient populations must be explored, and we need to improve targeting to increase the amount of drug that gets to the affected organ and cells.

We think the ability of SNAs to access so many different tissues is game-changing and will be central to the emergence and ultimate widespread use of such medicines. SNAs are the product of three core capabilities: the ability to make large quantities of oligonucleotides, an understanding of genetic disease pathways, and the ability to get such oligonucleotides into tissues and cells that matter. The first two are important, but without the third the process is like making software without hardware it needs to run on. SNAs may be that crucial and versatile hardware—a platform able to be reused for many different types of illness, one that begins to move the pharma industry away from the difficult search for entirely new molecules for every new treatment. An SNA simply needs a different set of oligonucleotides to be sent after a new disease. And we are just getting started.

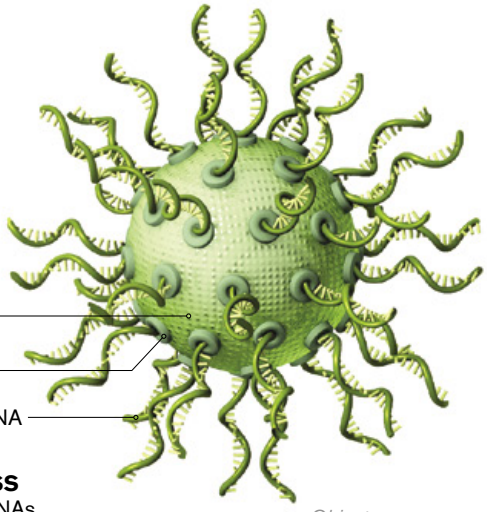
Chad A. Mirkin is director of the International Institute for Nanotechnology and holds professorships in chemistry, chemical and biological engineering, biomedical engineering, materials science and medicine at Northwestern University. He is a founder of Exicure, a company developing spherical nucleic acids for use as drugs.

Christine Laramy received her Ph.D. in chemical and biological engineering from Northwestern and is now an analyst at the law firm Latham and Watkins.

Kacper Skakuj is a graduate student in the chemistry department at Northwestern.

DNA to Treat DNA

Within a cell, aberrant DNA—and the messenger RNA (mRNA) it uses to tell the cell what to do—can cause disease. Scientists can synthesize DNA that specifically binds to such problem molecules. When formed into spherical nucleic acids (SNAs), it penetrates cells and interferes with the trouble-causing molecules.



LINEAR LIMITS
DNA or RNA drugs have been tried with the more typical linear strands of the molecules. These can work but often have difficulty entering a cell or are destroyed by immune defenses. They usually need to be injected directly into a disease site, which limits use.

SPHERICAL SUCCESS
On the surface of the SNAs, the many strands of DNA show abundant attraction points to cell doorways called scavenger receptors, in contrast to the single "hook" of a free strand. Thus, the spheres are more easily taken inside the cell.

Objects not drawn to scale

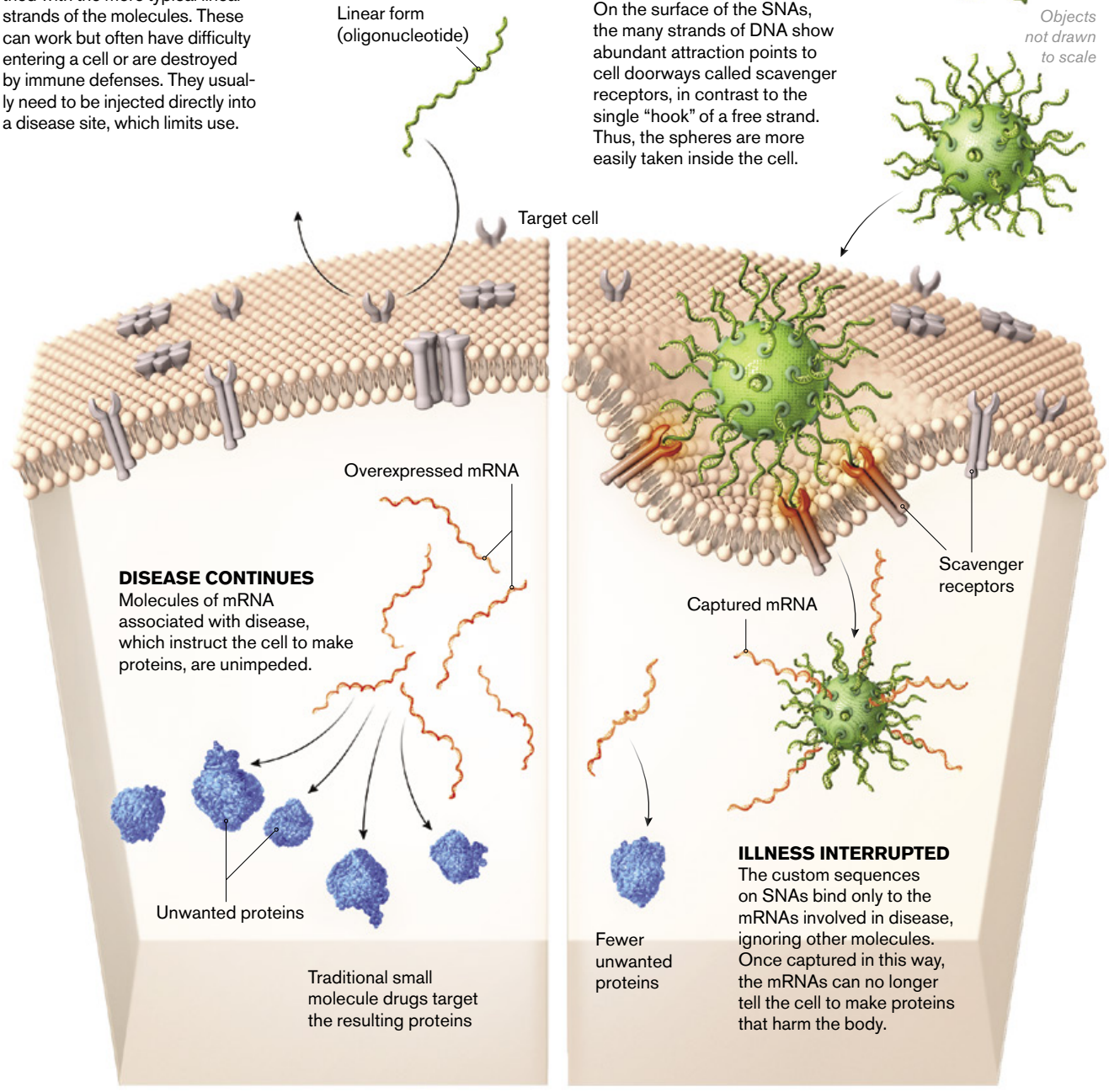
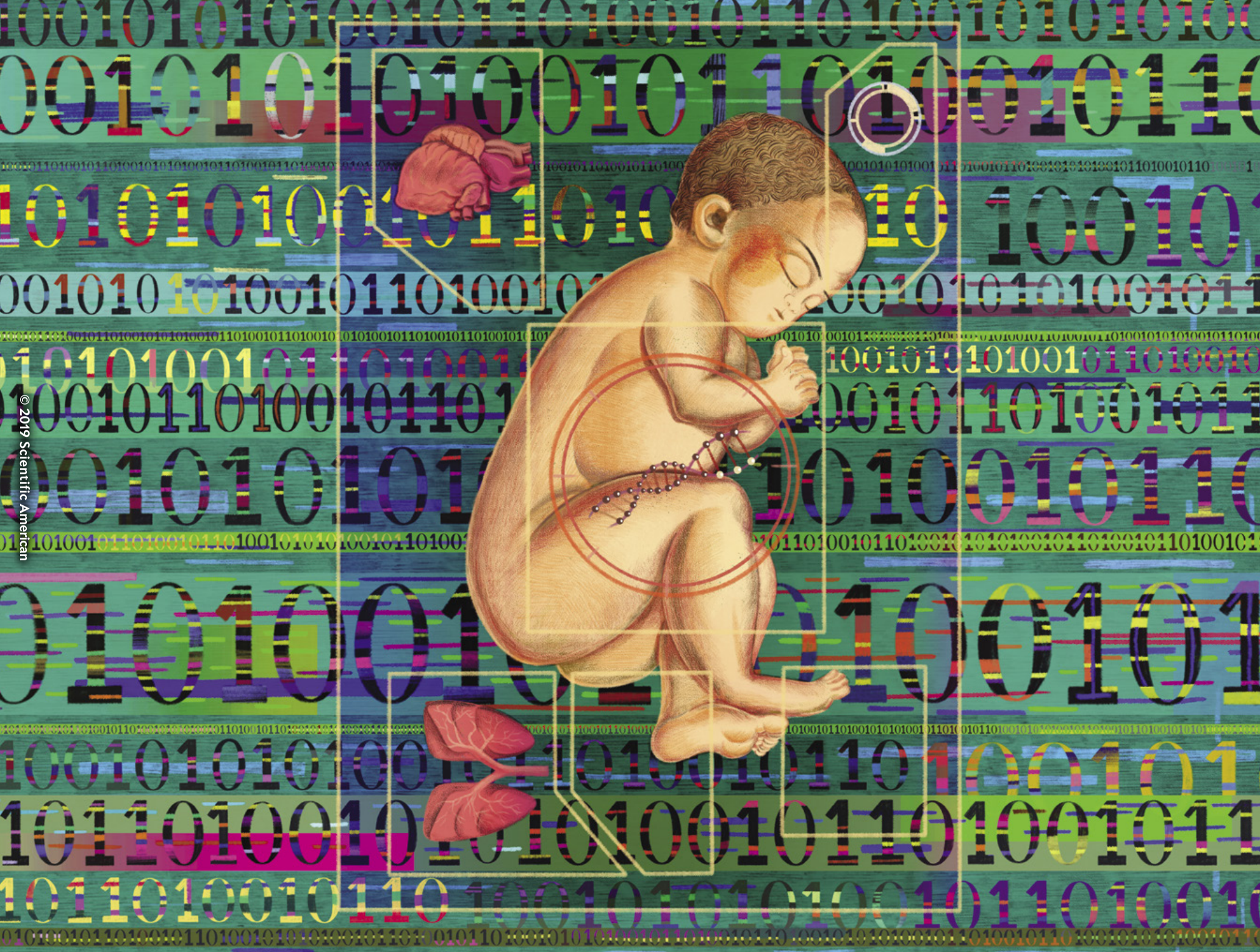


Illustration by Emily Cooper



MEDICAL TESTS

23 and Baby

We now have the ability to screen for thousands of genetic diseases in newborns. That may not always be the healthy thing to do

By Tanya Lewis

MITCHELL GORBY CAME INTO this world around 3 P.M. on August 9, 2019, at Balboa Naval Hospital in San Diego. The baby seemed healthy, and his parents, Tiffany and Rylan, were thrilled. But a few hours later a nurse noticed that Mitchell seemed lethargic and never cried, and monitors indicated that his body was not getting enough oxygen. Mitchell was rushed to the neonatal intensive care unit at nearby Rady Children's Hospital, where tests revealed that oxygen wasn't bonding to the molecule that carries it through the blood, hemoglobin, and his red blood cells were dying off. He wasn't nursing, so the hospital put in a feeding tube. Mitchell's doctor ordered CT and brain scans and tested for infectious diseases—but she could not figure out what was wrong with him. As a last resort, she suggested sequencing Mitchell's genome.

The results from Stephen Kingsmore's laboratory at the Rady Children's Institute for Genomic Medicine came back within about 48 hours. Mitchell had a rare genetic mutation known as hemoglobin Toms River, which prevents oxygen from bonding to the proteins in fetal red blood cells. The mutation—named after the New Jersey hometown of the first patient identified with the problem in 2011—affects only fetal hemoglobin; babies start making healthy adult hemoglobin within a few months. Doctors just had to keep Mitchell alive until that happened. Rady neonatologist Jeanne Carroll says that "having his whole genome allowed us to know the starting point" for treatment. She and Mitchell's team of physicians prescribed a series of blood transfusions, and the baby improved rapidly. In just under a month he was strong enough to go home.

For children like Mitchell who are born with a genetic disease, it used to take years to get a diagnosis, and by then it often was too late. Now, however, advances in the speed of genetic sequencing and steeply falling costs have made it possible to screen for hundreds or even thousands of childhood-onset genetic diseases. Within the past year or so a few dozen hospitals have started offering the ability to rapidly sequence a newborn's genome to help diagnose a life-threatening condition soon after birth. Researchers are studying whether such sequencing should be offered to all newborns as part of standard health screening. And companies such as Sema4 and BabyGenes are now marketing 23andMe-style direct-to-consumer tests to parents simply seeking to know more about the health of their baby. Prenatal and newborn genetic sequencing is expected to grow to an $11.2-billion industry by 2027, up from a $4-billion market in 2018.

Proponents say that genetic testing of newborns can help diagnose a life-threatening childhood-onset disease in urgent cases and could dramatically increase the number of genetic conditions all babies are screened for at birth, enabling earlier diagnosis and treatment. It could also inform parents of conditions they could pass on to future children or of their own risk of adult-onset diseases. Genetic testing could detect hundreds or even thousands of diseases, an order of magnitude more than current heel-stick blood tests—which all babies born in the U.S. undergo at birth—or confirm results from such a test.

But others caution that genetic tests may do more harm than good. They could miss some diseases that heel-stick testing can detect and produce false positives for others, causing anxiety and leading to unnecessary follow-up testing. Sequencing children's DNA also raises issues of consent and the prospect of genetic discrimination.

Regardless of these concerns, newborn genetic testing is already here, and it is likely to become only more common. But is the technology sophisticated enough to be truly useful for most babies? And are families—and society—ready for that information?

IN THE 1960S MICROBIOLOGIST Robert Guthrie developed a test for phenylketonuria (PKU), a genetic disorder that causes the amino acid phenylalanine to build up in the body. PKU is easily treated with a phenylalanine-restricted diet, but without intervention it can cause brain damage and mental disabilities. Within a few years other U.S. states required that Guthrie's test be administered to newborns, and tests for other conditions were soon to follow. By the mid-1980s most states had mandatory screening programs. In 2002 the federal government asked

the American College of Medical Genetics to develop guidelines for newborn screening, which culminated in the Recommended Universal Screening Panel, a set of 35 core conditions and 25 secondary ones that are treatable. Most states now test for a subset of these conditions.

There are roughly 14,000 known genetic diseases in humans, ranging from childhood-onset diseases such as PKU and congenital heart disease to adult-onset conditions such as Huntington's disease and heritable forms of cancer. Some childhood diseases, such as PKU, are treatable if caught early. Heel-stick tests look for only a tiny fraction of these diseases, hence the appeal of genetic testing.

In the early 2010s researchers at the National Institute of Child Health and Human Development and the National Human Genome Research Institute launched a program, called NSIGHT (short for Newborn Sequencing in Genomic Medicine and Public Health), to explore the risks and benefits of DNA screening of newborns. Rady's Kingsmore led one of four projects funded by NSIGHT, which explored the use of rapid, whole-genome sequencing in extremely sick newborns suspected of having a genetic disease.

Standard sequencing can take weeks, but using a rapid sequencing method and software that compared the genome with the patient's disease characteristics, Kingsmore's team could get a genetic diagnosis back in as little as a day or two. For these babies, hours or days can be the difference between life and death or severe disability. The first of two trials led by Kingsmore took place from 2014 to 2016 at Children's Mercy Hospital in Kansas City. The second ran from 2017 to 2019 at Rady Children's. Within the past year the group has started offering newborn sequencing at 23 hospitals around the country, and lawmakers from California have introduced federal legislation to cover the cost of sequencing critically ill babies through Medicaid. As of last November, Kingsmore and his colleagues had sequenced more than 1,100 babies with suspected genetic diseases. About one in three of them received a diagnosis that identified an illness, and one in four had their existing treatment changed as a result.

Mitchell Gorby was one of those sequenced at Rady (but not as part of NSIGHT). Carroll, the Rady neonatologist, says the information "helped us more confidently give him more transfusions and hold off on other testing." It is possible Mitchell may have survived and outgrown his disorder without the test and diagnosis. But in other cases, sequencing has very likely saved lives. Moreover, sequencing probably significantly reduced the diagnostic odyssey such children have to take, Kingsmore says.

EXTREMELY SICK BABIES are not the only ones who could benefit from genetic testing. Another NSIGHT project investigated whether sequencing could also be used in clinical settings to screen newborns with no obvious signs of disease.

For this study, called the BabySeq Project, Robert Green of Brigham and Women's Hospital, Alan Beggs of Harvard Medical School and their colleagues recruited families and randomly assigned half of them to have their babies' genomes sequenced. They developed a list of about 1,500 genes that were highly associated with diseases that begin in childhood or adolescence, then returned information about a subset of those genes to the families. The goal was to do the most

35

genetic diseases can be spotted by blood tests for newborns used in many states. The tests look for parts of proteins or other molecules linked to treatable gene-associated ailments.

193

illnesses can now be identified through DNA itself, using one of the more popular commercial genetic test panels for newborns, Sema4's Natalis. Like state blood tests, Natalis screens for diseases that are treatable.

1,514

genes, each responsible for a different childhood disease, were identified in a research study on newborns called BabySeq. It looked for DNA tied to treatable illnesses, for genes that can affect responses to drugs, and for genes that would not affect the particular baby but could be passed on and cause disease in future generations.

comprehensive testing possible—to see anything and everything that could be discovered about gene-based risks. Last January the group reported sequencing results from 159 newborns—mostly healthy babies but also some ill ones in the neonatal ICU. The scientists found that 9.4 percent of the healthy group were at risk of developing a childhood-onset disease that was not known from their medical or family history, and 88 percent were carriers for recessive diseases.

"Whenever you have the chance to learn about the health of your child, there's an opportunity for anxiety." ***—Natalie, BabySeq parent***

So was the testing worth it for parents? A mother named Natalie, who requested we use only her first name out of concern for her family's privacy, has a son who was enrolled in BabySeq. Natalie, who is a physician and lives in Washington, D.C., admits she felt some nervousness about the testing. "Whenever you have the chance to learn about the health of your child, there's an opportunity for anxiety," she says. But overall, she and her husband were comfortable with the project. "Because they were looking at only genetic defects that affect childhood and only illnesses that had some preventive measures, we felt it could potentially be useful," she says.

Fortunately, the results of tests on her son, Russell, did not turn up any childhood-onset genetic disorders. The exams did indicate that he may be a carrier for a recessive metabolic disorder called Gaucher disease, but the sequencing of this gene is particularly prone to error, so he will need follow-up testing to confirm. For other families, the benefits of sequencing were more clear-cut: one child had a disorder—missed by standard screening—that makes the body unable to recycle a vitamin called biotin; the condition can cause coma and death if left untreated, but it can easily be treated by supplementation.

Although BabySeq was initially focused only on childhood-onset disorders, one baby in the study was found to carry a variant of the *BRCA2* gene, which is associated with a high risk of breast and other cancers, so the researchers asked parents for permission to inform them of the risk of adult-onset disorders if they chose. Natalie and her husband opted not to receive this information but said they would leave it up to Russell if he wanted to be tested when he was older. "We felt it should be our son's decision," Natalie says.

BECAUSE OF ITS COMPLEXITY and cost, BabySeq was never intended to be a feasible addition to standard newborn screening. "We have not tried to advocate for this in clinical practice," Green of Brigham and Women's says. But sequencing tests are no longer confined to clinical practice. Several companies now offer direct-to-consumer DNA tests for newborns. The firm Sema4 sells a test for $379 that it says screens for more than 190 genetic conditions that can occur before the age of 10 and that can be treated with medication, diet or other interventions. The company gives results to parents in a genetic-counseling session about four to six weeks after the test. Sema4's CEO, Eric Schadt, says the test can detect disease-related genetic variants with 99 percent accuracy. Sema4 only reports results for diseases that have a greater than 80 percent penetrance—the proportion of people with a genetic variant who end up developing the disease. It also discloses information about the child's sensitivity to certain drugs, although the U.S. Food and Drug Administration has recently been pressuring companies not to make such information available, because it says that it has not reviewed the tests and that they may not be backed up by clinical evidence.

Another company, BabyGenes, offers a test that scours 100 genes for more than 72 conditions. It is offered in the form of either a cheek swab or dried-blood spot test and retails for $349.

Schadt admits Sema4 doesn't know whether the kind of testing it offers leads to an overall benefit for patients, although he says the company is doing studies to find out. There are reasons to wonder. The accuracy of these tests in detecting disease is still uncertain. In a third NSIGHT project, led by Jennifer Puck, Barbara Koenig and Pui-Yan Kwok of the University of California, San Francisco, researchers sequenced the DNA of dried spots of blood left over from newborn heel-stick tests (California has kept all its blood spots since the early 1980s). Although the sequencing did detect some genetic conditions that the standard newborn screening panel does not test for, it missed some of those that standard screening caught. And it flagged a lot of genetic variants of unknown significance, Puck says: "Newborn screening is very different from having a sick individual in front of you for whom you're trying to arrive at a diagnosis."

When combined with the standard screening, DNA testing did reduce the number of false positives, however. Puck thinks sequencing could be an add-on to standard screening when there's an abnormal result, but she doesn't think it should be used to screen all healthy babies. "We're just not at the point where we can interpret the sequence with sufficient predictive value to say 'yes' or 'no,' this is a disease or not," she says.

Another issue that concerns physicians and medical ethicists is the possibility that genetic testing will cause unnecessary anxiety for parents about diseases that may appear later in life or never show up at all. "When it comes to genetic information about your child, a lot of people aren't in a position to well interpret what the results mean," says Nita Farahany, a professor of law and philosophy at Duke University School of Law, who is an expert in genetics and bioethics. "If they're told their child has a four times greater risk [of some condition], but the population risk is 1 percent, how do they treat their children?" There is already a shortage of genetic counselors in the U.S., so there would not be enough people to help parents understand their child's genetic results.

Then there's the issue of privacy. If the child's genetic information is stored on file, who has access to it? If the information becomes public, it could lead to discrimination by employers or insurance companies. The Genetic Information Nondiscrimination Act (GINA), passed in 2008, prohibits such discrimination. But GINA does not

apply to employers with fewer than 15 employees and does not cover insurance for long-term care, life or disability. It also does not apply to people employed and insured by the military's Tricare system, such as Rylan Gorby. When his son's genome was sequenced, researchers also obtained permission to sequence Rylan's genome, to determine if he was a carrier for the rare hemoglobin condition. Because it manifests itself only in childhood, Gorby decided taking the test was worth the risk of possible discrimination.

Cost is another consideration. Clinical sequencing is still about $500 to $800, and interpretation can be upward of $1,000, according to Brigham and Women's Green. For families who can't afford health insurance, this is out of reach. Some experts have also raised concerns that genetic testing could lead to a lot of follow-up testing with specialists, which could overburden an already resource-strapped health care system. If sequencing turns out to save money in the long run, insurance companies may cover it, but there's no guarantee.

Yet another problem is that the majority of the sequencing to date has been done in babies whose families are well-off and white, raising concerns that this could become the province of only the privileged. And the racial homogeneity could skew the results: diseases more prevalent in Caucasian individuals could be overrepresented in test panels, whereas illnesses more common in racial minorities may be underrepresented. (New medical data projects intend to address this disparity [see "All of Us," on page S14].)

THE U.C.S.F. NSIGHT PROJECT included a working group that investigated some of these ethical and policy issues, which culminated in a 2018 report by the Hastings Center, a bioethics nonprofit in Garrison, N.Y. The report concluded that newborn sequencing has many benefits in helping diagnose sick babies and could expand the number of conditions that meet the stringent newborn screening criteria. But using genome sequencing as a replacement for newborn screening is "at best premature," the authors say, and direct-to-consumer sequencing should not be used for diagnosis or screening purposes.

Barbara Koenig, a professor of medical anthropology and bioethics at U.C.S.F. and one of the report's co-authors, underscores the fact that sequencing, while promising, is not yet mature enough to be routinely used to screen healthy children. "This is not a technology that's ready for prime time for use in healthy infants," Koenig says.

Despite these concerns, the era of newborn sequencing is now upon us, and the practice will likely become more widespread as costs come down and the results become more accurate and useful. In the meantime, the risks and benefits of sequencing must be weighed on an individual basis. Extremely sick newborns are a completely different case from apparently healthy children of worried parents susceptible to marketing from genetic-testing firms.

For Mitchell Gorby, sequencing was certainly worth it. Two months after leaving the hospital, he is doing fine and has doubled his weight. His parents are settling into their new routine, somewhat sleep-deprived, but happy to be home with their healthy baby boy.

Tanya Lewis is an associate editor who covers health and medicine at *Scientific American.*

Gene Therapy Arrives

After false starts, drugs that manipulate the code of life are finally changing lives

By Jim Daley

The idea for gene therapy—a type of DNA-based medicine that inserts a healthy gene into cells to replace a mutated, disease-causing variant—was first published in 1972. After decades of disputed results, treatment failures and some deaths in experimental trials, the first gene therapy drug, for a type of skin cancer, was approved in China in 2003. The rest of the world was not easily convinced of the benefits, however, and it was not until 2017 that the U.S. approved one of these medicines. Since then, the pace of approvals has accelerated quickly. At least nine gene therapies have been approved for certain kinds of cancer, some viral infections and a few inherited disorders. A related drug type interferes with faulty genes by using stretches of DNA or RNA to hinder their workings. After nearly half a century, the concept of genetic medicine has become a reality.

GENE INSERTION

These treatments use a harmless virus to carry a good gene into cells, where the virus inserts it into the existing genome, canceling the effects of harmful mutations in another gene.

GENDICINE: China's regulatory agency approved the world's first commercially available gene therapy in 2003 to treat head and neck squamous cell carcinoma, a form of skin cancer. Gendicine is a virus engineered to carry a gene that has instructions for making a tumor-fighting protein. The virus introduces the gene into tumor cells, causing them to increase the expression of tumor-suppressing genes and immune response factors.The drug is still awaiting FDA approval.

GLYBERA: The first gene therapy to be approved in the European Union treated lipoprotein lipase deficiency (LPLD), a rare inherited disorder that can cause severe pancreatitis. The drug inserted the gene for lipoprotein lipase into muscle cells. But because LPLD occurs in so few patients, the drug was unprofitable. By 2017 its manufacturer declined to renew its marketing authorization; Glybera is no longer on the market.

IMLYGIC: The drug was approved in China, the U.S. and the E.U. to treat melanoma in patients who have recurring skin lesions following initial surgery. Imlygic is a modified genetic therapy inserted directly into tumors with a viral vector, where the gene replicates and produces a protein that stimulates an immune response to kill cancer cells.

KYMRIAH: Developed for patients with B cell lymphoblastic leukemia, a type of cancer that affects white blood cells in children and young adults, Kymriah was approved by the FDA in 2017 and the E.U. in 2018. It works by introducing a new gene into a patient's own T cells that enables them to find and kill cancer cells.

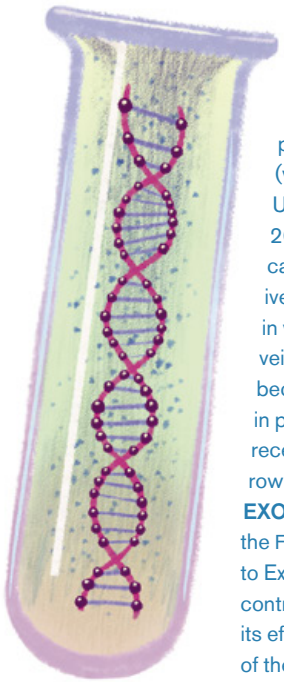
LUXTURNA: The drug was approved by the FDA in 2017 and in the E.U. in 2018 to treat patients with a rare form of inherited blindness called biallelic RPE65 mutation-associated retinal dystrophy. The disease affects between 1,000 and 2,000 patients in the U.S. who have a mutation in both copies of a particular gene, RPE65. Luxturna delivers a normal copy of RPE65 to patients' retinal cells, allowing them to make a protein necessary for converting light to electrical signals and restoring their vision.

STRIMVELIS: About 15 patients are diagnosed in Europe every year with severe immunodeficiency from a rare inherited condition called adenosine deaminase deficiency (ADA-SCID). These patients' bodies cannot make the ADA enzyme, which is vital for healthy white blood cells. Strimvelis, approved in the E.U. in 2016, works by introducing the gene responsible for producing ADA into stem cells taken from the patient's own marrow. The cells are then reintroduced into the patient's bloodstream, where they are transported to the bone marrow and begin producing normal white blood cells that can produce ADA.

YESCARTA: Developed to treat a cancer called large B cell lymphoma, Yescarta was approved by the FDA in 2017 and in the E.U. in 2018. It is in clinical trials in China. Large B cell lymphoma affects white blood cells called lymphocytes. The treatment, part of an approach known as CAR-T cell therapy, uses a virus to insert a gene that codes for proteins called chimeric antigen receptors (CARs) into a patient's T cells. When these cells are reintroduced into the patient's body, the CARs allow them to attach to and kill cancer cells in the bloodstream.

ZOLGENSMA: In May 2019 the FDA approved Zolgensma for children younger than two years with spinal muscular atrophy, a neuromuscular disorder that affects about one in 10,000 people worldwide. It is one of the leading genetic causes of infant mortality. Zolgensma delivers a healthy copy of the human SMN gene to a patient's motor neurons in a single treatment.

ZYNTEGLO: Granted approval in the E.U. in May 2019, Zynteglo treats a blood disorder called beta thalassemia that reduces a patient's ability to produce hemoglobin, the protein in red blood cells that contains iron, leading to life-threatening anemia. The therapy has been approved for individuals12 years and older who require regular blood transfusions. It employs a virus to introduce healthy copies of the gene for making hemoglobin into stem cells taken from the patient.The cells are then reintroduced into the bloodstream and transported to the bone marrow, where they begin producing healthy red blood cells that can manufacture hemoglobin.



GENE INTERFERENCE

This approach uses a synthetic strand of RNA or DNA (called an oligonucleotide) that, when introduced into a patient's cell, can attach to a specific gene or its messenger molecules, effectively inactivating them. Some treatments use an antisense method, named for one DNA strand, and others rely on small interfering RNA strands, which stop instruction molecules that go from the gene to the cell's protein factories.

DEFITELIO: This drug contains a mixture of single-strand oligonucleotides obtained from the intestinal mucosa of pigs. It was approved (with limitations) in the U.S. and the E.U. in 2017 to treat severe cases of veno-occlusive disease, a disorder in which the small veins of the liver become obstructed, in patients who have received a bone marrow transplant.

EXONDYS 51: In 2016 the FDA granted approval to Exondys 51 amid some controversy regarding its efficacy; two members of the FDA review panel resigned in protest of the decision. The therapy is designed to treat a form of Duchenne muscular dystrophy caused by mutations in the RNA that codes for the protein that helps to connect muscle fibers' cytoskeletons to a surrounding matrix. Exondys 51 is effective in treating about 13 percent of the Duchenne population.

KYNAMRO: Approved by the FDA in in 2013, Kynamro is designed to inhibit—or effectively shut down production of—a protein that helps to produce low-density lipoprotein (LDL). Injected subcutaneously, this therapy is used to lower LDL levels in patients who have dangerously high cholesterol.

MACUGEN: Age-related macular degeneration is the leading cause of vision loss in people age 60 and older. It is caused by deterioration of the center of the retina due to leaking blood vessels. Approved in the U.S., Macugen inhibits these blood vessels from growing under the retina, thus treating the disorder.

SPINRAZA: With its FDA approval in 2016, Spinraza became the first gene-based therapy for spinal muscular atrophy. The inherited disorder is caused by low levels of SMN, a key protein for the maintenance of motor neurons. Spinraza binds to RNA from a "backup" gene called SMN2, converting that RNA into instructions for making fully functioning SMN proteins.

Jim Daley is a freelance journalist based in Chicago.

BIG DATA

All of Us

DNA-based medicine needs more diversity to avoid harmful bias. One big research project is fixing that

By Stephanie Devaney

WHEN THE RACE TO sequence the first human genome was rushing toward the finish line about 20 years ago, I remember feeling mesmerized by what was about to happen. It was the dawn of a new century, and it seemed we were on the cusp of unlocking the meaning behind the blueprint of life, DNA. Once we could line up all 3.1 billion base pairs of the molecule in our genome, I thought—I was an undergraduate student at the time, dazzled by science—we would understand everything there is to know about human health and disease.

What I didn't know was that those first decades of genetic medicine would leave a lot of people behind. So I was taken aback several years later, in 2009, just after I got my doctorate in molecular genetics, when researchers at Duke University reported that 96 percent of the genomic data we had gathered came from people of European ancestry. This was not the result of small numbers: they calculated the percentage using the more than 1.7 million individual genome samples analyzed at the time, but the samples were lacking diversity. Over the next few years things did not get much better, and as recently as four years ago genomic databases were still way out of balance, with more representation of Europeans and less of everyone else.

This inequity, if it is not fixed, will turn into tremendous health inequality. Today more and more people are getting answers about the underlying causes of their diseases because of medicine's ability to mine their genomes. There are hundreds of drugs that contain genetic information in their labeling because gene variants affect how bodies process these drugs, and knowing the variants that patients have helps doctors set the most beneficial dose for their patients. Moreover, today improved knowledge about the genomic drivers of different cancers has paid dividends in how physicians diagnose and treat many tumors. Yet people who are not white and not male have different sets of genes that do not always fit into these treatment regimens.

For example, African-Americans and Latinos have the highest rate of asthma in the U.S., but studies show that common drugs used in inhalers do not help them as well as they help whites. Asians who take the antiseizure drug carbamazepine have a higher risk of a severe, sometimes fatal, reaction. Nobody developing these drugs, or prescribing them when they first came into use, anticipated these problems. If DNA is one important factor in our quest for more effective medical treatment, we need to address the lack of diversity in genetic data.

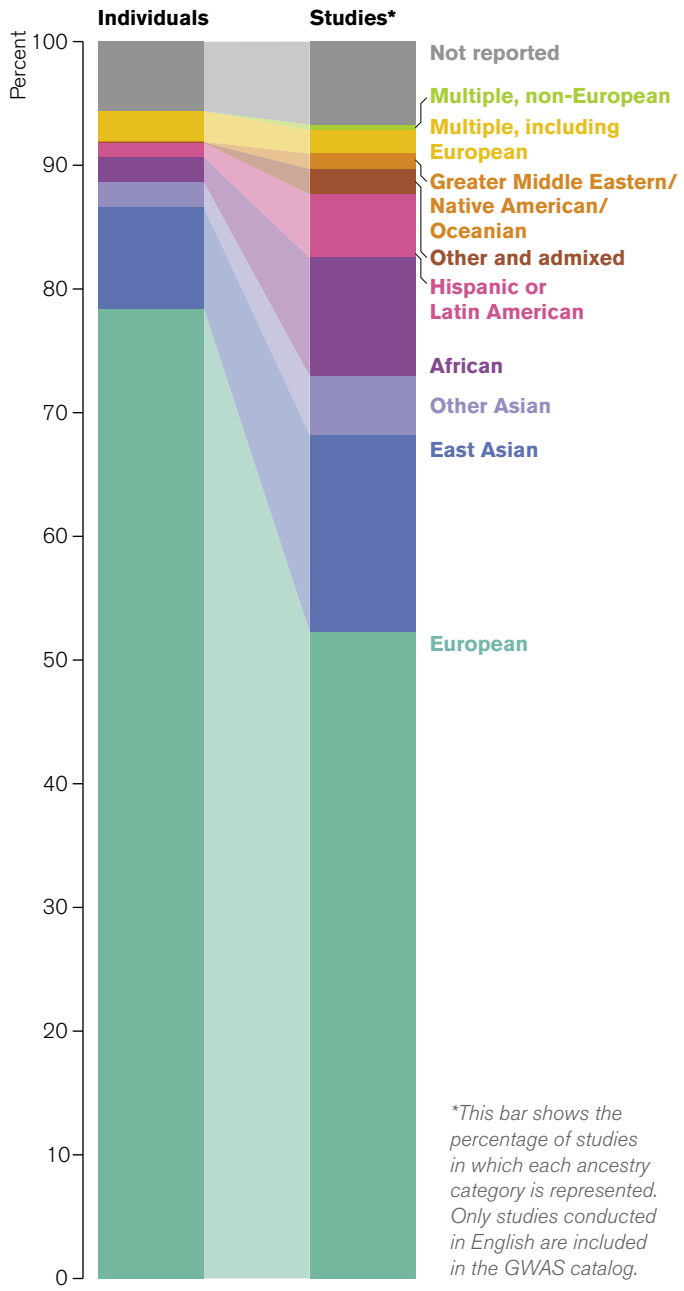
That is where the *All of Us* Research Program, where I work, hopes to help. Set up by the National Institutes of Health and launched in 2018, we are asking a million or more people from all backgrounds to join us as partners in research, not as human subjects, and share all kinds of health information over the course of their lives. Already we have more than 250,000 participants. More than 51 percent belong to racial and ethnic minorities, more than 10 percent are sexual and gender minorities, and overall more than 80 percent represent a group that has been historically underrepresented in research data sets.

People can join All of Us by going to our program Web site (www.joinallofus.org) and clicking "Join Now." After agreeing to participate, respondents can offer us their medical records, answer a variety of surveys about their health

Biased Gene Studies

To link genes to disease risk and other traits, hundreds of genome-wide association studies (GWAS) have looked at the DNA of thousands of different people as of 2018. But in terms of racial background, these people are not so different. Taking all the projects together, 78 percent of the people in them are white Europeans, whereas just 2 percent are African and 1 percent are Hispanic or Latin American. The studies themselves also predominantly focused on Europeans and rarely on other populations. So gene variants that appear in non-European people and may be linked to illness rarely show up in this research. The scarcity makes it hard to analyze and understand the significance of the variants.

Racial Backgrounds in Published Gene-Association Studies



and lifestyle, and participate in other activities such as syncing their fitness tracker data to our program. We also have hundreds of enrollment sites at local hospitals and health centers across the country where participants can provide samples of blood and urine to help researchers study their DNA. Our hope is for people to stick with us for 10 years or more because, as the program grows, we will regularly add new ways for them to learn about themselves and contribute to research.

THE MOMENT IS RIGHT

A LOT OF THIS PARTICIPANT-RESEARCHER collaboration is linked to advances in technology. Sequencing that first human genome had a $1-billion price tag. Today such a sequence costs less than $1,000 and can take less than 24 hours to complete. It is also easier to integrate this information with other crucial medical data. Health care organizations have been turning their patients' paper-based medical records into electronic versions. As of 2017, 96 percent of all U.S. hospitals and 80 percent of all office-based doctors are using a certified electronic health record system. New apps on smartphones and other digital health technologies such as smart watches collect data from nearly anywhere and directly from a person. These trends all make it easier to store, share and mine large data sets for answers to questions about disease causes and effects. Such trends also raise big and disturbing issues about privacy, making it important for projects such as ours to have both strong security and full transparency to all our participants.

And it is crucial to treat these people as partners. The actions of past medical researchers have earned much distrust in minority communities, after causing harm in the Tuskegee Syphilis Study, where researchers misled African-American men with syphilis and never gave them adequate treatment, and with the widespread use of HeLa cells, which were taken from a patient named Henrietta Lacks without her knowledge or permission. People wanted to see research go forward but *with* them rather than about them. To overcome this kind of distrust, All of Us is using a new model for research, one that invites input from participants as well as researchers with science degrees. Participants serve on the program's advisory and governing bodies, working groups, and task forces. We have also partnered with local health care organizations, hospitals, and community groups to advise us and help find people to participate. Community engagement is not familiar ground for large medical research projects, and we are still learning the best ways to do it.

Some studies have provided us with blueprints for developing long-term relationships like the ones we hope to have, studies that have changed medicine for the better. The Framingham Heart Study, for example, started in 1948 with 5,209 men and women, largely white, from one town in Massachusetts. With a 99 percent retention rate, the study continues to this day. As participants share data year after

SOURCE: "THE MISSING DIVERSITY IN HUMAN GENETIC STUDIES," BY GIORGIO SIRUGO ET AL., IN *CELL*, VOL. 177; MARCH 21, 2019

year, researchers can see how their heart health changes over time. The risk factors for heart disease identified by the Framingham study—such as high blood pressure, high cholesterol, smoking and obesity—are so ingrained in our collective consciousness and our approach to health care that they feel like common sense.

GOING FURTHER

THIS KIND OF MEDICAL DISCOVERY is what we envision for All of Us, but we want to take it further, with participants who are not all white and who represent diversity in many dimensions, not just traditional race labels that, in reality, encompass a lot of different backgrounds. If we're going to get at the root causes of health and disease, this means understanding the differences and similarities among us all. For example, sickle cell disease occurs when someone inherits two mutated genes for the oxygen-carrying protein hemoglobin. It affects 100,000 African-Americans and more than 20 million people around the world. In contrast, sickle cell trait—meaning just one of these genes is mutated—actually gives people an advantage in surviving malaria, which makes evolutionary sense if your ancestors came from areas such as Africa where malaria is prevalent. New studies, however, have found that sickle cell trait might not be as benign as doctors used to believe, because it may increase the risk for kidney disease. Some African-Americans are more susceptible to this risk and some less. There's clearly more to learn about why this might be the case and about how different DNA variants might interact to affect the health of people with sickle cell trait. The DNA information from more than a million All of Us participants could help researchers learn much more about complex traits like this.

We do have to start with some of the broad-brush categories to recruit enough people to start recognizing the more fine-grained groups among them. Currently we are exceeding our goal of overrepresenting groups that have been historically underrepresented in research. For instance, African-Americans make up about 13 percent of the U.S. population but just 3 percent of the samples previously used in genome studies. In All of Us, 21.5 percent of participants so far are African-American. Similarly, Hispanics constitute about 18 percent of the U.S. population but in 2016 made up less than 1 percent of the data in our genomic databases. Today 17.6 percent of All of Us participants are Hispanic.

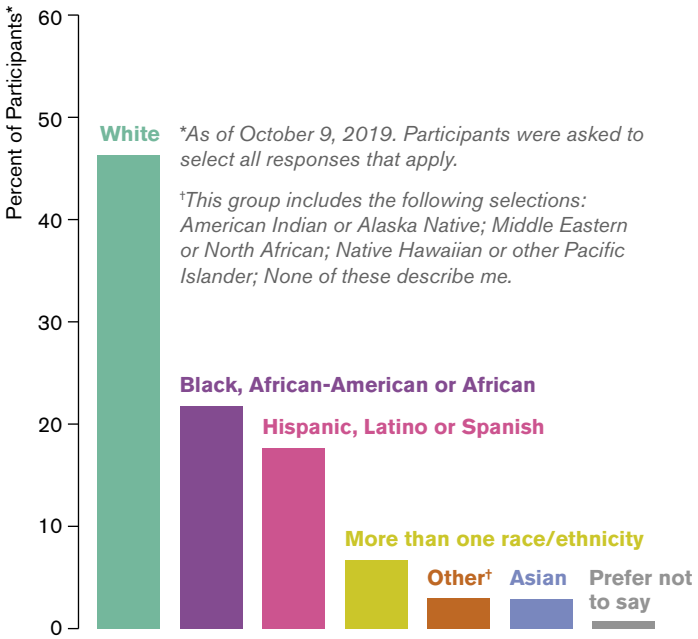
That diversity will help us discover more about how DNA affects health across different communities, but the molecule will not be our sole focus. Many factors beyond our genes are at play when it comes to disease. We know that where you were born, what you eat, the stress you feel, and other clinical and biological factors affect health, but we still don't understand by how much. For example, when we think about some of the most common chronic diseases that afflict our population—high blood pressure is one example—many of them disproportionately affect the most socially and economically disadvantaged people in our country. And from what we can tell at the moment, the determinants are not simply their race or ethnicity. Risks also include family structure, socioeconomic status, stressors such as trauma, sex and gender inequality, availability of nutrient-rich foods, access to health care, and many other factors that we can capture in the All of Us data set.

Within the next several years, we should be able to compare this rich set of information with participants' DNA. When we do so, scientists such as myself, the All of Us participants and all of you will start to get a clearer picture of the roles that biology and environment play in disease development, and—most important of all—what we can do about it.

Molecular geneticist **Stephanie Devaney** is deputy director of the All of Us research program at the National Institutes of Health. She was the staff lead for the White House Precision Medicine initiative.

A Better Balance

A new precision medicine project, All of Us, has much larger populations of groups that have been historically underrepresented in genetics research. The project, sponsored by the U.S. National Institutes of Health, began recruiting participants in 2018. More than 250,000 people enrolled by October 2019, and just over 20 percent are black, African-American or African. About 18 percent are Latino, Hispanic or Spanish. Nearly 3 percent are Asian, and 6.7 percent are of mixed races. Slightly less than half of the people are white. The project's goal is to get DNA and other health information from more than one million people.



SOURCE: NATIONAL INSTITUTES OF HEALTH, ALL OF US RESEARCH HUB, OCTOBER 9, 2019

Graphics by Amanda Montañez

SPECIAL REPORT FROM
SCIENTIFIC AMERICAN
nature

ScientificAmerican.com/InnovationsIn/dna-drug-revolution

Close to Birds:
An Intimate Look at Our Feathered Friends

by Roine Magnusson, Mats Ottosson and Åsa Ottosson. Roost Books, 2019 ($39.95)

LONG-EARED OWL poses for a portrait.

In 2019 a disturbing report ran in *Science* that global bird populations have plummeted by 29 percent—some three billion birds lost—since 1970. That birds provide vital services to hold most ecosystems together is undoubtable; their decline is either the canary of coming ecosystem disaster or evidence that it might be too late to save many of Earth's diverse biomes. Photographer Magnusson and nature writers Ottosson and Ottosson teamed up to create this striking collection of bird portraits paired with intimate, lesser-known details about the subjects. The arresting red ring around a common gull's eye and the tiny dinosaurlike talon of the thrush nightingale remind us of all that we stand to lose if more birds disappear.

Love Drugs: The Chemical Future of Relationships

by Brian D. Earp and Julian Savulescu. Stanford University Press, 2020 ($25)

What if you could take a pill to fix a broken relationship—or get over one? MDMA (aka Ecstasy) was used in psychotherapy in the early 1980s, but since the drug was made illegal in 1985, the practice has gone underground. And early studies of the "bonding" hormone oxytocin's effects on interpersonal relationships are promising, but the findings are too preliminary to recommend taking it for therapeutic use. Ethicists Earp and Savulescu make the case that existing pharmaceuticals already unintentionally influence relationships (some antidepressants can affect sexual desire and function, for example), so why not explore the use of "love drugs" on relationships explicitly? Such drugs should never be given to oppress or "convert" sexual minorities, the authors clarify—but when taken consensually to have a desired effect on a relationship, they could be just what the doctor ordered. *—Tanya Lewis*

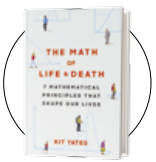
The Contact Paradox: Challenging Our Assumptions in the Search for Extraterrestrial Intelligence

by Keith Cooper. Bloomsbury, 2020 ($28)

For decades we have turned an eye upward to look for alien worlds, so far without success. Not to worry, says space journalist Cooper; we are just beginning the search for extraterrestrial intelligence (SETI). But where should we look for signs of aliens? And what happens if we actually find them? Cooper investigates different ways that a technological civilization might signal us, from radio waves to neutrino beams, and considers life-forms that could inhabit icy moons. He also ponders the gruesome history of conquistadors on Earth as an example of the kind of culture clash that could follow first contact. Although he criticizes many traditional notions of SETI scientists—such as assuming alien intelligence will look like our own—Cooper leaves us with an optimistic outlook: even if we don't find aliens, we will learn a lot about ourselves just by looking. *—Kelso Harper*

The Math of Life and Death: 7 Mathematical Principles That Shape Our Lives

by Kit Yates. Scribner, 2020 ($26)



Many people assume that the closest math gets to their daily lives is when it's time to calculate the tip at a restaurant or the discount being offered at a store. But mathematician Yates shows that everyone—even the most math-phobic among us—interacts with math much more often and deeply than we realize. He untangles the interesting (and chilling) mathematics involved in the courtroom, for instance, explaining how an erroneous statistic presented during a trial wrongly put a woman behind bars for murder. He also dives into how exponential growth dooms pyramid schemes, how gynecologists mistakenly interpret the rate of false positives in breast cancer screenings, and how binary code errors cost soldiers' lives during the First Gulf War. Math "leads us," Yates writes, "on the myriad paths of our lives." *—Clara Moskowitz*

Don't Fact-Check Judgment Calls

They're not meant to be taken as gospel truths

By Naomi Oreskes

With the election cycle in full swing, it's open season for journalists hell-bent on catching candidates out in lies and misrepresentations. In a world that has become relentlessly "truthy," to borrow Stephen Colbert's apt neologism, we need journalists, scientists and other experts to stand up for facts and keep the public debate honest. But when it comes to climate change, there is a tricky gray zone between facts and expert judgments.

One such zone has been on display since the release of a 2018 Intergovernmental Panel on Climate Change (IPCC) special report entitled *Global Warming of 1.5 °C,* whose authors concluded that we had 12 years left (now 11) to achieve radical reductions in greenhouse gas emissions to limit global warming. This alert has been widely cited, and politicians who have invoked it have been repeatedly fact-checked. But some of this checking makes the dialogue feel more like ice hockey—where "checking" is intended to disrupt play and establish dominance—than like an effort to help the public understand a complex but crucial issue.

In last July's second Democratic debate, for example, former U.S. Representative Beto O'Rourke of Texas said, "I listen to scientists on this, and they are very clear. We don't have more than 10 years to get this right." And Pete Buttigieg, mayor of South Bend, Ind., said, "Science tells us we have 12 years before we reach the horizon of catastrophe when it comes to our climate." The *New York Times* declared that both statements were "misleading," insisting that any claim "that there are 12 or just 10 years until the point of no return goes beyond what the [IPCC] report itself says." The *Washington Post* called 12 years "a figure that is frequently cited but often misused," implying that Mayor Buttigieg was among those referencing it in error. And in September, after the CNN town hall on climate change, the Associated Press similarly fact-checked a statement by Senator Elizabeth Warren of Massachusetts that "we've got, what, 11 years, maybe, to reach a point where we've cut our emissions in half," claiming that it was "out of step with science."

But the IPCC wasn't stating a fact in the first place. It was presenting a collective expert judgment—in this case, the consensus of 86 authors and review editors from 39 countries. Given this accounting, there will inevitably be a range of legitimate interpretations, and any translation will necessarily be a simplification subject to differences of individual opinion. With the finding understood in this way, the dynamic of fact-checking is misplaced. It's as if, after 9/11, the media were fact-checking how politicians characterized the threat to America.

Moreover, consider the headlines that news outlets themselves offered when the report came out. From the *New York Times:* "Major climate report describes a strong risk of crisis as early as 2040." The *Washington Post:* "The world has just over a decade to get climate change under control, [United Nations] scientists say." The AP: "UN report on global warming carries life-or-death warning." And just for fun, here's what the *New York Post* had to say: "Terrifying climate change warning: 12 years until we're doomed."

Call me unfussy, but these headlines don't strike me as substantively different from what the politicians said. They use the same language of crisis, of time limits, and of life and death that the fact-checkers rejected. And contrary to the AP report, scientists did, in fact, agree on a time frame.

Politicians do sometimes say things that are egregiously at odds with expert consensus; the overt denial of climate change is the obvious case in point. We should call out conspicuously false claims, such as an assertion that the world will end tomorrow (it might, but not from anthropogenic climate change) or that we can leave it to the marketplace to innovate a way out of the problem (theoretically possible, but practically impossible without the right government policies to drive and guide that innovation).

But let's not fact-check things that aren't facts. There is a world of interpretation—and therefore a range of justifiable readings—built into any expert judgment. We should discuss that reasonable range and flag claims that are obviously unreasonable. But we should not confuse judgments with facts. Doing so turns what should be a serious discussion into a score-driven hockey brawl. SA

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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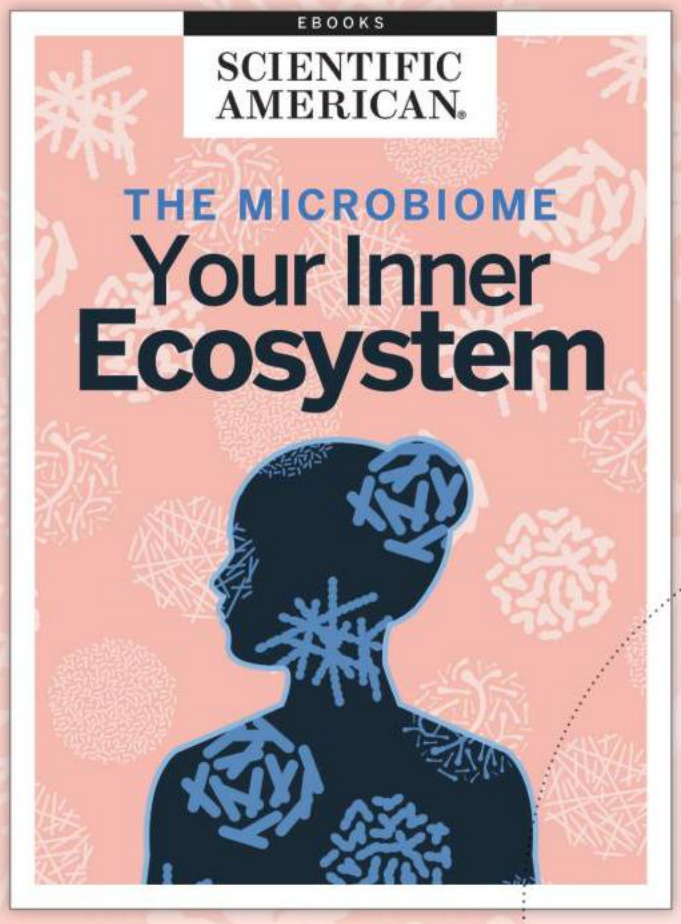
Illustration by Marco Melgrati



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

Uber Rat

On the road with rodents

By Steve Mirsky

One way to kill time in New York City while waiting for a subway train is to look for rats. You can often find one or two down at track level, although I've also seen the occasional *Rattus norvegicus* up on the platform just standing around with its weary fellow mammalians. One enterprising subway rat went viral in 2015, when it was videoed dragging an entire slice of pizza down a flight of stairs. But when you leave the big city, the major mode of transportation becomes the car. And that's why rats in Richmond, Va., have learned to drive.

Okay, that's not completely accurate—Richmond's mass-transit system is not what forced rodents to get behind the wheel. In fact, their little custom-made cars don't even have steering wheels. But the rats are definitely driving. For science.

Researchers at the University of Richmond built what they called an ROV, which you might assume stands for "Really? Oh, Very" but which is actually an acronym for Rodent-Operated Vehicle. The ROV is fashioned from a one-gallon clear plastic food container, which provides excellent visibility both for and of the driver, and a commercially available robot car kit.

Of course, you can't simply tell a rat to take the ROV out for a spin. So the scientists connected a battery to an aluminum plate on the inside bottom of the cab. They also attached copper wire to the other terminal of the battery and bent that wire to form a series of thin bars placed at the inside front of the cab. When a rat with its rear feet on the plate placed its front feet on the wires, it completed an electrical circuit that powered the car's motor. And Mario And*rat*ti was off.

According to the researchers' article last October online in *Behavioural Brain Research,* "Driving training began when the animals were approximately 5 months of age." That might seem young, but male rats reach sexual maturity at six weeks, so their wait for a car must seem endless. By moving their front paws to different positions on the copper wire, the rats quickly learned to steer their really-mini vans. Although rats clearly could acquire the ability to drive, not one could pass the written test. Seems that writing a parking ticket may be harder than parking.

The motivation for the furry chauffeurs was to get a reward much loved by rats and graduate students alike: Froot Loops. The rats got a quarter of a torus of the sugary treat; their driving instructors no doubt threw back a few handfuls when rotating and balancing the tires. Video of the vehicular vermin can be found online, and, frankly, I've seen worse driving in Florida shopping center parking lots.

So why go to all this trouble when rats are happy to run mazes for their cereal? The answer is in the title of the study: "Enriched Environment Exposure Accelerates Rodent Driving Skills." (The magazine *New Scientist* had the more pedestrian headline, "Scientists Have Trained Rats to Drive Tiny Cars to Collect Food." Actually most human driving is also about food collection. Or money-earning. For food collection.)

Some of the rats were reared in "enriched environments" that provided their little brains with stimulation. Others were reared in "standard laboratory housing." (Still others were rear-ended.) And the rats that grew up in the well-to-do neighborhoods were quicker to learn to drive and maintained the skill longer than did their downbeat comrades.

As the researchers note in their write-up: "The complex driving task was viewed as a model for human-machine interactions such as driving a car or operating other technological devices." So Dale Earnhrat could serve as a model for research about "learning and skill acquisition."

Another finding: based on analyses of the ratio of the levels of two hormones, it appears that the rats found driving to be relaxing. Of course, they were in a controlled setting, not trying to go west on 42nd Street at 5 P.M. on a weekday. In that situation, your savvy rat knows that the shuttle train from Grand Central to Times Square takes much less of a toll. Even without traffic, a train-riding rat will probably beat a car-driving rat by a whisker. SA

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Illustration by Matt Collins

JANUARY

1970 Rules of Chemical Warfare

"President Nixon's announcement concerning chemical and biological weapons renounced germ warfare and the first use of lethal and 'incapacitating' chemical weapons. The statement did not, however, change U.S. policy on two major weapons currently in routine use in Vietnam: tear gas and chemical defoliants. With regard to biological warfare the renunciation was unilateral and unequivocal. The President indicated that biological-warfare research would be confined to defensive measures and that the U.S. stockpile of bacteriological weapons would be destroyed."

1970

1920

1870

1920 Stamp Licking

"A discussion of 'The Postage Stamp as a Possible Source of Infection' appears in the *Medical Times* for October, 1919. Laboratory tests showed that no stamp was free from germs. Among the germs were colon bacilli, staphylococci, streptococci, pneumococci and diphtheroid bacilli. The amount of danger presented by these organisms cannot be stated, as, unfortunately, no tests were made to determine the virulence of the germs. In commenting on these results, *American Medicine,* while not encouraging the common practice of moistening stamps with the tongue, points out that if stamps were a grave source of infection a very large percentage of the population would undoubtedly be suffering from infections due to this cause."

1

1870: A patented (and mostly superfluous) reading stand.

1870 Reading Technology

"The improvement we herewith illustrate will be found a luxury which few, either sick or well, having once enjoyed, will be willing to resign. These devices enable reading either while a person is sitting or reclining, so that the printed matter is placed directly in front of the eyes, and in such a position that no muscular effort is required to sustain the book or to keep the body in a position of restraint. This invention was patented through the Scientific American Patent Agency, by Edward Conley, of Cincinnati, Ohio."

Petroleum Furnaces

"Henri St.-Claire Deville was instructed by the French Academy to conduct a series of experiments upon this important subject, and he has succeeded in inventing a furnace that satisfactorily accomplishes the object. This may safely be regarded as one of the most important inventions of the year."

EPIC TALES

2

Digital entertainment: "personal theater" from 2000.

CELEBRATING 175 YEARS

Technology of Entertainment

By the late 19th century reading for fun had become popular because of advances in the art of the novel, cheaper paper and mass printing, and more leisure time. The patented reading stand we illustrated above probably had zero effect. Another technology leap was the phonograph (you know, like a record player). Thomas Edison wrote in our issue of May 18, 1878, that he thought it would be good for dictation in the office, but allowed it could be "liberally devoted to music." In 1906 radio broadcasting for entertainment began; by July 1925 we advocated bringing your radio while camping "far from the madding crowd." The April 1939 issue proclaimed "Here Comes Television!"—with "entertainment" as top priority. Inventions often need other practical inputs to transform society: our modern entertainment emerged after we harnessed the power of the computer, the Internet and the smartphone, then commercialized a way to provide (and pay for!) content viewable or playable on these gizmos. By November 2000 we knew "digitizing everything audio and video will disrupt the entertainment industry's social order."

SCIENTIFIC AMERICAN, VOL. XXII, NO. 2; JANUARY 8, 1870 (1); *SCIENTIFIC AMERICAN*, VOL. 283, NO. 5; NOVEMBER 2000; TERRY RENNA *AP Photo (2)*

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Ken Albala teaches food history and the history of early modern Europe, is the creator of the Great Courses' *Food: A Cultural Culinary History* and has written or edited 25 books, including cookbooks, popular histories, encyclopedia and reference works, winning awards for *Beans: A History* and *Three World Cuisines: Italian, Mexican, Chinese.*

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David Christian, Ph.D.

Distinguished Professor of Modern History
Macquarie University

David Christian began teaching courses in Big History in the 1980s and has been at the forefront of many educational initiatives since, including co-founding The Big History Project with Bill Gates, directing Macquarie University's Big History Institute and co-creating their Big History School for K-12 online courses.

Big History: A "Short" History of the Universe and Everything

- The Cosmos
- A Living Planet
- Humans
- The Future: Where Is It All Going?

Robert Hazen, Ph.D.

Clarence Robinson Professor of Earth Sciences
George Mason University

Robert Hazen is also Senior Staff Scientist at the Carnegie Institution's Geophysical Laboratory and Executive Director of the Deep Carbon Observatory, where his recent research focuses on the role of minerals in the origin of life and the interactions between biomolecules and mineral surfaces.

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Millie Hughes-Fulford, Ph.D.
Professor of Medicine
University of California Medical Center

Millie Hughes-Fulford was selected as a Scientist-Astronaut on the first Spacelab mission dedicated to biomedical studies in 1991 and has since continued her research into the mechanisms of cell growth and activation in spaceflight, winning an award from NASA in 2012 for discovering why the immune system is weakened in zero gravity.

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- Living and Working in Space
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- The Future

Jill Tarter, Ph.D.
Emeritus Chair for SETI Research, SETI Institute

Jill Tarter achieved recognition for her work searching for evidence of extraterrestrial life, which entered public consciousness through the movie *Contact*, and has won several awards including the Lifetime Achievement Award from Women in Aerospace, two NASA Public Service Medals, *Time* Magazine's Top 100 Most Influential People in 2004 and many more for her dedication to communicating science to the public.

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Text by Jen Christiansen | Graphic by Nicholas Rougeux

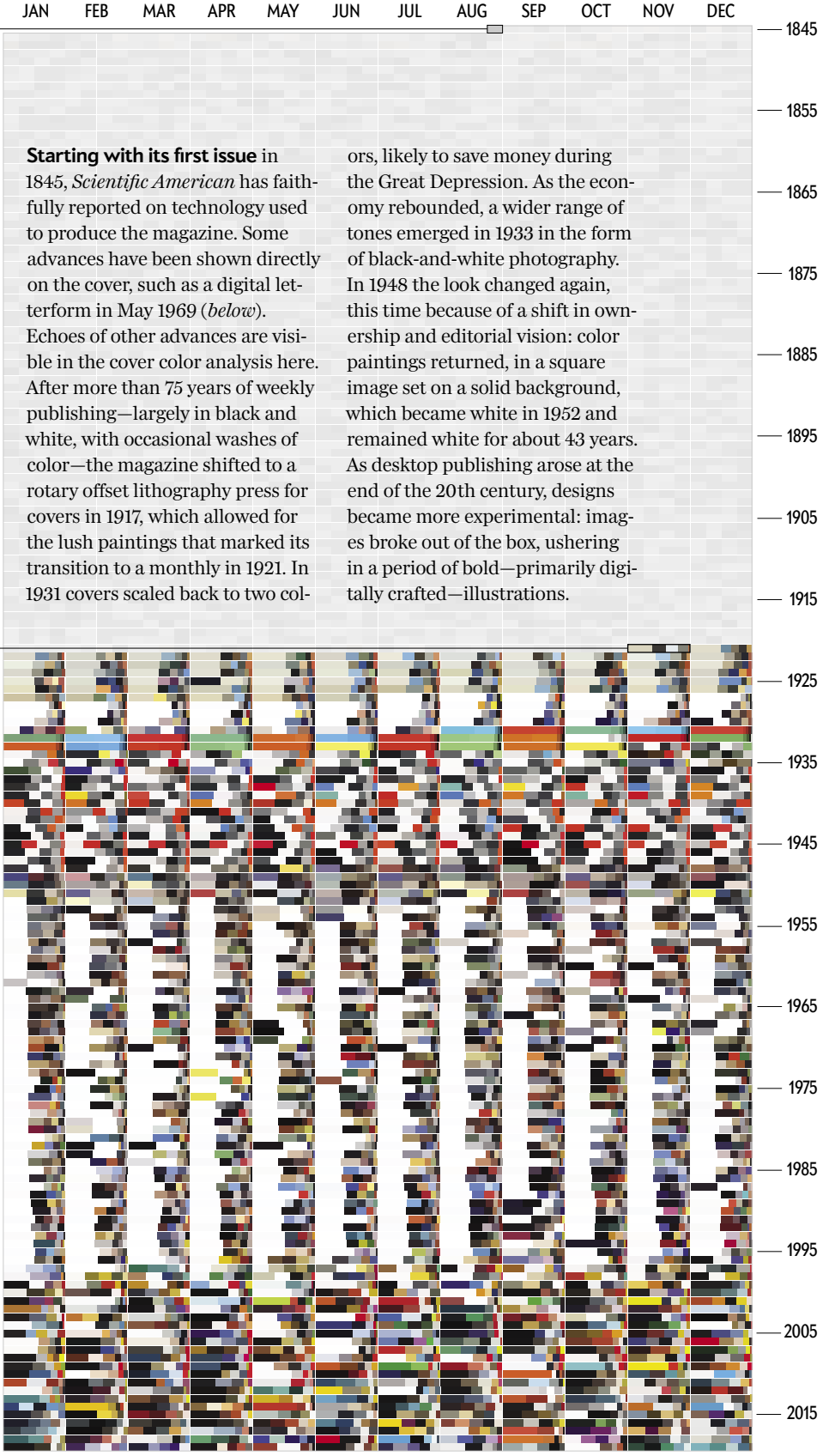
Scientific American began as a four-page black-and-white broadsheet paper, published weekly.

Aug. 28, 1845

Covering Color

Hues on *Scientific American*'s covers provide a 175-year record of publishing trends

Starting with its first issue in 1845, *Scientific American* has faithfully reported on technology used to produce the magazine. Some advances have been shown directly on the cover, such as a digital letterform in May 1969 (*below*). Echoes of other advances are visible in the cover color analysis here. After more than 75 years of weekly publishing—largely in black and white, with occasional washes of color—the magazine shifted to a rotary offset lithography press for covers in 1917, which allowed for the lush paintings that marked its transition to a monthly in 1921. In 1931 covers scaled back to two colors, likely to save money during the Great Depression. As the economy rebounded, a wider range of tones emerged in 1933 in the form of black-and-white photography. In 1948 the look changed again, this time because of a shift in ownership and editorial vision: color paintings returned, in a square image set on a solid background, which became white in 1952 and remained white for about 43 years. As desktop publishing arose at the end of the 20th century, designs became more experimental: images broke out of the box, ushering in a period of bold—primarily digitally crafted—illustrations.



The publication became a monthly magazine in November 1921. Here each month's horizontal bar represents a single issue. The tiles show the top five colors on each cover, arranged from the color used most (*at left*) to least (*at right*).

Nov. 1921

May 1932

Jan. 1942

A May 1948 redesign established the iconic square cover image, combined with a stacked, left-justified logo—features that persisted, with slight modifications, for nearly five decades.

May 1948

May 1969

In the late 1990s desktop publishing eased the process of composing covers, resulting in striking imagery integrated with dynamic type.

March 1997

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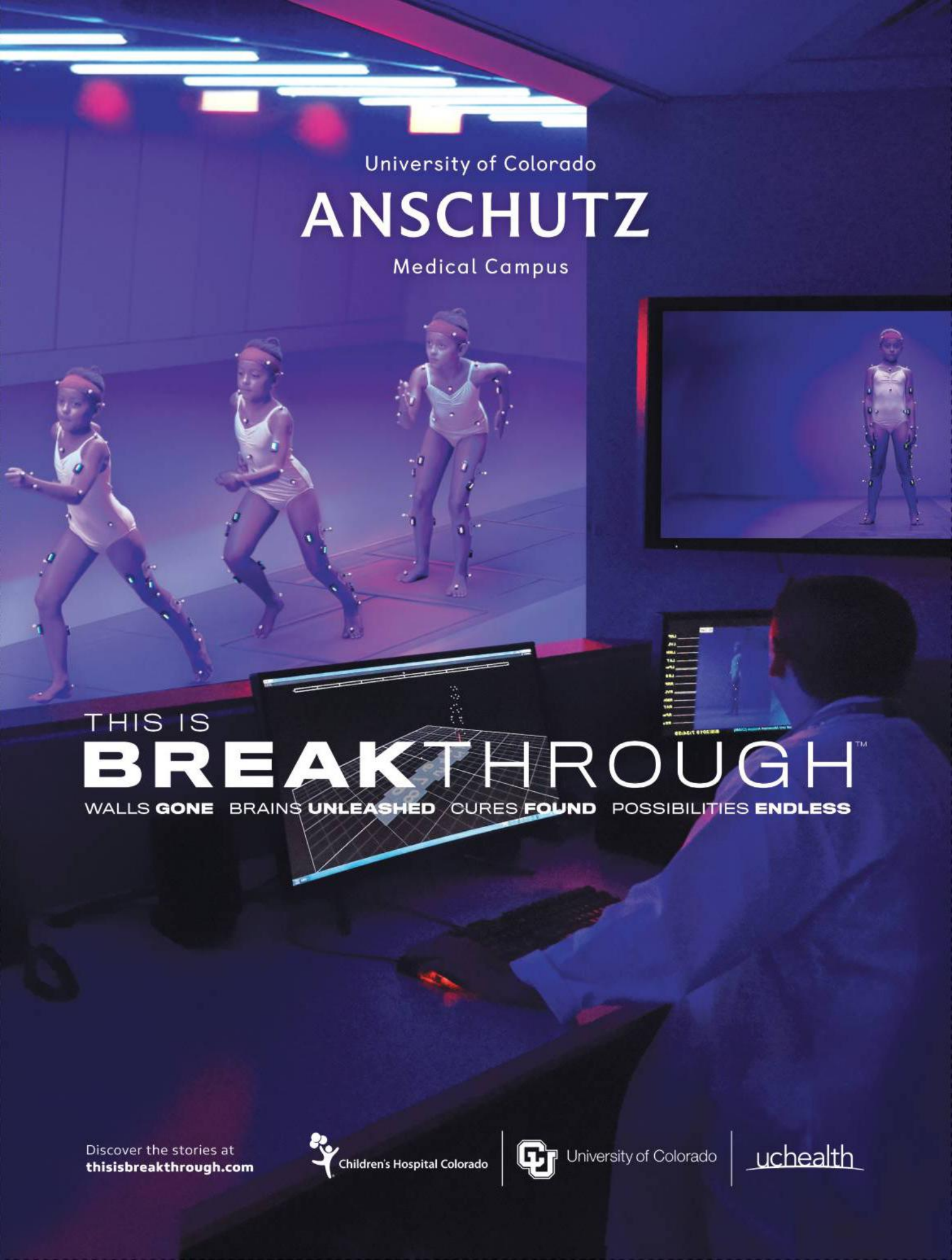
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