SOCIAL MEDIA SCARE
Fears about kids and tech are wildly overblown PAGE 44

PHAGE FIGHTERS
Fresh hope for drug-resistant infections PAGE 50

SONGBIRD GENETICS
Solving the mystery of their immense diversity PAGE 58

SCIENTIFIC AMERICAN

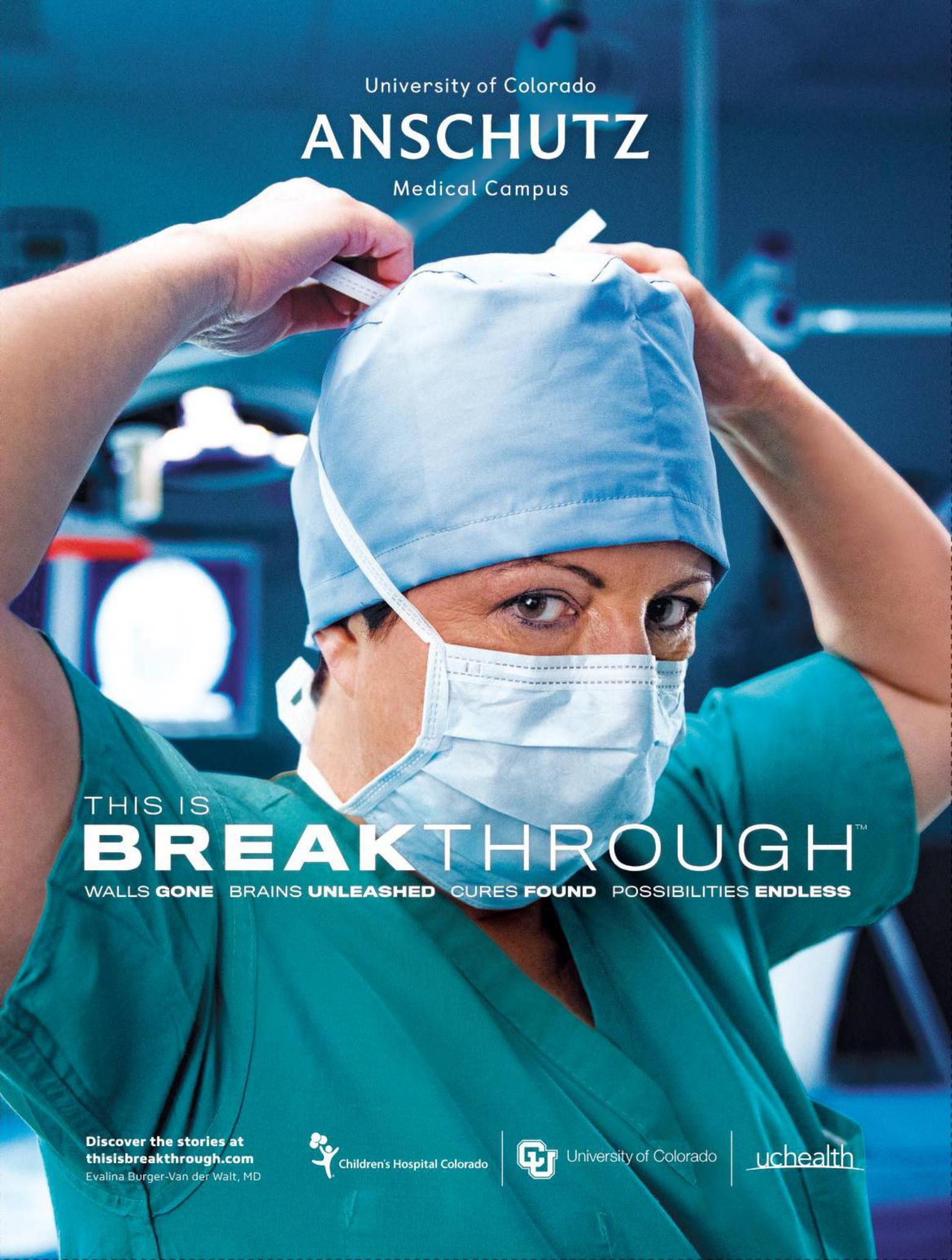
TIME CRYSTALS
Exotic new states of matter contain patterns that repeat like clockwork

PLUS

GRAVITATIONAL WAVES
Inside the world's first underground detector PAGE 62

IS INEQUALITY INEVITABLE?
An intriguing mathematical model PAGE 70

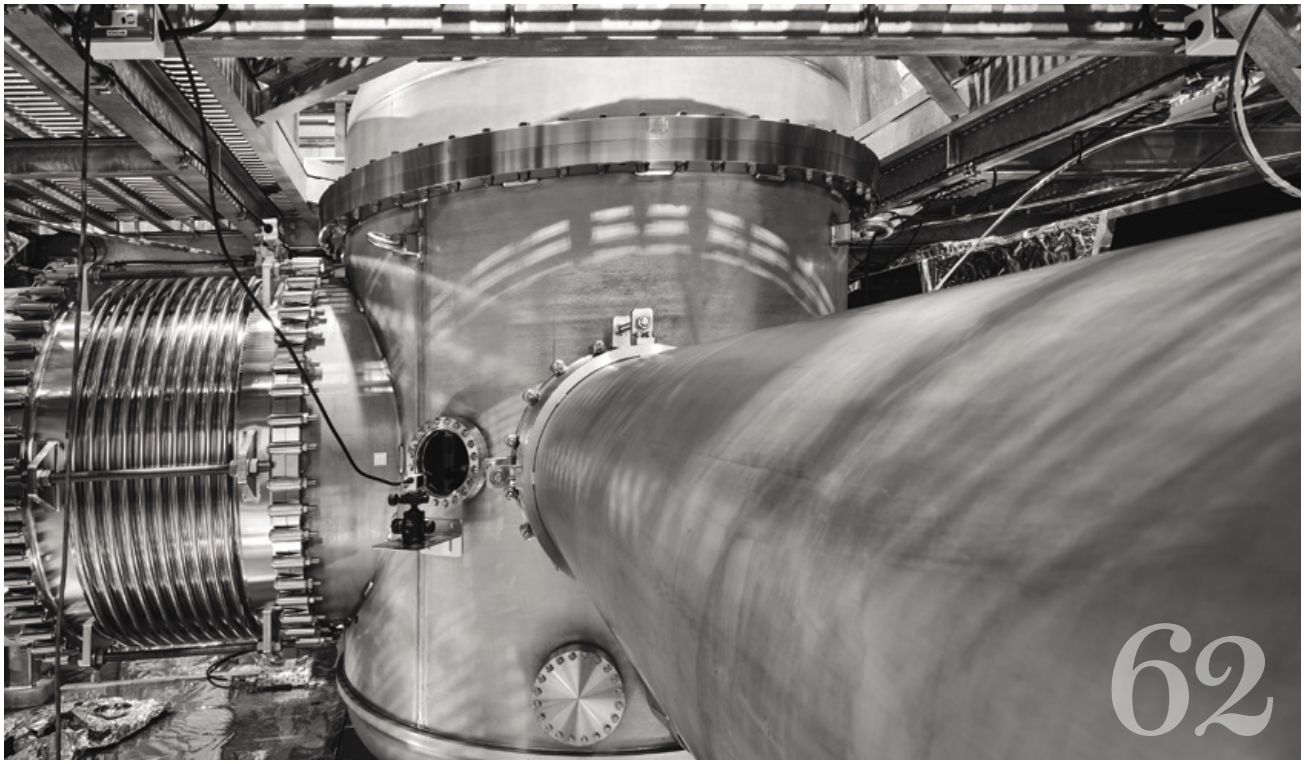
NOVEMBER 2019
ScientificAmerican.com


University of Colorado
ANSCHUTZ
Medical Campus
THIS IS
BREAKTHROUGH™
WALLS GONE BRAINS UNLEASHED CURES FOUND POSSIBILITIES ENDLESS
Discover the stories at
thisisbreakthrough.com
Evalina Burger-Van der Walt, MD
Children's Hospital Colorado
University of Colorado
uchealth

NOVEMBER 2019

VOLUME 321, NUMBER 5

SCIENTIFIC AMERICAN



ENRICO SACCHETTI

ON THE COVER
Physicists recently discovered the first real-world time crystals, states of matter in which patterns repeat over time. Materials of this kind could be used in new, ultra-accurate clocks, and the study of time crystals in general could lead to insights in fundamental physics and cosmology.
Illustration by Mark Ross Studio.

SCIENTIFIC AMERICAN

10

14

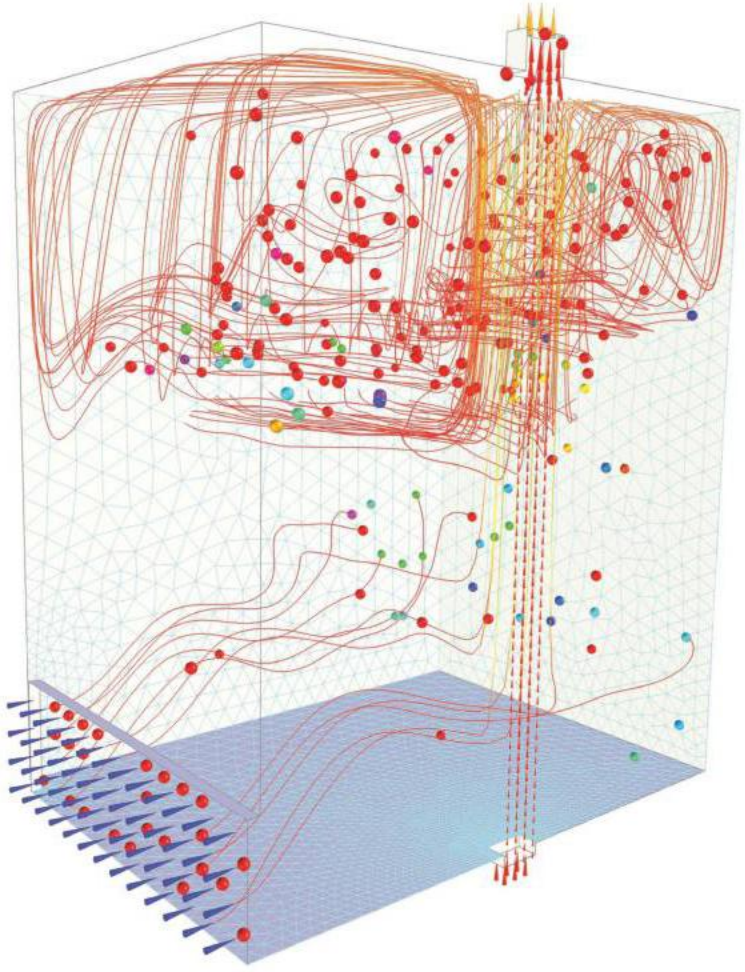
82

SPECIAL REPORT

S1 Nature Outlook: Influenza
The "flu" is annoying to many and lethal to some. This report, from *Nature,* looks at our latest defenses: better vaccines and treatments, speedier diagnosis of the sick, and closer monitoring of the natural reservoir of the virus.

Scientific American (ISSN 0036-8733), Volume 321, Number 5, November 2019, published monthly by Scientific American, a division of Nature America, Inc., 1 New York Plaza, Suite 4600, New York, N.Y. 10004-1562. Periodicals postage paid at New York, N.Y., and at additional mailing offices. Canada Post International Publications Mail (Canadian Distribution) Sales Agreement No. 40012504. Canadian BN No. 127387652RT; TVQ1218059275 TQ0001. Publication Mail Agreement #40012504. Return undeliverable mail to Scientific American, P.O. Box 819, Stn Main, Markham, ON L3P 8A2. **Individual Subscription rates:** 1 year $49.99 (USD), Canada $59.99 (USD), International $69.99 (USD). **Institutional Subscription rates:** Schools and Public Libraries: 1 year $84 (USD), Canada $89 (USD), International $96 (USD). Businesses and Colleges/Universities: 1 year $399 (USD), Canada $405 (USD), International $411 (USD). Postmaster: Send address changes to Scientific American, Box 3187, Harlan, Iowa 51537. **Reprints inquiries: (212) 451-8415. To request single copies or back issues, call (800) 333-1199. Subscription inquiries: U.S. and Canada (800) 333-1199; other (515) 248-7684. Send e-mail to scacustserv@cdsfulfillment.com.**

Prevent epidemic outbreaks with mathematical modeling and simulation.



Visualization of the motion of bacteria particles in a room with a displacement ventilation system.

Using math to analyze the spread of epidemic diseases is not a new concept. One of the first compartmental models of mathematical epidemiology dates back to 1760 and was presented by Daniel Bernoulli for studying the mortality rate of smallpox. Today, medical researchers and public health officials continue to use mathematical modeling and simulation to prevent and control epidemic outbreaks in the modern world.

The COMSOL Multiphysics® software is used for simulating designs, devices, and processes in all fields of engineering, manufacturing, and scientific research. See how you can apply it to analyzing the spread of epidemic diseases.

comsol.blog/epidemiology-simulation

COMSOL

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

Lucy in the Sky with Crystals

When our creative director, Michael Mrak, sent around the illustration for this month's cover story—a conceptual rendering of so-called time crystals—our features editor, Seth Fletcher, responded, "Cool. Very prog rock." The artwork certainly seems ready-made for a Pink Floyd album (Roger Waters, if you're reading this, the offer's on the table) or at least one of those velvet blacklight posters. And time crystals are indeed pretty trippy stuff.

Whereas conventional crystals are orderly states of matter whose patterns repeat at regular intervals in space, these more exotic materials have patterns that repeat at regular intervals in time. Theoretical physicist and Nobel laureate Frank Wilczek and his wife, Betsy Devine, coined the term "time crystals" in 2012, and scientists created the first bona fide examples in the lab in 2017. Still a nascent field of research, it is one that could lead to unprecedentedly precise measurements of time and distance, with myriad applications. For more mind-bending details, turn to Wilczek's article, "Crystals in Time," on page 28.

Coincidentally, a few of the concepts that appear in Wilczek's story—phase transitions, symmetry breaking and "exquisite" accuracy—also come up, in a more disheartening context, in mathematician Bruce M. Boghosian's piece about the origins of economic inequality, "The Inescapable Casino," on page 70. It turns out that they have been "hiding in plain sight," he writes. Models developed by physicists and mathematicians, which display features of physical systems, reveal that in free-market economies capital naturally trickles up from the poor to the rich, leading to oligarchy. And these models match the extreme concentration of wealth that we see in the world today.

Inequality is also at the heart of journalist Rachel Nuwer's account of biodiversity research in postconflict Colombia ("Conservation after Conflict," on page 36). The country, which emerged from decades of civil war in 2016, is home to nearly 63,000 known species and likely many more. Ironically, the years of strife acted to protect this rich natural history, which is now coming under threat as farmers, extractive industries and others move into once dangerous areas. But biologists can now travel more freely as well, and the race is on to tally Colombia's abundant fauna. Yet documentation alone won't save those species. Economic disparity led to war in the first place, so putting biodiversity in service of better livelihoods for Colombians is a critical part of the equation.

Almost everywhere we look, science and society are inextricably intertwined, which is why we must hold researchers to such high standards. Take, for instance, contributing editor Lydia Denworth's description (*page 44*) of efforts to improve studies of social media's impact on young people. Science will only ever suggest how to resolve our problems, however—the rest is up to us.

Fortunately, the next generation appears up to the challenge, and we were proud to sponsor the Scientific American Innovator Award at the Google Science Fair, held in August. The 16-year-old winner was Tuan Dolmen of Turkey, who found a way to harness energy from tree vibrations to power digital applications in agriculture. Explore Tuan's project at www.googlesciencefair.com. SA

Illustration by Nick Higgins


BECAUSE SOMEDAY
I'll throw out the syllabus.
Every someday needs a plan.®
Together, we'll help you achieve what matters most for retirement.
• Develop a long-term financial game plan.
• Get, and stay, on track toward your goals.
• Live the life you want today, and through retirement.
Talk with Fidelity today about retirement. Because you don't have to know all the answers—that's why we're here to help.
Fidelity INVESTMENTS
Fidelity.com/retirementready
866.715.2058
Investing involves risk, including the risk of loss.
The trademarks and/or service marks appearing above are the property of FMR LLC and may be registered.
Fidelity Brokerage Services LLC, Member NYSE, SIPC. 900 Salem Street, Smithfield, RI 02917
© 2017 FMR LLC. All rights reserved. 813868.2.0

July 2019

WOMEN'S SPACE

"One Small Step Back in Time," by Clara Moskowitz, includes a picture of the firing room for *Apollo 11*'s launch in 1969. I found, amid a sea of crew cuts, white shirts and dark ties, NASA engineer JoAnn Morgan seated at her console. Against the far wall, I could make out three other women. I, and undoubtedly other readers, would like to know more about the women in the control room that day—who they were and why they were there.

ISAAC FREUND *Department of Physics, Bar-Ilan University, Israel*

MORGAN REPLIES: I cannot identify the women against the wall. They came in the back door to hear the VIP speeches, which occurred 40 minutes or longer after launch. I did not know them, and they could have been clerical staff, procedure or mail-delivery distribution employees, or any variety of administrative contractors in the building.

There were very few NASA women at the facility. In tests, Judy Kersey, the first female guidance systems engineer, would come in to brief her division chief, who sat in my row. But I think she may have been in the Central Instrumentation Facility during the Apollo 11 *launch. Note that the firing room doors are unlocked within 30 minutes after launch and once the engine burns of the first and second stages are successful. I also remember Boeing had a woman writer who helped its engineers with procedures.*

"It is no mystery why the nuclear power industry has been in decline: it is ultimately dirty and inherently dangerous."

GARY D. LAVER *LOS OSOS, CALIF.*

NUCLEAR POWER DEBATE

For the second time in three months, *Scientific American* has published an item promoting the promise of a revival in nuclear energy. In "Reactor Redo" [May 2019], Rod McCullum describes current research on "safer and more efficient" reactor designs. In "I've Come Around on Nuclear Power" [Ventures], Wade Roush shares how his fear of global warming converted him to support "the nuclear industry's rebirth in the U.S." Both articles ignore some long-term, practical shortcomings of nuclear power: First, the failure to develop reliable technology and policy regarding spent nuclear fuel. And second, the ongoing cost of nuclear plants once they stop generating electricity.

Nuclear plants may not generate carbon dioxide, but they certainly produce radioactive waste. Regardless of how fuel is initially processed or actually used within a reactor, the radioactive properties of spent nuclear fuel remain fundamentally hazardous. If we feel carbon dioxide is dangerous, let's consider the consequences of a growing worldwide cache of spent uranium.

Roush claims that if the social cost of carbon were properly considered, nuclear power would become more economical than fossil-fuel plants. Besides promoting the false dichotomy of fossil fuels versus nuclear energy, he ignores the substantial cost of nuclear plants even after their utility has passed. Consider how the citizens of California will be charged billions of dollars for decommissioning the San Onofre and Diablo Canyon nuclear plants. Consider as well the costs of Chernobyl and Fukushima.

It is no mystery why the nuclear power industry has been in decline: it is ultimately dirty and inherently dangerous, and it meets its exorbitant costs with a blank check from taxpayers.

GARY D. LAVER *Los Osos, Calif.*

Having had responsibility for the licensing of several nuclear plants, I agree with Roush that we have far more to fear from climate change than nuclear power. Its continued use makes sense and should be part of the solution, so long as it pencils out.

But Roush is wrong that carbon tax is a "political nonstarter." As of early September, the Energy Innovation and Carbon Dividend Act (H.R. 763) pending in the U.S. House of Representatives already had 62 House members signed on. It is a revenue-neutral, free-market approach that would impose an effective accelerant to the transition to clean energy.

DOUG NICHOLS *via e-mail*

MOON EVOLUTION

"Origin Story," by Simon J. Lock and Sarah T. Stewart, asserts that Earth's moon was formed from a doughnut-shaped mass of rock vapor—a synestia—after a collision with a Mars-sized body.

The Fermi paradox asks why we haven't detected technologically capable extraterrestrials yet. There are many suggested answers, but among the least far-fetched are "rare Earth" theories that posit aliens might not exist because the conditions that allowed humans the time to evolve are very rare. One such possible condition is the existence of a moon that can help stabilize a planet's rotational axis because an unstable axis implies a wildly fluctuating climate.

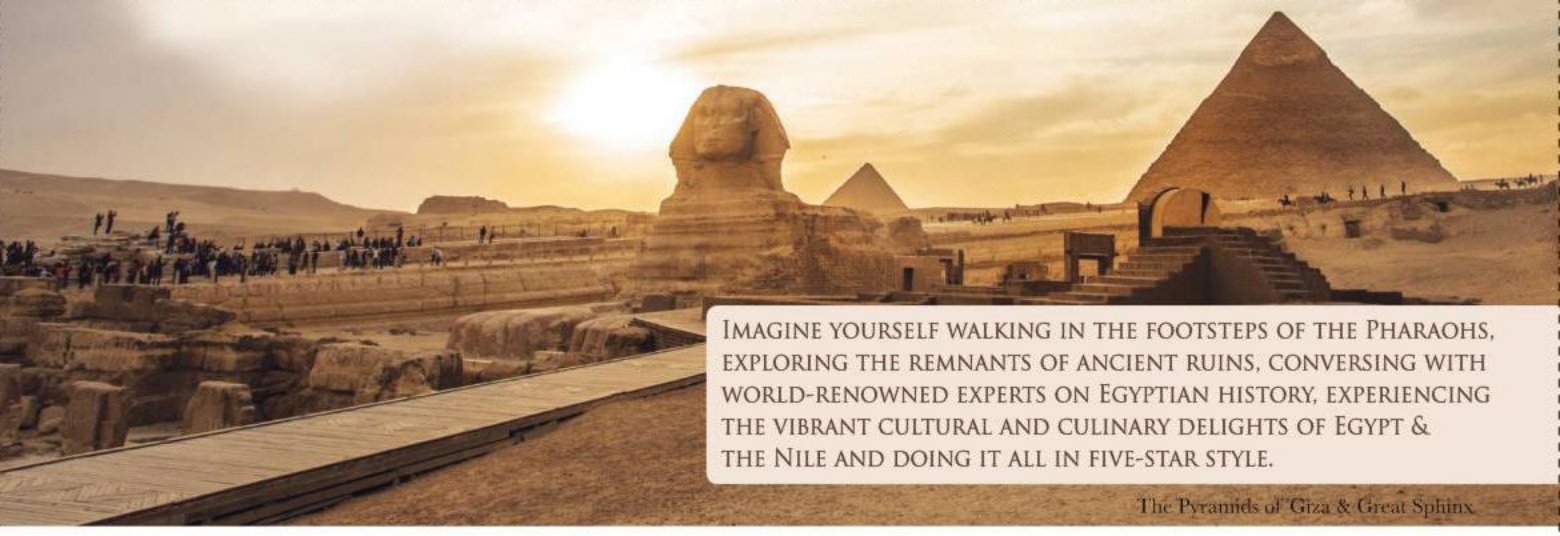
Lock and Stewart state that synestias might be the norm in new planetary systems. If they are indeed common, does this increase or decrease the probability that extrasolar planets might have a "dual planet" system (akin to our Earth and moon)?

JOHN TAKAO COLLIER *via e-mail*

THE AUTHORS REPLY: Although synestias are common, not all of them will

ARCHAEOLOGICAL PATHS

EXCLUSIVE. EDUCATIONAL. EXTRAORDINARY. EGYPT.



IMAGINE YOURSELF WALKING IN THE FOOTSTEPS OF THE PHARAOHS, EXPLORING THE REMNANTS OF ANCIENT RUINS, CONVERSING WITH WORLD-RENOWNED EXPERTS ON EGYPTIAN HISTORY, EXPERIENCING THE VIBRANT CULTURAL AND CULINARY DELIGHTS OF EGYPT & THE NILE AND DOING IT ALL IN FIVE-STAR STYLE.

The Pyramids of Giza & Great Sphinx

THE ROYAL TOUR TO EGYPT WITH DR. ZAHI HAWASS

EXCLUSIVE

Unlike conventional tours, only The Royal Tour offers its participants VIP entry to areas of the ancient sites that are not open to the general public. These exclusive adventures include:

- ▲ VISITING THE GIZA PYRAMIDS & LUXOR TEMPLE OUTSIDE OF REGULAR OPENING HOURS FOR A MORE INTIMATE & CROWD-FREE EXPERIENCE
- ▲ ONCE-IN-A-LIFETIME CHANCE TO STAND BETWEEN THE PAWS OF THE GREAT SPHINX AND HAVE A CLOSER LOOK INSTEAD OF WATCHING IT FROM THE VIEWING PLATFORM
- ▲ TOURING THE TOMBS OF THE PYRAMID BUILDERS IN GIZA – AN ACTIVE EXCAVATION SITE DISCOVERED BY DR. HAWASS & CLOSED TO TOURISTS
- ▲ PRIVATE ADMISSION TO THE GREAT PYRAMID OF KHUFU WITH A VISIT TO THE QUEEN'S & SUBTERRANEAN CHAMBERS – BOTH CLOSED TO THE PUBLIC
- ▲ A SOUGHT-AFTER CAMERA PERMIT ALLOWING PHOTOGRAPHY IN SACRED SPACES LIKE THE VALLEY OF KINGS & EGYPTIAN MUSEUM IN CAIRO

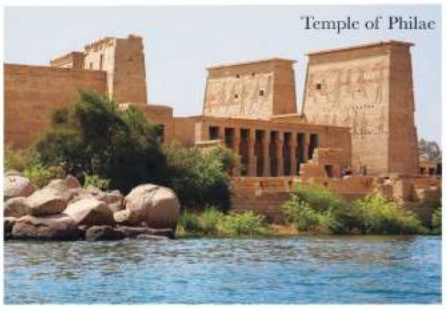
EDUCATIONAL

Led by the world's most famous archaeologist, Dr. Zahi Hawass, The Royal Tour to Egypt offers unparalleled access to the wonders and complexities of Ancient Egypt. An expert with decades of expertise, Dr. Hawass will take you on curated and informative tours of Egypt's most prized cultural institutions and offer insights and perspective into Egypt's highly valued artifacts and relics. In addition, you will hear secrets never told before and spend time in the esteemed company of Dr. Mostafa Waziri, Egypt's Head of Antiquities. You will be hosted by the former First Lady, Mrs. Jehan Sadat, in the residence of Egypt's late president Anwar Sadat – an experience normally reserved for royalty and heads of state.

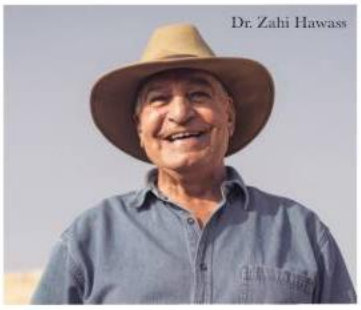
EXTRAORDINARY

First-class service from start to finish awaits you on The Royal Tour. Beginning in Cairo, The Royal Tour provides opulent accommodations in the city's finest five-star hotels. After leaving Cairo behind, participants will fly to Luxor to board a luxury cruise ship for a grand eight-day Nile Cruise. While cruising the Nile, you will visit Egypt's greatest ancient monuments and enjoy the modern-day amenities of a sun deck, pool, lounges, bar, gym, spa and fine dining.

BOOK YOUR TOUR TODAY AT: **royalegypt.com**
CONTACT US: **contact@archaeologicalpaths.com** **917-719-1974**



Temple of Philae



Dr. Zahi Hawass

form a large moon. They come in a wide variety of shapes, sizes, and thermal and rotational states. Key to the size of the satellite that can be formed from a synestia is the amount of mass that is injected into orbit in the outer regions of the body. Only a small fraction of impacts will inject enough mass into orbit to form a moon as large as ours, and we are still working out what range of conditions could make it.

Synestias are a new part of the grand mystery of how rare life on Earth is. And whether a "dual planet" system like our own is common is still very much an open question. We will keep working to understand which of our planet's special characteristics were determined during its formation.

LUNAR LITTER

I read "Mapping the Mission," Edward Bell's breakdown of *Apollo 11*'s landing, with great interest. Could you clarify what happened to the equipment and to the Stars and Stripes banner that was left on the moon's surface? Were they blown away by the exhaust gases and hidden by dust when the explorers departed in the lunar module?

Jacques Van Geersdaele *Belgium*

THE EDITORS REPLY: According to NASA, the American flag indeed was likely knocked over by the rocket blast as the lunar module lifted off from the moon. Either way, its stars and stripes are probably long gone, faded by the intense ultraviolet radiation on our natural satellite. The lunar module's descent stage and scientific instruments are thought to remain on the moon, albeit weathered by micrometeorites, radiation and extreme temperature changes.

ERRATUM

"Lunar Land Grab," by Adam Mann, should have said that 109 countries are now party to the Outer Space Treaty, not 107. Additionally, the article refers to 2012 as the original deadline for the Google Lunar XPRIZE. To clarify: in the initial competition, participants had until the end of that year to win the full grand prize, after which a reduced prize would be available until the end of 2014.

SCIENTIFIC AMERICAN®
ESTABLISHED 1845

ACTING EDITOR IN CHIEF
Curtis Brainard

COPY DIRECTOR **Maria-Christina Keller** CREATIVE DIRECTOR **Michael Mrak**

EDITORIAL
CHIEF FEATURES EDITOR **Seth Fletcher** CHIEF NEWS EDITOR **Dean Visser** CHIEF OPINION EDITOR **Michael D. Lemonick**

FEATURES
SENIOR EDITOR, SUSTAINABILITY **Mark Fischetti**
SENIOR EDITOR, CHEMISTRY / POLICY / BIOLOGY **Josh Fischman**
SENIOR EDITOR, SPACE / PHYSICS **Clara Moskowitz**
SENIOR EDITOR, SCIENCE AND SOCIETY **Madhusree Mukerjee**
SENIOR EDITOR, TECHNOLOGY / MIND **Jen Schwartz**
SENIOR EDITOR, EVOLUTION / ECOLOGY **Kate Wong**

NEWS
SENIOR EDITOR, MIND / BRAIN **Gary Stix**
SENIOR EDITOR, SPACE / PHYSICS **Lee Billings**
ASSOCIATE EDITOR, TECHNOLOGY **Sophie Bushwick**
ASSOCIATE EDITOR, SUSTAINABILITY **Andrea Thompson**
ASSOCIATE EDITOR, HEALTH AND MEDICINE **Tanya Lewis**
ASSISTANT NEWS EDITOR **Sarah Lewin Frasier**

MULTIMEDIA
SENIOR EDITOR, MULTIMEDIA **Jeffery DelViscio**
ENGAGEMENT EDITOR **Sunya Bhutta**
SENIOR EDITOR, MULTIMEDIA **Steve Mirsky**
SENIOR EDITOR, COLLECTIONS **Andrea Gawrylewski**

ART
ART DIRECTOR **Jason Mischka**
PHOTOGRAPHY EDITOR **Monica Bradley**
ASSOCIATE GRAPHICS EDITOR **Amanda Montañez**
SENIOR GRAPHICS EDITOR **Jen Christiansen**
ART DIRECTOR, ONLINE **Ryan Reid**
ASSISTANT PHOTO EDITOR **Liz Tormes**

COPY AND PRODUCTION
SENIOR COPY EDITOR **Daniel C. Schlenoff**
SENIOR COPY EDITOR **Aaron Shattuck**
SENIOR COPY EDITOR **Angelique Rondeau**
MANAGING PRODUCTION EDITOR **Richard Hunt**
PREPRESS AND QUALITY MANAGER **Silvia De Santis**

DIGITAL
PRODUCT MANAGER **Ian Kelly**
SENIOR WEB PRODUCER **Jessica Ramirez**

CONTRIBUTORS
EDITORS EMERITI **Mariette DiChristina, John Rennie**
EDITORIAL **David Biello, Lydia Denworth, W. Wayt Gibbs, Ferris Jabr, Anna Kuchment, Robin Lloyd, Melinda Wenner Moyer, George Musser, Christie Nicholson, Ricki L. Rusting**
ART **Edward Bell, Zoë Christie, Lawrence R. Gendron, Nick Higgins, Katie Peek**

EDITORIAL ADMINISTRATOR **Ericka Skirpan**
EXECUTIVE ASSISTANT SUPERVISOR **Maya Harty**

SCIENTIFIC AMERICAN CUSTOM MEDIA
MANAGING EDITOR **Cliff Ransom**
MULTIMEDIA EDITOR **Kris Fatsy**
ENGAGEMENT EDITOR **Dharmesh Patel**
CREATIVE DIRECTOR **Wojtek Urbanek**
MULTIMEDIA EDITOR **Ben Gershman**

PRESIDENT
Dean Sanderson

EXECUTIVE VICE PRESIDENT **Michael Florek**

CLIENT MARKETING SOLUTIONS
VICE PRESIDENT, COMMERCIAL **Andrew Douglas**
PUBLISHER AND VICE PRESIDENT **Jeremy A. Abbate**
MARKETING DIRECTOR, INSTITUTIONAL PARTNERSHIPS AND CUSTOMER DEVELOPMENT **Jessica Cole**
PROGRAMMATIC PRODUCT MANAGER **Zoya Lysak**
DIRECTOR, INTEGRATED MEDIA **Jay Berfas**
DIRECTOR, INTEGRATED MEDIA **Matt Bondlow**
MANAGER, GLOBAL MEDIA ALLIANCES **Brendan Grier**
SENIOR ADMINISTRATOR, EXECUTIVE SERVICES **May Jung**

CONSUMER MARKETING
HEAD, MARKETING AND PRODUCT MANAGEMENT **Richard Zinken**
MARKETING MANAGER **Chris Monello**
SENIOR COMMERCIAL OPERATIONS COORDINATOR **Christine Kaelin**

ANCILLARY PRODUCTS
ASSOCIATE VICE PRESIDENT, BUSINESS DEVELOPMENT **Diane McGarvey**
CUSTOM PUBLISHING EDITOR **Lisa Pallatroni**
RIGHTS AND PERMISSIONS MANAGER **Felicia Ruocco**

CORPORATE
HEAD, COMMUNICATIONS, USA **Rachel Scheer**

PRINT PRODUCTION
PRODUCTION CONTROLLER **Madelyn Keyes-Milch**
ADVERTISING PRODUCTION CONTROLLER **Dan Chen**

LETTERS TO THE EDITOR
Scientific American, 1 New York Plaza, Suite 4600, New York, NY 10004-1562 or editors@sciam.com
Letters may be edited for length and clarity. We regret that we cannot answer each one.
Join the conversation online—visit *Scientific American* on Facebook and Twitter.

HOW TO CONTACT US

Subscriptions
For new subscriptions, renewals, gifts, payments, and changes of address: U.S. and Canada, 800-333-1199; outside North America, 515-248-7684 or www.ScientificAmerican.com

Submissions
To submit article proposals, follow the guidelines at www.ScientificAmerican.com. Click on "Contact Us." We cannot return and are not responsible for materials delivered to our office.

Reprints
To order bulk reprints of articles (minimum of 1,000 copies): Reprint Department, Scientific American, 1 New York Plaza, Suite 4600, New York, NY 10004-1562; 212-451-8415. For single copies of back issues: 800-333-1199.

Permissions
For permission to copy or reuse material: Permissions Department, Scientific American, 1 New York Plaza, Suite 4600, New York, NY 10004-1562; randp@SciAm.com; www.ScientificAmerican.com/permissions. Please allow three to six weeks for processing.

Advertising
www.ScientificAmerican.com has electronic contact information for sales representatives of Scientific American in all regions of the U.S. and in other countries.

Apollo 11
Masterpiece Tribute

Celebrate the definitive achievement in space exploration with this superbly crafted

50th Anniversary

illuminated presentation!

LISTEN as it plays a sound bite from President John F. Kennedy's inspiring "We choose to go to the Moon" speech!

Shown smaller than impressive size of appr. 7.5" H x 8.5" W. Product subject to change

Fine collectible. Not intended for children under 14.

LIMITED EDITION OF ONLY 5,000 WORLDWIDE!

After a decade of triumph, tragedy and bold ingenuity, the world watched as astronauts Neil Armstrong, Michael Collins and Buzz Aldrin landed the "Eagle" on the surface of the Moon on July 20, 1969. It was an historic achievement that fulfilled the late President John F. Kennedy's ambitious pledge to put a man on the Moon.

To celebrate the ***50th Anniversary*** of one of mankind's greatest technological achievements, Hawthorne proudly presents the *Apollo 11 Masterpiece Tribute*. **Limited to only 5,000 worldwide**, this one-of-a-kind illuminating sculpture features a faithfully handcrafted, hand-painted replica sculpture of the Apollo 11 Lunar Module, the first manned spacecraft to land anywhere beyond our planet. This handsome base features archival NASA photos from the Apollo 11 mission, the mission insignia, and Armstrong's famous statement as he first set foot on the lunar surface..."one small step for man, one giant leap for mankind." At the flip of a switch, this detailed sculpture plays a sound bite from President John F. Kennedy's stirring "We choose to go to the Moon" speech! It also proudly features a miniature replica of the American flag planted by Armstrong and Aldrin in the Sea of Tranquility and a textured lunar surface complete with the astronauts' bootprints.

Not available in any store. ACT NOW!

PRE-ORDER this 50th Anniversary illuminated edition of the *Apollo 11 Masterpiece Tribute* at the attractive price of only $99.99, payable in four installments of just $24.99 each*, the first billed before shipment. You can pre-order with confidence as our best-in-the-business guarantee assures your satisfaction. To pre-order yours, send no money now. Simply complete and mail the Reservation Application today!

www.bradfordexchange.com

RESERVATION APPLICATION **RESPOND PROMPTLY**

THE BRADFORD EXCHANGE

HAWTHORNE VILLAGE DIVISION

9345 Milwaukee Avenue · Niles, IL 60714-1393

YES! Please enter my Pre-Order for the *Apollo 11 Masterpiece Tribute* for me as described in this announcement. **SEND NO MONEY NOW.**

CERTIFICATE OF AUTHENTICITY & 365-DAY GUARANTEE

Signature

Mrs. Mr. Ms.

Name (Please Print Clearly)

Address

City

State Zip

Email

14-02005-002-E67701

*Plus a total of $14.99 shipping and service, plus sales tax (see bradfordexchange.com).
All sales subject to acceptance and product availability. Pre-Order - product will ship November 2019.

End Vaccine Exemptions

Religious and philosophical exceptions are too dangerous to public health

By the Editors

As of late August, there had been more than 1,200 cases of measles across 31 U.S. states this year. It's a dispiriting comeback for a disease that was declared eliminated in this country in 2000. If the disease has not stopped spreading by the time you read this, the U.S. will likely have lost this status. The illness has been cropping up mainly in pockets of unvaccinated people. Those who choose not to immunize their families are placing at risk not only themselves and their children but also others who cannot be vaccinated because they are too young or have medical issues.

There isn't an iota of doubt that vaccines are an overwhelmingly safe and effective way to prevent measles and other diseases, including mumps, rubella, poliomyelitis and pertussis. All 50 states mandate that children entering school get immunized unless they have a medical exemption. Yet almost every state also offers religious exemptions, and more than a dozen offer personal belief/philosophical ones as well. California, Mississippi, West Virginia, Maine and, most recently, New York State have gotten rid of all nonmedical waivers. The others must follow suit. It's imperative for protecting public health.

It doesn't take many unvaccinated people to cause an outbreak. Measles was one of the first vaccine-preventable diseases to reappear because it is so contagious; the threshold for resistance to a disease conferred by sufficient community-wide levels of immunity or vaccination—so-called herd immunity—is 93 to 95 percent. If vaccination levels fall below that threshold, an infected person can cause an outbreak.

Hesitancy about vaccines is nothing new. People have questioned inoculations since Edward Jenner discovered the smallpox vaccine in 1796. Today vaccines are partly a victim of their own resounding success. People rarely, if ever, see once common diseases such as measles and polio, so they don't understand their potential danger. On top of that, relentless misinformation campaigns have touted such false claims as the idea that vaccines cause autism. Numerous studies have shown they do not. The discredited researcher Andrew Wakefield introduced this idea in a now refuted study, and celebrities such as Jenny McCarthy and Robert F. Kennedy, Jr., have given it credence. And social media has made it easier than ever for vaccine deniers to find like-minded networks of people to confirm their false beliefs.

Despite the existence of religious exemptions to vaccines, most major faith groups in the U.S. do not prohibit vaccination, and many religious leaders encourage it. Nevertheless, a large number of this year's measles cases occurred in ultra-Orthodox Jewish communities in the neighborhood of Williamsburg in Brooklyn and in Rockland County, New York. (It's not just the Jewish community: the majority of New York City schools with relatively low rates of measles vaccination among students were Muslim or Christian academies or alternative-learning institutions.) The outbreak in New York City was declared over in September, but cases have persisted in Rockland County.

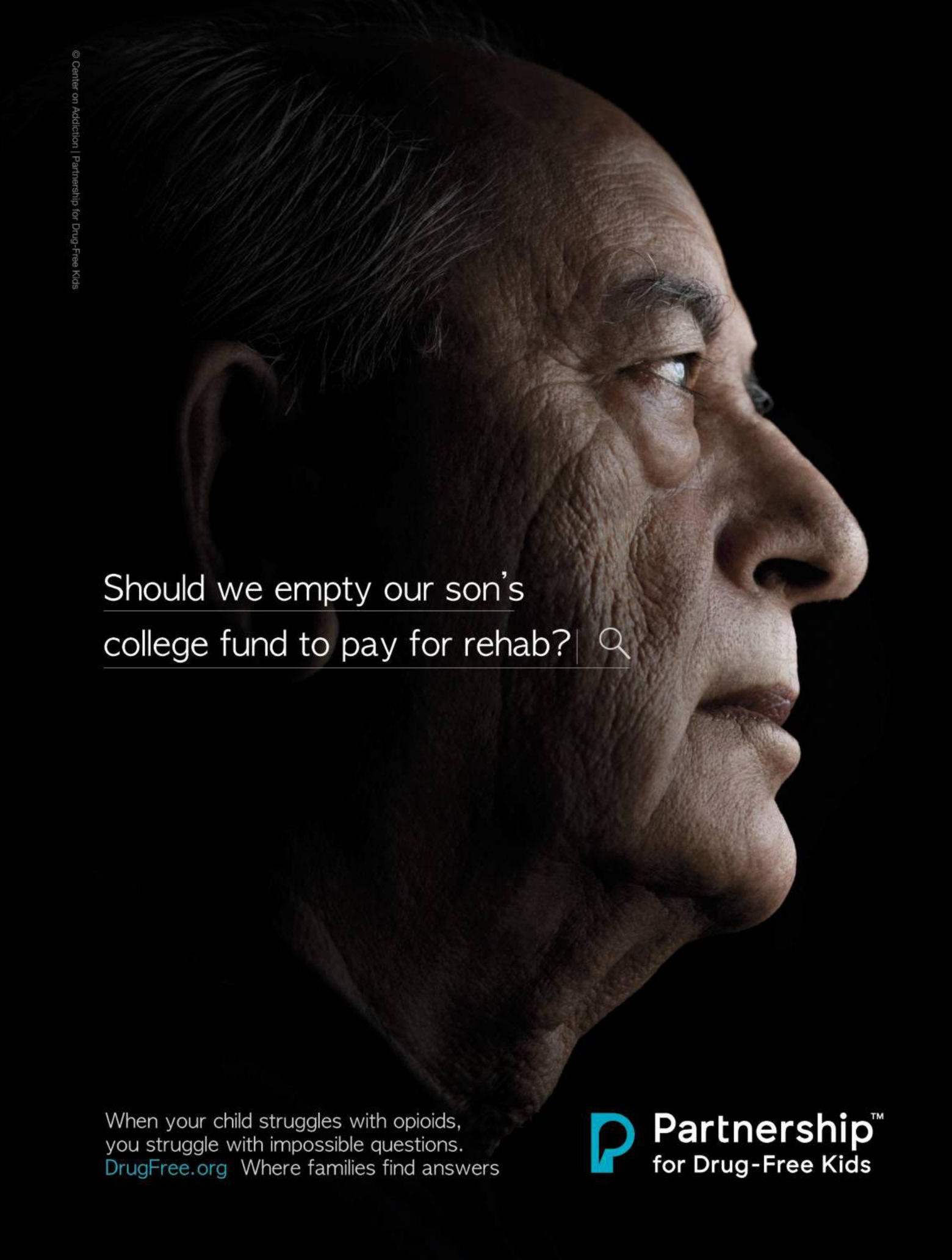
Many people who choose not to vaccinate believe no government should force them to put medicine into their bodies or their children's. They frame the choice as a personal right, but they are not taking into account the rights of others, including their own children, to be free of disease. When it comes to balancing the two, we need to consider the needs of the community as well as those of the individual. The Supreme Court ruled in *Jacobson v. Massachusetts* that states have the authority to require vaccination against smallpox, and in *Prince v. Massachusetts* it reaffirmed that the right to religious liberty does not include the right to expose a child or the community to disease.

Some experts argue we should just make it more difficult to obtain religious and philosophical exemptions. But unless the exemptions are removed completely, there will always be people who want to use them. Partial elimination, as the Washington State Senate enacted in the case of philosophical exemptions for the MMR (measles, mumps and rubella) vaccine alone, is also shortsighted because it sends the message that some immunizations are less important than others. The only surefire solution is to eliminate nonmedical exemptions to recommended vaccines.

People who cannot be vaccinated for medical reasons—such as those with compromised immune systems—should of course remain exempt. But there is no legitimate argument against vaccination for the vast majority of healthy people, and there are many powerful arguments in favor of it. Refusing to vaccinate is not a matter of freedom. It's a matter of public safety. SA

JOIN THE CONVERSATION ONLINE
Visit *Scientific American* on Facebook and Twitter
or send a letter to the editor: editors@sciam.com

Illustration by Rafa Alverez


© Center on Addiction | Partnership for Drug-Free Kids
Should we empty our son's
college fund to pay for rehab?
When your child struggles with opioids,
you struggle with impossible questions.
DrugFree.org Where families find answers
Partnership™
for Drug-Free Kids

The U.S. Needs a Mental Health Czar

The country is facing a psychological crisis—and nobody is really in charge

By Kirk J. Schneider

The U.S. is experiencing a mental health crisis. According to recent surveys, rates of depression, anxiety and opioid addiction, particularly among young people, are alarmingly high. Also mounting are rates of suicide, hate crimes and rampage killings, as is the demand for mental health services. A survey published in January by the California Health Care Foundation and the Kaiser Family Foundation found that more than half of those surveyed thought their communities lacked adequate mental health care providers and that most people with mental health conditions are unable to get needed services.

These statistics indicate that there is a gap in state and federal oversight of public mental health. The federal office of the surgeon general oversees operations of the U.S. Public Health Service, which communicates health recommendations to the public, but that is a huge portfolio that ranges from nutrition to vaccines to environmental hazards to mental health. The Substance Abuse and Mental Health Services Administration (SAMHSA) oversees and provides support to mental health services specifically, but it tends to focus on addiction and shorter-term, behavioral modalities. Moreover, it appears to be dominated by a medical orientation, which may not be adequate to address the intense psychological needs of many in the nation. And neither office appears to have the staff, budget and expertise to tackle the diversity of problems in the mental health sector.

For that reason, Congress should create an office dedicated to public mental health—the office of a "psychologist general." He or she would coordinate closely with the office of the surgeon general, as well as related government agencies such as SAMHSA, to oversee and advise the public regarding strictly psychological (that is, nonmedical) approaches to public mental health care. Such a position could be filled by a psychologist, a counselor, a social worker, a researcher or a psychiatrist—but he or she must have specific expertise in *psychological* approaches to public mental health. In addition, the psychologist general should be a distinguished professional who has a superlative knowledge of evidence-based approaches to health care and who has a collaborative view of how psychology and medicine can work together to optimize it.

Some of my colleagues have asked why we shouldn't have a psychiatrist general rather than a psychologist general as overseer of public mental health. My answer is that although these specialists are integral to the health care system, the statistics demonstrate that their contributions do not appear to be sufficient. Moreover, there are indications that many in our society are overmedicated and that potent psychological methodologies could give people the resources to function more sustainably on their own or in conjunction with appropriate medical care.

A psychologist general at the forefront of mental health research and delivery would send a strong message that psychological well-being is prized on a par with physical health—a message in keeping with the phrase "Life, Liberty and the pursuit of Happiness." More important, it is a message that resonates with contemporary needs. As a major review of the literature demonstrates, there is every indication that by addressing these needs our nation will save on medical costs as well.

Just as in the case of the surgeon general, the psychologist general would be nominated by the president, with the advice and consent of Congress. Candidates might come from the U.S. Public Health Service—or it might make more sense for Congress to authorize selections outside of this corps because there are many qualified psychologists, counselors, social workers, researchers and psychiatrists who may not officially be part of the corps but who hold equivalent, and perhaps in some cases superior, credentials in the promotion of psychological approaches to public mental health. In either case, the time is ripe for a psychologist general. It is both economically warranted and morally imperative. SA

Kirk J. Schneider is a psychologist and a current member of the Council of the American Psychological Association.

JOIN THE CONVERSATION ONLINE
Visit *Scientific American* on Facebook and Twitter or send a letter to the editor: editors@sciam.com

Illustration by Matt Harrison Clough

Celebrate America's Space Exploration

Space Mission
Men's Nylon Jacket

Apollo 11 Patch commemorates the 50th Anniversary of NASA's First Lunar Landing on July 20, 1969

Officially Licensed by NASA

☆

12 replica patches commemorating the 12 Apollo missions adorn the sleeves

☆

Features Apollo emblem, and American flag patches on the front and back

☆

Flight style jacket in water-resistant nylon

An Officially Licensed Exclusive from The Bradford Exchange

Honor a giant leap for mankind in a custom-designed flight-style jacket that commemorates NASA's Apollo Program of manned space missions. Officially Licensed by NASA and crafted of black nylon, this exclusive jacket proudly displays replica patches down the sleeves that represent 12 Apollo missions, six of which were lunar landing missions including Apollo 11, the historical first moon landing on July 20, 1969. On the Apollo 11 patch, you'll notice imagery of a bald eagle landing on the moon, a meaningful design inspired by the words spoken by the mission commander as their lunar module, The Eagle, touched down on the moon's surface for the very first time. All of the detailed designs were faithfully recreated from the official patches worn on the uniforms of our brave astronauts and depict many significant moments in the history of space exploration and the NASA program itself. From eagles and orbiting capsules to a clipper ship and the Greek god Apollo, you'll never get tired of studying the symbolism in the images on these 12 detailed patches!

And to complete the exciting space mission motif, an American flag and NASA logo patch adorn either side of the chest, while an Apollo emblem patch is seen on the back. This full zip jacket features a water-resistant outer shell with a quilted lining, rib knit cuffs, and hem. Two zippered front pockets and two snap slip pockets at the hip finish the look. Imported.

A Remarkable Value... Satisfaction Guaranteed

Available in men's sizes M-XXL, the *"Space Mission" Men's Nylon Jacket* can be yours now for $139.95* (sizes XXL, add $10), payable in 4 convenient installments of just $34.99 each, and backed by our 30-day, money-back guarantee. To reserve yours, send no money now; just return your Priority Reservation today!

*See bradfordexchange.com for information on all that is included in your one-time shipping and service charge.

Replica Patches on Sleeves

Order online at bradfordexchange.com/spacemissionjacket

 01-26712-001-BIBR3

PRIORITY RESERVATION **SEND NO MONEY NOW**

THE BRADFORD EXCHANGE
APPAREL & ACCESSORIES

9345 Milwaukee Avenue · Niles, IL 60714-1393

YES. Please reserve the ***"Space Mission" Men's Nylon Jacket*** for me in the size indicated below.

- ❑ **Medium** (38-40) 01-26712-011
- ❑ **Large** (42-44) 01-26712-012
- ❑ **XL** (46-48) 01-26712-013
- ❑ **XXL** (50-52) 01-26712-014

*Plus $15.99 shipping and service; see bradfordexchange.com. Please allow 2-4 weeks after initial payment for shipment. Sales subject to product availability and order acceptance.

Signature

Mrs. Mr. Ms.

Name (Please Print Clearly)

Address

City State Zip

E-Mail

E93411

ADVANCES

Boaters transport ice in Vietnam's Mekong Delta.

BRUNO DE HOGUES Getty Images

INSIDE

GEOGRAPHY

Delta Danger

Newly calculated elevation means millions of residents may need to leave Vietnam's Mekong Delta

A stunning 12 million people could be forced to retreat from rising seas in Vietnam's Mekong Delta within half a century. Geographer Philip Minderhoud and his colleagues at Utrecht University in the Netherlands arrived at this conclusion after analyzing ground-based topography measurements to which outside scientists' access was limited for years. The new analysis, published in August in *Nature Communications,* shows that the Mekong's elevation above sea level averages just 0.8 meter—almost two meters lower than commonly cited estimates.

The locally measured figures more than double the number of Vietnamese people living in low-lying areas that will be inundated as the earth's climate warms, with some places likely to be underwater in only a few decades.

For elevation readings in many developing countries, international researchers rely on freely available global satellite data because there are few on-the-ground records—and because some governments closely guard their own data. But satellite elevation readings can be notoriously unreliable in low-lying areas. Torbjörn E. Törnqvist, a geologist at Tulane University, says this is a concern not just for the Mekong but also for other mega deltas inhabited by tens of millions of people (such as the Ganges in Bangladesh and India and the Irrawaddy in Myanmar). "My hope is that these findings will wake people up to the fact that we're dealing with terrible data sets that aren't

Map by Mapping Specialists

appropriate for the problems these deltas are facing," he says.

Unlike rocky continental coasts, deltas are made of soft river sediments that are deposited over thousands of years and can easily compact and subside. Subsidence can grow worse when upstream dams block the incoming flow of new sediments in rivers or when groundwater or natural gas is pumped up from below, removing underlying support for the land. Urban infrastructure can also prevent water from seeping into the earth and refilling aquifers. All these forces are at play in the Mekong, which is subsiding in some areas at rates approaching five centimeters a year—and the rate at which the entire delta is subsiding is among the fastest in the world. According to Nguyen Hong Quan, a hydrogeologist at Vietnam National University, flooding has grown more common all across the delta.

Numerous international assessments of deltas are based on topography information gathered in February 2000 by the space shuttle *Endeavour.* Known as the Shuttle Radar Topography Mission, this global survey was sponsored in part by the U.S. Department of Defense, and data from the project are now publicly available. Elevation assessments use other space-based measurements as well, but in general they are prone to vertical errors ranging up to 10 meters or more. "Not so bad if you're modeling the Himalayas," Törnqvist says. "But for a low-lying delta, that's a whole different story." Organizations such as the World Bank rely on these assessments when making policy decisions, including where to allocate flood-preparedness resources.

The gold-standard remote-sensing system used for measuring delta heights—lidar, which is often mounted on aircraft—is accurate to within a few centimeters. But it is expensive and generally unavailable in developing countries.

Space shuttle data had put the Mekong's average elevation at 2.6 meters. But Minderhoud, who was on-site with a Dutch research team studying the delta, was skeptical. He found that those measurements had strange elevation patterns that were inconsistent with the local terrain. Minderhoud says his Vietnamese colleagues knew their government had been collecting ground-based survey data and even some lidar measurements. Vietnamese academics, however, had not published the data in international journals, according to Minderhoud.

Robert Nicholls, a coastal engineer at the University of Southampton in England, says it is not unusual for governments to withhold topography measurements for national security reasons. Because those data can be used to support strategic military operations, "they are not in the public domain," Nicholls says. And governments may simply not want to stir drama among local populations, Törnqvist notes.

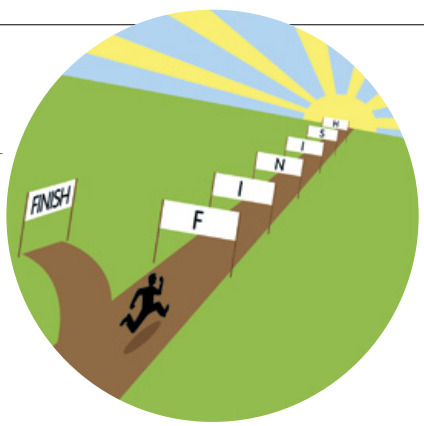
To gain access to the Vietnamese data, Minderhoud first had to build trust with government institutions and identify opportunities for cooperation. "I tried to find out how my own research might contribute to their goals," he says. "The key was to make this a combined effort." In time, he wound up with almost 20,000 elevation points measured throughout the delta.

Minderhoud's team also performed a crucial step that is frequently neglected in regional assessments: the researchers calibrated the data to a local benchmark for zero elevation at an island town called Hon Dau. This was necessary because ocean

HUMAN BEHAVIOR

Procrastination Tech Support

"Cognitive prosthesis" motivates people to finish tasks



Choosing between instant gratification and future benefit can easily lead to shortsighted decisions: streaming TV instead of going to the gym, for example, or scrolling through social media rather than working on a challenging project. "Because of this misalignment between immediate reward and long-term value, people often struggle to do what's best for them in the long run," says Falk Lieder, a cognitive scientist at the Max Planck Institute for Intelligent Systems in Tübingen, Germany.

To guide individuals toward optimal choices, Lieder and his colleagues designed a digital tool they call a "cognitive prosthesis." It helps to match a decision's immediate reward with its long-term worth—using artificial intelligence to augment human decision-making through a to-do list. The researchers developed a set of models and algorithms that consider various elements such as a list of tasks, an individual's subjective aversion to each and the amount of time available. The system then assigns reward points to each task in a way that is customized to encourage that person to complete them all.

"The idea was to turn the challenging projects that people pursue in the real world into a gamelike environment," Lieder says. "The point system [gives] people proximal, attainable goals that signal that they're making progress."

The team tested the setup in a series of experiments with human subjects. The results, published online in August in *Nature Human Behaviour,* revealed that the AI support system helped people make better, faster decisions and procrastinate less—and it made them more likely to complete all the assigned tasks. In one experiment, in which the researchers presented 120 participants with a list of several writing assignments, they found that

Illustration by Thomas Fuchs

currents and other forces can cause water to "pile up" along certain local coastlines, making sea surfaces higher in some areas. The more typical approach is to use a global benchmark for zero elevation, which may not reflect local sea-surface height. By combining average rates for sea-level rise and for subsidence, Minderhoud estimates the water will effectively rise by 0.8 meter on average in 57 years.

A similar fate may await other major deltas. Heri Andreas, a researcher at the Bandung Institute of Technology in Indonesia, says Jakarta—coastal home to 10 million people and one of the fastest-sinking cities on earth—has been modeled extensively with lidar. Scientists estimate that almost all of the city's northern district could be submerged by 2050, and President Joko Widodo announced plans to build a new capital on the island of Borneo. "But many other cities in Indonesia are also experiencing subsidence, and we don't have accurate elevation models for most of them," Andreas says.

Although the locally measured elevations are disturbing to outside experts, Nguyen maintains that they were not a surprise to scientists in Vietnam. He also says the Vietnamese government is developing what he claims is a new and even more precise elevation map. As for relocation, Nguyen says he is unaware of any plans to that effect. "The challenge is to convince people if the prediction is reliable enough to take action," he says. *—Charles Schmidt*

85 percent of individuals who used the tool completed all their tasks; the rate was only 56 percent for those not using it.

The difference in completion rates was "quite impressive," says Mike Oaksford, a psychologist at Birkbeck, University of London, who was not involved in the study. "That seems to me to be a convincing demonstration that procrastination is something that this strategy [can] help with quite a lot."

Lieder says one of the current tool's limitations is that it can handle only short to-do lists, so he and his team are trying to scale it up for a larger number of tasks. At the same time, they are working with a company called Complice to integrate the tool into an existing to-do list app. The researchers also plan to run field experiments to see how well their cognitive prosthesis fares in the real world.

—Diana Kwon

CLIMATE CHANGE

The Price of Warming

Countries rich and poor will take a financial hit

When a major heat wave engulfed western Europe in late July, Paris and other cities recorded their highest temperatures ever. The furnacelike weather did not just cause sweaty brows—it also exacted a financial toll in infrastructure damage, lost labor productivity and potentially lower agricultural yields. The situation illustrates how even relatively wealthy countries can take an economic blow from climate change.

That is a key message of a new study from the nonprofit National Bureau of Economic Research (NBER). Much earlier research has suggested that climate-related losses would be higher for poorer, hotter countries and that colder countries could even see economic benefits from warming. But the new analysis indicates financial suffering will be widespread. "It doesn't matter what kind of country you are, you are going to get hit by climate change," says study co-author Kamiar Mohaddes of the University of Cambridge.

In a preliminary report for NBER, Mohaddes and other economists compiled per capita gross domestic product (GDP) and temperature data for 174 countries going back to 1960 to capture how above-normal temperatures have impacted income levels historically. They then projected that relation into the future to see how further warming could affect GDP, a measure of all the goods and services a country produces.

If greenhouse gas emissions continued to grow along their current trajectory, about 7 percent of global GDP would be lost by 2100, the researchers found. Rich and poor countries, as well as those with hot and cold climates, would all see GDP losses (*graphic*). The U.S. would lose 10.5 percent of its GDP, whereas Canada—which some economists say could benefit from warming because of expanded agriculture—would lose 13 percent.

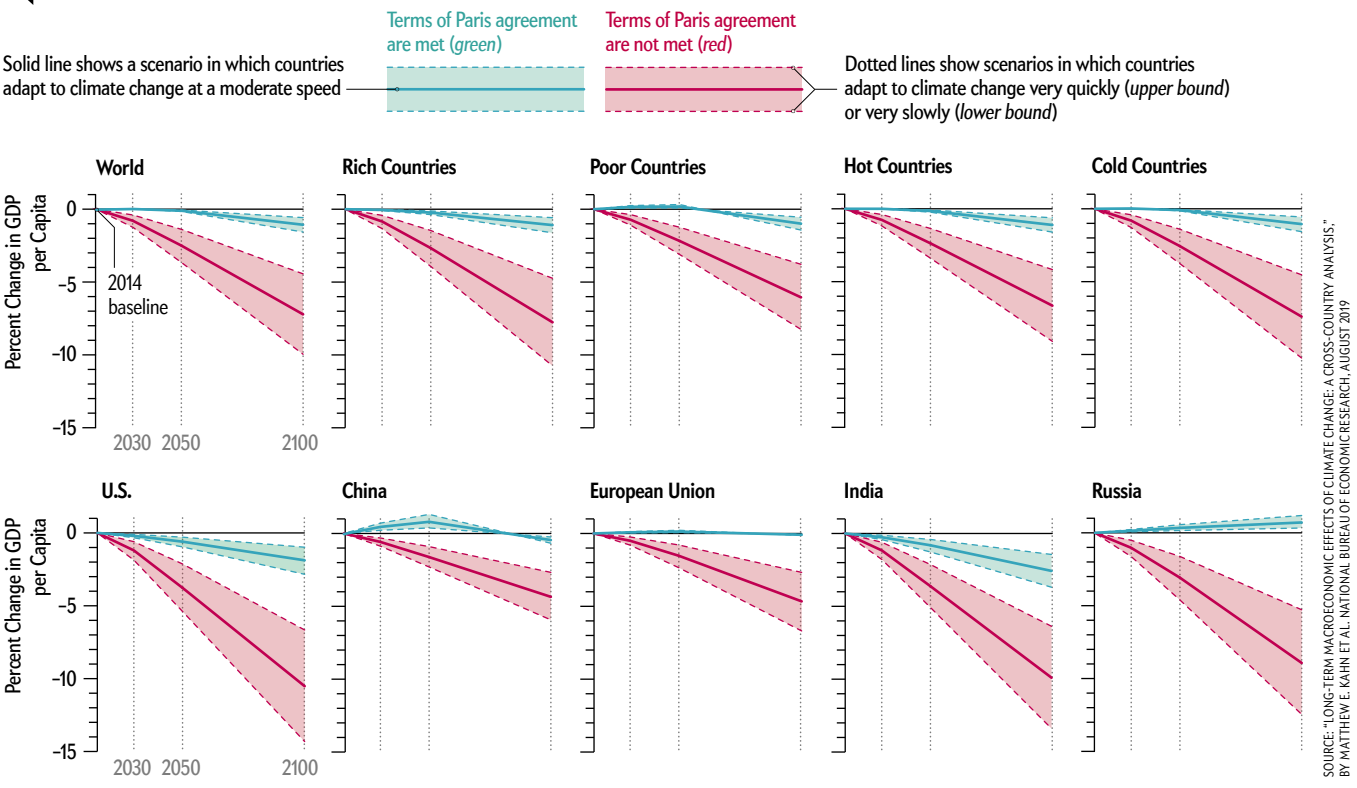
Limiting emissions in accordance with the Paris climate agreement (which aims to keep global temperature rise below two degrees Celsius by 2100) would substantially stem the losses. Globally, the decline in GDP would be a mere 1 percent; in the U.S. and Canada, it would about 2 percent.

Unlike earlier studies, this one looked not just at temperatures but at how they deviate from the normal conditions to which societies have adapted. Although rich countries such as the U.S. may have more resources to compensate for swings away from those norms, the study results make clear that adaptation alone will not prevent major losses, Mohaddes says. "All of the infrastructure and the technology that we have mitigates the cost but cannot conceal it fully," says World Bank economist Stéphane Hallegatte, who was not involved with the study.

Both Mohaddes and Hallegatte say the projections most likely underestimate GDP losses because the study does not take into account the bigger variations in climate extremes expected in the future.

—Andrea Thompson

The Costs of Climate Change in Lost GDP



SOURCE: "LONG-TERM MACROECONOMIC EFFECTS OF CLIMATE CHANGE: A CROSS-COUNTRY ANALYSIS," BY MATTHEW E. KAHN ET AL. NATIONAL BUREAU OF ECONOMIC RESEARCH, AUGUST 2019

Graphic by Amanda Montañez

IN THE NEWS

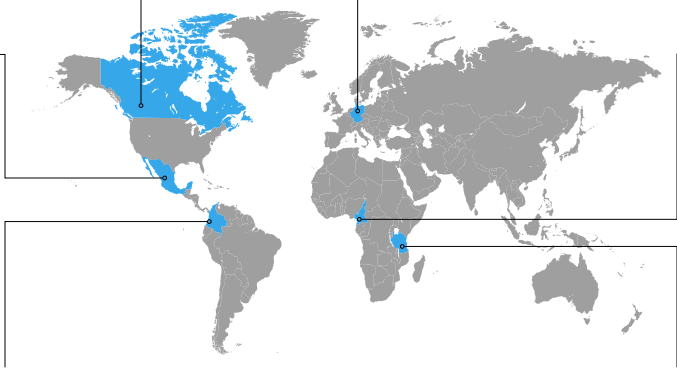
Quick Hits

By Jennifer Leman

CANADA
In the famed Burgess Shale rock formation, paleontologists discovered hundreds of fossils from a horseshoe crab–shaped, prehistoric predator that lived in the ocean 506 million years ago. It measured up to a foot long.

GERMANY
A vengeful crowd attacked two intoxicated German men who killed a western capercaillie they said attacked them. The bird is endangered in Germany; species populations have shrunk because of habitat loss and stress from increased human contact.

MEXICO
Researchers have rationed electricity and cut temporary employees' jobs after Mexico's president lowered funding for federal institutions, including those supported by the National Council of Science and Technology, by 30 to 50 percent in certain budget items.



CAMEROON AND EQUATORIAL GUINEA
Scientists found that Goliath frogs, which are Earth's largest living frogs and can be longer than a football, construct protected ponds for their young by pushing heavy rocks across streams. They live only in this region.

COLOMBIA
Scientists confirmed a destructive fungus targeting banana plants has arrived in the country. No treatment is available, so officials put potentially infected crops under quarantine to stop its spread.

TANZANIA
Marine biologists discovered a colorful fish species, dubbed the vibranium fairy wrasse, during a biodiversity assessment of largely unstudied deep reefs off Zanzibar's coast.

For more details, visit www.ScientificAmerican.com/nov2019/advances

ANIMAL BEHAVIOR

Feather Trap

Brazilian ants build an unusual pitfall for bugs

Pheidole oxyops nest entrance is surrounded by feathers.

RICARDO SOLAR

Fallen feathers may appear innocuous, but bugs in tropical Brazilian savannas should think twice about approaching them. New research suggests *Pheidole oxyops* ants sometimes place feathers around their underground nest's single entrance as bait for other creatures, which then tumble in. This behavior is an unusual example of ants using lures or traps rather than actively hunting down their prey.

Inácio Gomes, an ecologist at the Federal University of Viçosa in Brazil, had never seen any description in scientific studies of ants building traps. He first noticed feathers around ant nest entrances in city parks and on his college campus, and he found two hypotheses in scientific literature: the feathers could collect morning dew in dry areas, or they could act as lures.

Gomes is lead author on an August study in *Ecological Entomology* that experimentally tested both ideas. The researchers provided a ready supply of wet cotton balls but found the ants still collected feathers, suggesting they were not being used for water. And the team found that artificial traps with feathers around them captured more wandering arthropods than those without.

Gomes says that once prey such as mites, springtails or other species of ants fall in, the nest entrance's soft walls make it hard for them to climb out, and the inhabitants quickly subdue them.

Helen McCreery, a biologist at Harvard University, who was not involved in Gomes's research, says the study is "really cool" and well done. "It's a very charismatic, conspicuous behavior," McCreery adds. "There are certainly very few examples of ants acquiring food without leaving their nest."

McCreery wonders why prey are attracted to the feathers in the first place; Gomes suggests smell and shape are potential draws. "In general, soil insects are very curious—that's why pitfall traps are so effective," Gomes says. Scientists use similar traps to capture wild specimens.

P. oxyops forage alone or in groups like other ant species—Gomes once saw them take down a praying mantis—but he said they most likely supplement hunting with the feather traps to get through long dry seasons with scarcer prey. —*Joshua Rapp Learn*

BIOLOGY

Hatchlings with Vision

Jumping spider babies are the size of a grain of sand but see surprisingly well

Adult jumping spiders are littler than a fingernail, but their vision is as clear as a small dog's. And the babies, with heads a hundredth the size of their parents', may see in almost as much clarity. Researchers have now discovered a mechanical secret behind this remarkable hatchling ability.

"Even arachnophobic people find these little jumping spiders to be compelling—they dance, they sing vibratory songs to each other," says Nathan Morehouse, a co-author of the study published in July in *Vision Research.* (Morehouse started the research at the University of Pittsburgh and finished it at the University of Cincinnati.) And the spiders' extraordinary visual ability captivates many scientists.

"Everyone I know who works on vision just loves jumping spiders," says Jamie Theobald, who studies insect vision at Florida International University and was not involved in the new study. "How they accommodate such amazing visual behaviors is a pretty important question."

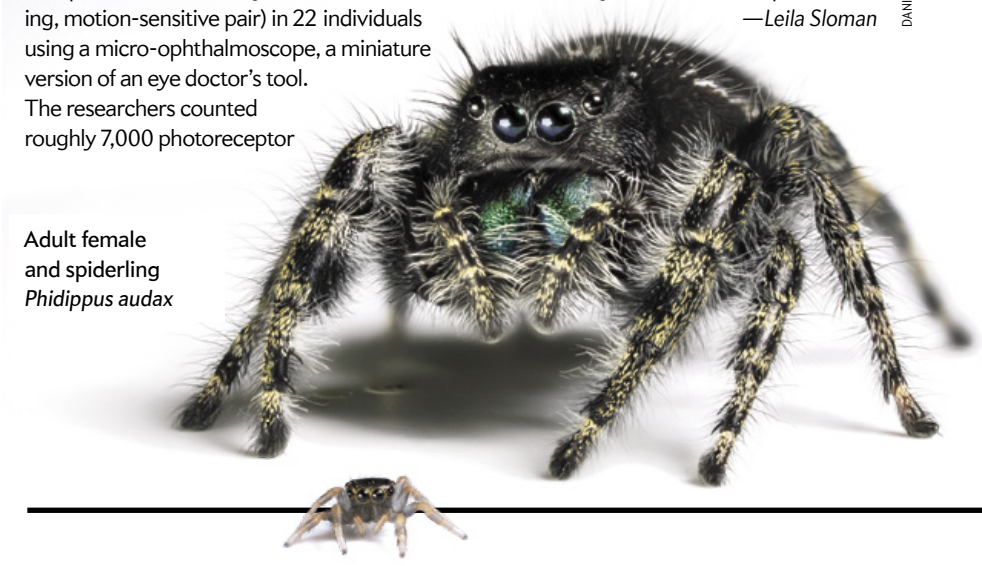
Researchers have observed that young jumping spiders can use complex visual cues while hunting. To find out how youngsters' vision is so close to adults', Morehouse and his colleagues peered into one of the spiders' four sets of eyes (a forward-facing, motion-sensitive pair) in 22 individuals using a micro-ophthalmoscope, a miniature version of an eye doctor's tool. The researchers counted roughly 7,000 photoreceptor cells per eye in early juvenile, late juvenile and adult spiders. They also examined seven of the spiders twice, four months apart, and found that none of them produced new photoreceptors.

That measurement indicates the spiders do not add receptors as they grow but cram in all these cells by the time they hatch—"Which is a crazy thing to do!" Morehouse says. According to the team's earlier genetic research, the tiny spiders most likely share an "ancient genetic tool kit" with insects: their bodies first construct the photoreceptors, then top them off with lenses. That mechanism makes sense for certain insects that add new photoreceptors, capped with separate lenses, to their eyes as they grow larger. But it is developmentally cumbersome for spiders, whose eyes each accommodate only one lens and so need all their photoreceptors in place early in life.

These results suggest spiderlings see as much detail as adults, with a comparable field of vision—although there are drawbacks. For instance, baby spiders' tiny photoreceptors provide poor light sensitivity. Morehouse has seen evidence of this himself: "They're a little bit stumbly," he says.

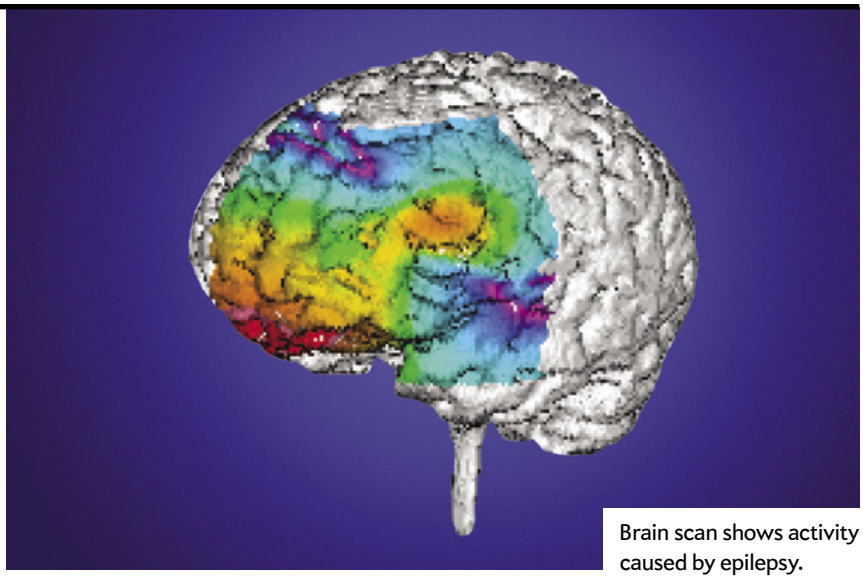
The eyes' biological structure cannot tell scientists everything about how the spiders see. "They may be making trade-offs at the neural level," Theobald says, such as restoring some sensitivity at the expense of spatial or temporal detail. For that reason, behavioral studies are necessary to fully understand spiders' vision. But the biological results alone are surprising, Theobald says: "To have to have all your photoreceptors right from the beginning? It's not the way I would build a spider."

—Leila Sloman



DANIEL ZUREK *Morehouse Lab*

Adult female and spiderling *Phidippus audax*



Brain scan shows activity caused by epilepsy.

SCIENCE SOURCE

MEDICINE

Seizure Warnings

Molecules in the blood could alert those with epilepsy hours ahead

More than 50 million people worldwide have epilepsy, and one of its harshest aspects is its unpredictability. Sufferers rarely know when a seizure will occur.

But molecular biologist Marion Hogg of FutureNeuro, a research institute hosted at the Royal College of Surgeons in Ireland, and her colleagues have found molecules whose levels in the bloodstream differ before and after a seizure. This discovery could lead to a blood test that gauges when seizures are likely to strike, enabling patients to take fast-acting preventive drugs. The study, published in July in the *Journal of Clinical Investigation,* may even offer clues about epilepsy's causes.

The researchers analyzed plasma samples from the blood of people with epilepsy and found that certain fragments of transfer RNA (tRNA)—a molecule involved in translating RNA into proteins—appear to spike hours before a seizure, then return to a normal level afterward. These fragments form when enzymes cut tRNAs in response to stress, possibly caused by increased brain activity in the run-up to a seizure.

Neurologist Mark Cook of St. Vincent's Hospital in Melbourne, Australia, who was not involved in the work, says the tRNA fluctuations could reflect the rhythms of biological clocks. "In adults with chronic epilepsy, we see cycles running over seven, 28, 40 days," Cook says. "These patterns control brain excitability, making you more or less liable to seizures." The new findings may thus ultimately lead to a better understanding of the causes of epilepsy. "We haven't known what's driving the cycles, but there may be a clue here that there are genes driving the system, generating these fragments, which allow prediction of seizures," Cook says. "That's very exciting because it tells you something not only about epilepsy but about how the brain works."

Cook's group previously predicted seizures by monitoring brain activity, but that required invasive surgery. FutureNeuro researchers are working on a seizure-prediction device that uses pinprick blood tests at home, similar to a glucose monitor. The study's analysis needed relatively large amounts of plasma separated from blood—so an immediate challenge is developing a device that works both with small samples and with whole blood. "We anticipate such a device may be available for patients to use in the next five years," Hogg says.

Advance warnings could make a major difference in patients' lives. "If you had an indication, perhaps you wouldn't go into work, or drive, or go swimming," Hogg says. And although some epilepsy drugs are fast-acting, most are for long-term management—but nearly a third of patients do not respond to the latter. Cook says that accurate seizure prediction would encourage drug development for acute use, which could mean fewer side effects as compared with a daily regimen.

—Simon Makin

SPACE ARCHAEOLOGY

History in Orbit

Space junk documents humanity's expansion into new frontiers

After two years on the moon, Surveyor 3 has visitors from the *Apollo 12* mission.

NASA

The word "archaeology" typically brings to mind crumbling ruins from ancient civilizations—not gleaming rocket ships or high-tech spacecraft. But more than 60 years of space missions have scattered countless artifacts throughout Earth orbit and across the solar system, creating a historic legacy of exploration for current and future generations. Alice Gorman, a researcher at Flinders University in Adelaide, Australia, is one of a few pioneering "space archaeologists" studying the Space Age. She is also the author of a new book, *Dr Space Junk vs the Universe: Archaeology and the Future* (MIT Press, 2019).

Scientific American spoke with Gorman about assessing the cultural significance of orbital debris and how to preserve space artifacts as a heritage for all humankind. An edited excerpt follows. —*Lee Billings*

What is "space archaeology?"

Space archaeology uses the physical material and the places associated with space exploration to learn about the human behaviors behind them. So this covers infrastructure on Earth, objects in Earth orbit and even sites on other worlds. The *Apollo* lunar landing areas are good examples—to me, those are archaeological sites. And that feeds into the related concept of "space heritage," which assigns different categories of significance—historical, aesthetic, social, spiritual and scientific—to certain artifacts and sites for past, present or future generations. Much of my work involves gathering the information to help make those judgments.

You're sometimes called Dr. Space Junk, but I get the sense you don't actually like the term.

That's right. Even though I strongly identify with that persona, the term "space junk" is problematic. From an archaeological per-

GEOLOGY

Birth of the Sahara

Dust on nearby islands hides secrets of the desert's origins

The Sahara is the world's largest and most legendary subtropical desert, but knowledge about it is surprisingly limited. Even estimates of when it formed vary widely, from more than five million years ago to mere thousands. Now, however, geologists studying wind-carried Saharan dust on the Canary Islands have come closer to pinning this down: it is, they report, close to five million years old.

One reason for the uncertainty over the Sahara's age is that researchers use such different methods to estimate it; these include studying desert dust found in sediment under the Atlantic Ocean, analyzing sandstone and modeling the ancient climate. To help settle things, geomorphologist Daniel Muhs of the U.S. Geological Survey (lead author on the new research) and his colleagues looked at sediment on Spain's Fuerteventura and Gran Canaria islands, where they found evidence of Saharan dust. The dust appeared in ancient soil layers, whose age they assessed on the basis of fossils found in the same layers—and that age agreed with earlier marine sediment studies. The researchers reported their finding in November in *Palaeogeography, Palaeoclimatology, Palaeoecology.*

"The conclusion of the study is very good," says Zhongshi Zhang, a climate modeler at the University of Bergen in Norway, who was not involved in the work. Because the dust found on the

spective, junk can be very valuable. When we call orbital debris "space junk," we're closing off the idea that it might have some positive qualities, now or in the future. Some space junk is still functional—satellites that still have fuel and can still transmit. They're only junk because no one is using them at this point in time. Not that these things must be gathering and relaying data to be useful; space artifacts can have primarily social rather than scientific functions, like Elon Musk's now interplanetary red Tesla sports car, or Vanguard 1, the oldest satellite [remaining] in space. Most of their value comes from shaping people's ideas of what space is and how they are connected to it.

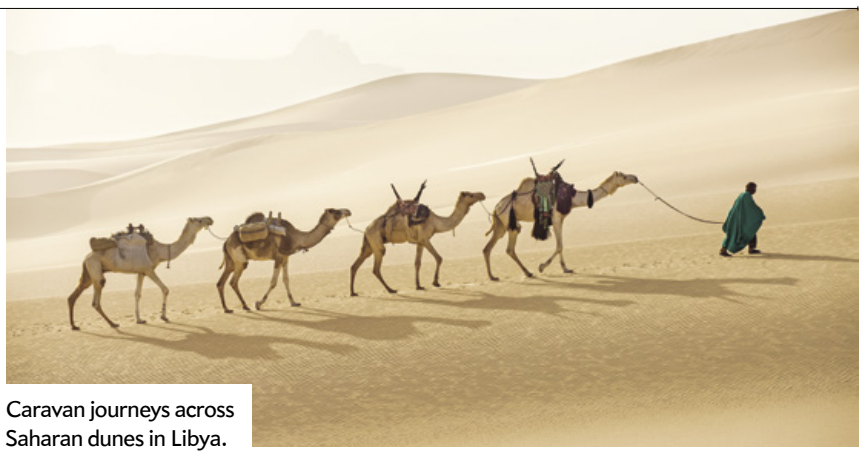
In your book, you argue that orbital debris should be left in place when there's no risk of collision with operational satellites and spacecraft. But why not bring something like Vanguard 1 down and put it in a museum?

I don't think putting Vanguard 1 or other superlative artifacts in a museum is the best strategy for preserving value.

An artifact's setting can be an important part of its significance. Some of Vanguard 1's significance depends on its being the oldest human-made object in orbit. Brought back to Earth, it can't be the oldest thing in orbit anymore—something else would gain that status. And, in terms of scientific significance, the longer we leave it up there, the more precious it becomes as a resource telling us the effects of long-term exposure to the space environment. We can and do study this remotely, measuring via reflectance how rough Vanguard 1's once smooth surface is becoming over time. Also, if you put Vanguard 1 in a museum, most people will never see it, only locals or tourists. But left as is, anyone can go look for it in the sky.

Are there any space artifacts or sites that merit special protections?

I'm very worried about lunar sites, particularly those of the *Apollo* landings. Everyone seems to be talking about going to the moon again, and people have talked about visiting or approaching these places. If we don't make a solid case for their protection, then some cowboy might just send a rover right up to *Apollo 11*'s landing site and drive over Armstrong's and Aldrin's footprints. Even if they only get close enough for a photo from a distance, that can still stir up lots of lunar dust, which can be very damaging for past exploration sites. On Earth the archaeological principle is to not unnecessarily destroy things and to always leave more for future researchers who may use better, more advanced techniques.



Caravan journeys across Saharan dunes in Libya.

ANNA SERDYUK *Getty Images*

islands is distinct from the marine record, Zhang adds, it helps to build the case for a multimillion-year age.

The Sahara is the biggest source of airborne dust in the world—and that dust's journey does not end in the Canary Islands, which lie just off the western coast of Africa. It continues on to places such as the Caribbean and the Amazon rain forest, Muhs notes. Amazon soils are poor in nutrients, and he says the new results help to show how nourishing dust from Africa could have been supporting the South American region's incredible biodiversity for millions of years—adding to the Amazon's own origin story. —*Lucas Joel*

A Dilemma with New Drugs

Most of the time we don't know if they are better than the old ones

By Claudia Wallis

"New and improved." These words have been yoked together in so many marketing campaigns that we tend to accept them as inexorably linked. But when it comes to new medications, don't swallow them without a healthy dose of skepticism. Many or most new drugs are not—or at least not provably—an improvement over the best existing drug for a given condition, and the fast-track drug-approval processes that have prevailed in recent years have added to the uncertainty about their advantages.

A recent report in the *British Medical Journal,* entitled "New Drugs: Where Did We Go Wrong and What Can We Do Better?," offers an analysis of the issue. The authors looked at 216 drugs approved by German regulators between 2011 and 2017; 152 were newly developed, and 64 were existing medications approved for new uses. Only 25 percent of the medications were deemed as offering a "considerable" or "major" advantage over the established treatment (termed the "standard of care"), and 16 percent had a minor or nonquantifiable advantage. Fully 58 percent had no proven added benefit in terms of lowering mortality, reducing symptoms or side effects, or improving health-related quality of life.

"This doesn't mean we are sure there's no added benefit," lead author Beate Wieseler said in an interview. "It just means we have no positive proof. Either we have no studies at all [comparing the new medicine with the standard of care] or we have studies, but they aren't good enough." The record was "particularly egregious," she and her colleagues wrote, for drugs that treat psychiatric and neurological disorders and those for diabetes, with only 6 and 17 percent, respectively, offering a confirmed added benefit.

Wieseler and her co-authors work for Germany's Institute for Quality and Efficiency in Health Care, which evaluates new treatments and advises on whether the country's health care system should pay a premium for them. Such organizations, known as health technology assessment (HTA) agencies, have become "enormously more powerful" in many countries' efforts to manage the spiraling cost of new drugs, says Sean Tunis of the not-for-profit Center for Medical Technology Policy in Baltimore. HTA works a little differently in the U.S., he explains: "If payers think a new drug is not any better than a drug that we already have, they will do things like requiring you try the cheaper drug first." Insurers and Medicaid will often insist on this kind of "step therapy."

Germany's HTA is probably the most persnickety about demanding head-to-head trials to prove that a new treatment beats the existing standard. This is not always practical. For one thing, such studies can be hugely expensive and time-consuming, with no guarantee of success. "What the authors are focused on is getting new, differentiated medicines at a low cost, and what they are missing is a sense of the complex economic underpinning of developing new medicines," says Ken Moch, president and CEO of Cognition Therapeutics, a biotech firm in Pittsburgh. Requiring trials that prove superiority, he says, can discourage companies from even attempting to develop new alternatives. This is already happening. Drug developers are increasingly focused on niches where there are no good treatments to compete with, such as rare diseases and advanced cancers. The sky's the limit on prices for these first-to-market drugs, which are often rushed through FDA approval with limited data on efficacy. Many new cancer drugs are approved when it is shown they can shrink tumors by 30 percent, even if there is no proof that they boost survival.

This lack of meaningful data to guide patients is a major point of Wieseler's paper. Tunis shares her concern: with accelerated approval, "there are more products approved, with a greater amount of uncertainty about risks and benefits." But there are other solutions besides head-to-head drug trials. One idea is for regulators and payers to require postmarket studies to track the effectiveness of newly approved drugs—a step too often neglected.

Tunis's center is taking another approach. Last year it helped to convene the makers of seven experimental gene therapies for hemophilia with patient groups, regulators, HTA agencies and others to agree on a set of meaningful end points for the companies' final studies before they seek approval. Patients, for example, asked that improvements in chronic pain and mental health be measured along with the frequency of bleeding episodes. The center is now looking at sickle cell therapies. If developers all use the same outcome metrics, it will be possible to compare the various products. Patients and their doctors won't be left in the dark. SA

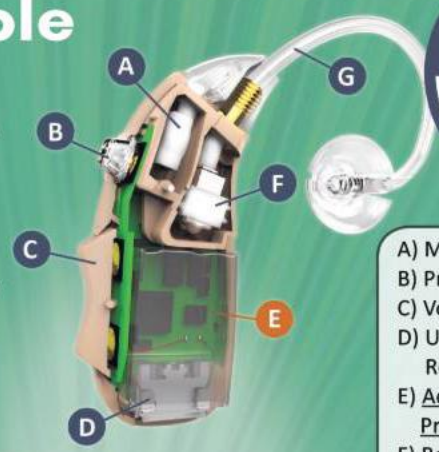
Claudia Wallis is an award-winning science journalist whose work has appeared in the *New York Times, Time, Fortune* and the *New Republic.* She was science editor at *Time* and managing editor of *Scientific American Mind.*

Illustration by Celia Krampien

Advanced Rechargeable Digital Hearing Aid Technology Only $229!*

(*Each when you buy a pair)

The new Advanced HearClear™ **HCR3 rechargeable** hearing aid combines advanced technology with a low price to provide you with outstanding value.



NEW ADVANCED R3 Digital Processor™

A) Microphone
B) Program Button
C) Volume Control
D) USB Charging Port & Rechargeable Battery
E) Advanced Digital Processor
F) Receiver (Speaker)
G) Sound Tube

5 Star Reviews! ★★★★★

Outstanding Product! "This product is outstanding. Dad loves it, my mom loves it, and I am grateful! Don't believe that you have to spend a lot of money to get a quality hearing aid"
- Gilmore B.

HCR3 Features!

- New Advanced Third Generation **American Technology**
- Digital sound processing chip provides **clear sound and makes speech easier to understand** with less feedback than old analog technology
- Don't worry about replacing batteries! **Full Charge Gives 16 Hours of Use! (Charger Included)**
- Easy **On / Off Button**
- Automatic Noise Reduction and Feedback Cancellation
- **100% Money Back Guarantee**
- **4 Programs** for different listening situations

Even Better In Pairs!

Your brain is designed to use both ears working together. In fact, studies show that you may be able to **hear up to 3 times better** in noisy situations when using two hearing aids. Buy a pair for the best results and maximum savings!

Simple. Affordable. Rechargeable Digital Hearing Aid - For Only $229!*

The new HearClear™ HCR3 Rechargeable Digital Hearing Aids features **advanced third generation digital technology** at an unbelievably affordable Price! The HCR3 is packed with the same key technologies that all high end digital hearing aids share while leaving out the extra bells and whistles that increase cost and require expensive adjustments. This **helps you hear better, while saving you a lot of money.**

NOW ON SALE!
~~List Price: $849~~
Sale Price: $229*

Your new HearClear HCR3 hearing aids work at a fraction of the cost of name-brand hearing aids, and you won't have to keep changing the batteries! You will love the discreet, comfortable, lightweight Open-fit design. The HCR3 is pre-programmed for most moderate to significant hearing losses, so you won't need professional appointments to make costly adjustments. **It is shipped directly to you and will help you hear better right out of the box!**

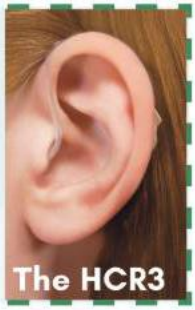
You can spend thousands for an expensive hearing aid, or you can spend just **$249** for a hearing aid that is great for most hearing losses **(only $229 each when you buy a pair – hear up to 3 times better than wearing just one)**. We are so sure you will love your hearing aids that we offer a **100% Money Back Guarantee - Risk Free** if you are not satisfied for any reason.

MONEY SAVING OFFER!

Use Coupon Code: **SA9A**

1-877-518-1813

***Only $229 Each When You Buy A Pair!**
(Coupon Code & Price Valid For A Limited Time Only)



Advanced Affordable Hearing™
Affordable Quality Since 1996!

A+ BBB ACCREDITED BUSINESS | 100% MONEY BACK GUARANTEE | RISK • FREE • Trial | US Company Owned And Operated | FDA REGISTERED

Visit and Save: **www.AdvancedHearing.com/SA9A**

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.

Requiem for the Telephone Call

Can you really "reach out and touch someone" via text?

By Wade Roush

The world's first telephone call—"Mr. Watson, come here, I want to see you"—was a request for a face-to-face meeting.

I live in Boston, where Alexander Graham Bell made that historic call in 1876, and on a recent trip I passed through Brantford, Ontario, where Bell first dreamed up his telephone in 1874. In Brantford, which bills itself as the "Telephone City," there's a giant memorial to Bell that includes a bronze casting with figures meant to represent Knowledge, Joy and Sorrow—the varieties of information spread by the telephone.

Today maybe we should reserve a bit of sorrow for the weakening of the personal connections fostered by Bell's miraculous invention.

We own more "phones" than ever, but we don't use them primarily for voice calls. In 2010 Americans spent 2.24 trillion minutes talking on their mobile devices—which averages out to 7,813 minutes per mobile line. By 2017 that had dropped to just 5,539 minutes per line, or 6,686 minutes per U.S. resident.

That's still 18 minutes per person per day, but it's a small slice of the *five hours a day* we spend doing other things on our mobile devices: watching YouTube and TikTok, browsing Facebook and Twitter, sending text messages, and all the rest. So at the inquest over the falloff in voice communication, Exhibit A is digital data. We consumed 28.6 trillion megabytes of data on our phones in 2018, a dramatic 82 percent increase over 2017 levels, according to the wireless industry group CTIA.

Exhibit B is robocalls. YouMail, which makes a robocall-blocking app, says that 4.7 billion calls were placed to U.S. phone numbers in July 2019 alone, an average of 14 per person. My own phone log shows that I got 36 spam calls that month—so many that I've started ignoring all unscheduled or unidentified calls.

In July the U.S. House of Representatives voted 429–3 to approve a bill that would allow carriers to block suspected robocallers and require them to implement authentication technology to screen out calls from spoofed numbers. The Senate had already passed a similar bill, and the White House is expected to approve a joint version this fall. Representative Frank Pallone, Jr., of New Jersey, chair of the Energy and Commerce Committee, predicted the measure will "restore Americans' confidence in the telephone system."

But the truth is, it's too late for that. An entire generation of Americans has grown up using phones as glorified pagers. Many people in this group would rather not receive calls at all; speaking on the phone "demands their full attention when they don't want to give it," as Sherry Turkle observed in *Alone Together,* her incisive 2011 book about the social price of the mobile revolution.

And to *make* a call is often seen as tantamount to aggression—a point that's satirized in a recent episode of Netflix's *Tales of the City.* Sixtysomething Brian is about to call a potential blind date when his fortysomething neighbor Wren grabs his phone out of his hand. "What the hell are you doing?" she exclaims. "I said reach out! That's text! I mean, this is the 21st century. Who's calling someone, you damn psychopath?"

But what's lost when texts and posts replace conversation is, briefly put, Joy and Sorrow: the emotional content conveyed by the human voice. Stripped of this real-time engagement, we're left only with Knowledge, which, as the past few years have shown, is so easily warped and misrepresented. Our telephones may have evolved into machines for 24/7 tweeting and texting, but we're more alone than ever. SA

JOIN THE CONVERSATION ONLINE
Visit *Scientific American* on Facebook and Twitter or send a letter to the editor: editors@sciam.com

Illustration by Jay Bendt

Incredible Africa

A PRIVATE JET EXPEDITION

EARLY BOOKING
book by Dec. 31, 2019 and earn a
$5,000 CREDIT
per person

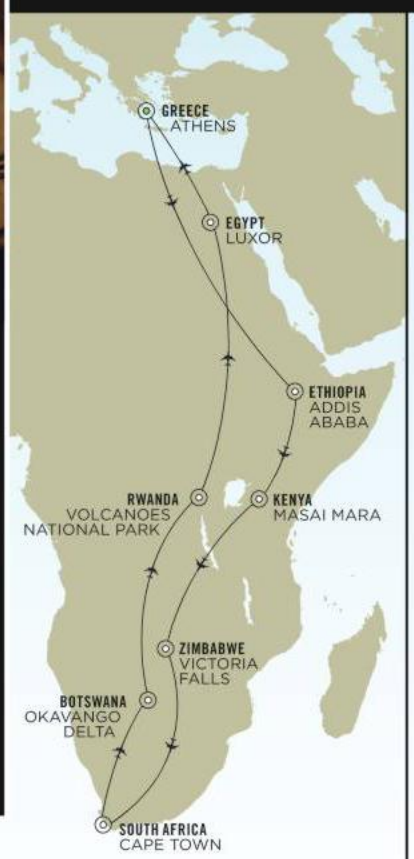
TRAVEL WITH EXPEDITION HOST

Donald Johanson

Best known for his 1974 discovery of **'Lucy,'** one of the most complete skeletons of *Australopithecus afarensis* known, Donald Johanson is one of four expert leaders of Incredible Africa.

46 GUESTS | **22** DAYS | **8** COUNTRIES

SEPTEMBER 4-25 | 2020



BUSHTRACKS
BY PRIVATE AIR

- Travel in comfort and security on a privately chartered Boeing 737 jet in an all-business class configuration
- Connect 5 UNESCO World Heritage Sites: the Acropolis, Ethiopia's subterranean churches, Victoria Falls, Botswana's Okavango Delta, and ancient Thebes with its necropolis in Luxor, Egypt
- Spot migrating wildebeest herds in the Masai Mara, track gorillas in Rwanda, and observe penguins, seals and more in Cape Town
- Led by Bushtracks founder David Tett, Craig Sholley (Senior Vice president at the African Wildlife Foundation), and naturalist Lisa Stevens

Learn more at: **bushtracks.com/by-private-air** or call for a **BROCHURE** 800.995.8689

GREECE	ETHIOPIA	KENYA	ZIMBABWE	SOUTH AFRICA	BOTSWANA	RWANDA	EGYPT
ATHENS	ADDIS ABABA	MASAI MARA	VICTORIA FALLS	CAPE TOWN	OKAVANGO DELTA	VOLCANOES NATIONAL PARK	LUXOR

Scientific American Unlimited

Perfect for science fans, gain access to all of our publications, apps & the full website experience.

Digital archive access back to 1845 including articles by Einstein, Curie and other timeless luminaries in more than 7,000 issues!

12 print and digital issues of *Scientific American* per year

More than 150 eBooks and Collector's Editions

Access to *Scientific American Mind*, *Space & Physics* and *Health & Medicine*

More than 200 articles per month, including news and commentary, on ScientificAmerican.com

sciam.com/unlimited

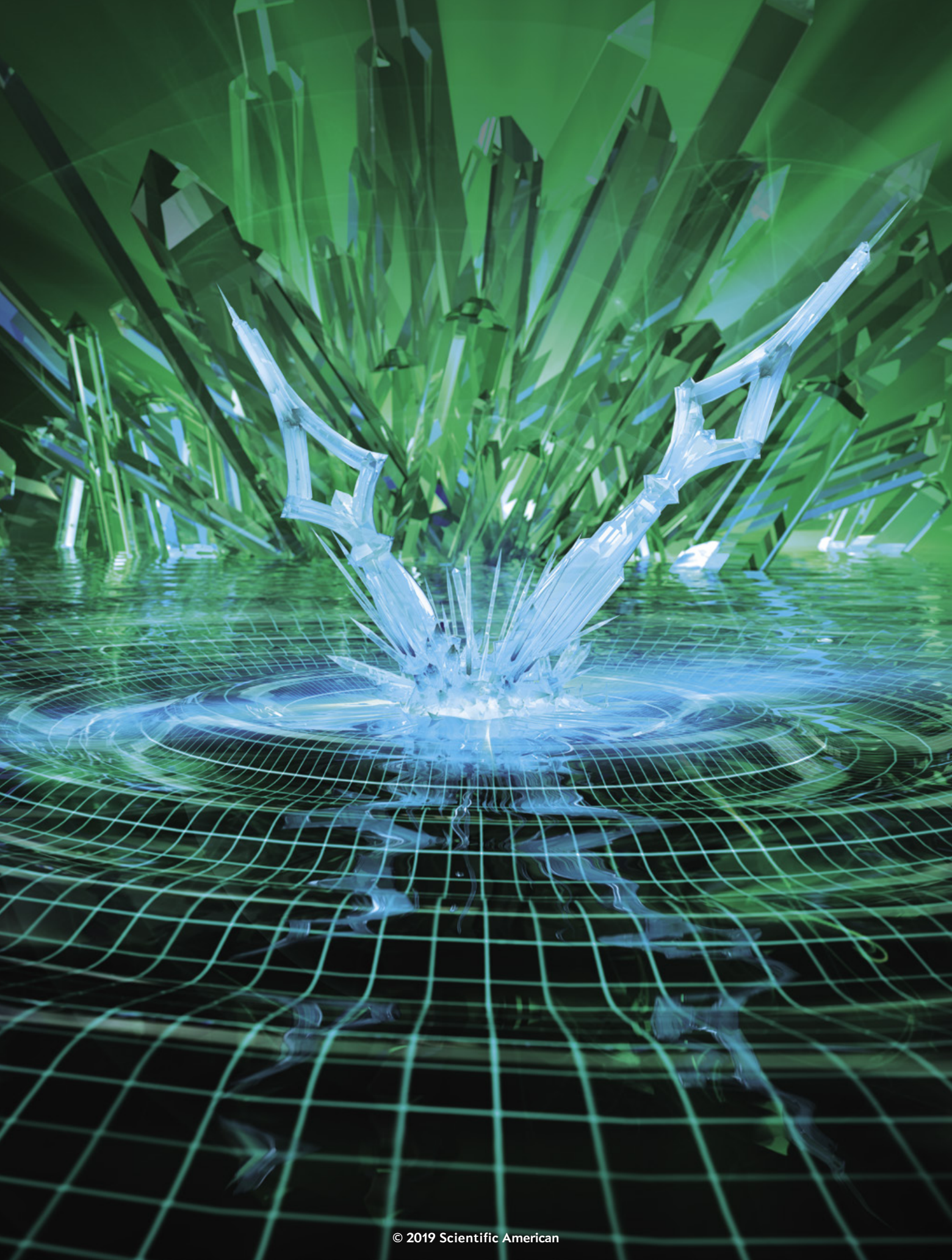
PHYSICS

CRYSTALS IN TIME

Surprising new states of matter called time crystals show the same symmetry properties in time that ordinary crystals do in space

By Frank Wilczek

Illustration by Mark Ross Studio



Frank Wilczek is a theoretical physicist at the Massachusetts Institute of Technology. He won the 2004 Nobel Prize in Physics for his work on the theory of the strong force, and in 2012 he proposed the concept of time crystals.

CRYSTALS

ARE NATURE'S MOST ORDERLY SUBSTANCES. INSIDE THEM, ATOMS and molecules are arranged in regular, repeating structures, giving rise to solids that are stable and rigid—and often beautiful to behold.

People have found crystals fascinating and attractive since before the dawn of modern science, often prizing them as jewels. In the 19th century scientists' quest to classify forms of crystals and understand their effect on light catalyzed important progress in mathematics and physics. Then, in the 20th century, study of the fundamental quantum mechanics of electrons in crystals led directly to modern semiconductor electronics and eventually to smartphones and the Internet.

IN BRIEF

Crystals are orderly states of matter in which the arrangements of atoms take on repeating patterns. In the language of physics, they are said to have "spontaneously broken spatial symmetry."

Time crystals, a newer concept, are states of matter whose patterns repeat at set intervals of time rather than space. They are systems in which time symmetry is spontaneously broken.

The notion of time crystals was first proposed in 2012, and in 2017 scientists discovered the first new materials that fully fit this category. These and others that followed offer promise for the creation of clocks more accurate than ever before.

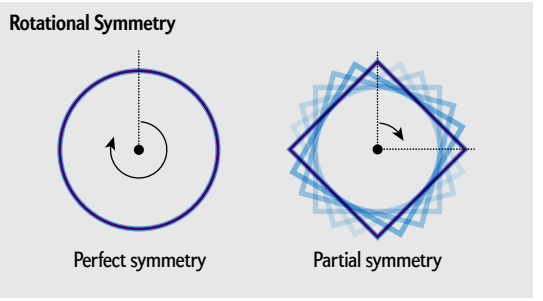
The next step in our understanding of crystals is occurring now, thanks to a principle that arose from Albert Einstein's relativity theory: space and time are intimately connected and ultimately on the same footing. Thus, it is natural to wonder whether any objects display properties in time that are analogous to the properties of ordinary crystals in space. In exploring that question, we discovered "time crystals." This new concept, along with the growing class of novel materials that fit within it, has led to exciting insights about physics, as well as the potential for novel applications, including clocks more accurate than any that exist now.

SYMMETRY

BEFORE I FULLY EXPLAIN this new idea, I must clarify what, exactly, a crystal is. The most fruitful answer for scientific purposes brings in two profound concepts: symmetry and spontaneous symmetry breaking.

In common usage, "symmetry" very broadly indicates balance, harmony or even justice. In physics and mathematics, the meaning is more precise. We say that an object is symmetric or has symmetry if there are transformations that could change it but do not.

That definition might seem strange and abstract at first, so let us focus on a simple example: Consider a circle. When we rotate a circle around its center, through any angle, it remains visually the same, even though every point on it may have moved—it has perfect rotational symmetry. A square has some symmetry but less than a circle because you must rotate a square through a full 90 degrees before it regains its initial appearance. These examples show that the mathematical concept of symmetry captures an essential aspect of its common meaning while adding the virtue of precision.



A second virtue of this concept of symmetry is that it can be generalized. We can adapt the idea so that it applies not just to shapes but more widely to physical laws. We say a law has symmetry if we can change the context in which the law is applied without changing the law itself. For example, the basic axiom of special relativity is that the same physical laws apply when we view the world from different platforms that move at constant velocities relative to one another. Thus, relativity demands that physical laws display a kind of symmetry—namely, symmetry under the platform-changing transformations that physicists call "boosts."

A different class of transformations is important for crystals, including time crystals. They are the very simple yet profoundly important transformations known as "translations." Whereas relativity says the

Illustrations by Jen Christiansen

same laws apply for observers on moving platforms, spatial translation symmetry says the same laws apply for observers on platforms in different places. If you move—or "translate"—your laboratory from one place to another, you will find that the same laws hold in the new place. Spatial translation symmetry, in other words, asserts that the laws we discover *anywhere* apply *everywhere*.

Time translation symmetry expresses a similar idea but for time instead of space. It says the same laws we operate under now also apply for observers in the past or in the future. In other words, the laws we discover at any time apply at every time. In view of its basic importance, time translation symmetry deserves to have a less forbidding name, with fewer than seven syllables. Here I will call it tau, denoted by the Greek symbol τ.

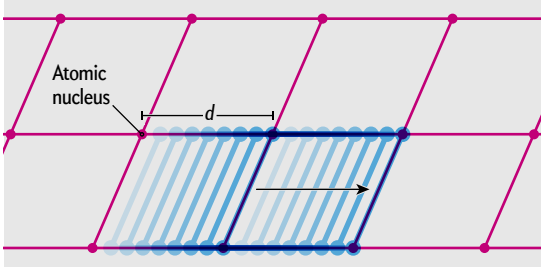
Without space and time translation symmetry, experiments carried out in different places and at different times would not be reproducible. In their everyday work, scientists take those symmetries for granted. Indeed, science as we know it would be impossible without them. But it is important to emphasize that we can test space and time translation symmetry empirically. Specifically, we can observe behavior in distant astronomical objects. Such objects are situated, obviously, in different places, and thanks to the finite speed of light we can observe in the present how they behaved in the past. Astronomers have determined, in great detail and with high accuracy, that the same laws do in fact apply.

SYMMETRY BREAKING

FOR ALL THEIR AESTHETIC SYMMETRY, it is actually the way crystals lack symmetry that is, for physicists, their defining characteristic.

Consider a drastically idealized crystal. It will be one-dimensional, and its atomic nuclei will be located at regular intervals along a line, separated by the distance d. (Their coordinates therefore will be nd, where n is a whole number.) If we translate this crystal to the right by a tiny distance, it will not look like the same object. Only after we translate through the specific distance d will we see the same crystal. Thus, our idealized crystal has a reduced degree of spatial translation symmetry, similarly to how a square has a reduced degree of rotation symmetry.

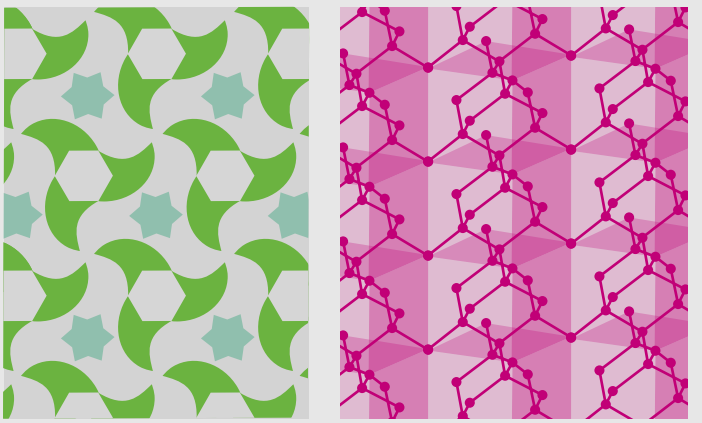
Translational Symmetry



Physicists say that in a crystal the translation symmetry of the fundamental laws is "broken," leading to a lesser translation symmetry. That remaining symmetry conveys the essence of our crystal. Indeed, if we know that a crystal's symmetry involves translations through multiples of the distance d, then we know where to place its atoms relative to one another.

Crystalline patterns in two and three dimensions can be more complicated, and they come in many varieties. They can display partial rotational and partial translational symmetry. The 14th-century artists who decorated the Alhambra palace in Granada, Spain, discovered many possible forms of two-dimensional crystals by intuition and experimentation, and mathematicians in the 19th century classified the possible forms of three-dimensional crystals.

Complex Crystalline Pattern Examples



Two dimensions (from the Alhambra palace) Three dimensions (diamond crystal structure)

In the summer of 2011 I was preparing to teach this elegant chapter of mathematics as part of a course on the uses of symmetry in physics. I always try to take a fresh look at material I will be teaching and, if possible, add something new. It occurred to me then that one could extend the classification of possible crystalline patterns in three-dimensional space to crystalline patterns in four-dimensional spacetime.

When I mentioned this mathematical line of investigation to Alfred Shapere, my former student turned valued colleague, who is now at the University of Kentucky, he urged me to consider two very basic physical questions. They launched me on a surprising scientific adventure:

What real-world systems could crystals in spacetime describe?

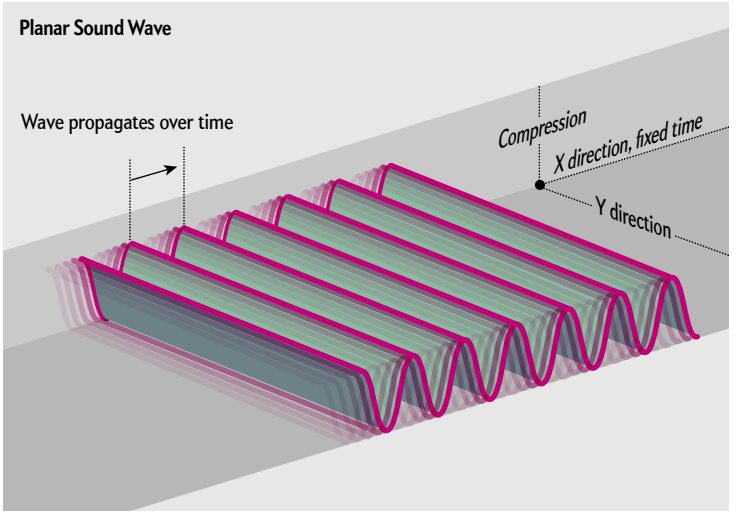
Might these patterns lead us to identify distinctive states of matter?

The answer to the first question is fairly straightforward. Whereas ordinary crystals are orderly arrangements of objects in space, spacetime crystals are orderly arrangements of events in spacetime.

As we did for ordinary crystals, we can get our bearings by considering the one-dimensional case, in

which spacetime crystals simplify to purely time crystals. We are looking, then, for systems whose overall state repeats itself at regular intervals. Such systems are almost embarrassingly familiar. For example, Earth repeats its orientation in space at daily intervals, and the Earth-sun system repeats its configuration at yearly intervals. Inventors and scientists have, over many decades, developed systems that repeat their arrangements at increasingly accurate intervals for use as clocks. Pendulum and spring clocks were superseded by clocks based on vibrating (traditional) crystals, and those were eventually superseded by clocks based on vibrating atoms. Atomic clocks have achieved extraordinary accuracy, but there are important reasons to improve them further—and time crystals might help, as we will see later.

Some familiar real-world systems also embody higher-dimensional spacetime crystal patterns. For example, the pattern shown here can represent a planar sound wave, where the height of the surface indicates compression as a function of position and time. More elaborate spacetime crystal patterns might be difficult to come by in nature, but they could be interesting targets for artists and engineers—imagine a dynamic Alhambra on steroids.



These types of spacetime crystals, though, simply repackage known phenomena under a different label. We can move into genuinely new territory in physics by considering Shapere's second question. To do that, we must now bring in the idea of *spontaneous* symmetry breaking.

SPONTANEOUS SYMMETRY BREAKING

WHEN A LIQUID or gas cools into a crystal, something fundamentally remarkable occurs: the emergent solution of the laws of physics—the crystal—displays less symmetry than the laws themselves. As this reduction of symmetry is brought on just by a decrease in temperature, without any special outside intervention, we can say that in forming a crystal the material breaks spatial translation symmetry "spontaneously."

An important feature of crystallization is a sharp change in the system's behavior or, in technical language, a sharp phase transition. Above a certain critical temperature (which depends on the system's chemical composition and the ambient pressure), we have a liquid; below it we have a crystal—objects with quite different properties. The transition occurs predictably and is accompanied by the emission of energy (in the form of heat). The fact that a small change in ambient conditions causes a substance to reorganize into a qualitatively distinct material is no less remarkable for being, in the case of water and ice, very familiar.

The rigidity of crystals is another emergent property that distinguishes them from liquids and gases. From a microscopic perspective, rigidity arises because the organized pattern of atoms in a crystal persists over long distances and the crystal resists attempts to disrupt that pattern.

The three features of crystallization that we have just discussed—reduced symmetry, sharp phase transition and rigidity—are deeply related. The basic principle underlying all three is that atoms "want" to form patterns with favorable energy. Different choices of pattern—in the jargon, different phases—can win out under different conditions (for instance, various pressures and temperatures). When conditions change, we often see sharp phase transitions. And because pattern formation requires collective action on the part of the atoms, the winning choice will be enforced over the entire material, which will snap back into its previous state if the chosen pattern is disturbed.

Because spontaneous symmetry breaking unites such a nice package of ideas and powerful implications, I felt it was important to explore the possibility that τ can be broken spontaneously. As I was writing up this idea, I explained it to my wife, Betsy Devine: "It's like a crystal but in time." Drawn in by my excitement, she was curious: "What are you calling it?" "Spontaneous breaking of time translation symmetry," I said. "No way," she countered. "Call it time crystals." Which, naturally, I did. In 2012 I published two papers, one co-authored by Shapere, introducing the concept. A time crystal, then, is a system in which τ is spontaneously broken.

One might wonder why it took so long for the concepts of τ and spontaneous symmetry breaking to come together, given that separately they have been understood for many years. It is because τ differs from other symmetries in a crucial way that makes the question of its possible spontaneous breaking much subtler. The difference arises because of a profound theorem proved by mathematician Emmy Noether in 1915. Noether's theorem makes a connection between symmetry principles and conservation laws—it shows that for every form of symmetry, there is a corresponding quantity that is conserved. In the application relevant here, Noether's theorem states that τ is basically

equivalent to the conservation of energy. Conversely, when a system breaks τ, energy is not conserved, and it ceases to be a useful characteristic of that system. (More precisely: without τ, you can no longer obtain an energylike, time-independent quantity by summing up contributions from the system's parts.)

The usual explanation for why spontaneous symmetry breaking occurs is that it can be favorable energetically. If the lowest-energy state breaks *spatial* symmetry and the energy of the system is conserved, then the broken symmetry state, once entered, will persist. That is how scientists account for ordinary crystallization, for example.

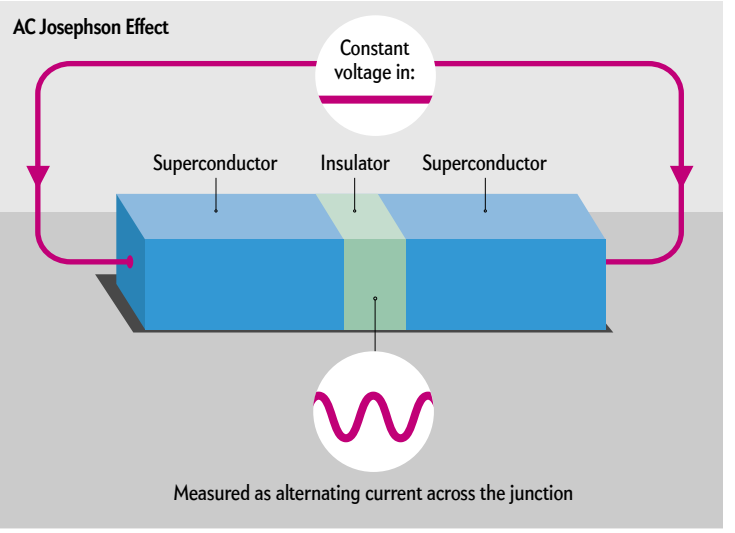
But that energy-based explanation will not work for τ breaking, because τ breaking removes the applicable measure of energy. This apparent difficulty put the possibility of spontaneous τ breaking, and the associated concept of time crystals, beyond the conceptual horizon of most physicists.

There is, however, a more general road to spontaneous symmetry breaking, which also applies to τ breaking. Rather than spontaneously reorganizing to a lower-energy state, a material might reorganize to a state that is more stable for other reasons. For instance, ordered patterns that extend over large stretches of space or time and involve many particles are difficult to unravel because most disrupting forces act on small, local scales. Thus, a material might achieve greater stability by taking on a new pattern that occurs over a larger scale than in its previous state.

Ultimately, of course, no ordinary state of matter can maintain itself against all disruptions. Consider, for example, diamonds. A legendary ad campaign popularized the slogan "a diamond is forever." But in the right atmosphere, if the temperature is hot enough, a diamond will burn into inglorious ash. More basically, diamonds are not a stable state of carbon at ordinary temperatures and atmospheric pressure. They are created at much higher pressures and, once formed, will survive for a very long time at ordinary pressures. But physicists calculate that if you wait long enough, your diamond will turn into graphite. Even less likely, but still possible, a quantum fluctuation can turn your diamond into a tiny black hole. It is also possible that the decay of a diamond's protons will slowly erode it. In practice, what we mean by a "state of matter" (such as diamond) is an organization of a substance that has a useful degree of stability against a significant range of external changes.

OLD AND NEW TIME CRYSTALS

THE AC JOSEPHSON EFFECT is one of the gems of physics, and it supplies the prototype for one large family of time crystals. It occurs when we apply a constant voltage V (a difference in potential energy) across an insulating junction separating two superconducting materials (a so-called Josephson junction, named after physicist Brian Josephson). In this situation, one observes that an alternating current at frequency $2eV/\hbar$ flows across the junction, where e is the charge of an electron and $\hbar$ is the reduced Planck's constant. Here, although the physical setup does not vary in time (in other words, it respects τ), the resulting behavior does vary in time. Full time translation symmetry has been reduced to symmetry under time translation by multiples of the period $\hbar/2eV$. Thus, the AC Josephson effect embodies the most basic concept of a time crystal. In some respects, however, it is not ideal. To maintain the voltage, one must somehow close the circuit and supply a battery. But AC circuits tend to dissipate heat, and batteries run down. Moreover, oscillating currents tend to radiate electromagnetic waves. For all these reasons, Josephson junctions are not ideally stable.



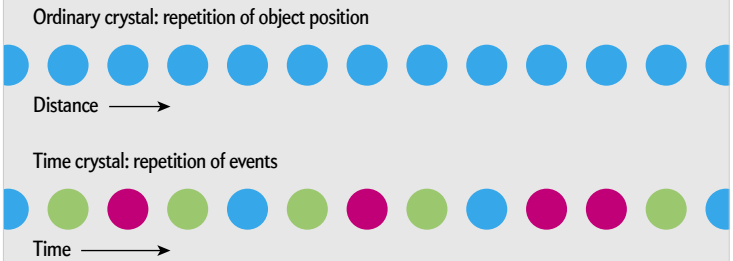
By using various refinements (such as fully superconducting circuits, excellent capacitors in place of ordinary batteries and enclosures to trap radiation), it is possible to substantially reduce the levels of those effects. And other systems that involve superfluids or magnets in place of superconductors exhibit analogous effects while minimizing those problems. In very recent work, Nikolay Prokof'ev and Boris Svistunov have proposed extremely clean examples involving two interpenetrating superfluids.

Thinking explicitly about τ breaking has focused attention on these issues and led to the discovery of new examples and fruitful experiments. Still, because the central physical idea is already implicit in Josephson's work of 1962, it seems appropriate to refer to all these as "old" time crystals.

"New" time crystals arrived with the March 9, 2017, issue of *Nature,* which featured gorgeous (metaphorical) time crystals on the cover and announced "Time crystals: First observations of exotic new state of matter." Inside were two independent discovery papers. In one experiment, a group led by Christopher Monroe of the University of Maryland, College Park, created a time crystal in an engineered system of a chain of ytterbium ions. In the other, Mikhail Lukin's group at Harvard University realized a time crystal in a system

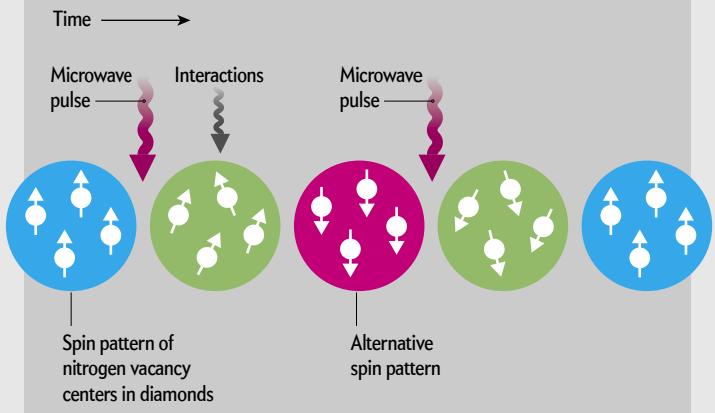
Making a Time Crystal

Just as the atoms in regular crystals repeat their arrangements over certain distances, time crystals are states of matter that repeat over specific periods of time. The first new materials that fit into this category were discovered in 2017 by two research teams, one led by Mikhail Lukin of Harvard University and the other by Christopher Monroe of the University of Maryland, College Park.



The Lukin Experiment

Lukin's group created a time crystal by manipulating the spins of atoms in so-called nitrogen vacancy centers—impurities in a diamond lattice. The researchers periodically exposed the diamond to laser pulses. Between pulses, the spins continued to interact with one another. The entire system repeated its overall configuration periodically—but not with the same period as the microwave pulses. Rather the system took on its own timing period, cycling at a fraction of the frequency of the pulses.



of many thousands of defects, called nitrogen vacancy centers, in a diamond.

In both systems, the spin direction of the atoms (either the ytterbium ions or the diamond defects) changes with regularity, and the atoms periodically come back into their original configurations. In Monroe's experiment, researchers used lasers to flip the ions' spins and to correlate the spins into connected, "entangled" states. As a result, though, the ions' spins began to oscillate at only half the rate of the laser pulses. In Lukin's project, the scientists used microwave pulses to flip the diamond defects' spins. They observed time crystals with twice and three times the pulse spacing. In all these experiments, the materials received external stimulation—lasers or microwave pulses—but they displayed a different period than that of their stimuli. In other words, they broke time symmetry spontaneously.

These experiments inaugurated a direction in materials physics that has grown into a minor industry. More materials utilizing the same general principles—which have come to be called Floquet time crystals—have come on the scene since then, and many more are being investigated.

Floquet time crystals are distinct in important ways from related phenomena discovered much earlier. Notably, in 1831 Michael Faraday found that when he shook a pool of mercury vertically with period T, the resulting flow often displayed period $2T$. But the symmetry breaking in Faraday's system—and in many other systems studied in the intervening years prior to 2017—does not allow a clean separation between the material and the drive (in this case, the act of shaking), and it does not display the hallmarks of spontaneous symmetry breaking. The drive never ceases to pump energy (or, more accurately, entropy), which is radiated as heat, into the material.

In effect, the entire system consisting of material plus drive—whose behavior, as noted, cannot be cleanly separated—simply has less symmetry than the drive considered separately. In the 2017 systems, in contrast, after a brief settling-down period, the material falls into a steady state in which it no longer exchanges energy or entropy with the drive. The difference is subtle but physically crucial. The new Floquet time crystals represent distinct phases of matter, and they display the hallmarks of spontaneous symmetry breaking, whereas the earlier examples, though extremely interesting in their own right, do not.

Likewise, Earth's rotation and its revolution around the sun are not time crystals in this sense. Their impressive degree of stability is enforced by the approximate conservation of energy and angular momentum. They do not have the lowest possible values of those quantities, so the preceding energetic argument for stability does not apply; they also do not involve long-range patterns. But precisely because of the enormous value of energy and angular momentum in these systems, it takes either a big disturbance or small disturbances acting over a long time to significantly change them. Indeed, effects that include the tides, the gravitational influence of other planets and even the evolution of the sun do slightly alter those astronomical systems. The associated measures of time such as "day" and "year" are, notoriously, subject to occasional correction.

In contrast, these new time crystals display strong rigidity and stability in their patterns—a feature that offers a way of dividing up time very accurately, which could be the key to advanced clocks. Modern atomic clocks are marvels of accuracy, but they lack the guaranteed long-term stability of time crystals. More accurate, less cumbersome clocks based on these emerging

states of matter could empower exquisite measurements of distances and times, with applications from improved GPS to new ways of detecting underground caves and mineral deposits through their influence on gravity or even gravitational waves. DARPA—the Defense Advanced Research Projects Agency—is funding research on time crystals with such possibilities in mind.

THE TAO OF τ

THE CIRCLE OF IDEAS and experiments around time crystals and spontaneous τ breaking represents a subject in its infancy. There are many open questions and fronts for growth. One ongoing task is to expand the census of physical time crystals to include larger and more convenient examples and to embody a wider variety of spacetime patterns, by both designing new time crystal materials and discovering them in nature. Physicists are also interested in studying and understanding the phase transitions that bring matter into and out of these states.

Another task is to examine in detail the physical properties of time crystals (and spacetime crystals, in which space symmetry and τ are both spontaneously broken). Here the example of semiconductor crystals, mentioned earlier, is inspiring. What discoveries will emerge as we study how time crystals modify the behavior of electrons and light moving within them?

Having opened our minds to the possibility of states of matter that involve time, we can consider not only time crystals but also time quasicrystals (materials that are very ordered yet lack repeating patterns), time liquids (materials in which the density of events in time is constant but the period is not) and time glasses (which have a pattern that looks perfectly rigid but actually shows small deviations). Researchers are actively exploring these and other possibilities. Indeed, some forms of time quasicrystals and a kind of time liquid have been identified already.

So far we have considered phases of matter that put τ into play. Let me conclude with two brief comments about τ in cosmology and in black holes.

The steady-state-universe model was a principled attempt to maintain τ in cosmology. In that model, popular in the mid-20th century, astronomers postulated that the state, or appearance, of the universe on large scales is independent of time—in other words, it upholds time symmetry. Although the universe is always expanding, the steady-state model postulated that matter is continuously being created, allowing the average density of the cosmos to stay constant. But the steady-state model did not survive the test of time. Instead astronomers have accumulated overwhelming evidence that the universe was a very different place 13.7 billion years ago, in the immediate aftermath of the big bang, even though the same physical laws applied. In that sense, τ is (perhaps spontaneously) broken by the universe as a whole. Some cosmologists have also suggested that ours is a cyclic universe or that the universe went through a phase of rapid oscillation. These speculations—which, to date, remain just that—bring us close to the circle of ideas around time crystals.

Finally, the equations of general relativity, which embody our best present understanding of spacetime structure, are based on the concept that we can specify a definite distance between any two nearby points. This simple idea, though, is known to break down in at least two extreme conditions: when we extrapolate big bang cosmology to its initial moments and in the central interior of black holes. Elsewhere in physics, breakdown of the equations that describe behavior in a given state of matter is often a signal that the system will undergo a phase transition. Could it be that spacetime itself, under extreme conditions of high pressure, high temperature or rapid change, abandons τ?

It occurred to me that one could extend the classification of possible crystalline patterns in three-dimensional space to crystalline patterns in four-dimensional spacetime.

Ultimately the concept of time crystals offers a chance for progress both theoretically—in terms of understanding cosmology and black holes from another perspective—and practically. The novel forms of time crystals most likely to be revealed in the coming years should move us closer to more perfect clocks, and they may turn out to have other useful properties. In any case, they are simply interesting, and offer us opportunities to expand our ideas about how matter can be organized. SA

MORE TO EXPLORE

Classical Time Crystals. Alfred Shapere and Frank Wilczek in *Physical Review Letters,* Vol. 109, No. 16, Article No. 160402; October 2012.

Quantum Time Crystals. Frank Wilczek in *Physical Review Letters,* Vol. 109, No. 16, Article No. 160401; October 2012.

Observation of a Discrete Time Crystal. Jiehang Zhang et al. in *Nature,* Vol. 543, pages 217–220; March 9, 2017.

Observation of Discrete Time-Crystalline Order in a Disordered Dipolar Many-Body System. Soonwon Choi et al. in *Nature,* Vol. 543, pages 221–225; March 9, 2017.

Time Crystals: A Review. Krzysztof Sacha and Jakub Zakrzewski in *Reports on Progress in Physics,* Vol. 81, No. 1, Article No. 016401; January 2018.

Time Crystals in Periodically Driven Systems. Norman Y. Yao and Chetan Nayak in *Physics Today,* Vol. 71, No. 9, pages 40–47; September 2018.

FROM OUR ARCHIVES

Anyons. Frank Wilczek; May 1991.

scientificamerican.com/magazine/sa

BIOLOGISTS ARE RACING to record new species at sites across Colombia. They are using the data to recommend economic policy that supports biodiversity instead of destroying it.

SUSTAINABILITY

Conservation after Conflict

Now that 50 years of war are over, Colombia wants to create an economy based on its biodiversity

By Rachel Nuwer

Rachel Nuwer is a freelance journalist and author of *Poached: Inside the Dark World of Wildlife Trafficking* (Da Capo Press, 2018). She lives in Brooklyn, N.Y.

FAT PURPLE CLOUDS HAD BEEN GATHERING ALL DAY ABOVE CUBARÁ, kicking up a dusty wind and cloaking the forested hills in shadow and mist. When the rain finally came, it came as a torrent, hammering metal roofs, overflowing ditches and transforming roads into rivers. A team of biologists, freshly arrived from Bogotá, could do little besides huddle on a porch in anticipation of their mission: find and document as many bird species as possible.

Not since 1961 had such a survey been undertaken in this remote northeastern Colombian town, primarily because until a few years ago, it was simply too dangerous.

Cubará is in the center of an infamous no-go zone, an area that was notorious for frequent clashes among guerrillas, paramilitary forces and the Colombian army. In 2016 the government signed a cease-fire agreement with the Revolutionary Armed Forces of Colombia (FARC), the country's largest rebel group, bringing an end to the longest-running conflict in the Western Hemisphere. Although gunshots no longer ring out, memories of the violence are still at the forefront of many people's minds. As Cubará's vice mayor told me when we met, "Congratulations for making it. Just a small number of people come here because everyone is afraid of visiting."

Now that a delicate peace has arrived, Cubará—and thousands of other Colombian towns like it—is slowly coming back to life. The fighting's end marked a new beginning not only for communities eager to rebuild but also for the scientists at the Alexander von Humboldt Biological Resources Research Institute, an independent nonprofit group that hopes to finally take stock of its nation's formidable natural history. Sandwiched between two continents and two oceans and crossed by both the equator and the Andes, Colombia contains 311 different ecological zones, from rain forests and mountains to mangrove stands and coral reefs. Already researchers have documented nearly 63,000 species there—a whopping 10 percent of global biodiversity. Only Brazil has more species than Colombia, and it is more than seven times larger.

This abundance was obvious even while the team took shelter from the rain. Tropical kingbirds flitted around a streetlight, and invasive giant African snails inched along the porch. A beetle as large as a human hand scuttled by, probably on the search for a mate, and a grapefruit-sized toad lapped up dinner from a cloud of termites. A strange wormlike creature that biologist Orlando Acevedo-Charry snatched from the flooded driveway turned out to be not a snake or a caecilian, as he originally hypothesized, but a marbled swamp eel.

IN BRIEF

Colombia has some of the highest biodiversity in the world. But a half-century of conflict blocked field research, and science stagnated. A 2016 peace treaty opened up regions once inaccessible, and biologists are racing to catalogue new species.

Scientists from Colombia's Humboldt Institute are in a unique position to show how preserving the richness of biodiversity can be a core building block of a sustainable economy. They are making policy recommendations to the government.

Peacetime also ushered in rapid deforestation. So Humboldt scientists are urgently promoting an economy rooted in industries such as agroforestry and ecotourism, which will help rural areas recover and grow without destroying the environment.

PRECEDING PAGES: FELIPE VILLEGAS *Humboldt Institute*

SCIENTISTS ARE TEAMING UP with local experts such as Saul Sanchez (*1, 2*) to survey bird diversity and develop ecotourism. Another researcher picks up bird calls with a parabolic microphone (*3*).

RACHEL NUWER

It is likely that many more species still await discovery. In nine major expeditions conducted across the country since 2015, scientists have documented hundreds of plants, animals and fungi, dozens of which appear to be new to science—including a freshwater ray with leopardlike polka dots, a peculiar sponge that wraps itself around mangrove tree branches like an insect nest, and a fish with no eyes. "Can you imagine it's 2019 and we're still discovering what we have?" remarks Gisele Didier Lopez, leader of the development unit at Humboldt. "It gives us goosebumps, like, 'Oh, my God, this was there and we didn't even know it!'"

But as peacetime opens up places such as Cubará for exploration, it simultaneously makes way for development. Roads are being constructed, land is being cleared and forests are disappearing. "The rate of landscape change is faster than our capacity to do research," says Acevedo-Charry, who curates the Collection of Environmental Sounds at Humboldt. "If we do not categorize biodiversity quickly and continuously around Colombia, we will lose it before we even know what we need to protect."

Acevedo-Charry, Didier and their colleagues at Humboldt are at the forefront of efforts not only to discover the breadth of Colombia's biodiversity but also to find ways to turn it into the centerpiece of a society bolstered by sustainability, resilience and green economics. "This is not the classical do-not-touch approach to biodiversity," Didier says. "Instead we want to use biodiversity as an ingredient in the recipe for economic growth—without destroying it." The ultimate goal, she says, is "to make biodiversity a capital asset for development."

Since 2016 the institute's 123 experts, along with other scientists and nonprofit organizations from Colombia and beyond, have frantically worked to draw up a vision of what a green Colombia might look like—and to create a roadmap for getting there. Didier and her colleagues may be in a unique position to do so. By law, Humboldt—which receives half its funding from the government and the other half from fundraising—is in charge of studying and reporting on Colombia's biodiversity. Its mission goes beyond cataloguing: the staff also are responsible for pursuing applied science that informs policy-making decisions and ultimately bridges the gap between society and government. Diego J. Lizcano, a biodiversity specialist at the Nature Conservancy, explained that because the institute is directly connected to the government, officials take its findings more seriously than those of NGOs and university researchers.

But as Colombia races forward with postconflict development, the window is quickly closing on realizing a rosy future in

which biodiversity is both cherished and sustainably capitalized. Despite Humboldt's relative influence, observers say that the environment remains low on the government's priority list and that deforestation continues to ravage much of the country. Didier describes this trajectory as "putting in a bulldozer and chopping down everything in front of it. Everything is at stake."

WAR AND (GREEN) PEACE

THAT SO MUCH WILDLIFE and habitat remain in Colombia today is, in part, a serendipitous side effect of conflict. Civil war officially broke out in 1964, when members of the peasant class, a group largely composed of small farmers, miners and land workers, rose up to fight gross inequality and formed FARC. The half-century of fighting froze not just ecological exploration but, in some places, ecological destruction.

Millions of rural residents fled the countryside to take refuge in cities, giving nature time to reclaim their properties. Rebels commanded those who stayed behind to keep out of certain tracts of forest and forbade them from hunting and cutting down trees. What began as an ideological struggle for a Marxist-Leninist government morphed into a conflict largely fueled by profit, especially from narcotics. Coca fields and cocaine labs sprang up alongside forest camps. "The guerrillas benefited from having forest they could hide in, and other people didn't dare go there," Didier says. "As a result, biodiversity remained high in hotspots for conflict."

As narcotics trafficking spread, violence followed. Any scientist who dared venture into rebel-controlled areas did so at the risk of his or her life. Nearly every field researcher in the country today seems to have a story of being kidnapped, interrogated at gunpoint or otherwise scared away from study sites. "Ten years ago the most dangerous thing you could come across in the field was a person," says Lizcano, who was held hostage for two days by rebels who kidnapped him while he was out looking for tapirs. Lizcano continued his work at a different location, but other studies were abandoned or never attempted in the first place, and many researchers chose to either leave Colombia or change careers. Ecological knowledge stagnated.

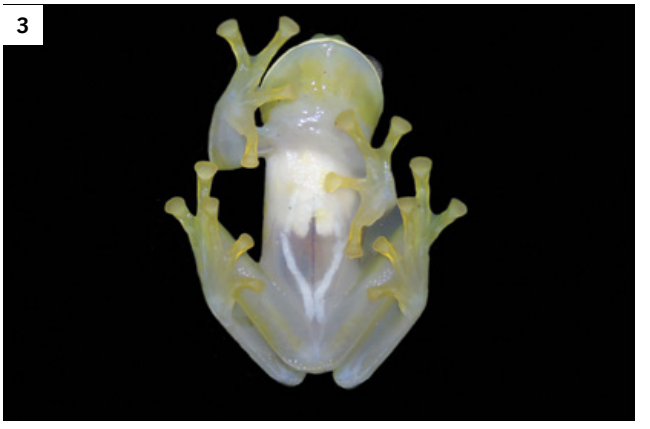
Hope for a reversal of this trend came from one of the nearly 600 stipulations of the 2016 peace agreement: the country must develop sustainably to improve the lives of all Colombians—not just urbanites, who compose at least three quarters of the population. This point was largely meant to address the rural discontent that ignited the conflict to begin with, and it promises marginalized countryside residents—many of whom are members of Colombia's 112 ethnic minority groups—access to education and clean water, subsidies for development programs in former rebel-held territories, and new roads to connect their communities to the rest of the country. It also encourages illegal coca growers to switch to legal crops in exchange for cash payments and government assistance.

"Because many of our problems come from lack of better livelihoods, education and health care in rural areas, that was the main part of the agreement for me," says Julia Miranda Londoño, director general of the Colombian National Park System. "If our development was more equitable, people would not need

Colombia's Hotspots

With 311 different ecological zones, Colombia is a biodiversity powerhouse: 10 percent of all species on Earth are found here. After a half-century of civil war, scientists are racing to document and preserve Colombia's natural heritage. But peacetime means deforestation has ramped up, as formerly rebel-occupied territories open up to mining, logging and resettlement. Of the country's nine hotspots for deforestation, five are located in the Amazon basin.

Map by Mapping Specialists



UVALDINO VILLAMIZAR (*1*) grows cacao using agroforestry practices. Such sustainable methods help to preserve Colombia's biodiversity, including species (*2, 3, 4*) discovered in the past few years.

RACHEL NUWER (*1*); DIRK WEINMANN (*2*); FROM "THE POVERTY OF ADULT MORPHOLOGY: BIOACOUSTICS, GENETICS, AND INTERNAL TADPOLE MORPHOLOGY REVEAL A NEW SPECIES OF GLASSFROG (ANURA: CENTROLENIDAE) *(KAKOG)* FROM THE SIERRA NEVADA DE SANTA MARTA, COLOMBIA," BY MARCO RADA ET AL., IN *PLOS ONE*, VOL. 14, NO. 5, ARTICLE E0215349; MAY 8, 2019; (*3*); MARTA KOLANOWSKA (*4*)

to look for other ways of living like growing coca crops and undertaking illegal mining."

Although Humboldt scientists and other researchers believe that biodiversity can play a key role in this equitable development, the question is how to actually make that happen across an entire nation. Colombians do not want their country to go the way of San Martín in Peru—a postconflict region that developed quickly yet now is completely deforested and suffers from frequent and severe fires, landslides and flooding as a result. They also cannot base their plans entirely on positive case studies of environmental conservation in places such as Costa Rica and Rwanda, both of which are much smaller and did not experience 50 years of war. Nordic countries provide leading examples of sustainable energy and natural resource use, but unlike Colombia, they benefit from having some of the strongest economies in the world.

So Colombia plans to forge its own path, led by the National Planning Department and backed by the country's scientists. In addition to growing a thriving ecotourism industry, ideas for this new bioeconomy range from helping indigenous and rural communities benefit from bioprospecting—the search for medicinal, edible and otherwise commercially useful plant and animal species—to using technology to boost aquaculture production and increase recycling, which is nearly nonexistent in the region. The Ministry of Finance is considering a bill that would expand Colombia's carbon tax, which currently applies to six liquid fuels, to include coal and gas. The government also aims to establish its first serious fleet of renewable energy sources through a special task force dedicated to energy transition.

The biggest focus is on reforming Colombian agriculture, a sector set to grow by 2.5 percent annually and increase its land use area by 44 percent over the next 15 years. "The way we use land is very, very destructive," says Brigitte Baptiste, who directed Humboldt for 10 years before recently taking up a position as head of EAN University in Bogotá. Ranchers clear-cut forests to graze just a couple of cows per acre. Irrigation systems are woefully out of date and wasteful—something even the producers acknowledge, Baptiste says. And pesticide use ranks among the highest worldwide, poisoning farmers and contaminating the environment.

Agroforestry, which could be huge in Colombia, is one alternative, according to Baptiste and her colleagues. This agricultural method incorporates livestock and crops into forests rather than cutting the trees down and in doing so brings benefits such as water provision and mitigation of floods and droughts. Cattle account for about 70 percent of Colombia's agricultural land use, but the country is also the third-largest coffee produc-

er, the fourth-largest oil palm producer and a major exporter of cacao, which is used to make chocolate. If agroforestry were implemented across Colombia, the nation's future forests would be not just islands of biodiversity dotting an otherwise human-dominated landscape but an interconnected matrix of nature supported by private landowners.

In Cubará, much of the road into town is lined by barren fields sheared of trees, where cattle graze alongside the stumps. As in many areas of rural Colombia, the shift to agroforestry is happening slowly, although here it is driven mainly by grassroots movements that are not waiting for the government to lead the charge. When organic farmers Monica and Uvaldino Villamizar decided to branch out into commercial cacao farming in 2006, they designed their fields to accommodate around 20 species of trees. Guided by information provided by the National Federation of Cacao Growers, they allowed their property to remain dense with vegetation and the cacophony of birdsong. The diverse growing space has also brought comparatively higher yields, they say, because the shade-to-sun ratio is better for the plants. "We're definitely happy with this system; it's why my family is eating and my daughter is studying," Uvaldino says. "She wants to be a civil engineer."

Globally, agroforestry and other "payment for ecosystem service" schemes are frequently incentivized by tax breaks or direct payment from governments or nonprofit groups. For the past decade the Nature Conservancy, for example, with funding from the World Bank and the U.K. government, has worked with more than 4,000 farmers to convert 66,500 acres of high-biodiversity, low-income land across Colombia for agroforestry—specifically for sustainable cattle ranching. Under this system, farmers plant trees from a list of more than 50 native species, which provide shade and food for their cows. At the same time, the trees serve as habitats for other species and provide carbon capture and storage services.

Since the Nature Conservancy project began, participating ranchers have reported an increase of up to 80 percent in milk and meat production. Farmers' profits have also gone up because sustainable products fetch higher prices in cities such as Bogotá, where an increasing number of people are willing to pay a premium for organic, responsibly produced meat, milk, chocolate, and more. Two Colombian meat and dairy companies are already purchasing and advertising deforestation-free products, and a rising number of restaurants—including a popular national chain called Crepes & Waffles—are signing up as well, oftentimes as a direct result of pressure from clientele. "The market here is ready for milk, meat and crops free of deforestation," Lizcano says.

Colombia's Ministry of Agriculture is aiming to have a new sustainable cattle-ranching policy signed by the end of 2019—a move scientists and NGOs have been pushing for several years. Carolina Jaramillo, a representative of Colombia at the Global Green Growth Institute, says implementing a policy that provides economic incentives and logistical guidance would represent "a whole cultural, financial and technological transformation across the country."

If agroforestry is implemented across rural Colombia, it will be not just islands of biodiversity but an interconnected matrix of nature supported by private landowners.

UNCERTAIN FORECAST

FOR ALL OF ITS PROMISE, Colombia has "the same blocks or lack of political will as any country trying to create a sustainable economy," says Andrés Gómez, a senior biodiversity researcher at ICF International, a global consulting services company. And then there are the issues specific to Colombia: narcotrafficking continues to plague a number of regions; tensions remain high between many of Colombia's 112 ethnic minorities and the government; and Colombia is facing a migration crisis ignited by turmoil and economic collapse in neighboring Venezuela. Meanwhile the National Liberation Army, another rebel group, has yet to agree to a peace treaty.

Of all the threats to the country's biodiversity, deforestation is the most dangerous. Nationwide it jumped 44 percent from 2015 to 2016, and although Colombia has doubled the size of its protected areas over the past eight years, 84 percent of the deforestation has taken place on these lands. According to Humboldt, more than 100,000 acres of national parks were cut between 2013 and 2017.

The scientists did not analyze the drivers behind those losses, but they name a number of contributing forces. In some areas, it is illegal gold mining or logging; in others, it is coca production. Land grabs and subsequent sales are commonly used to launder money from illegal activities, Baptiste says, and corruption greases the process. In addition, many of Colombia's 6.9 million internally displaced persons have begun returning to their former rural homelands, where they stake claims on land. Displaced persons undertaking deforestation "argue that they have suffered from the war," Miranda Londoño says. "But there is no right to commit a crime to solve your needs." Jaramillo suggests the need for "profound land reform," which could give poor people access to land that has already been deforested. But a project of this scale is not currently being considered, she says.

Trying to slow the forest losses, no matter the source, can be deadly. More than 30 environmental defenders were murdered in Colombia in 2017, and park rangers who interfere with land grabs regularly receive death threats. Colombia's laws are clear on the illegality of deforestation, and its courts are well equipped to prosecute those who engage in it, Baptiste explains, but the country still has little capacity for enforcement on the ground. Despite many arrests, there are few signs that deforestation is being curtailed. In a paper in preparation, Humboldt researchers

ECOLOGIST BRIGITTE BAPTISTE, who led the Humboldt Institute until September 2019, has become famous in Colombia for advocating for a green economy.

FELIPE VILLEGAS *Humboldt Institute*

analyzed deforestation patterns from 2000 to 2015 to identify contributing factors, including road expansion, coca plantation presence, and conflict. They used those data to build a predictive model and found that if conditions do not change, Colombia will lose an additional 18 million acres of forest—7 percent of the country's total forest cover—by 2050. More than 50 percent of the losses will occur in postconflict zones.

Ultimately the fate of these forests and other natural resources depends on whether Colombians embrace the environment as a pillar of the new green economy rather than seeing it as an obstacle to improving their well-being. "Unless we create real opportunities for them based on value they can get out of biodiversity, conservation is not going to work," says Jose Manuel Ochoa Quintero, a program coordinator at Humboldt.

Baptiste has become something of a celebrity for taking on a leading role in pushing this agenda. She is famous in Colombia for both her charismatic evangelizing about the environment and her status as a transgender woman in a conservative country. She regularly appears on television and is quoted in the media—as are an increasing number of celebrities who have aligned themselves with antideforestation initiatives.

The culture seems to be shifting. When Colombia's new president, Iván Duque Márquez, took office in August 2018, his administration's plan to end deforestation entailed dousing coca crops in herbicide and allowing that thousands of square miles of wild nature would still inevitably be lost. But the announcement received major condemnation from the public and the media, and the Duque administration began preparing a new approach. Deforestation is now considered a national security threat.

If there is a cultural signal that national enthusiasm for biodiversity is on the rise, it might be associated with the fact that Colombia is home to 20 percent of the world's recorded bird species. Birding tourism holds "immense potential" for the country, according to a 2017 paper in *Tropical Conservation Science*. (Peru, the authors write, doubled its bird-watching tourism from 2012 to 2013 and now enjoys $89 million of annual revenue, much of which remains in local communities.) Despite this wealth of bird life, it was not until 2015 that Colombia participated in Cornell University's Global Big Day, an annual event in which birders around the world compete to see which nation can log the most species in 24 hours. In 2017, after two years of "dysfunctional participation," as Acevedo-Charry puts it, the country emerged victorious, with 1,486 species sighted. National pride soared.

Confident Colombia could hold on to the title in 2018, national radio stations ran commercials encouraging participation, and television media and newspapers featured stories about the event. The blitz worked: Some 4,500 birders, including members of the air force and police, turned out at 730 sites. In Cubará, Acevedo-Charry, Johana Zuluaga-Bonilla, president of the Ornithologist Association of Boyacá-Ixobrychus, and Saul Sanchez, a former hunter turned local conservationist, recorded 111 species among the three of them, transforming the region from a question mark on the map to one rich in verified biodiversity. Across the nation birders saw and heard 1,546 species—an "unfathomable" number for a single country in a single day, the competition organizers wrote. In 2019 Colombia took the gold yet again.

This enthusiasm is translating into economically viable options for rural residents, where former hunters, monocrop farmers and timber harvesters are turning to birding, ecotourism and agroforestry. Less than a decade ago Colombians could not conceive of coming together to celebrate their biodiversity through birding, let alone becoming a country powered by its natural heritage, Acevedo-Charry says. As more people gradually embrace this vision, there are signs it might be making a difference: Satellite imagery recently analyzed by researchers at the University of Medellín indicates that deforestation rates, compared with the beginning of 2018, are going down. "The biodiversity-based economy is injecting hope for those who need it most," Acevedo-Charry says. "It is already changing lives." SA

MORE TO EXPLORE

Chocolate of Peace. Documentary directed by Gwen Burnyeat and Pablo Mejía Trujillo, 2016. Available at https://vimeo.com/179038624

Greening Peace in Colombia. Brigitte Baptiste et al. in *Nature Ecology & Evolution*, Vol. 1, Article No. 0102; March 1, 2017.

Colombia: After the Violence. Sara Reardon in *Nature*, Vol. 557; May 2, 2018.

FROM OUR ARCHIVES

Can Sustainable Management Save Tropical Forests? Richard E. Rice et al.; April 1997.

The Race to Save Colombia's Uncontacted Tribes from Outsiders. Adam Piore; February 2019.

scientificamerican.com/magazine/sa

TECHNOLOGY

THE KIDS ARE ALL RIGHT

New findings suggest that the angst over social media is misplaced and that more nuance is required to understand its effects on well-being

By Lydia Denworth

Illustrations by Mark Zingarelli

Lydia Denworth is a contributing editor for *Scientific American* and is author of *Friendship: The Evolution, Biology, and Extraordinary Power of Life's Fundamental Bond* (W. W. Norton, in press).

IT WAS THE HEADLINES THAT MOST UPSET AMY ORBEN. IN 2017, WHEN SHE WAS A GRADUATE student in experimental psychology at the University of Oxford researching how social media influences communication, alarming articles began to appear. Giving a child a smartphone was like giving a kid cocaine, claimed one. Smartphones might have destroyed a generation, said another. Orben didn't think such extreme statements were warranted. At one point, she stayed up all night reanalyzing data from a paper linking increases in depression and suicide to screen time. "I figured out that tweaks to the data analysis caused major changes to the study results," Orben says. "The effects were actually tiny."

She published several blog posts, some with her Oxford colleague Andrew K. Przybylski, saying so. "Great claims require great evidence," she wrote in one. "Yet this kind of evidence does not exist." Then Orben decided to make her point scientifically and changed the focus of her work. With Przybylski, she set out to rigorously analyze the large-scale data sets that are widely used in studies of social media.

The two researchers were not the only ones who were concerned. A few years ago Jeff Hancock, a psychologist who runs the Social Media Lab at Stanford University, set an alert to let him know when his research was cited by other scientists in their papers. As the notifications piled up in his in-box, he was perplexed. A report on the ways that Facebook made people more anxious would be followed by one about how social media enhances social capital. "What is going on with all these conflicting ideas?" Hancock wondered. How could they all be citing his work? He decided to seek clarity and embarked on the largest meta-analysis to date of the effects of social media on psychological well-being. Ultimately he included 226 papers and data on more than 275,000 people.

The results of Orben's, Przybylski's and Hancock's efforts are now in. Studies from these researchers and others, published or presented in 2019, have brought some context to the question of what exactly digital technology is doing to our mental health. Their evidence makes several things clear. The results to date have been mixed because the effects measured are themselves mixed. "Using social media is essentially a trade-off," Hancock says. "You get very small but significant advantages for your well-being that come with very small but statistically significant costs." The emphasis is on "small"—at least in terms of effect size, which gauges the strength of the relation between two variables. Hancock's meta-analysis revealed an overall effect size of 0.01 on a scale in which 0.2 is small. Przybylski and Orben measured the percent of variance in well-being that was explained by social media use and found that technology was no more associated with decreased well-being for teenagers than eating potatoes. Wearing glasses was worse. "The monster-of-the-week thing is dead in the water," Przybylski says.

Furthermore, this new research reveals serious limitations and shortcomings in the science of social media to date. Eighty percent of studies have been cross-sectional (looking at individuals at a given point in time) and correlational (linking two measures such as frequency of Facebook use and level of anxiety but not showing that one causes the other). Most have relied on self-reported use, a notoriously unreliable measure. Nearly all assess only frequency and duration of use rather than content or context. "We're asking the wrong questions," Hancock says. And results are regularly overstated—sometimes by the scientists, often by the media. "Social media research is the perfect storm showing us where all the problems are with our scientific methodology," Orben says. "This challenges us as scientists to think about how we measure things and what sort of effect size we think is important."

To be clear, it is not that social media is never a problem. Heavy use is associated with potentially harmful effects on well-being. But effects from social media appear to depend on the

IN BRIEF

Anxiety about the effects of social media on young people has risen to such an extreme that giving children smartphones is sometimes equated to handing them a gram of cocaine. The reality is much less alarming.

A close look at social media use shows that most young texters and Instagrammers are fine. Heavy use can lead to problems, but many early studies and news headlines have overstated dangers and omitted context.

Researchers are now examining these diverging viewpoints, looking for nuance and developing better methods for measuring whether social media and related technologies have any meaningful impact on mental health.

user—age and mental health status are two important factors that make a difference. Also, cause and effect appear to go in both directions. "It's a two-way street," Hancock says.

The hope is that the field will use these new findings to embark on a new science of social media that will set higher standards for statistical analysis, avoid preposterous claims, and include more experimental and longitudinal studies, which track people at multiple time points. "We don't want to be a field in which we say that potato eating has destroyed a generation," says clinical neuropsychologist Tracy Dennis-Tiwary of Hunter College. "Despite our concerns, we need to pull ourselves together and act like scientists. We have to have adequate evidence."

FEAR OF TECHNOLOGY

ANXIETY AND PANIC over the effects of new technology date back to Socrates, who bemoaned the then new tradition of writing things down for fear it would diminish the power of memory. Thomas Hobbes and Thomas Jefferson both warned that communal relationships would suffer as industrial societies moved from rural to urban living. "Before we hated smartphones, we hated cities," write sociologists Keith Hampton of Michigan State University and Barry Wellman of the NetLab Network, based in Toronto, both of whom study the effects of technological innovation. Radio, video games and even comic books have all caused consternation. Television was going to bring about the dumbing down of America.

Even so, the change that came about from mobile phones, the Internet and social networking sites feels seismic. Cell phones were first widely adopted in the 1990s. By 2018, 95 percent of American adults were using them. Smartphones, which added instant access to the Internet, entered the mainstream with the introduction of the iPhone in 2007, and now more than three quarters of U.S. adults have them. Eighty-nine percent of those adults use the Internet. There is near saturation for all things digital among adolescents and adults younger than 50 and among higher-income households. Nonusers tend to be older than 65, poor, or residents of rural areas or other places with limited service. Between 2005, when the Pew Research Center began tracking social media use, and 2019, the proportion of Americans using social media to connect, keep up with the news, share information and be entertained went from 5 to 72 percent—that means it jumped from one in 20 adults to seven in 10.

Because social media is so new, the science investigating its effects is also new. The earliest study Hancock could find that examined social media use and psychological well-being was done in 2006. It came as no surprise that early approaches were limited. Physician Brian Primack, who headed the Center for Research on Media, Technology, and Health at the University of Pittsburgh until moving to the University of Arkansas this year, likens the field to initial research on nutrition: "It took a while to say, 'Let's split out fats and proteins and carbohydrates, and not just that, but let's split out trans-fats and polyunsaturated fats,'" he says. "It's important for anyone who is doing good research to adapt to what's going on." Primack points to his own early work, such as studies that looked only at overall social media use, as examples of what will not cut it anymore. "You might be spending two hours a day clicking 'like' on pictures of cute puppies, and I might be spending two hours a day having violent clashes about politics and religion and other hot-button issues. Studies like my early one would count [those activities] the same."

Many people in the field have been particularly critical of work by psychologist Jean M. Twenge of San Diego State University. In addition to her research papers, Twenge's popular 2017 article in the *Atlantic,* based on her book *iGen,* was the one that asked: "Has the Smartphone Destroyed a Generation?" Twenge is hardly the only researcher to publish negative findings about social media use, but the publicity around her work has made her one of the most high profile. She points to a steep rise in mental health issues among the group born between 1995 and 2012 and writes that "much of this deterioration can be traced to their phones." Her work compares rising rates of depression and anxiety among young people to the proliferation of smartphones in the same time period. Twenge acknowledges that the link is correlational but argues that her conclusions represent "a logical sequence of events" based on the evidence—and care is warranted: "When we're talking about the health of children and teens, it seems to me we should err on the side of caution."

The science of social media needs to set higher standards for statistical analysis, avoid preposterous claims and study people for a longer time.

No one disagrees about the importance of young people's health, but they do think that Twenge has gotten ahead of the science. "Why wait for causal evidence?" says Dennis-Tiwary. Because the story might not be so straightforward. She points to a longitudinal study done by researchers in Canada in response to one of Twenge's articles. They studied nearly 600 adolescents and more than 1,000 young adults over two and six years, respectively, and found that social media use did not predict depressive symptoms but that depressive symptoms predicted more frequent social media use among adolescent girls. "This is a much more nuanced story," Dennis-Tiwary says. "We know that problematic smartphone use may as likely be a result of mental health problems as a cause, and that calls for a different set of solutions."

Correlational studies have their uses, just as epidemiological research can suggest a link between pollution and increased cancer rates when a randomized clinical trial is not possible. While he thinks it is important not to overstate findings, economist Matthew Gentzkow of Stanford, who studies social media, says of Twenge's work that "there are some pretty striking facts there. They don't tell us whether smartphones are causing mental health problems, but they really shine some light on that

possibility. What we need now is to dig in and try to do more careful studies to isolate what's really going on."

A TWO-WAY STREET?

THAT IS WHAT the newest studies set out to do. Hancock's meta-analysis highlighted the fact that many studies on social media and psychological well-being did not measure the same outcomes. Effects generally fell into one of six categories. Three concern positive indicators of well-being: eudaemonic happiness (having a sense of meaning), hedonic happiness (joy in the moment) and relationships. And three are negative: depression, anxiety and loneliness. Hancock and his team found that more social media use was associated slightly with higher depression and anxiety (though not loneliness) and more strongly associated with relationship benefits (though not eudaemonic or hedonic well-being). (The largest effect, at 0.20, was the benefit of stronger relationships.) He and his colleagues also found that active rather than passive use was positively associated with well-being. (They found no effect for passive use, although others have found it to be negative.)

And how researchers asked questions mattered. Framing questions around "addiction" rather than more neutrally makes a negative finding more likely. In all the literature, there were only 24 longitudinal studies, the "gold standard" that allows researchers to compare the relation between well-being and social media use at two points in time and statistically assess which variable is driving change in the other. In these, Hancock's team found a further small but interesting result. "When you have higher well-being, you use social media less, which suggests that well-being is driving [how much use is made of] social media to some degree," Hancock says.

In a trilogy of papers about adolescent technology use, Orben and Przybylski tackled three major pitfalls they had identified in previous analyses of large-scale data sets. The first paper, published in January in *Nature Human Behaviour,* provided both context and a method for improving transparency. It included three data sets from the U.S. and Europe made up of more than 350,000 adolescents. Such data sets are valuable but make it easy to turn up statistically significant results that may not be of practical significance. Przybylski and Orben calculated that if they had followed standard statistical operating procedure, they could have produced roughly 10,000 papers showing negative screen effects, 5,000 indicating no effect and another 4,000 demonstrating positive technology effects on young people—all from the same data sets.

For their new analysis, they used a technique called specification curve analysis, a tool that examines the full range of possible correlations at once. It is the statistical equivalent of seeing the forest for the trees. Analyzed in this way, digital technology use was associated with only 0.4 percent of the variation in adolescent well-being. The wealth of information in the data allowed for the telling comparisons with potatoes and glasses. It also revealed that smoking marijuana and bullying had much larger negative associations for well-being (at 2.7 and 4.3 times worse, respectively, than the average in one of the data sets), whereas positive behaviors such as getting enough sleep and regularly eating breakfast were much more strongly linked to well-being than technology use. "We're trying to move from this mindset of cherry-picking one result to a more holistic picture," Przybylski says. "A key part of that is being able to put these extremely minuscule effects of screens on young people in a real-world context." (Twenge and others question the usefulness of explaining percentages of variation and say it will always turn up small numbers that might mask practical effects.)

Their second paper, published in April in *Psychological Science,* included stronger methods for measuring screen time. They used three data sets from the U.S., the U.K. and Ireland that included time-use diaries in addition to self-reported media usage and measures of well-being. Over a period of five years the more than 17,000 teenagers in the studies were given a diary one day each year. They filled in 10- to 15-minute windows all day long about exactly what they were doing, including use of digital technologies. When Orben and Przybylski applied their statistical technique to the data, there was little evidence for substantial negative associations between digital engagement and well-being. The diaries also allowed them to look at *when* during the day adolescents were using digital media, including before bed. Even that did not make a difference in well-being, although they

did not look at hours of sleep as an outcome, only more general psychological measures.

And finally, in May, with psychologist Tobias Dienlin of the University of Hohenheim in Germany, Orben and Przybylski published a paper in the *Proceedings of the National Academy of Sciences USA,* incorporating longitudinal data to analyze the effect of social media on adolescents' life satisfaction over time. This approach allowed them to ask whether adolescents who are on social media more in a given year than average feel better or worse at year's end and whether feeling better or worse than normal changes social media use in the coming year. Here, too, the result was small and nuanced. "The change in social media use in one year only predicts about 0.25 percent of the variance in the change in life satisfaction over one year," Orben says. "We're talking about fractions of 1 percent changes." The researchers did, however, see slightly stronger effects in girls than in boys, a finding Orben intends to investigate further. The question of individual risk will also be important. "We really want to see if there are reproducible profiles of young people who are more or less vulnerable or resilient to different forms of technology," Przybylski says.

WHAT ABOUT GENERATION Z?

TEENAGE MEDIA use has been a particular concern because of the ubiquity of smartphones today and because adolescence is such a formative period of development. In choosing what to worry about, parents have followed scientists' lead, says psychologist Candice Odgers of the University of California, Irvine. They worry mainly about how much time their children spend online without giving equal attention to the critical question of what they are doing there. Odgers's own work suggests that amount of use is not the problem. In a study published online this summer in *Clinical Psychological Science,* Odgers, Michaeline Jensen of the University of North Carolina at Greensboro and their colleagues followed nearly 400 adolescents for two weeks, sending questions to the teenagers' cell phones three times a day. The study design allowed them to compare mental health symptoms and technology immersion daily as well as over the weeks of the study.

Was media use associated with individual adolescents' well-being? The answer was not really. Routines in place at the start did not predict later mental health symptoms, and mental health was not worse on days teenagers reported spending more or less time on technology.

"It's ironic that in the end the real danger is not smartphones—it's the level of misinformation that's being directed at the public and at parents," Odgers says. "It's consuming so much of the airtime that it's causing us to miss potentially some of the real threats and problems around digital spaces." For her part, Odgers is far more worried about privacy and unequal access to technology for kids from families with lower socioeconomic status. She also suspects that some adolescents find much needed social support online and that adults should pay closer attention to what works in that regard.

SOCIAL MEDIA 2.0

THESE STUDIES are just the beginning. They have helped clarify the big picture on social media usage, but far more work is needed. Variety in the types of studies conducted will help tease out nuance. In a recent experimental study, for instance, Stanford's Gentzkow asked more than 1,600 people to deactivate their Facebook accounts, which was verified electronically. He and his colleagues were surprised that substitution of other digital technologies went down, not up. "People perceive they're spending less time on all these things," Gentzkow says. The effect size was small, however, and masked a lot of individual variation. Some people loved the break; others really missed their online social world. "Facebook is delivering a lot of value to people, but nevertheless they may be using it more than is really optimal for them," Gentzkow says. "There are many people for whom scaling back their usage a little could make them happier and better off."

Several researchers are trying to better measure screen time. Stanford communications researcher Byron Reeves and his colleagues have developed a technique called Screenomics, which takes a picture of people's phones every five seconds (with permission). Technology companies also have a role to play. Corporations are better able than scientists to count how much time individuals are spending on different activities, but they consider that information proprietary, and there are privacy concerns for users to be addressed. Przybylski is pushing for that policy to change. "Companies shouldn't get a free pass," he says.

New research also seeks to do a better job of predicting individual variation. In Hancock's lab, Stanford undergraduate Angela Lee developed a creative approach. She applied the idea of mindsets—that beliefs shape people's realities—to social media. Through interviews, Lee found that views about social media fell into two general buckets: whether someone thought social media was good or bad for them (valence) and whether or not they thought they were in control of it (agency). Over the course of three studies, she and Hancock tested close to 700 people and found that social media mindsets predicted users' well-being. A sense of agency had the strongest effect. "The more you believe you are in control over your social media, the more social support you have, the less depression you report, the less stress, the less social anxiety, regardless of how much you're actually saying you use social media," says Lee, who is now a graduate student in Hancock's lab. She presented the work in May at the Association for Psychological Science meeting.

The power of mindset serves as a reminder of the power of perspective. In the 1980s people were wringing their hands about the time kids spent staring mindlessly at television screens, says Gentzkow, who has studied that era. He imagines asking those worrywarts about new technologies that would allow kids to instead interact with one another by sharing messages, photographs and videos. "Anybody then would have said, 'Wow, that would be amazing.'" SA

MORE TO EXPLORE

Has the Smartphone Destroyed a Generation? Jean M. Twenge in *Atlantic,* Vol. 320, pages 58–65; September 2017.

The Association between Adolescent Well-Being and Digital Technology Use. Amy Orben and Andrew K. Przybylski in *Nature Human Behaviour,* Vol. 3, No. 2, pages 173–182; February 2019.

Screens, Teens, and Psychological Well-Being: Evidence from Three Time-Use-Diary Studies. Amy Orben and Andrew K. Przybylski in *Psychological Science,* Vol. 30, No. 5, pages 682–696; May 2019.

FROM OUR ARCHIVES

Your Brain in the Smartphone Age. *Scientific American* eBooks; May 6, 2019.

scientificamerican.com/magazine/sa

Is Phage Therapy Here to Stay

A treatment from World War I is making a comeback in the struggle to beat deadly multidrug-resistant infections

By Charles Schmidt

Illustration by Ashley Mackenzie

Charles Schmidt is a freelance journalist based in Portland, Me., covering health and the environment. He has written for us about dangerous contaminants in drinking water and about multigenerational effects from Agent Orange in Vietnam.

BOBBY BURGHOLZER HAS CYSTIC FIBROSIS, A GENETIC DISEASE THAT throughout his life has made him vulnerable to bacterial infections in his lungs. Until a few years ago antibiotics held his symptoms mostly at bay, but then the drugs stopped working as well, leaving the 40-year-old medical device salesman easily winded and discouraged. He had always tried to keep fit and played hockey, but he was finding it harder by the day to climb hills or stairs. As his condition worsened, Burgholzer worried about having a disease with no cure. He had a wife and young daughter he wanted to live for. So he started looking into alternative treatments, and one captured his attention: a virus called a bacteriophage.

IN BRIEF

Harmful bacteria are becoming ever more resistant to antibiotics. Physicians are turning to phages—viruses that infect bacteria—as a new line of attack.

Doctors are testing several different phage therapies in clinical trials, which kill bacteria in different ways.

Researchers will have to significantly reduce the time and cost needed to find the right phage to defeat a bacterium, if the therapies are to succeed commercially.

Phages, as they are known, are everywhere in nature. They replicate by invading bacteria and hijacking their reproductive machinery. Once inside a doomed cell, they multiply into the hundreds and then burst out, typically killing the cell in the process. Phages replicate *only* in bacteria. Microbiologists discovered phages in the 1910s, and physicians first used them therapeutically after World War I to treat patients with typhoid, dysentery, cholera and other bacterial illnesses. Later, during the 1939–1940 Winter War between the Soviet Union and Finland, use of the viruses reportedly reduced mortality from gangrene to a third among injured soldiers.

Treatments are still commercially available in former Eastern Bloc countries, but the approach fell out of favor in the West decades ago. In 1934 two Yale University physicians—Monroe Eaton and Stanhope Bayne-Jones—published an influential and dismissive review article claiming the clinical evidence that phages could cure bacterial infections was contradictory and inconclusive. They also accused companies that manufactured medicinal phages of deceiving the public. But the real end of phage therapy came in the 1940s as doctors widely adopted antibiotics, which were highly effective and inexpensive.

Phage therapy is not approved for use in humans in any Western market today. Research funding is meager. And although human studies in Eastern Europe have generated some encouraging results—particularly those from the Eliava Institute in Tbilisi, Georgia, the field's research epicenter—many Western scholars say the work does not meet their rigorous standards. Furthermore, a smattering of clinical trials in Western Europe and the U.S. have produced some high-profile failures.

Yet despite the historical skepticism, phage therapy is making a comeback. Attendance at scientific conferences on the treatment is skyrocketing. Regulators at the U.S. Food and Drug Administration and other health agencies are signaling renewed interest. More than a dozen Western companies are investing in the field. And a new wave of U.S. clinical trials launched this year. Why the excitement? Phage treatments have been curing patients with multidrug-resistant (MDR) infections that no longer respond to antibiotics. The FDA has allowed petitioning doctors to administer these experimental treatments on a "compassionate use" basis when they could show that their patients had no other options—exactly what Burgholzer was hoping to prove.

MDR infections are a rapidly growing public health nightmare. At least 700,000 people worldwide now die from these incurable maladies every year, and the United Nations predicts that number could rise to 10 million by 2050. In the meantime, the drug industry's antibiotic pipeline is running dry.

Like all viruses, phages are not really alive—they cannot grow, move or make energy. Instead they drift along until by chance they stick to bacteria. Unlike antibiotics, which kill a range of helpful bacteria as they kill the strains making a person sick, a phage attacks a single bacterial species, and perhaps a few of its closest relatives, and spares the rest of the microbiome. Most phages have an icosahedral head—like a die with 20 triangular faces. It contains the phage's genes and connects to a long neck that ends in a tail of fibers, which bind to receptors on a bacterium's cell wall. The phage then plunges a kind of syringe through the wall and injects its own genetic material, which co-opts the bacterium into making more phage copies. Other types of phages, not used medically, enter the same way but live dormantly, reproducing only when the cell divides.

Phages have co-evolved with bacteria for billions of years and are so widespread that they kill up to 40 percent of all the bacteria in the world's oceans every day, influencing marine oxygen production and perhaps even Earth's climate. The spotlight on phages as medical tools is getting brighter as technological advances make it possible to match the viruses to their targets with better accuracy. The few facilities that are technically able to provide phage therapy, under strict regulatory protocols, are being overwhelmed with requests.

Clinical trials underway are beginning to generate the high-quality data needed to convince regulators that phage therapy is viable, but considerable questions remain. The biggest is whether phage therapy can tackle infections on a large scale. Clinicians have to match phages to the specific pathogens in a patient's body; it is not clear whether they can do that cost-effectively and with the speed and efficiency needed to bring phages into routine use. Also problematic is a shortage of regulatory guidelines governing the production, testing and use of phage therapy. "But if it has the potential to save lives, then we as a society need to know whether it will work and how best to implement it," says Jeremy J. Barr, a microbiologist at Monash University in Melbourne, Australia. "The antibiotic-resistance crisis is too dire to not embrace phage therapy now."

TRADING VULNERABILITIES

BURGHOLZER LEARNED about phages by talking to other people with cystic fibrosis around the country. While scouring the Internet for more information, he came on a YouTube video made by phage researchers at Yale University. Soon he was corresponding with Benjamin Chan, a biologist in Yale's department of ecology and evolutionary biology. Since arriving there in 2013, Chan has accumulated a "library" of phages, harvested from sewage, soil and other natural sources, that he makes available to doctors at Yale New Haven Hospital and elsewhere.

Chan's first case, in 2016, was a resounding success. He isolated a phage from pond water, and doctors used it to cure Ali Khodadoust, a prominent eye surgeon. Khodadoust had been suffering from a raging MDR infection in his chest, a complication from open-heart surgery four years earlier. He was taking massive daily doses of antibiotics to try to fight his invading pathogen, the tenacious bacterium *Pseudomonas aeruginosa*. The virus Chan selected latches on to what is known as an efflux pump on the bacterial cell wall. The pumps expel antibiotics and are frequently found in drug-resistant bacteria. Most of the *P. aeruginosa* in Khodadoust's body had the pumps, and the phage killed them. The relatively few remaining *P. aeruginosa* faced an evolutionary trade-off: their lack of efflux pumps meant they survived the virus attack, but it made them defenseless against antibiotics. By taking the phages and antibiotics together, Khodadoust gradually recovered in just a few weeks. He died two years later, at age 82, from noninfectious illnesses.

After that first case, Chan supplied phages for nearly a dozen more experimental treatments at Yale, most involving cystic fibrosis patients with *P. aeruginosa* lung infections. He asked Burgholzer to send a sputum sample by overnight delivery so he could identify phages that might help.

I visited Chan at Yale last December, after the screening had begun. He was wearing a checkered oxford shirt, khakis and loafers, and before long he was calling me "dude," his preferred moniker. After chatting briefly in his office, we headed for an adjacent laboratory, where Chan showed me a petri dish. Burgholzer's bacteria had developed into a gray lawn spanning the dish, but two thin, clear rows cut across it. The bacteria that had been in those rows were all dead, Chan told me, killed by drips of a phage solution Burgholzer would soon be treated with. Burgholzer's infection was caused by three species of the bacterial genus *Achromobacter,* and Chan planned to select individual phages that could pick them off one by one—an approach known as sequential monophage therapy. "We're essentially playing chess in an antimicrobial war," Chan said. "We need to make calculated moves."

Chan hoped to induce an evolutionary trade-off similar to the one he believes worked for Khodadoust. Unable to find a phage that targets efflux pumps on *Achromobacter* bacteria, he instead selected one that targets a large protein called lipopolysaccharide (LPS) in the microbe's cell wall. LPS has side chains of molecules known as O antigens, which vary in length. The longer the chain, the better the bacteria's ability to resist not only antibiotics but also the host's immune system. Chan planned to kill the hardy long-chain strains with phages, leaving the weaker short-chain pathogens behind. In the best scenario, he said, a succession of phages would shift the bacterial population toward short-chain strains that might be more easily controlled by drugs and Burgholzer's own immune defenses. "Bacteria compete for real estate in the body," Chan said. "After large numbers of one species are suddenly killed by phage, in many cases, others move in." He wanted the new occupants to be less virulent than their predecessors.

Chan's boss, Paul Turner, has devoted his career to studying evolutionary trade-offs in the microbial world. A professor in Chan's department, he explained later on the day of my visit that phage treatments can work without completely ridding the body of a disease-causing bacteria. Especially when treating chronic conditions, doctors can use phages to selectively shape the population of the bad bacteria so it develops other vulnerabilities. "Should those vulnerabilities be toward antibiotics, then so much the better," he told me. Combining antibiotics with phages to achieve optimal effects for patients, he says, "makes it easier to move forward with phage therapy quickly."

I drove with Chan to Yale New Haven Hospital to watch as Burgholzer's phage treatment got underway. We took an elevator to the second floor, where we waited for Chan's clinical collaborator, Jonathan Koff, to arrive. A pulmonologist and director of the Adult Cystic Fibrosis Program, Koff soon came bounding in, a

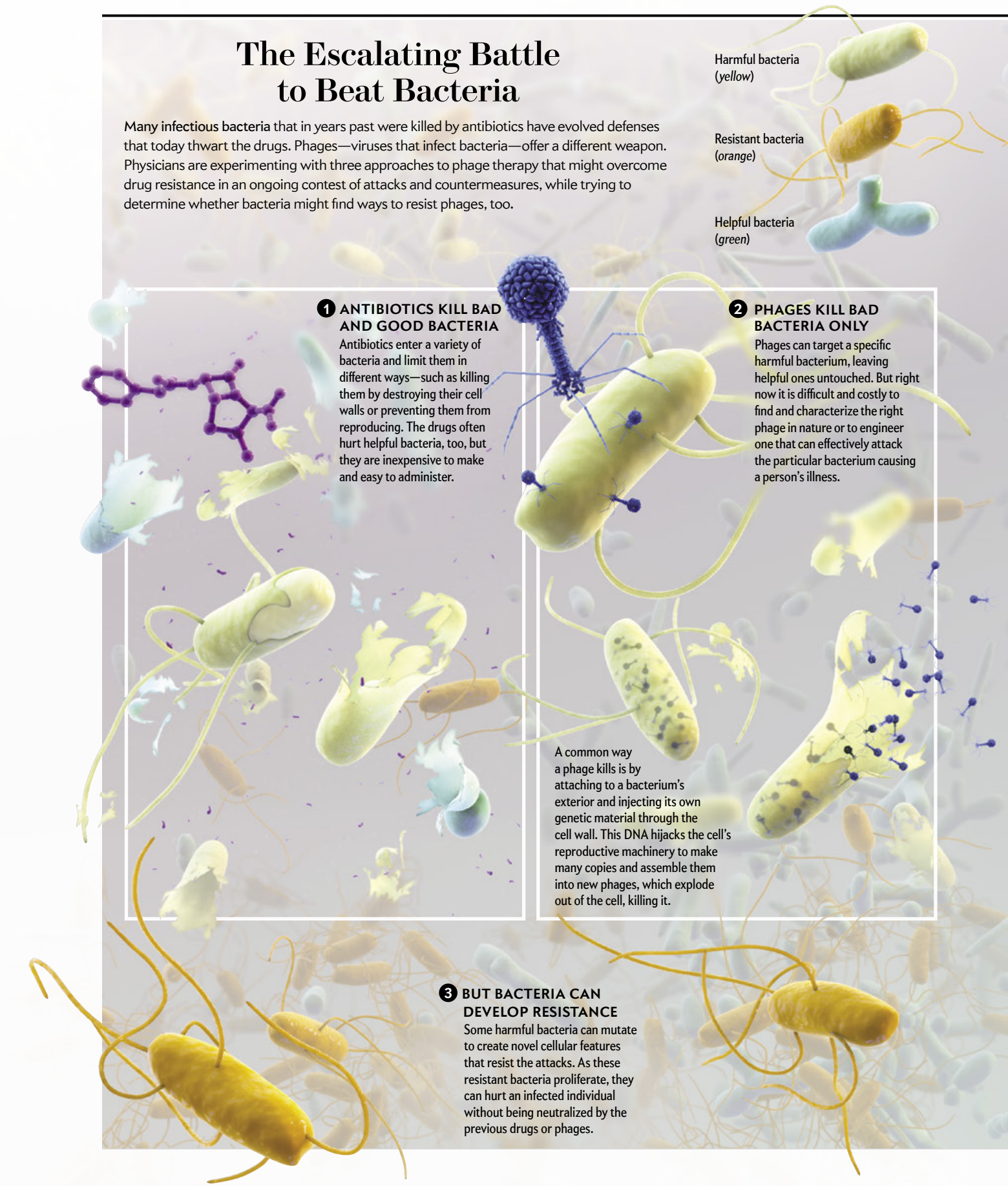
The Escalating Battle to Beat Bacteria

Many infectious bacteria that in years past were killed by antibiotics have evolved defenses that today thwart the drugs. Phages—viruses that infect bacteria—offer a different weapon. Physicians are experimenting with three approaches to phage therapy that might overcome drug resistance in an ongoing contest of attacks and countermeasures, while trying to determine whether bacteria might find ways to resist phages, too.

Harmful bacteria (*yellow*)

Resistant bacteria (*orange*)

Helpful bacteria (*green*)



1 ANTIBIOTICS KILL BAD AND GOOD BACTERIA

Antibiotics enter a variety of bacteria and limit them in different ways—such as killing them by destroying their cell walls or preventing them from reproducing. The drugs often hurt helpful bacteria, too, but they are inexpensive to make and easy to administer.

2 PHAGES KILL BAD BACTERIA ONLY

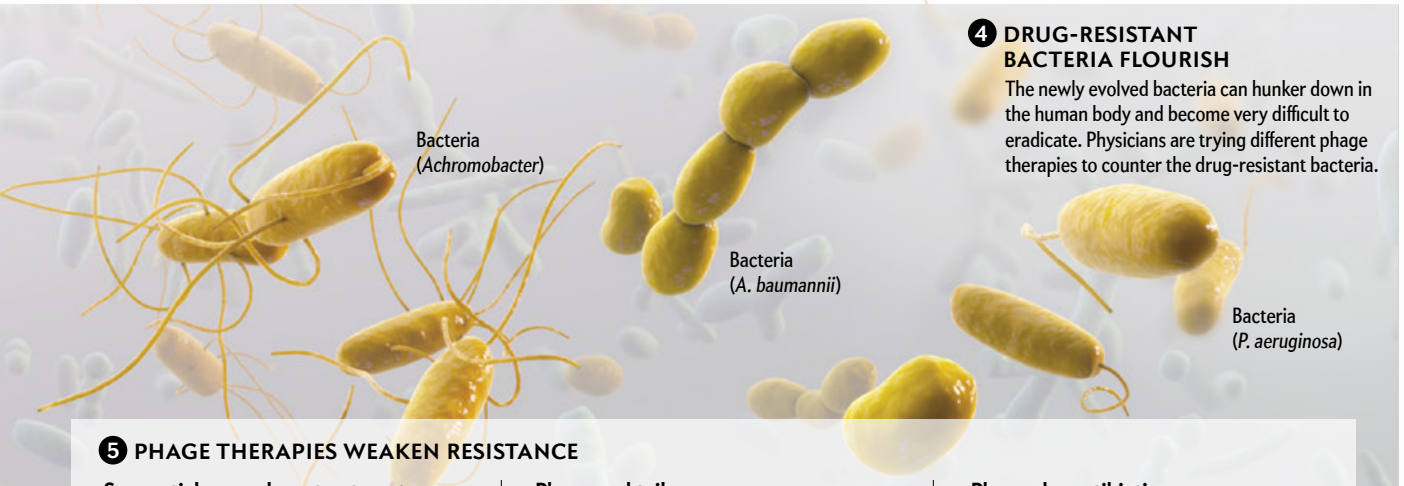
Phages can target a specific harmful bacterium, leaving helpful ones untouched. But right now it is difficult and costly to find and characterize the right phage in nature or to engineer one that can effectively attack the particular bacterium causing a person's illness.

A common way a phage kills is by attaching to a bacterium's exterior and injecting its own genetic material through the cell wall. This DNA hijacks the cell's reproductive machinery to make many copies and assemble them into new phages, which explode out of the cell, killing it.

3 BUT BACTERIA CAN DEVELOP RESISTANCE

Some harmful bacteria can mutate to create novel cellular features that resist the attacks. As these resistant bacteria proliferate, they can hurt an infected individual without being neutralized by the previous drugs or phages.

Illustration by AXS Biomedical Animation Studio

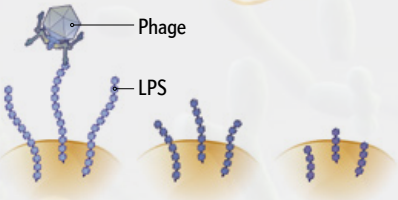


4 DRUG-RESISTANT BACTERIA FLOURISH

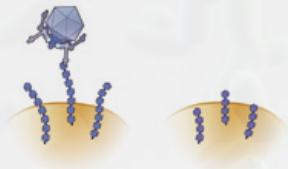
The newly evolved bacteria can hunker down in the human body and become very difficult to eradicate. Physicians are trying different phage therapies to counter the drug-resistant bacteria.

5 PHAGE THERAPIES WEAKEN RESISTANCE

Sequential monophage treatment



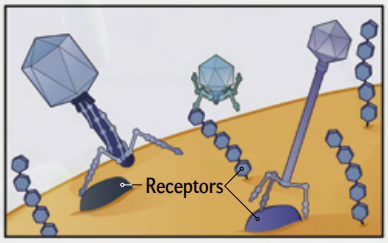
Phage 1 is given to a patient. It destroys *Achromobacter* species 1, which has long lipopolysaccharide (LPS) chains.

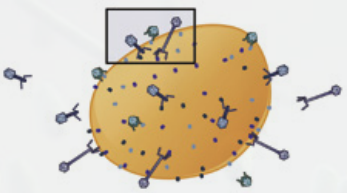


Phage 2 is then given to destroy *Achromobacter* species 2, which has moderately long LPS chains.

The immune system, which struggles against the longer-chain species, destroys the remaining short-chain *Achromobacter* species.

Phage cocktails

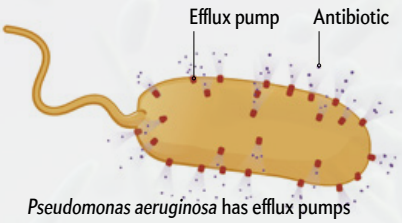




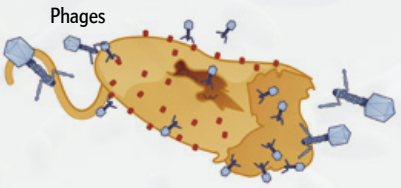
Several different phages are given simultaneously to a patient. Each phage targets a different receptor on *Acinetobacter baumannii*.

The *A. baumannii* cells cannot modify all types of receptors at once to resist the different phages and are killed.

Phage plus antibiotics



Pseudomonas aeruginosa has efflux pumps that expel antibiotics that sneak inside it.



Phages attach to the efflux pumps, shutting them down.

Antibiotics can now persist inside the *P. aeruginosa* cells and kill them.

6 BACTERIAL BALANCE IS RESTORED

By killing only harmful bacteria, phages allow helpful bacteria to dominate a person's microbiome—at least until bad bacteria evolve again.

knapsack slung over his shoulder. Burgholzer met the three of us in a treatment room and spoke with a rasp—the only outward sign of his disease. As Koff and Chan compared notes, he told me he wanted to stay healthy for his three-year-old daughter. When treatment time arrived, he tossed his cell phone to his wife. "Here, take a photo for my mother," he said with a grin. Then he raised a nebulizer over his mouth and nose and began inhaling a vaporized phage solution into his lungs.

PHAGE COCKTAILS

ACCORDING TO KOFF, sequential monophage therapy makes sense for treating cystic fibrosis and certain other chronic diseases that sequester bad bacteria in the body. When there is no proven way to eliminate the pathogens completely, he says, the tactic is to chip away at the harmful strains.

Some clinicians are choosing a different approach: They give patients multiple phages in a therapeutic cocktail, trying to knock out an infection completely by targeting a variety of bacterial resistance mechanisms simultaneously. Ideally, each phage in a cocktail will glom on to a different receptor, so if bacteria evolve resistance to one virus in the mixture, other viruses will keep up the attack.

Experts cannot say which of the phage therapies may win out. What is needed now are results from clinical trials that can help overcome residual skepticism.

Chan and Koff argue that phage interactions with bacteria are unpredictable and that when exposed to cocktails, pathogens might develop resistance to all the viruses in the mixture at once, which could limit future treatment options. "Splitting the cocktail into sequential treatments allows you to treat patients for longer durations," Koff says.

Jessica Sacher, co-founder of the Phage Directory, an independent platform for improving access to phages and phage expertise, says convincing arguments can be made for either method. "The science isn't there yet to say one is necessarily better than the other." She notes that cocktails might be more appropriate for acutely ill patients, who cannot always wait for doctors to develop a sequential strategy.

Urgency was paramount in the now famous case of Tom Patterson, a professor at the University of California, San Diego, who in 2016 was saved by phage cocktails after being stricken by an MDR infection during a trip to Egypt. The invader was *Acinetobacter baumannii,* a notoriously drug-resistant microbe that is common in Asia and is spreading steadily toward the West. Patterson was in multiorgan failure by the time doctors delivered mixtures of four viruses through a catheter into his abdomen and a fifth intravenously. The physicians treated him twice a day for four weeks, and he was cleared of infection within three months. He still needed extensive rehabilitation, but he remains healthy today.

The case drew worldwide media attention. The treating physicians were Robert Schooley, a friend of Patterson's and chief of infectious diseases at U.C. San Diego, and Patterson's wife, Steffanie Strathdee, then director of the university's Global Health Institute. Two years later, with an initial investment of $1.2 million, Schooley and Strathdee launched the Center for Innovative Phage Applications and Therapeutics at U.C. San Diego to fund clinical research and promote the field.

Each phage Patterson was treated with was screened for its ability to kill *A. baumannii* in infectious samples obtained from his body, using assays at the Naval Medical Research Center at Fort Detrick, Md., and at Texas A&M University. The assays can test hundreds of phages against bacterial pathogens simultaneously in just eight to 12 hours, according to Biswajit Biswas, chief of the bacteriophage division at the center, which supplied some of the phages used in Patterson's treatment. Biswas, who developed the assay and created the center's phage bank, says the assay allows new viruses to be easily swapped in to counter the onset of resistance. Patterson did develop resistance to his first cocktail within two weeks, prompting the navy to prepare a second one with longer-lasting effects. A company called Adaptive Phage Therapeutics in Gaithersburg, Md., has since licensed the navy's assay and its phage bank and will soon take them both into clinical trials in patients with urinary tract infections.

The navy assay checks only for bacterial cell death; it does not reveal which receptors are targeted. Whether cocktails should target known receptors is in debate. Ry Young, a phage geneticist at Texas A&M, who supplied viruses for Patterson, argues they should. "We don't even know if phages were responsible for his successful outcome," he says. "Our best guess is that phage treatment lowered his infectious load to a level where his immune system took over." The better approach to cocktails, Young says, is to combine three or four viruses targeting distinct receptors on the same bacterial strain. The odds of a bacterium evolving resistance to a single phage are about a million to one, he says, whereas the odds of it losing or developing mutant forms of receptors targeted by all the phages in a cocktail "are essentially zero." Furthermore, the identification of important receptors is critical if clinicians hope to make bacteria sensitive to antibiotics again.

Barr says scientists are working to identify the receptors targeted by Patterson's cocktails, but he disagrees on the need to identify the receptors prior to use. "It's an understandable viewpoint and a hot topic in the field," he says. "We know very little about these phages, and we need checks and balances before using them in therapy. Does that mean we need to identify host receptors? That is a huge amount of work currently, so I would say it's not required but definitely desirable."

ENGINEERED PHAGES

GIVEN THE VAGARY OF COCKTAILS, some researchers say phages should be genetically engineered to bind to specific receptors and also to kill bacteria in novel ways. The vast majority of

phages used thus far have been natural, harvested from the environment, but phage engineering is an emerging frontier with a new success story under its belt. Isabelle Carnell, a British teenager with cystic fibrosis, was suffering from life-threatening infections in her liver, limbs and torso after undergoing a double lung transplant in 2017. Her bacterial nemesis—*Mycobacterium abscessus*—was not responding to any antibiotics. Yet this year, in a first for the field, researchers from several institutions successfully treated the girl with an engineered cocktail of three phages. One naturally rips apart *M. abscessus* as it replicates. The other two also kill bacteria but not as completely, leaving 10 to 20 percent surviving the process. So the team, led by Graham Hatfull, a professor of biological sciences at the University of Pittsburgh, deleted a single gene from each of those two phages, turning them into engineered assassins. The cocktail of three phages cleared Carnell's infection within six months.

Researchers at Boston University first developed engineered phages in 2007. They coaxed one into producing an enzyme that more effectively degrades the sticky biofilms secreted by certain infectious bacteria for protection. Scientists have since modified phages to kill broader ranges of harmful bacteria or potentially to deliver drugs and vaccines to specific cells. These lab-designed viruses are also more patentable than natural phages, which makes them more desirable to drug companies. As if to underscore that point, a division of the pharmaceutical giant Johnson & Johnson struck a deal in January with Locus Biosciences, worth up to $818 million, to develop phages engineered with the gene-editing tool CRISPR.

Developing a phage therapy that is commercially viable will not be easy. Barr and other scientists point out that it takes a tremendous amount of time, money and effort to engineer a phage, and after all that the target bacteria might soon evolve resistance to it. Furthermore, regulatory approval for an engineered phage "could be a tough sell," says Barr, echoing the view of several scientists interviewed for this story. But FDA spokesperson Megan McSeveney, in an e-mail, claimed the agency does not distinguish between natural and engineered phages as long as therapeutic preparations are deemed safe.

FUTURE PROSPECTS

COMPANIES ARE NOW testing different ways to bring phages to broader markets. Some companies want to supply patients with personalized therapies matched specifically to their infections. That is the strategy at Adaptive Phage Therapeutics. The company's chief executive officer, Greg Merril, says assays used to screen the navy's phages against infectious samples could be offered at diagnostic labs and major medical centers worldwide. Phages effective against locally prevalent bacteria in each region could be supplied in kiosks, bottled in FDA-approved, ready-to-use vials. Merril says doctors could continually monitor treated patients for resistance, swapping in new phages as needed until the infections are under control. He estimates that the per-patient cost under the current compassionate-use system is approximately $50,000, an expense that should fall with economies of scale.

Other companies reject this personalized strategy in favor of fixed phage products more akin to commercial antibiotics. Armata Pharmaceuticals' lead product is a cocktail of three natural phages targeted at *Staphylococcus aureus* bacteria, the cause of common staph infections often contracted at hospitals. It is in clinical trials in patients who have infected mechanical heart pumps. Armata's plan is to monitor for treatment-resistant staph in the general population, then introduce new cocktails as needed, in much the same way that influenza vaccines are tuned every year to match the latest circulating strains. Pharmaceutical executives said it was too soon to estimate what the costs would be.

Experts still cannot say which of the current strategies—sequential monotherapy, cocktails, engineered phages, and general or personalized treatments—may ultimately win out, assuming any do. An optimal approach "might not even exist," says Barr, considering that "phage treatments in each case could depend on complicating issues, such as the target pathogen, the disease and the patient's medical history."

Phage therapy is still saddled by geopolitical biases, too, says Strathdee. What is really needed now, she says, are positive results from well-controlled clinical trials that can help overcome residual skepticism. Alan Davidson, a biochemist at the University of Toronto, speculates that within a decade phage therapy might be cheaper, easier and faster than it is today. He leans toward the engineering approach, saying sequencing the whole genome of a patient's bacteria and then synthesizing a phage to cure an infection could be quicker and less expensive "than screening the pathogens against a battery of viruses drawn from nature."

Meanwhile Burgholzer, who was self-administering phage therapy with a nebulizer at home until March 2019, has not yet experienced the clinical improvements he was hoping for. In March, Chan and Koff introduced a second phage targeted at another *Achromobacter* strain. By April the bacterial counts in Burgholzer's lungs had fallen by more than two orders of magnitude since the initial treatment began. "So it does appear we can pick off those strains successively," Koff told me. Yet Koff acknowledged that Burgholzer was not noticing a dramatic change in lung function. When I asked why, Koff responded, "We know a lot more about the phage we use against *P. aeruginosa* than we do about phages targeting *Achromobacter*." The ability to manipulate the infection "is less informed."

The next step, Koff says, will be to genetically sequence mucus samples from Burgholzer's lungs. "We really need to understand what's happening with his bacteria so we can get to the high level of sophistication we have with *P. aeruginosa*. Bobby is letting us take a chance to see if, at a minimum, we can help." Frustrated but still eager, Koff says, "Some patients respond better than others. We need to understand those dynamics." SA

MORE TO EXPLORE

Global Priority List of Antibiotic-Resistant Bacteria to Guide Research, Discovery, and Development of New Antibiotics. World Health Organization, 2017.

Engineered Bacteriophages for Treatment of a Patient with a Disseminated Drug-Resistant *Mycobacterium abscessus*. Rebekah M. Dedrick et al. in *Nature Medicine*, Vol. 25, pages 730–733; May 2019.

Phage Directory: https://phage.directory

FROM OUR ARCHIVES

Infectious Drug Resistance. Tsutomu Watanabe; December 1967.

scientificamerican.com/magazine/sa

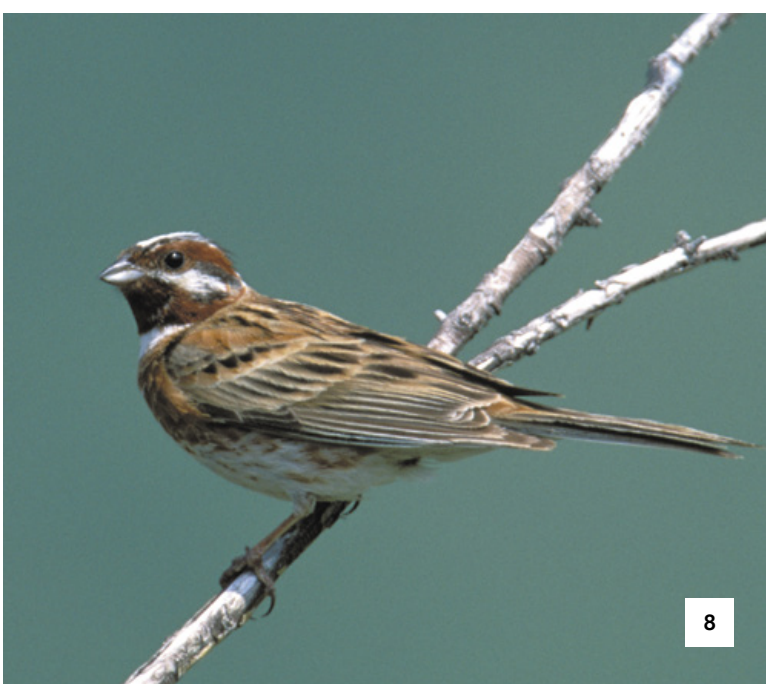

1


2


4


5


7


8

3

6

9

EVOLUTION

Winged Victory

The discovery of a strange chromosome in songbirds might explain their astonishing diversity

By Kate Wong

When a 10-kilometer-wide hunk of burning space rock slammed into what is now the Gulf of Mexico 66 million years ago, it touched off widespread destruction, wiping out more than 75 percent of life on Earth. The Chicxulub asteroid, as it is called, is best known as the dinosaur killer. But although it doomed *Tyrannosaurus rex* and *Triceratops,* the sauropods and the hadrosaurs, the asteroid actually set one lineage of dinosaurs on a path to glory: that of modern birds.

SONGBIRD SPECIES found to have the extra chromosome include the Gouldian finch (*1*), Blyth's reed warbler (*2*), Eurasian skylark (*3*), Eurasian bullfinch (*4*), rook (*5*), European siskin (*6*), common canary (*7*), pine bunting (*8*) and barn swallow (*9*).

Birds got their start more than 150 million years ago, evolving from meat-eating dinosaurs called theropods, and they attained an impressive degree of diversity in the first 85 million years or so of their existence. But the ancestors of today's birds—members of the neornithine lineage—were mere bit players compared with archaic birds such as the enantiornithines, which ruled the roost. When the asteroid struck, however, neornithine fortunes shifted. The impact extinguished all of the nonbird dinosaurs and most birds. Only the neornithines made it through that apocalyptic event. This clutch of survivors would give rise to one of the greatest evolutionary radiations of all time.

Today there are more than 10,000 bird species, making them the second most speciose class of vertebrate creatures alive, outnumbered only by the bony fish. They come in every shape and size—the land-bound ostrich tips the scales at more than 136 kilograms; the ever whirring bee hummingbird, less than two grams. They have colonized virtually every major body of land and water on the planet, from the sweltering tropics to the frozen poles. And they have diversified to fill a vast array of dietary niches, evolving adaptations to eating everything from microscopic algae to large mammals.

Incredibly, roughly half of these species are songbirds, which are characterized by a special voice box. The group includes the warblers, canaries, larks and other mellifluous singers but also the strident (to human ears, anyway) crows and their kin. To put that number in perspective, there are approximately as many living species of songbirds as there are of mammals.

How did this particular group of birds come to be so extraordinarily diverse? Biologists have long sought to answer this question, scouring the fossil record and DNA sequences of modern birds for clues. But apart from pinpointing where songbirds originated (Australia), many of these studies produced inconclusive or conflicting results. A detailed picture of where and when the lineages leading to modern songbirds split off from one another—and thus the factors driving this radiation—remained elusive.

In the absence of conclusive evidence to show how it all transpired, researchers have advanced a number of competing theories for songbird diversification that center variously on climate change, plate tectonics and sexual selection, in which mate preferences spur evolution.

Now a new finding has set the field atwitter. All songbirds, it seems, have a weird extra chromosome that does not appear to exist in other birds. The discovery suggests a genetic mechanism for creating barriers to reproduction between populations of a species, which promotes speciation. Much remains to be learned about this auxiliary package of DNA, but already some researchers are wondering whether it just might be the secret of the songbirds' dazzling evolutionary success.

BACK POCKET GENES

THE CHROMOSOME in question is called the germ-line-restricted chromosome (GRC), so named for its presence in reproductive cells—eggs, sperm and their precursors—but not the rest of the body's cells, called somatic cells. Progenitors of both eggs and sperm contain GRC, but by the time a sperm cell has developed fully, the GRC has been eliminated from it. The chromosome is thus transmitted to offspring via the mother exclusively.

Until recently the GRC was known only from two songbirds: the zebra finch and its close relative the Bengalese finch. It seemed to be an oddity of these two species, nothing more. But when researchers decided to look for it in other lineages of birds, a striking pattern emerged. In a paper published in the June 11 *Proceedings of the National Academy of Sciences USA,* Anna Torgasheva and Pavel Borodin of the Russian Academy of Sciences, Denis Larkin of the University of London and their colleagues report that all 16 of the songbird species they examined—a sample that included representatives from across the family tree of songbirds—had the GRC; none of the eight species representing other major bird groups did. What is more, the GRCs they found differed considerably from species to species—even between closely related ones—suggesting that the chromosome has evolved quickly in these different songbird lineages since it first appeared in their common ancestor an estimated 35 million years ago.

Cells of other organisms have previously been found to carry extra chromosomes called B chromosomes. But their occurrence is erratic, varying between members of the same species or even between different cells in the same individual. GRC, in contrast, is "an obligatory element in the germ line of song birds," Larkin says. This ubiquity suggests that GRC is more influential than B chromosomes.

Exactly what GRC is influencing is largely a mystery, however—researchers know very little about what its genes actually do. But some hints have come to light. In another recent GRC study, which has been posted to the bioRxiv preprint server but not yet published in a peer-reviewed scientific journal, Cormac M. Kinsella and Alexander Suh of Uppsala University in Sweden and their colleagues found that the zebra finch GRC contains at least 115 genes, including some that have been shown to make proteins and RNA in the ovaries and testes of adult birds. This expression pattern hints that these genes may help guide the development of sperm and eggs. Other genes on the zebra finch GRC are comparable to genes that are known from mouse studies to be involved in early embryonic development.

To Borodin and Larkin, these findings suggest that the GRC may have allowed songbirds to circumvent key constraints on

Kate Wong is a senior editor for evolution and ecology at *Scientific American.*

IN BRIEF

Songbirds are the most species-rich bird group, accounting for roughly half of the more than 10,000 bird species alive today.

Biologists have long wondered how songbirds came to be so diverse. Traditional explanations have focused on factors such as climate change.

Recent studies show that songbirds have an extra chromosome not found in other birds, suggesting that it might have been the key to their diversification.

CYRIL LAUBSCHER *Getty Images* (1); OLEG MINITSKIY *Getty Images* (2); LES STOCKER *Getty Images* (3); REINHARD HOLZL *Getty Images* (4); KIM TAYLOR *Getty Images* (5); ALAMY (6); FERNANDO SANCHEZ DE CASTRO *Getty Images* (7); HANNE AND JENS ERIKSEN *Nature Picture Library* (8); DP WILDLIFE VERTEBRATES *Alamy* (9)

bird evolution. "The avian genome in general is very compact and conserved compared with, for example, the mammalian genome," Larkin explains. The genomes of today's mammals range in size from less than two picograms to more than eight picograms and are packaged into anywhere from six chromosomes to 102. In the tens of millions of years over which they have been evolving, their chromosomes have been sliced and diced and reshuffled and rejoined many times. These rearrangements have altered gene expression in ways that have produced diverse traits. Birds, in contrast, have genomes ranging from just under one picogram to just over two. And they usually have right around 80 chromosomes, with comparatively little of the "junk" DNA found in most mammals.

The reason bird genomes are small and streamlined, some experts surmise, has to do with flight. Flying is an energetically expensive activity. Larger genomes require larger cells, and both are metabolically costlier than their smaller counterparts. The intense metabolic demands of flying may have therefore limited bird genome size. Because the GRC occurs only in germ-line cells and not the far more numerous somatic cells, it could have provided songbirds with a rare chunk of extra DNA—fodder for the evolution of new traits—without the metabolic costs associated with having a larger somatic genome.

The GRC could have provided songbirds with a rare chunk of extra DNA—fodder for the evolution of new traits.

"Birds need additional copies of germ-cell-specific genes for a very short breeding period only to produce a lot of sperm and load [egg cells] with large amounts of proteins. They have no reason to carry these genes throughout the year and in [the rest of the body's] cells when and where they are of no use," Borodin says. If songbirds found a way to obtain additional genes on a temporary basis that could work during early stages of development while keeping their basic genome intact, Larkin adds, such an arrangement would be tremendously advantageous and could lead to the huge variety seen in songbirds compared with other bird groups.

In theory, the GRC could have created the reproductive isolation needed for new species to evolve by rendering those individuals that carried the extra chromosome unable to interbreed and produce fertile offspring with those that did not. Once the GRC originated in the last common ancestor of songbirds, members of that ancestral species that carried the GRC could produce fertile offspring only with mates that also had the GRC. As the GRC evolved, acquiring new genes, songbirds with a particular variant of GRC could produce fertile offspring only with mates that carried that same GRC variant.

ENGINE OF CHANGE?

ACCORDING TO BORODIN AND LARKIN, the discovery that GRC is widespread among songbirds and absent in other birds dovetails with the results of another recent study. In April, Carl Oliveros of Louisiana State University and his colleagues reported on the results of their analysis of DNA from dozens of members of the passerine order of birds, which comprises the songbirds and some other, far less speciose groups. Based on the DNA sequences and a handful of fossils of known age, the team reconstructed how the various passerine families were related and when they branched off. It then compared this time line of diversification against climate and geologic records to see if the passerine diversification trends correlated with events in Earth history, as predicted by some hypotheses. On the whole, fluctuations in the diversification rates of these birds did not track changes in global temperature or dispersals of the birds into new continents. The findings prompted the authors to suggest that more complex mechanisms than temperature or ecological opportunity were the main drivers of passerine speciation. "These conclusions are very much in line with our hypothesis of GRC contribution to songbird diversification," Larkin asserts.

Not everyone is ready to embrace the suggestion that GRC drove songbird diversification, however. "In general, it is hard to establish causation between any one given trait, like the presence of GRCs, and the evolutionary success of a particular group," Oliveros says. "The presence of the trait could by chance have coincided with another trait—nesting behavior, for example—that may have played a larger role in a group's evolutionary success."

But other researchers not involved in the new studies find the notion intriguing. "The fact that [GRCs] have been maintained over long evolutionary periods and also contain putatively functional genes … suggests that they could play a role in reproductive isolation in birds," observes David Toews of Pennsylvania State University. If the sky-high diversification rate of songbirds compared with that of other birds was promoted by a genomic mechanism such as GRCs, "it would definitely be exciting and not something that I would have predicted," Toews says. He cautions, though, that "we need to know more about what they are actually doing to make that link with confidence."

The work could have implications for understanding organisms beyond birds. "We thought we knew a lot about how bird genomes are organized," Suh reflects, "but the GRC has been right before our eyes yet has been overlooked." Scientists have found similar extra chromosomes in hagfishes and some insects. What if GRCs are more widespread in the tree of life, he wonders: "The findings in songbirds open up a bunch of new directions for thinking about evolution and development." SA

MORE TO EXPLORE

Programmed DNA Elimination of Germline Development Genes in Songbirds. Cormac M. Kinsella et al. Posted to Biorxiv preprint server December 22, 2018. www.biorxiv.org/content/10.1101%444364v2

Germline-Restricted Chromosome Is Widespread among Songbirds. Anna Torgasheva et al. in *Proceedings of the National Academy of Sciences USA*, Vol. 116, No. 24, pages 11,845–11,850; June 11, 2019.

FROM OUR ARCHIVES

Taking Wing. Stephen Brusatte; January 2017.

scientificamerican.com/magazine/sa

IN THE PIPELINE

Cocooned in stainless steel and surrounded by water-logged rock, one of two three-kilometer-long vacuum chambers sprawls down a damp, dripping tunnel bored underneath Mount Ikenoyama in Japan. An intricate system of lasers and mirrors inside the chambers is designed to tune in to gravitational waves moving through our planet from across the cosmos.

ENRICO SACCHETTI

CENTER OF GRAVITY

ASTROPHYSICS

The first major gravitational-wave observatory to be built under Earth's surface—KAGRA in Japan—is set to turn on

By Lee Billings

GRAVITATIONAL WAVES—ripples in spacetime produced by merging black holes, colliding neutron stars, detonating supernovae and other cosmic cataclysms—have sparked a revolution in astrophysics. First observed in 2015, a century after Albert Einstein predicted their existence, these elusive whispers in the fabric of reality are already revealing otherwise hidden details of the exotic objects that produce them. Studies of gravitational waves have provided researchers with the first direct evidence that black holes exist, produced new estimates of the cosmic expansion rate, and shown that neutron stars are the main sources of the universe's supply of gold, platinum and other heavy elements. Eventually they could allow researchers to glimpse the universe as it was in the first fractions of a second after the big bang.

Lee Billings is a senior editor for space and physics at *Scientific American*.

The forefront of this promising future can be found in a subterranean complex of darkened tunnels. There more than 200 meters below Mount Ikenoyama in the Gifu prefecture of central Japan, an international team of scientists, engineers and technicians is finishing almost a decade of steady construction, readying the Kamioka Gravitational-Wave Detector (KAGRA) to begin operations by the end of this year. Soon KAGRA will join the world's three other active gravitational-wave detectors—the twin stations of the U.S.-based Advanced Laser Interferometer Gravitational-Wave Observatory (LIGO) in Hanford, Wash., and in Livingston, La., and the Advanced Virgo facility near Pisa, Italy. KAGRA's location in Japan and orientation with respect to LIGO and Virgo will independently check and enhance those detectors' observations, allowing researchers to better measure the orientations and spins of merging black holes and neutron stars.

Collectively, this quartet of detectors will reach new heights of sensitivity and precision, finding fainter gravitational-wave events than ever before and pinpointing their celestial coordinates with unprecedented acuity for follow-up with conventional telescopes. Here selected photographs capture some of the final technical preparations before KAGRA is unleashed on the sky.

To find gravitational waves, KAGRA relies on the same method used by LIGO and Virgo, a technique called laser interferometry. In this approach, a laser beam bounces between mirrors suspended at the ends of two pipelike vacuum chambers. The chambers are several kilometers long and oriented perpendicularly to each other, forming what looks like a giant **L**. The laser acts as a measuring stick, revealing when a passing gravitational wave briefly stretches and shrinks spacetime, altering the chambers' lengths (and thus

IN BRIEF

Studies of gravitational waves using three observatories are revolutionizing our understanding of black holes, neutron stars and other astrophysical objects.
A fourth observatory, the Kamioka Gravitational-Wave Detector (KAGRA), is set to begin operations by the end of 2019.
The first observatory of its kind to be built underground and kept at extremely low temperatures to increase sensitivity, KAGRA is demonstrating innovations crucial for constructing a new generation of even more advanced gravitational-wave detectors.

ENRICO SACCHETTI

SHIELDING VIBRATIONS

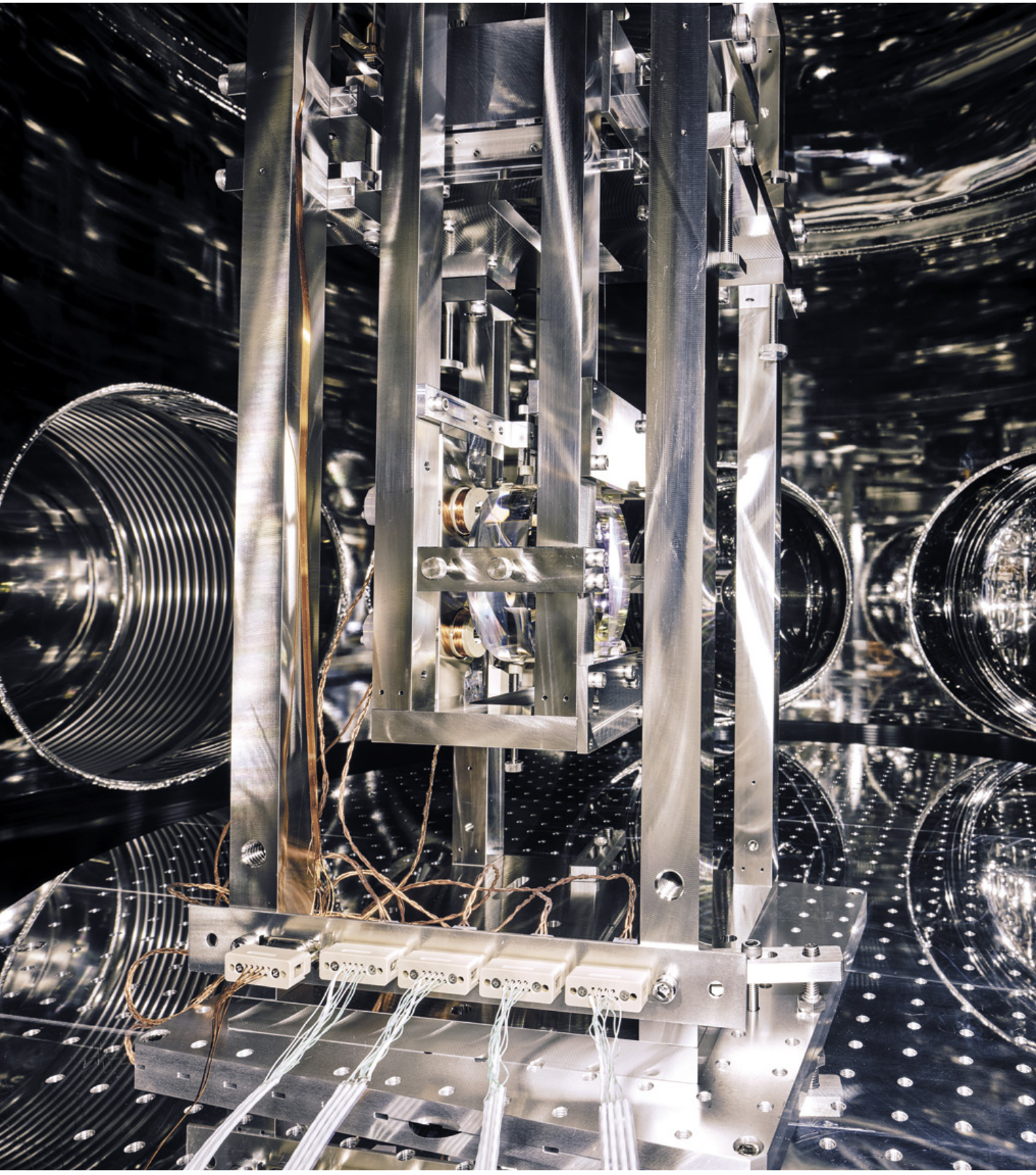
A technician squats beside the uppermost section of a 14-meter-tall vibration isolation system for one of KAGRA's polished sapphire mirrors. Such systems are necessary shields against outside noises, allowing a passing gravitational wave's minuscule signature—a mirror's shift by a fraction of a thousandth of the width of a proton—to be detected.

the total distance a beam of light travels). Such perturbations are inconceivably tiny, far smaller than the diameter of a single proton—meaning that each facility must somehow account for or suppress an almost countless assortment of contaminating noises, from the enormous seismic motions of earthquakes and tides to the softer vibrations caused by airplanes overhead, passing cars, nearby wildlife or even a mirror's jiggling atoms. Distinguishing between legitimate gravitational-wave signals and noise-induced "glitches" is an almost overwhelming task—and one that has contributed to numerous false alarms mixed in with the dozens of authentic detections collaboratively announced to date by LIGO and Virgo.

Buried deep below its mountain, KAGRA will be the first major laser interferometer built and operated entirely underground, far from the cacophony of background noise at the terrestrial surface. It is also the first to use cryogenically cooled mirrors—each a polished 23-kilogram cylinder of sapphire crystal—which can dramatically reduce thermal vibrations and deliver corresponding boosts in sensitivity. LIGO's and Virgo's mirrors are kept at room temperature; KAGRA's will be maintained at a frigid 20 degrees above absolute zero.

Although these two advances could in principle allow KAGRA to find fainter sources of gravitational waves than LIGO or Virgo, they are not without drawbacks: Mechanical coolers keep the laser-bathed mirrors cold but also introduce their own vibrational noise into measurements, and water from rain and melting snow regularly infiltrates KAGRA's tunnels, forcing workers to install plastic sheets to protect delicate equipment. Even with protection, the moisture may halt operations during the wettest times of year.

If all goes according to plan, KAGRA will not only help make additional major discoveries but also demonstrate the new technologies likely to be used by the next generation of more advanced gravitational-wave observatories around the globe. SA



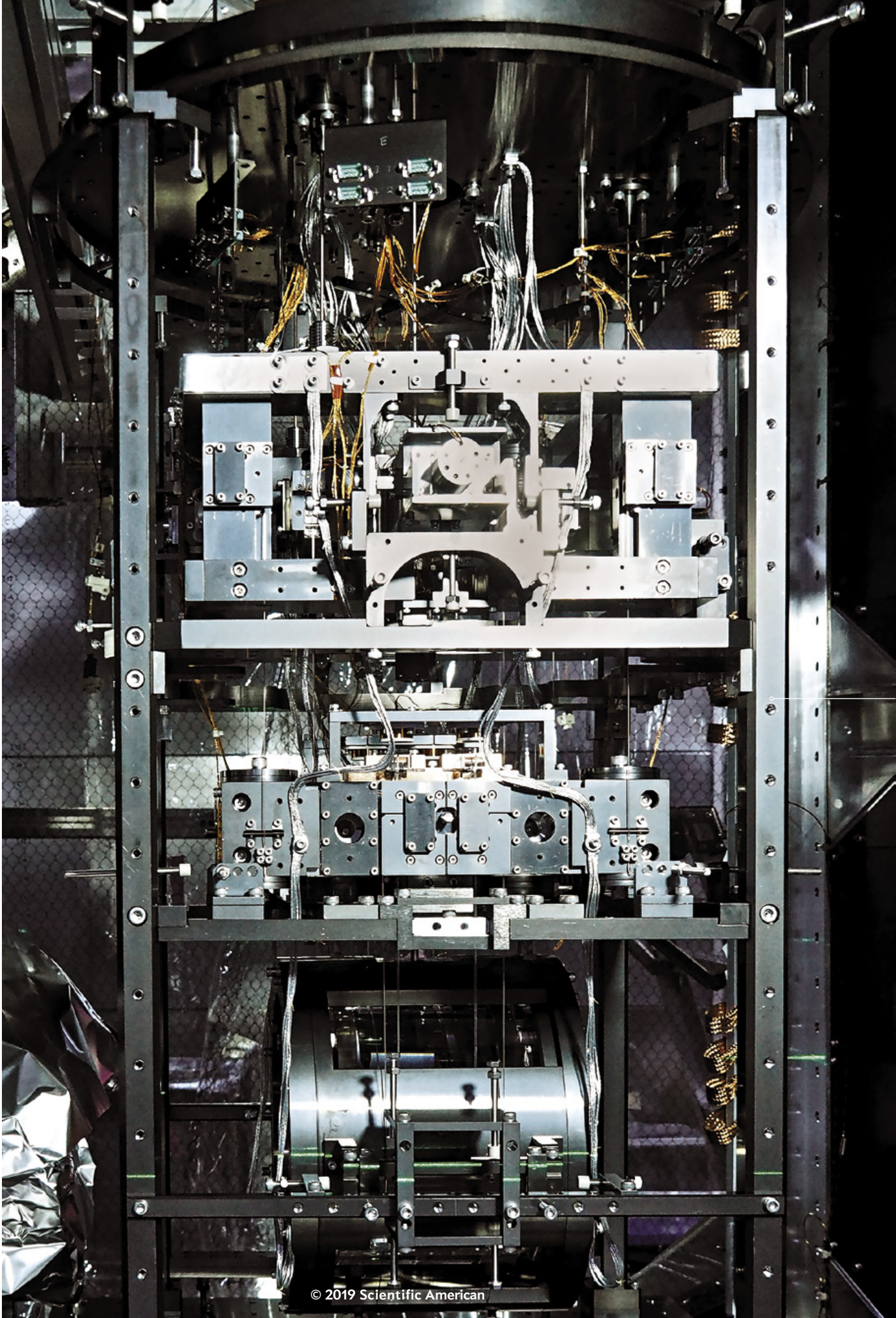
OPPOSITE PAGE: ENRICO SACCHETTI; THIS PAGE: ROHAN MEHRA

TIGHT BEAM

To ensure that KAGRA's lasers can accurately register the almost imperceptible distortions of its mirrors caused by gravitational waves, scientists must precisely control the location and brightness of the laser beam. This requires feeding the laser through what is effectively a telescope (*shown here*) mated to another vibration isolation device and housed inside a vacuum vessel.

KEEPING COOL

A technician checks a mirror's suspension system before its installation inside KAGRA's cryogenic containers. Once inside, the mirror and its mounting are cooled to almost absolute zero—all in an effort to minimize the thermal vibrations of their constituent atoms, allowing signatures of fainter gravitational waves to be seen.



MIRROR, MIRROR

Another view of the delicate apparatus that keeps a mirror in place, before installation in KAGRA's cryogenic system. The sapphire mirror is held in the cylindrical chamber in the bottommost stage, suspended by four thin sapphire fibers. The remaining three vertical stages contain components to isolate the mirror assembly from seismic noise and are fabricated with a variety of materials that can withstand KAGRA's extremely cold operating conditions.

COMMAND CENTER

All of KAGRA's instruments are controlled from this room at the surface, a 10-minute drive from the underground cavern's entrance. A wall-mounted bank of six large screens displays the temperature, humidity and operational conditions of the KAGRA site, and smaller screens along the room's right wall show snapshots of laser light cascading through the vacuum tunnels, as well as information about seismic activity throughout Japan.

OPPOSITE PAGE: INSTITUTE FOR COSMIC RAY RESEARCH, UNIVERSITY OF TOKYO; THIS PAGE: ENRICO SACCHETTI

MORE TO EXPLORE

The Detection of Gravitational Waves with LIGO. Barry C. Barish. Paper presented at the American Physical Society Division of Particles and Fields Conference, Los Angeles, Calif., January 5–9, 1999. Preprint available at **https://arxiv.org/abs/gr-qc/9905026**

Observation of Gravitational Waves from a Binary Black Hole Merger. The LIGO Scientific Collaboration and the Virgo Collaboration in *Physical Review Letters,* Vol. 116, No. 6, Article No. 061102; February 12, 2016.

KAGRA: 2.5 Generation Interferometric Gravitational Wave Detector. The KAGRA Collaboration in *Nature Astronomy,* Vol. 3, pages 35–40; January 2019.

FROM OUR ARCHIVES

The Future of Gravitational Wave Astronomy. Lee Billings; ScientificAmerican.com, February 12, 2016.

scientificamerican.com/magazine/sa

ECONOMICS

THE INESCAPABLE CASINO

A novel approach developed by physicists and mathematicians describes the distribution of wealth in modern economies with unprecedented accuracy

By Bruce M. Boghosian

Illustrations by Hanna Barczyk

WEALTH INEQUALITY IS ESCALATING AT an alarming rate not only within the U.S. but also in countries as diverse as Russia, India and Brazil. According to investment bank Credit Suisse, the fraction of global household wealth held by the richest 1 percent of the world's population increased from 42.5 to 47.2 percent between the financial crisis of 2008 and 2018. To put it another way, as of 2010, 388 individuals possessed as much household wealth as the lower half of the world's population combined—about 3.5 billion people; today Oxfam estimates that number as 26. Statistics from almost all nations that measure wealth in their household surveys indicate that it is becoming increasingly concentrated.

Bruce M. Boghosian is a professor of mathematics at Tufts University, with research interests in applied dynamical systems and applied probability theory.

Although the origins of inequality are hotly debated, an approach developed by physicists and mathematicians, including my group at Tufts University, suggests they have long been hiding in plain sight—in a well-known quirk of arithmetic. This method uses models of wealth distribution collectively known as agent-based, which begin with an individual transaction between two "agents" or actors, each trying to optimize his or her own financial outcome. In the modern world, nothing could seem more fair or natural than two people deciding to exchange goods, agreeing on a price and shaking hands. Indeed, the seeming stability of an economic system arising from this balance of supply and demand among individual actors is regarded as a pinnacle of Enlightenment thinking—to the extent that many people have come to conflate the free market with the notion of freedom itself. Our deceptively simple mathematical models, which are based on voluntary transactions, suggest, however, that it is time for a serious reexamination of this idea.

In particular, the affine wealth model (called thus because of its mathematical properties) can describe wealth distribution among households in diverse developed countries with exquisite precision while revealing a subtle asymmetry that tends to concentrate wealth. We believe that this purely analytical approach, which resembles an x-ray in that it is used not so much to represent the messiness of the real world as to strip it away and reveal the underlying skeleton, provides deep insight into the forces acting to increase poverty and inequality today.

OLIGARCHY

IN 1986 SOCIAL SCIENTIST John Angle first described the movement and distribution of wealth as arising from pairwise transactions among a collection of "economic agents," which could be individuals, households, companies, funds or other entities. By the turn of the century physicists Slava Ispolatov, Pavel L. Krapivsky and Sidney Redner, then all working together at Boston University, as well as Adrian Drăgulescu, now at Constellation Energy Group, and Victor Yakovenko of the University of Maryland, had demonstrated that these agent-based models could be analyzed with the tools of statistical physics, leading to rapid advances in our understanding of their behavior. As it turns out, many such models find wealth moving inexorably from one agent to another—even if they are based on

fair exchanges between equal actors. In 2002 Anirban Chakraborti, then at the Saha Institute of Nuclear Physics in Kolkata, India, introduced what came to be known as the yard sale model, called thus because it has certain features of real one-on-one economic transactions. He also used numerical simulations to demonstrate that it inexorably concentrated wealth, resulting in oligarchy.

To understand how this happens, suppose you are in a casino and are invited to play a game. You must place some ante—say, $100—on a table, and a fair coin will be flipped. If the coin comes up heads, the house will pay you 20 percent of what you have on the table, resulting in $120 on the table. If the coin comes up tails, the house will take 17 percent of what you have on the table, resulting in $83 left on the table. You can keep your money on the table for as many flips of the coin as you would like (without ever adding to or subtracting from it). Each time you play, you will win 20 percent of what is on the table if the coin comes up heads, and you will lose 17 percent of it if the coin comes up tails. Should you agree to play this game?

You might construct two arguments, both rather persuasive, to help you decide what to do. You may think, "I have a probability of ½ of gaining $20 and a probability of ½ of losing $17. My expected gain is therefore:

$$½ \times (+\$20) + ½ \times (-\$17) = \$1.50$$

which is positive. In other words, my odds of winning and losing are even, but my gain if I win will be greater than my loss if I lose." From this perspective it seems advantageous to play this game.

Or, like a chess player, you might think further: "What if I stay for 10 flips of the coin? A likely outcome is that five of them will come up heads and that the other five will come up tails. Each time heads comes up, my ante is multiplied by 1.2. Each time tails comes up, my ante is multiplied by 0.83. After five wins and five losses in any order, the amount of money remaining on the table will be:

$$1.2 \times 1.2 \times 1.2 \times 1.2 \times 1.2 \times 0.83 \times 0.83 \times 0.83 \times 0.83 \times 0.83 \times \$100 = \$98.02$$

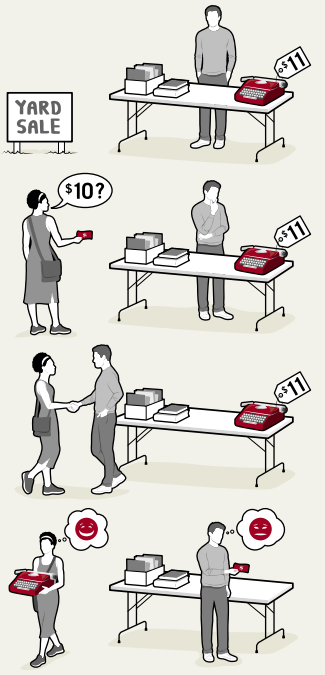
so I will have lost about $2 of my original $100 ante." With a bit more work you can confirm that it would take about 93 wins to compensate for 91 losses. From this perspective it seems disadvantageous to play this game.

The contradiction between the two arguments presented here may seem surprising at first, but it is well known in probability and finance. Its connection with wealth inequality is less familiar, however. To extend the casino metaphor to the movement of wealth in an (exceedingly simplified) economy, let us imagine a system of 1,000 individuals who engage in pairwise exchanges with one another. Let each begin with some initial wealth, which could be exactly equal. Choose two agents at random and have them transact, then do the same with another two, and so on. In other words, this model assumes sequential transactions between randomly chosen pairs of agents. Our plan is to conduct millions or billions of such transactions in our population of 1,000 and see how the wealth ultimately gets distributed.

What should a single transaction between a pair of agents look like? People have a natural aversion to going broke, so we assume that the amount at stake, which we call Δw (Δw is pronounced "delta w"), is a mere fraction of the wealth of the poorer person, Shauna. That way, even if Shauna loses in a transaction with Eric, the richer person, the amount she loses is always less than her own total wealth. This is not an unreasonable assumption and in fact captures a self-imposed limitation that most people instinctively observe in their economic life. To begin with—just because these numbers are familiar to us—let us suppose Δw is 20 percent of Shauna's wealth, w, if she wins and –17 percent of w if she loses. (Our actual model assumes that the win and loss percentages are equal, but the general outcome still holds. Moreover, increasing or decreasing Δw will just extend the time scale so that

Winners, Losers

The yard sale, a simple mathematical model developed by physicist Anirban Chakraborti, assumes that wealth moves from one person to another when the former makes a "mistake" in an economic exchange. If the amount paid for an object exactly equals what it is worth, no wealth changes hands. But if one person overpays or if the other accepts less than the item's worth, some wealth is transferred between them. Because no one wants to go broke, Chakraborti assumed that the amount that can potentially be lost is some fraction of the wealth of the poorer person. He found that even if the outcome of every transaction is chosen by a fair coin flip, many such sales and purchases will inevitably result in all the wealth falling into the hands of a single person—leading to a situation of extreme inequality. —*B.B.*



IN BRIEF

Wealth inequality is escalating in many countries at an alarming rate, with the U.S. arguably having the highest inequality in the developed world.

A remarkably simple model of wealth distribution developed by physicists and mathematicians can reproduce inequality in a range of countries with unprecedented accuracy.

Surprisingly, several mathematical models of free-market economies display features of complex macroscopic physical systems such as ferromagnets, including phase transitions, symmetry breaking and duality.

Illustration by Brown Bird Design

more transactions will be required before we can see the ultimate result, which will remain unaltered.)

If our goal is to model a fair and stable market economy, we ought to begin by assuming that nobody has an advantage of any kind, so let us decide the direction in which Δw is moved by the flip of a fair coin. If the coin comes up heads, Shauna gets 20 percent of her wealth from Eric; if the coin comes up tails, she must give 17 percent of it to Eric. Now randomly choose another pair of agents from the total of 1,000 and do it again. In fact, go ahead and do this a million times or a billion times. What happens?

If you simulate this economy, a variant of the yard sale model, you will get a remarkable result: after a large number of transactions, one agent ends up as an "oligarch" holding practically all the wealth of the economy, and the other 999 end up with virtually nothing. It does not matter how much wealth people started with. It does not matter that all the coin flips were absolutely fair. It does not matter that the poorer agent's expected outcome was positive in each transaction, whereas that of the richer agent was negative. Any single agent in this economy could have become the oligarch—in fact, all had equal odds if they began with equal wealth. In that sense, there was equality of opportunity. But only one of them *did* become the oligarch, and all the others saw their average wealth decrease toward zero as they conducted more and more transactions. To add insult to injury, the lower someone's wealth ranking, the faster the decrease.

This outcome is especially surprising because it holds even if all the agents started off with identical wealth and were treated symmetrically. Physicists describe phenomena of this kind as "symmetry breaking" [*see box on page 76*]. The very first coin flip transfers money from one agent to another, setting up an imbalance between the two. And once we have some variance in wealth, however minute, succeeding transactions will systematically move a "trickle" of wealth upward from poorer agents to richer ones, amplifying inequality until the system reaches a state of oligarchy.

If the economy is unequal to begin with, the poorest agent's wealth will probably decrease the fastest. Where does it go? It must go to wealthier agents because there are no poorer agents. Things are not much better for the second-poorest agent. In the long run, all participants in this economy except for the very richest one will see their wealth decay exponentially. In separate papers in 2015 my colleagues and I at Tufts University and Christophe Chorro of Université Panthéon-Sorbonne provided mathematical proofs of the outcome that Chakraborti's simulations had uncovered—that the yard sale model moves wealth inexorably from one side to the other.

Does this mean that poorer agents never win or that richer agents never lose? Certainly not. Once again, the setup resembles a casino—you win some and you lose some, but the longer you stay in the casino, the more likely you are to lose. The free market is essentially a casino that you can never leave. When the trickle of wealth described earlier, flowing from poor to rich in each transaction, is multiplied by 7.7 billion people in the world conducting countless transactions every year, the trickle becomes a torrent. Inequality inevitably grows more pronounced because of the collective effects of enormous numbers of seemingly innocuous but subtly biased transactions.

THE CONDENSATION OF WEALTH

YOU MIGHT, OF COURSE, wonder how this model, even if mathematically accurate, has anything to do with reality. After all, it describes an entirely unstable economy that inevitably degenerates to complete oligarchy, and there are no complete oligarchies in the world. It is true that, by itself, the yard sale model is unable to explain empirical wealth distributions. To address this deficiency, my group has refined it in three ways to make it more realistic.

In 2017 Adrian Devitt-Lee, Merek Johnson, Jie Li, Jeremy Marcq, Hongyan Wang and I, all at Tufts, incorporated the redistribution of wealth. In keeping with the simplicity desirable in applied mathematics models, we did this by having each agent take a step toward the mean wealth in the society after each transaction. The size of the step was some fraction χ (or "chi") of his or her distance from the mean. This is equivalent to a flat wealth tax for the wealthy (with tax

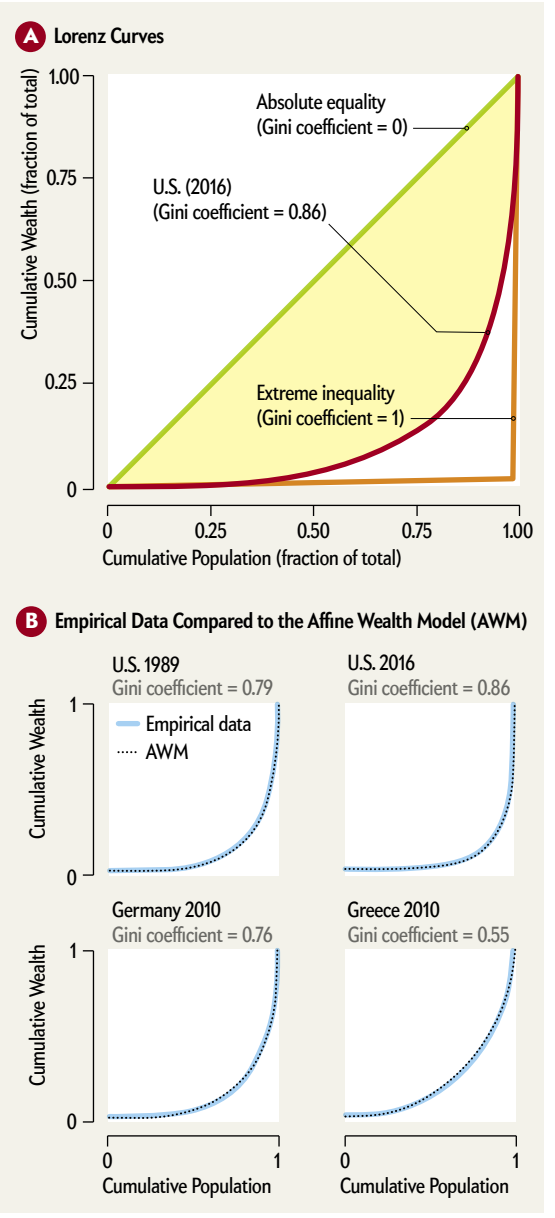
Measuring Inequality

In the early 20th century American economist Max O. Lorenz designed a useful way to quantify wealth inequality. He proposed plotting the fraction of wealth held by individuals with wealth less than *w* against the fraction of individuals with wealth less than *w*. Because both quantities are fractions ranging from zero to one, the plot fits neatly into the unit square. Twice the area between Lorenz's curve and the diagonal is called the Gini coefficient, a commonly used measure of inequality.

Let us first consider the egalitarian case. If every individual has exactly the same wealth, any given fraction of the population has precisely that fraction of the total wealth. Hence, the Lorenz curve is the diagonal (*green line in* A), and the Gini coefficient is zero. In contrast, if one oligarch has all the wealth and everybody else has nothing, the poorest fraction *f* of the population has no wealth at all for any value of *f* that is less than one, so the Lorenz curve is pegged to zero. But when *f* equals one, the oligarch is included, and the curve suddenly jumps up to one. The area between this Lorenz curve (*orange line*) and the diagonal is half the area of the square, or ½, and hence the Gini coefficient is one.

In sum, the Gini coefficient can vary from zero (absolute equality) to one (oligarchy). Unsurprisingly, reality lies between these two extremes. The red line shows the actual Lorenz curve for U.S. wealth in 2016, based on data from the Federal Reserve Bank's Survey of Consumer Finances. Twice the shaded area (*yellow*) between this curve and the diagonal is approximately 0.86—among the highest Gini coefficients in the developed world.

The four small figures in B show the fit between the affine wealth model (AWM) and actual Lorenz curves for the U.S. in 1989 and 2016 and for Germany and Greece in 2010. The data are from the Federal Reserve Bank (U.S., as mentioned above) and the European Central Bank (Germany and Greece). The discrepancy between the AWM and Lorenz curves is less than a fifth of a percent for the U.S. and less than a third of a percent for the European countries. The Gini coefficient for the U.S. (*shown in plot*) increased between 1989 and 2016, indicating a rise in inequality. —*B.B.*



SOURCE: FEDERAL RESERVE BANK'S SURVEY OF CONSUMER FINANCES (*U.S. empirical data*); EUROPEAN CENTRAL BANK (*German and Greek empirical data*)

rate χ per unit time) and a complementary subsidy for the poor. In effect, it transfers wealth from those above the mean to those below it. We found that this simple modification stabilized the wealth distribution so that oligarchy no longer resulted. And astonishingly, it enabled our model to match empirical data on U.S. and European wealth distribution between 1989 and 2016 to better than 2 percent. The single parameter χ seems to subsume a host of real-world taxes and subsidies that would be too messy to include separately in a skeletal model such as this one.

In addition, it is well documented that the wealthy enjoy systemic economic advantages such as lower interest rates on loans and better financial advice, whereas the poor suffer systemic economic disadvantages such as payday lenders and a lack of time to shop for the best prices. As James Baldwin once observed, "Anyone who has ever struggled with poverty knows how extremely expensive it is to be poor." Accordingly, in the same paper mentioned above, we factored in what we call wealth-attained advantage. We biased the coin flip in favor of the wealthier individual by an amount proportional to a new parameter, ζ (or "zeta"), times the wealth difference divided by the mean wealth. This rather simple refinement, which serves as a proxy for a multitude of biases favoring the wealthy, improved agreement between the model and the upper tail of actual wealth distributions.

The inclusion of wealth-related bias also yields—and gives a precise mathematical definition to—the

Graphics by Jen Christiansen

phenomenon of partial oligarchy. Whenever the influence of wealth-attained advantage exceeds that of redistribution (more precisely, whenever ζ exceeds χ), a vanishingly small fraction of people will possess a finite fraction, $1 - \chi/\zeta$, of societal wealth. The onset of partial oligarchy is in fact a phase transition for another model of economic transactions, as first described in 2000 by physicists Jean-Philippe Bouchaud, now at École Polytechnique, and Marc Mézard of the École Normale Supérieure. In our model, when ζ is less than χ, the system has only one stable state with no oligarchy; when ζ exceeds χ, a new, oligarchical state appears and becomes the stable state [*see box on preceding page*]. The two-parameter (χ and ζ) extended yard sale model thus obtained can match empirical data on U.S. and European wealth distribution between 1989 and 2016 to within 1 to 2 percent.

Such a phase transition may have played a crucial role in the condensation of wealth following the breakup of the Soviet Union in 1991. The imposition of what was called shock therapy economics on the former states of the U.S.S.R. resulted in a dramatic decrease of wealth redistribution (that is, decreasing χ) by their governments and a concomitant jump in wealth-attained advantage (increasing ζ) from the combined effects of sudden privatization and deregulation. The resulting decrease of the "temperature" χ/ζ threw the countries into a wealth-condensed state, so that formerly communist countries became partial oligarchies almost overnight. To the present day at least 10 of the 15 former Soviet republics can be accurately described as oligarchies.

As a third refinement, in 2019 we included negative wealth—one of the more disturbing aspects of modern economies—in our model. In 2016, for example, approximately 10.5 percent of the U.S. population was in net debt because of mortgages, student loans and other factors. So we introduced a third parameter, κ (or "kappa"), which shifts the wealth distribution downward, thereby accounting for negative wealth. We supposed that the least wealth the poorest agent could have at any time was $-S$, where S equals κ times the mean wealth. Prior to each transaction, we loaned wealth S to both agents so that each had positive wealth. They then transacted according to the extended yard sale model, described earlier, after which they both repaid their debt of S.

The three-parameter (χ, ζ, κ) model thus obtained, called the affine wealth model, can match empirical data on U.S. wealth distribution to less than a sixth of a percent over a span of three decades. (In mathematics, the word "affine" describes something that scales multiplicatively and translates additively. In this case, some features of the model, such as the value of Δw, scale multiplicatively with the wealth of the agent, whereas other features, such as the addition or subtraction of S, are additive translations or displacements in "wealth space.") Agreement with European wealth-distribution data for 2010 is typically better than a third to a half of a percent [*see box above*].

To obtain these comparisons with actual data, we had to solve the "inverse problem." That is, given the empirical wealth distribution, we had to find the values of (χ, ζ, κ) at which the results of our model most closely matched it. As just one example, the 2016 U.S. household wealth distribution is best described as having $\chi = 0.036$, $\zeta = 0.050$ and $\kappa = 0.058$. The affine wealth model has been applied to empirical data from many countries and epochs. To the best of our knowledge, it describes wealth-distribution data more accurately than any other existing model.

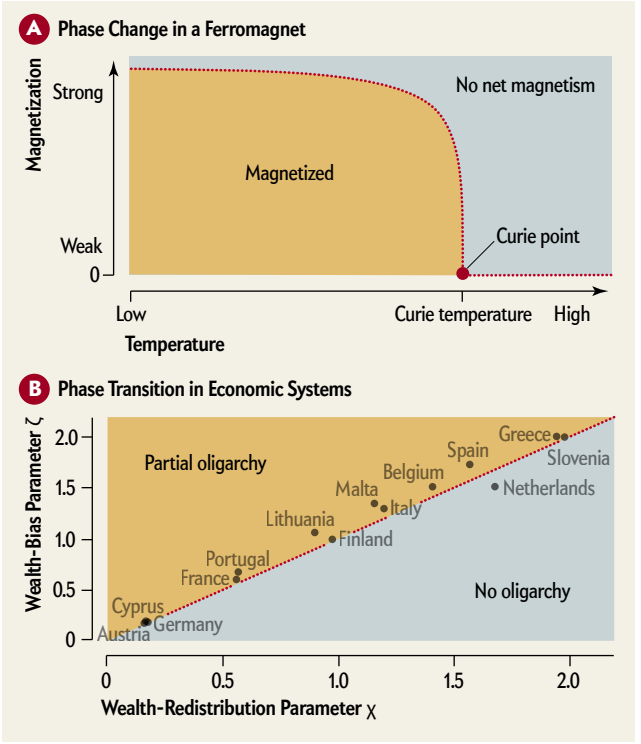
The Physics of Inequality

When water boils at 100 degrees Celsius and turns into water vapor, it undergoes a phase transition—a sudden and dramatic change. For example, the volume it occupies (at a given pressure) increases discontinuously with temperature. Similarly, the strength of a ferromagnet falls to zero (*orange line in* A) as its temperature increases to a point called the Curie temperature, T_c. At temperatures above T_c, the substance has no net magnetism. The fall to zero magnetism is continuous as the temperature approaches T_c from below, but the graph of magnetization versus temperature has a sharp kink at T_c.

Conversely, when the temperature of a ferromagnet is reduced from above to below T_c, magnetization spontaneously appears where there had been none. Magnetization has an inherent spatial orientation—the direction from the south pole of the magnet to the north pole—and one might wonder in which direction it develops. In the absence of any external magnetic field that might indicate a preferred direction, the breaking of the rotational symmetry is "spontaneous." (Rotational symmetry is the property of being identical in every orientation, which the system has at temperatures above T_c.) That is, magnetization shows up suddenly, with the direction of the magnetization being random (or, more precisely, dependent on microscopic fluctuations beyond our idealization of the ferromagnet as a continuous macroscopic system).

Economic systems can also exhibit phase transitions. When the wealth-bias parameter ζ of the affine wealth model is less than the redistribution parameter χ, the wealth distribution is not even partially oligarchical (*blue area in* B). When ζ exceeds χ, however, a finite fraction of the wealth of the entire population "condenses" into the hands of an infinitesimal fraction of the wealthiest agents. The role of temperature is played by the ratio χ/ζ, and wealth condensation shows up when this quantity falls below one.

Another subtle symmetry exhibited by complex macroscopic systems is "duality," which describes a one-to-one correspondence between states of a substance above and below the critical temperature, at which the phase transition occurs. For ferromagnetism, it relates an ordered, magnetized system at temperature T below T_c to its "dual"—a disordered, unmagnetized system at the so-called inverse temperature, $(T_c)^2/T$, which is above T_c. The critical temperature is where the system's temperature and the inverse temperature cross (that is, $T = (T_c)^2/T$). Duality theory plays an increasingly



important role in theoretical physics, including in quantum gravity.

Like ferromagnetism, the affine wealth model exhibits duality, as proved by Jie Li and me in 2018. A state with $\zeta < \chi$ is not a partial oligarchy, whereas a corresponding state with this relation reversed—that is, with the "temperature" χ/ζ inverted to ζ/χ—is. Interestingly, these two dual states have exactly the same wealth distribution if the oligarch is removed from the wealth-condensed economy (and the total wealth is recalculated to account for this loss).

Significantly, most countries are very close to criticality. A plot of 14 of the countries served by the European Central Bank in the χ–ζ plane in **B** shows that most lie near the diagonal. All except one (the Netherlands) lie just above the diagonal, indicating that they are just slightly oligarchical. It may be that inequality naturally increases until oligarchies begin to form, at which point political pressures set in, preventing further reduction of equality. —*B.B.*

SOURCE: BRUCE M. BOGHOSIAN; EUROPEAN CENTRAL BANK (*country data*)

TRICKLE UP

WE FIND IT NOTEWORTHY that the best-fitting model for empirical wealth distribution discovered so far is one that would be completely unstable without redistribution rather than one based on a supposed equilibrium of market forces. In fact, these mathematical models demonstrate that far from wealth trickling down to the poor, the natural inclination of wealth is to flow upward, so that the "natural" wealth distribution in a free-market economy is one of complete oligarchy. It is only redistribution that sets limits on inequality.

The mathematical models also call attention to the enormous extent to which wealth distribution is caused by symmetry breaking, chance and early advantage (from, for example, inheritance). And the presence of symmetry breaking puts paid to arguments for the justness of wealth inequality that appeal to "voluntariness"—the notion that individuals bear all responsibility for their economic outcomes simply because they enter into transactions voluntarily—or to the idea that wealth accumulation must be the result of cleverness and industriousness. It is true that an individual's location on the wealth spectrum correlates to some extent with such attributes, but the overall shape of that spectrum can be explained to better than 0.33 percent by a statistical model that completely ignores them. Luck plays a much more important role than it is usually accorded, so that the virtue commonly attributed to wealth in modern society—and, likewise, the stigma attributed to poverty—is completely unjustified.

Moreover, only a carefully designed mechanism for redistribution can compensate for the natural tendency of wealth to flow from the poor to the rich in a market economy. Redistribution is often confused with taxes, but the two concepts ought to be kept quite separate. Taxes flow from people to their governments to finance those governments' activities. Redistribution, in contrast, may be implemented by governments, but it is best thought of as a flow of wealth from people to people to compensate for the unfairness inherent in market economics. In a flat redistribution scheme, all those possessing wealth below the mean would receive net funds, whereas those above the mean would pay. And precisely because current levels of inequality are so extreme, far more people would receive than would pay.

Given how complicated real economies are, we find it gratifying that a simple analytical approach developed by physicists and mathematicians describes the actual wealth distributions of multiple nations with unprecedented precision and accuracy. Also rather curious is that these distributions display subtle but key features of complex physical systems. Most important, however, the fact that a sketch of the free market as simple and plausible as the affine wealth model gives rise to economies that are anything but free and fair should be both a cause for alarm and a call for action. SA

MORE TO EXPLORE

A Nonstandard Description of Wealth Concentration in Large-Scale Economies. Adrian Devitt-Lee et al. in *SIAM Journal on Applied Mathematics,* Vol. 78, No. 2, pages 996–1008; March 2018.

The Affine Wealth Model: An Agent-Based Model of Asset Exchange That Allows for Negative-Wealth Agents and Its Empirical Validation. Jie Li et al. in *Physica A: Statistical Mechanics and Its Applications,* Vol. 516, pages 423–442; February 2019.

FROM OUR ARCHIVES

A Rigged Economy. Joseph E. Stiglitz; November 2018.

scientificamerican.com/magazine/sa

Expertise. Insights. Illumination.

Discover world-changing science. Get 12 issues of *Scientific American* in print and explore our digital archive back to 1845, including articles by more than 150 Nobel Prize winners.

sciam.com/print&archive

Download on the App Store | GET IT ON Google Play

The Nature of Life and Death: Every Body Leaves a Trace

by Patricia Wiltshire. Putnam, 2019 ($27)

ONE OF DOZENS of decaying bodies studied at the University of Tennessee's Anthropological Research Facility.

For many, pollen is a nuisance, responsible only for sniffles and sneezes. For forensic ecologist Wiltshire, pollen is a portal, transporting her to the scene of a crime. Microscopic pollen particles that cling to a suspect's jacket or a victim's hair can reveal critical clues about a crime scene's ecosystem. Using this evidence, Wiltshire can often re-create, in brilliant detail, where a victim spent his or her final moments—often to the surprise of the detectives working with her. Between gripping case studies, Wiltshire weaves in charming tales from her childhood in Wales and hard-won lessons on navigating the male-dominated fields of science and law enforcement. *—Jennifer Leman*

You Look Like a Thing and I Love You: How Artificial Intelligence Works and Why It's Making the World a Weirder Place

by Janelle Shane. Voracious Books/ Little, Brown, 2019 ($28)

Training an AI to write pickup lines—the source of this book's title—might sound frivolous, but the process can illuminate the often opaque inner workings of these computer constructs. Shane is an optics researcher who also explores the strange creations of AI systems on her blog, and here she brings an analytical eye to explain how AIs operate, what problems they can solve, and what will likely remain too hard, or too dangerous, for them to tackle. The programs tend to carry over and enhance bias from data they are given, for instance, and their black box nature makes it difficult to catch errors and misinterpreted goals. Shane's humorous but weighty discussion reveals the promise and peril of an AI future. *—Sarah Lewin Frasier*

More Things in the Heavens: How Infrared Astronomy Is Expanding Our View of the Universe

by Michael Werner and Peter Eisenhardt. Princeton University Press, 2019 ($35)

Infrared light falls to the right of visible light on the electromagnetic spectrum, with longer wavelengths than what the eye can see. And because the expansion of the universe stretches the wavelength of light from distant objects, many of the farthest, oldest things in the cosmos are visible only in infrared. The best tool astronomers have for seeing the infrared universe is the Spitzer Space Telescope. Launched in 2003, it has glimpsed galaxies, planets, asteroids, and, especially, "the youngest, most distant galaxies yet discovered," write Spitzer scientists Werner and Eisenhardt. Now, before the telescope shuts down in January 2020, the authors recount the major sights that greeted Spitzer's infrared eyes on the skies. *—Clara Moskowitz*

The Great Pretender: The Undercover Mission That Changed Our Understanding of Madness

by Susannah Cahalan. Grand Central Publishing, 2019 ($28)

In a famed experiment, psychologist David Rosenhan and seven other "pseudopatients" faked their way into psychiatric hospitals, claiming to hear voices. He subsequently published a 1973 paper in *Science* detailing how hospital staff pathologized normal behavior, mistreated patients and kept the pseudopatients institutionalized for weeks. The paper caused an uproar and confirmed widespread mistrust of the mental health system. Although Rosenhan's work influenced the future of psychiatric care in the U.S., his paper did not tell the whole story. Writer Cahalan digs deeper—starting with the charismatic Rosenhan and his mysteriously unfinished book about the experiment. In her quest to track down the facts, Cahalan discovers that some of Rosenhan's claims were, at best, overstated and may have been completely untrue. *—Leila Sloman*

DAVID HOWELLS *Getty Images*

CRUISE WITH SCIENTIFIC AMERICAN Travel

Celebrate Scientific American's 175th Anniversary

Cruise the Pacific Rim of South and Central America to celebrate **Scientific American's 175th Anniversary**. Savor 20+ hours of exclusive onboard classes while we're at sea. While we're in port, take advantage of archaeology, fitness, food, history, and outdoor opportunities.

Survey the big history of the region. Get a cosmic perspective on the search for life in the universe. Enrich your knowledge of regional pre-Columbian peoples. And then head ashore and deepen your appreciation of the cultures and beauty of the area.

Join us! Hail the spirit of inquiry, the discipline of scientific theory, and the value of fact on *Scientific American*'s 175th birthday cruise. Get in on the action and book now.

THE AMERICAS, MARCH 15th – 30th, 2020

SPEAKERS & SEMINARS

The conference fee is $1,575 and includes all 90-minute seminars below.

Ken Albala, Ph.D.

Professor of History
University of the Pacific

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.*

Anthropology: Revelations of Cookbooks

- Gastronomy in the Ancient World
- The Medieval Culinary Aesthetic from Baghdad to Paris
- The Renaissance Kitchen
- Cookbooks for Mass Consumption

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.

Geology: Minerals and the Origins of Life

- How Rocks and Life Co-evolved
- Mysteries of the Evolving Mineral Realm
- Carbon and the Emergence of (Almost) Everything
- The Scientific Quest for Life's Origins

Cruise prices start at $2,019 per person (pp) based on double occupancy. Add'l pp fees, taxes, and gratuities apply. Cruise pricing is subject to change.

For more info email: Info@InsightCruises.com or visit: ScientificAmerican.com/AnniversaryCruise

Cruiseimage/Trevor Adeline

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.

Space: An Astronaut's Perspective

- Living and Working in Space
- ISS and Science
- The Right Stuff — Revised 2020 Edition
- 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.

Habitable Worlds: The Search for Life

- Extremophiles on Earth
- Exoplanets
- Biosignatures
- Technosignatures

For speakers' complete bios, visit http://InsightCruises.com/events/sa39/#SPEAKERS.html

Post-Cruise Land Tour March 30 – April 3, 2020

Join us in Los Angeles to visit the most exciting science sites that SoCal has to offer. We'll go behind the scenes into the prep lab at the Natural History Museum to learn how scientists process fossils. We'll also enjoy private tours at NASA's Jet Propulsion Lab, CalTech and the Mount Wilson Observatory, where we'll stay until after dark to observe the stars through the same Hooker telescope that Edwin Hubble used in 1923 to discover the Andromeda galaxy.*

NOTES: Maximum of 40 for our private telescope reservation. Mt. Wilson Observatory is at 5,700 feet of elevation and not ADA compliant.

CST# 2065380-40

For more info email: Info@InsightCruises.com or visit: ScientificAmerican.com/AnniversaryCruise

Zeynep Tufekci is an associate professor at the University of North Carolina School of Information and Library Science and a regular contributor to the *New York Times*. Her book, *Twitter and Tear Gas: The Power and Fragility of Networked Protest*, was published by Yale University Press in 2017.

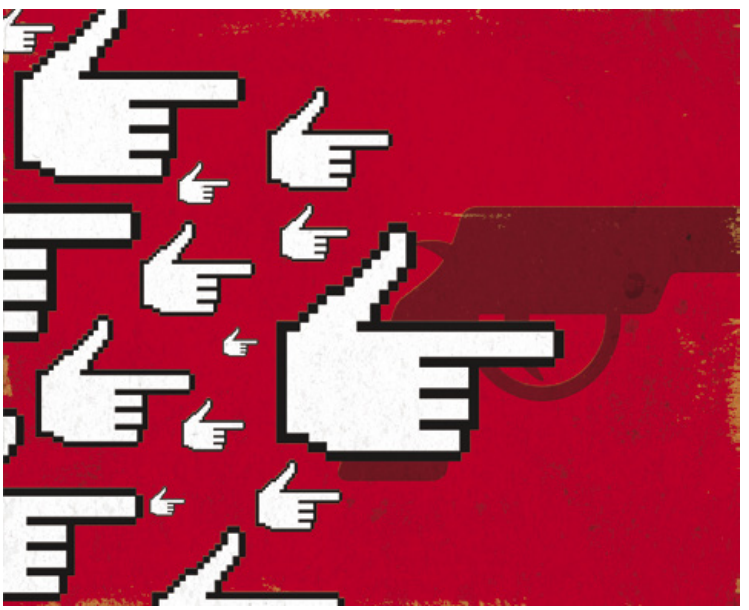
Shootings and Social Contagion

It's the one factor we keep overlooking

By Zeynep Tufekci

Tragically, more than 20 percent of mass shootings, as tracked by the National Institute of Justice for the past 50 years, have occurred in the past five. The past three have been the deadliest. In the U.S., there is well-deserved attention on the availability of guns (because the deadliness of method and ease of access to weapons matter greatly) and on whether we pay sufficient attention to mental health support for troubled young men.

But there is one more factor that is only recently getting some of the scrutiny it deserves: the role that social contagion plays in inspiring those troubled individuals to choose this course. People routinely underestimate how social humans are. We all have a viewpoint and an inner life, of course. But in the 20 years since Columbine and other mass shootings, we can say with increasing confidence what is, in retrospect, almost blindingly obvious: the shooters are inspired by those who came before—and how we react to shootings is part of the unfortunate cycle feeding them.



We can look all the way back to ancient Greece for the archetype: Herostratus, the arsonist who burned down the second Temple of Artemis in Ephesus to immortalize his name, albeit in infamy. As Roman writer Valerius Maximus noted, "A man was found to plan the burning of the temple of Ephesian Diana so that through the destruction of this most beautiful building his name might be spread through the whole world."

Indeed, here I am, spreading it. In response to his terrible act, Herostratus was given the *damnatio memoriae* treatment: he was removed from all official historical records, and all public mention of him was banned. The magnitude of his crime, however, meant that he eventually found his way to some accounts nonetheless.

Contrast *damnatio memoriae* with our own treatment of mass shooters. Most readers who were old enough when the Columbine tragedy happened almost certainly know the names of the shooters. It is understandable because when confronted with the seemingly unimaginable, we want to understand, so we turn our attention to the individuals. Mass shooters' names and faces dominate the media, and if they leave manifestos, those spread virally as well. Even if they are being condemned, they are noted, remembered and immortalized.

Unfortunately, not everyone reacts in horror. The man who murdered 26 people at an elementary school in Newtown, Conn., an almost unfathomable crime, was obsessed with the fame and attention the Columbine shooters received. He collected clippings about their act and downloaded videos and other material from other mass shootings, as well as gun suicides. He then went on to commit his own horror.

This is not an isolated case. We have quantitative evidence that reveals a spike in such shootings in the period following extensive mass media coverage of one, and reports and law-enforcement investigations show that many shooters study previous shooters, collect news stories about them and study their methods. In a terrible twist, they even focus on the numbers of their victims in an effort to up that count—realizing that the higher the number, the more coverage and attention they will receive in the "rankings," so to speak, as if it were a video-game scoreboard.

None of this is meant to make light of the other factors—availability of guns or mental health support—and does not necessarily speak to all mass shootings, some of which are more akin to terrorism. It does, however, tell us something important about ancient wisdom: *damnatio memoriae* may well be the correct method, as hard as it may seem.

In the modern world, we cannot and should not censor media coverage of the event; however, we can definitely change the way we report it and talk about it. Instead of profiling the murderers, we can focus on the victims; instead of publicizing their often incoherent ramblings, we can dismiss the content as the pathetic words of murderers, and we can certainly avoid plastering the faces and the names of the killers on media outlets and social media. That will not be a full solution, because the other factors need tackling as well, but it is one important step in denying these troubled men the one thing they seek above almost everything: posthumous infamy. SA

JOIN THE CONVERSATION ONLINE
Visit *Scientific American* on Facebook and Twitter or send a letter to the editor: editors@sciam.com

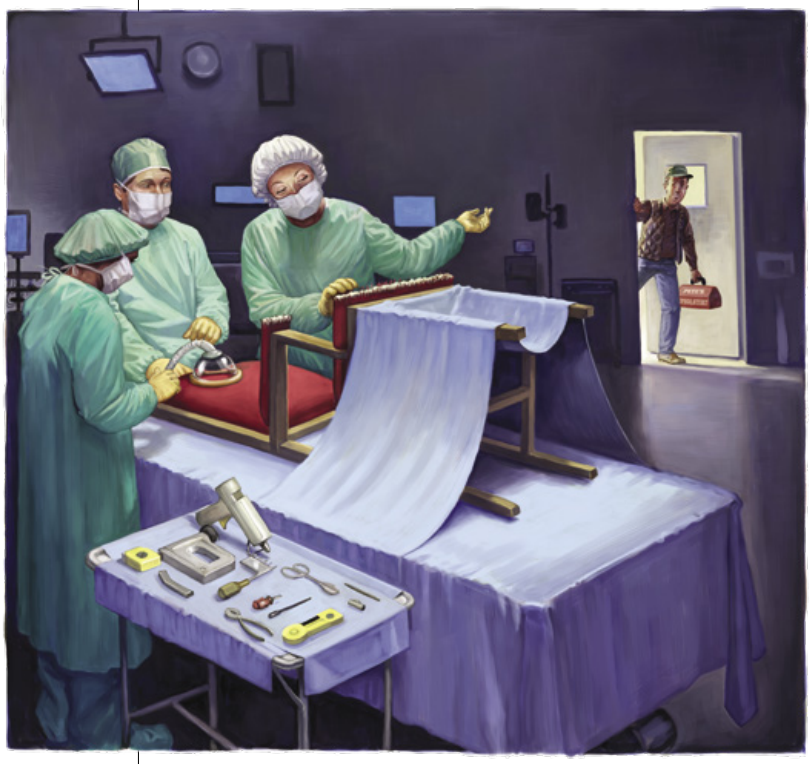
Illustration by Thomas Fuchs

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.

Chair Man

Cardiovascular disease's link to stress sat in plain sight

By Steve Mirsky



Rarely does a speaker at a conference have to abandon a talk because he's seasick. But I saw it happen in August on a *Scientific American*/Bright Horizons cruise around the U. K. and Ireland, as our ship hit rough seas. The nauseated narrator finished his talk a few days later in calmer waters. And for the porpoises of this ocean-going column, all you need to know is that he was not Robert Sapolsky. I mean purposes.

Sapolsky, a neurobiologist and primatologist at Stanford University, got through his talks with no lunch losses. One presentation dealt with the health effects of chronic stress. "This link between stress and cardiovascular disease is so solid," he said, "that it accounts for *the* most famous personality profile in all of medicine." Type A personality, that is. "And I would guess if you're using a cruise to sit and listen to *Scientific American* lectures, this applies to like 80 percent of us in this room."

Sapolsky continued, "Type A was first described by a pair of cardiologists, [Meyer] Friedman and [Ray] Rosenman, in the 1950s … time-pressured, hostile, poor self-esteem, joyless striving." The docs announced that these traits actually raise your risk of heart disease.

"[Other] cardiologists hated these guys. You're some 1950s cardiologist, all you think about is Ozzie and Harriet and heart valves … and instead here's these guys saying, 'No, you need to sit down your patients and talk to them.' Who wants to talk to their patients?!" Indeed, the happiest doctors I have ever met are pathologists.

"It wasn't till the 1980s that there were enough data in for people to say type A is for real," Sapolsky said. "It is a bigger risk factor for cardiovascular disease than if you smoke, than if you are overweight, than if you have elevated cholesterol levels."

So how did Friedman and Rosenman identify this condition? "I actually got to hear this story from the horse's mouth himself, Meyer Friedman," Sapolsky said. "He and his partner had this cardiology practice in San Francisco—everything was going great. They had this one problem, though. For some reason, they were wearing out chairs in the waiting room at an incredibly high rate…. Every month this upholsterer comes in, fixes a chair or two. One month the upholsterer is on vacation. A replacement upholsterer comes in, takes one look at the chairs and discovers type A personality. He says, 'What is wrong with your patients? Nobody wears out chairs this way.' "

Sapolsky then showed a photograph of one of the chairs, which you can see in his book *Why Zebras Don't Get Ulcers*. "The front two inches of the seat cushion and the arm rests are totally shredded. The rest of the seat is perfectly fine. It's like every night there's dwarf beavers, and they're clawing at the chairs. What is this? This is what [a type A person] does when they're sitting in the waiting room of their cardiologist's office waiting to find out if there's bad news. Not just figuratively but literally sitting on the edge of their seat and clawing and squirming.

"So what's supposed to happen at this point if things worked right: Friedman grabs him and says, 'Good God, man, what you've discovered!' [And there are] midnight conferences between upholsterers and cardiologists. And [there are] teams of idealistic young upholsterers going across America and coming back with the news that, no, you don't find chairs like these in podiatrists' offices."

What did the nonagenarian Friedman tell Sapolsky he actually did back in the 1950s? "He said, 'I told my nurse … get this man out of my face, he's wasting time, give him his damn check.' *He* was too type A to listen to the guy. And it wasn't until five years later, they were collaborating with psychologists, out popped the type A profile, and they said, 'Oh, my God, the upholsterer, he was right!'

"To this date, they have no idea who that man was. Now I'm willing to bet … go to some bar in the Mission District in San Francisco, and there's gonna be this 110-year-old retired upholsterer. And get him started, and he's gonna go on and on about how he discovered type A personality." And in so doing—you might want to take a seat yourself for this—changed the fabric of medicine. SA

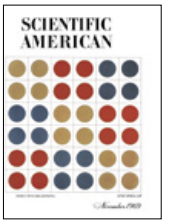
JOIN THE CONVERSATION ONLINE
Visit *Scientific American* on Facebook and Twitter or send a letter to the editor: editors@sciam.com

Illustration by Matt Collins

NOVEMBER

1969 Lung Support

"Respiratory failure is now reversible in a large percentage of cases if proper treatment is provided. Such treatment is available in respiratory intensive-care units: properly equipped hospital facilities directed by a new kind of medical specialist, the intensivist, and manned by teams of trained physicians. The increasing capability of respiratory intensive care is the result of an increasing discourse between respiratory physiologists and physicians who treat patients. Data that have long been available are now being brought to bear through active intervention to preserve the life of critically ill patients. Treatment of acute respiratory failure is probably as close to being a quantitative science as any field of clinical medicine can be today. In this situation, precise measurement approaches or exceeds in importance the 'clinical judgment' that for so many years has been the prime quality of the good physician."



1969

1919

1869

1919: A former military tank gets repurposed as an all-terrain vehicle for the amusement of tourists.

1919 Merry Mountaineers

"France's task of beating swords into ploughshares included the conversion of tanks into something having peacetime value. Some have been employed for towing canal barges; others have become agricultural tractors; others have made their way into the factory. But the most novel conversion is no doubt that of the mountain-climbing tanks, now available to tourists of the French Alps of Savoy. Shorn of its coat of armor and its fighting equipment, and provided with seats, it becomes an excellent passenger-carrying vehicle for traversing rough terrain. Our illustration offers some idea of the thrills of a ride in the mountain-climbing tank."

The Unemployed Horse

"Professional horse-breeders still boost for the business; but they are merely whistling to keep up their courage. The days of the horse as a beast of burden are numbered.

The automobile is taking the place of the carriage horse; the truck is taking the place of the dray horse; and the farm tractor the place of the farm horse. Nor is there any cause to bemoan this state of affairs. We all admit that the horse is one of the noblest of animals; and that is a very good reason why we should rejoice at his prospective emancipation from a life of servitude and suffering. That, of course, is the humanitarian side of it; the business side is more to the point: the machine is going to do the hard work of the world much easier and much cheaper than it ever has been done. At least 50 percent of the horses will have been laid off by January 1st, 1920."

1869 Vaccination

"A long article recently appeared in the *New York Times,* taking the strongest ground against vaccination, urging that it propagated disease, while as a prevention of mortality from smallpox, it was utterly inefficient. This article represented views now entertained by many upon this subject. The London *Lancet* in an article in favor of vaccination makes the following remarks: 'The fact is, that the only people injured by the Compulsory Vaccination Act are medical men. There is no disease which pays medical men better than smallpox. A good attack of it makes man, or child, a patient for a solid month.'"

"Cardiff Giant" Hoax

"Letter of John F. Boynton, Geologist, to Prof. Henry Morton, of the Pennsylvania University: 'Dear Sir: On Saturday last, some laborers engaged in digging a well on the farm of W. C. Newell, near the village of Cardiff, about 13 miles south of this city, discovered, lying about three feet below the surface of the earth, what they supposed to be the 'petrified body' of a human being of colossal size. Its length is ten feet and three inches, and the rest of the body is proportionately large. The excitement in this locality over the discovery is immense and unprecedented. Thousands have visited the locality within the last three days.

On a careful examination, I am convinced that it is not a fossil, but was cut from a piece of stratified sulphate of lime. It was quarried, probably, somewhere in this county [Onondaga, N.Y.], from our Gypsum beds. My conclusion regarding the object of the deposit of the statue in this place is as follows: It was for the purpose of hiding and protecting it from an enemy who would have destroyed it, had it been discovered.'"

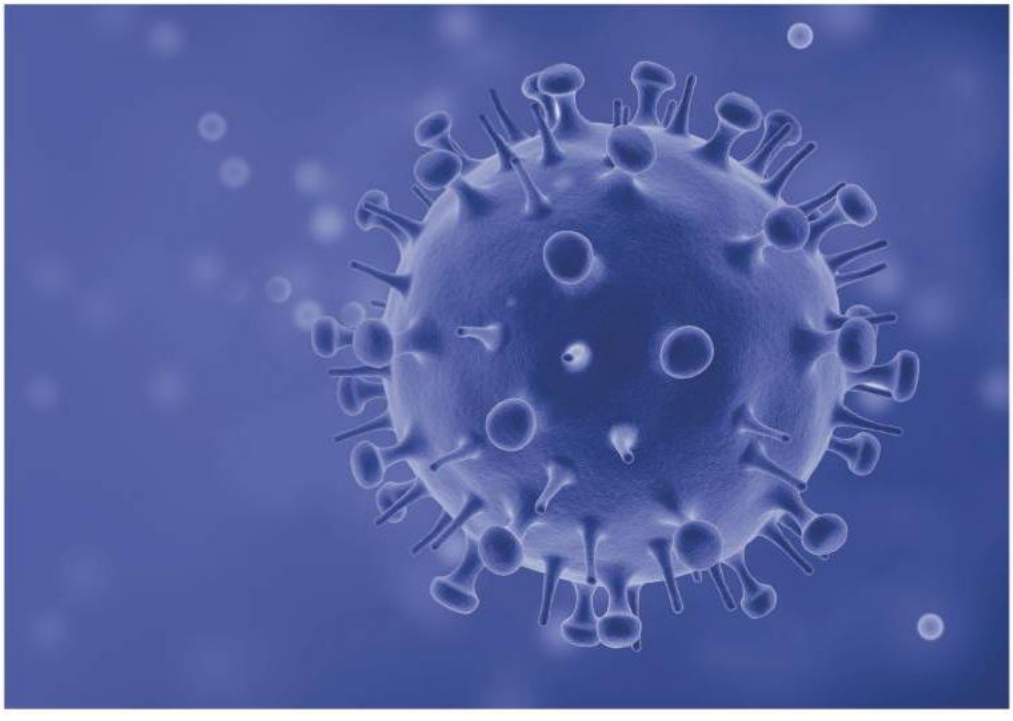
The statue had actually been sculpted the year before under the direction of one George Hull as either a joke or a hoax and buried on the property of his relative William C. Newell.

SCIENTIFIC AMERICAN, VOL. CXXI, NO. 21, NOVEMBER 22, 1919

Sanofi Pasteur: fighting influenza by improving today and innovating for tomorrow

AUTHORS
Timothy Alefantis, Mario Barro, Iris De Bruijn, Philippe-Alexandre Gilbert, Ana Goncalvez, Rosalind Hollingsworth, Harold Kleanthous, Armaghan Naik, Konstantin Pugachev, Deborah Rudin, John Shiver, Saranya Sridhar, William Warren & Jianxin Zhang
Sanofi Pasteur, 1 Discovery Drive, Swiftwater, PA 18370, USA
This article has been written and funded by Sanofi Pasteur

At Sanofi Pasteur, we believe in a world in which no one suffers or dies from a vaccine-preventable disease. As the world's leading manufacturer of influenza vaccines, we know influenza is still one of the most devastating, yet under-appreciated, diseases of modern society, despite the availability of effective vaccines. According to the World Health Organization (WHO), seasonal influenza epidemics are estimated to result in 3 to 5 million cases of severe illness worldwide and 290,000 to 650,000 deaths annually[1]. Among 31 human infectious diseases, influenza topped the list in burden of disease and disability-adjusted life years (DALYs)[2]. Because of this, work is urgently needed to reduce the effects of influenza on human suffering and death. We believe this is achievable by increasing the awareness of the serious and far-reaching impact influenza has on human health; by improving the understanding of the benefits of today's influenza vaccines; and by leading research and development efforts to provide new, more effective influenza vaccine options.



Influenza remains one of the most devastating diseases of modern society. ©iStock

INFLUENZA: MORE THAN AN ACUTE RESPIRATORY INFECTION

For more than 60 years, manufacturers have been tackling influenza infection and its significant consequences with effective vaccines. Studies describing the safety, efficacy and effectiveness of influenza vaccines unequivocally demonstrate the favourable benefit/risk ratio of immunization for those at high risk, such as the elderly or immunocompromised individuals. However, society still negates the seriousness of influenza by often considering it no worse than a bad cold.

Despite clear recommendations from national and international health authorities, vaccine coverage rates among eligible patients in many countries remain below 50%. There are several reasons for this, top among which are misinformation and misperceptions of the personal risk or the potential

serious outcomes of influenza infection. Sanofi Pasteur aims to increase the awareness of influenza as a severe disease, to ensure that the maximum public-health impact of current vaccines is achieved, while we continue research to develop new and more effective vaccines.

While the public-health burden associated with annual influenza epidemics and the positive impact of vaccines are well documented, communication efforts tend to focus on laboratory-confirmed cases. This is a diagnosis infrequently established in the day-to-day clinical setting, and one that hides a multitude of different clinical courses and outcomes. It is true that influenza starts with a sudden onset of symptoms associated with respiratory infection, and recovery can occur within a few days to weeks without further consequences. What many do not understand is that life-threatening complications can develop, even in the young and otherwise healthy.

An influenza infection can both trigger acute health conditions, such as pneumonia, myocardial infarction and stroke, and exacerbate chronic conditions, like diabetes and respiratory illness. However, influenza and its health complications are underdiagnosed. If more people were aware of these complications, and thus the value of vaccination, they would be more convinced to get vaccinated.

For almost 100 years, an association between influenza and cardiovascular disease has been recognized due to overlap in their peak incidence during winter months. Epidemiological studies have also described an increase in cardiovascular deaths during influenza epidemics. Taken together, these observations suggest cardiovascular complications of influenza infection can be significant. Vaccine studies have provided further support that influenza vaccination can help prevent or reduce the risk of many cardiovascular complications[3,4]. In fact, estimates of influenza vaccine effectiveness to help prevent acute myocardial infarction range from 15% to 45%, comparing favourably with other more routine coronary prevention measures, including smoking cessation (32–43%), statins (19–30%) and antihypertensive therapy (17–25%)[5].

Those with chronic lung disease, such as chronic obstructive pulmonary disease (COPD), often find their medical conditions worsen as a result of influenza infection. Influenza vaccination has been shown to be associated with reduced hospitalizations among people with diabetes, chronic lung disease and cardiovascular disease. Therefore, annual vaccination should be an obligatory component of chronic disease-management programmes.

If we are to ensure every patient receives an influenza vaccine whenever advocated, stakeholders must be convinced that an infection can not only be serious in its own right, but can also lead to acute health crises such as heart attack or stroke, and/or exacerbate underlying chronic conditions like diabetes or respiratory illnesses.

DETERMINANTS OF VACCINE EFFECTIVENESS

As evidenced, vaccination remains the cornerstone of preventing influenza infection and related complications. However, the overall vaccine effectiveness against influenza still varies considerably year over year. Over the last 15 years in the USA, estimates of vaccine effectiveness to prevent medically attended laboratory-confirmed influenza have varied between 10% and 60%[6]. Yet, even with modest vaccine effectiveness, the impact of annual vaccination campaigns is profound and should not be ignored. Following the 2017–2018 season, the US Centers for Disease Control and Prevention (CDC) reported influenza vaccine effectiveness of only 38%, which meant that vaccination still prevented an estimated 7.1 million illnesses, 3.7 million medical visits, 109,000 hospitalizations and 8,000 deaths[7]. To that end, efforts in influenza prevention should not lose focus on the benefits of today's vaccines, several of which have improved effectiveness compared to traditional influenza vaccines. The use of current vaccines is critical, while at the same time we continue to look for ways to develop even more effective, broadly protective vaccines.

To understand how to improve influenza vaccines we must take into account the variety of factors that result in suboptimal and variable effectiveness including antigenic drift of circulating viruses, immune waning following vaccination and weakened immune responses due to a number of potential human host factors.

ANTIGENIC DRIFT

The first of these, antigenic drift, occurs when the circulating influenza virus mutates and is no longer recognized by the antibodies induced by the vaccine. Current vaccines do not have a sufficient ability to induce broad cross-protection against drifted or shifted circulating strains; their effectiveness is driven by how well the strains in the vaccine are matched with the circulating strains. This is why, since 1952, the WHO and country regulatory authorities maintain an extensive influenza-surveillance system and select the recommended composition of vaccines for each season. Maintaining such an effort is necessary, but difficult and time-consuming. Despite best efforts and up-to-date information, the strains selected for vaccine production may not adequately match those circulating during the following influenza season, resulting in mismatch. New vaccines, including those being developed by Sanofi Pasteur, to induce an immune response that is not negatively impacted by viral antigenic drift would be a tremendous advance.

IMMUNE WANING

Second, multiple reports from Europe, Australia and the USA report that vaccine effectiveness wanes during the influenza season at varying degrees, and depends on the vaccine strain and, potentially, host factors. While the effect of waning may be, partially, explained by antigenic drift in circulating strains during the season, there is likely a host factor influencing the protection over time. Various reports show antibody titres in vaccine recipients decline over the course of the season, even reaching pre-vaccination levels after one year. To what extent a decline in antibody titre translates to actual insufficient protection remains somewhat speculative, since the relation between antibody titre and protection is not entirely understood and depends on factors such as age, health status and immune competence of the vaccine recipient.

If waning of antibody titres indeed causes reduction in vaccine effectiveness during the influenza season, it is essential that new vaccines induce the most optimal immune responses lasting at protective levels over time.

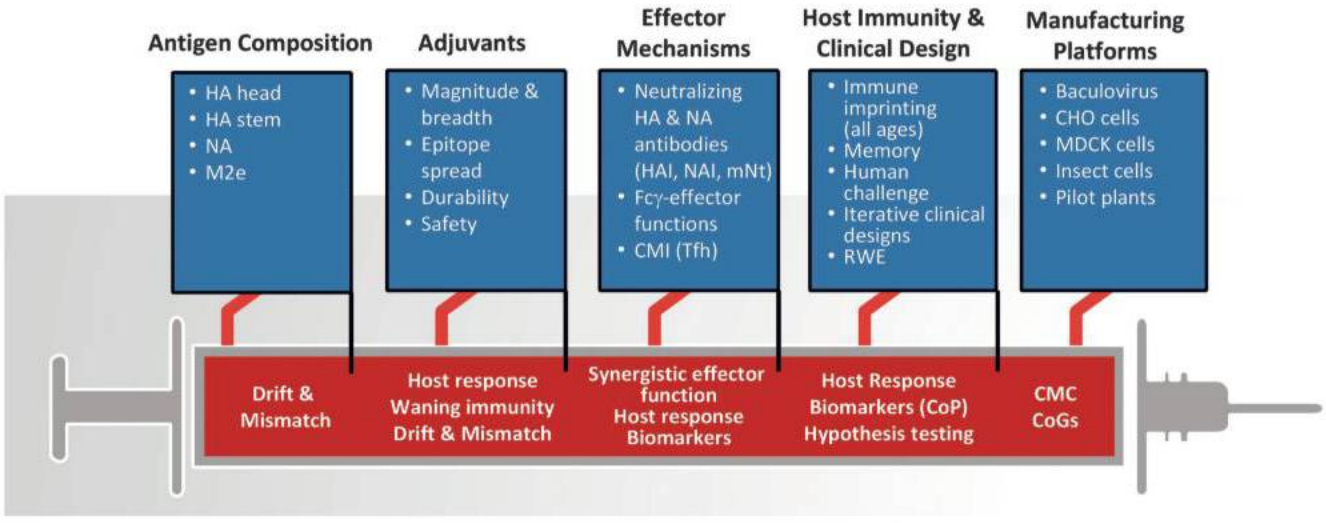


Figure 1. Improving influenza vaccine effectiveness will be driven through research and development across five pillars: antigen composition, adjuvants, effector mechanisms, host immunity and clinical design, and manufacturing platforms. CHO, Chinese hamster ovary cells; CMC, chemistry manufacturing and controls; CMI, cell-mediated immunity; CoGs, cost of goods; CoP, correlates of protection; Fcγ-effector, fragment crystallizable gamma receptor effector; HA, hemagglutinin; HAI, hemagglutinin inhibition; M2e, influenza virus matrix protein 2 ectodomain; MDCK, Madin-Darby canine kidney; mNt, microneutralization test; NA, neuraminidase; NAI, neuraminidase inhibition; RWE, real world evidence; Tfh, T follicular helper cell.

HUMAN HOST FACTORS

Third, increasing evidence shows that age, immunological fitness, exposure to previous influenza viruses and genetic makeup determine largely how well a certain vaccinee will develop a protective immune response at the outset of vaccination. Why does the influenza attack rate or protection after vaccination vary with age? One hypothesis is the antibody response against a given strain is influenced by the immunological memory induced against the strain or strains encountered for the first time early in life — the so-called phenomenon of 'original antigenic sin' or immunological imprinting[8]. It is also thought this decreased antibody response to subsequent exposures may be a result of 'antigen trapping', which means pre-existing, cross-reactive antibodies and memory cells 'capture' the new antigen and decrease the antigenic load available for priming naive B cells, which would lead to a diminished novel response[9]. Seemingly supporting this hypothesis is the observation that longitudinal exposure to antigenically drifting strains is potentially responsible for maintaining a strong memory response against strains encountered early in life[10].

Co-morbidity and frailty also impact the host's ability to mount an adequate vaccine response and contribute to a decrease of immunological fitness[11]. Immunological fitness is also affected by the intrinsic aging of the immune system itself (known as immunosenescence); by immune immaturity early in life; and by immune naivety to novel antigens early in life and to new pandemic strains. Various factors in the immune response have been reported to diminish in aged individuals. The multiplicity of these impairments, including decreased antibody levels and lowered antibody specificity, is thought to cause a reduction in influenza vaccine efficacy in the elderly.

In younger populations, particularly infants, immaturity of the immune system plays a significant role in suboptimal efficacy of influenza vaccines, which necessitates boosting of the immune response by repeated vaccinations, addition of adjuvants or other means. In newborns and up to 6 months of age it may be particularly difficult to find effective solutions for active immunization. However, maternal immunization has been shown to offer some protection in this age group, thereby closing the gap between birth and receipt of influenza vaccine at 6 months of age.

Thus, many facets, both intrinsic and extrinsic to the recipient, define the three main reasons for suboptimal and variable influenza vaccine effectiveness. An understanding of these mechanisms and finding innovative ways to address them with scientific advances and new vaccine approaches are crucially important to developing improved effectiveness.

INNOVATING BETTER VACCINES FOR TOMORROW

We know influenza remains a wily opponent, with scientists working to address the unpredictability and complexity of each season. To that end, differentiated and improved influenza vaccines, including high-dose vaccines, adjuvanted vaccines and those produced with new technology, such as recombinant protein and cell-based vaccines, are demonstrating greater efficacy within different age groups. To continue its leadership in research and development of improved influenza vaccines, Sanofi Pasteur is focusing its efforts on five key pillars: antigen composition; adjuvants; induction of synergistic immunological effector functions; understanding of host immunity to influenza; and the adoption of next-generation vaccine-manufacturing platforms (Fig. 1). Each pillar has the potential to address the three main reasons behind reduced influenza vaccine effectiveness.

The first pillar addresses vaccine composition, presenting a well-matched hemagglutinin (HA) to the human immune system, and potentially additional antigens with the ability to protect against heterologous viruses, such as the second most abundant glycoprotein, neuraminidase (NA). The importance of HA antigen selection and expression of a structurally intact molecule that targets immunity to conserved epitopes on the globular (HA1) head and the HA2 stalk could ensure greater breadth against evolving seasonal viruses. Eliciting immunity to antigens like NA may confer protection and reduce disease symptoms[12]. NA has been shown to elicit neutralizing and non-neutralizing antibodies with different immunological effector functions, acting synergistically to enhance protection and reduce disease severity.

The second pillar makes the case for inclusion of an immune enhancer or adjuvant to increase the magnitude of protective immune response and, in turn, address waning immunity. Ensuring antibody titres remain high throughout the influenza season is consistent with sustained protection and increased vaccine effectiveness. Additional attributes are the potential for epitope spread by increasing cross-reactivity to other virus strains, which can have a direct impact on breadth of virus coverage and enhanced cellular immunity[13]. With few adjuvants being part of today's licensed influenza vaccines, we aim to conduct more clinical research on novel candidate adjuvants, especially in key target populations such as the young, the elderly and the immunocompromised.

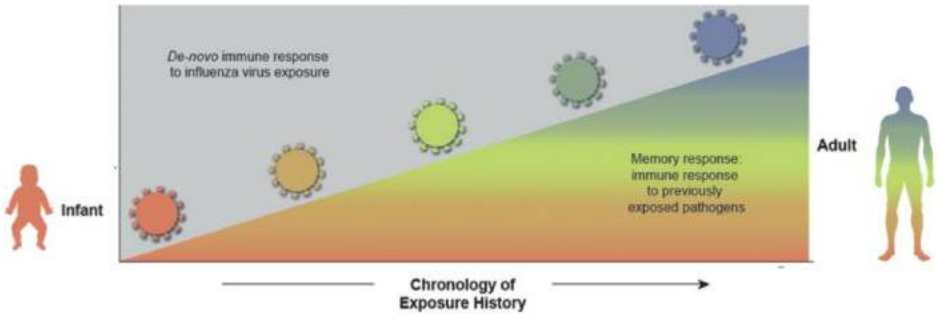


Figure 2. Host immunity influences response to vaccination. Age is an important determinant of the immune response to influenza virus

The third pillar concerns a shortfall in harnessing alternate effector functions. Today's licensed vaccines rely predominantly on HA inhibition (HAI) and neutralizing antibodies. While HAI is an established correlate of protection, there is an opportunity to target synergistic effector functions. Classical virology teaches us the importance of neutralizing antibodies in preventing infection, but the roles of Fc-dependent non-neutralizing antibodies targeting both HA and NA are only now being understood and have shown a significant bearing on disease modulation. Therefore, the inclusion of other antigens and the use of an adjuvant that can elicit different immunological effector functions are expected to maximize protection, both at the initial infection stage and during virus spread.

The fourth pillar relies on understanding the influence of the host's pre-existing influenza immune history on subsequent vaccination. As mentioned, natural exposure to influenza early in life imprints the host and shapes immunity to subsequent vaccination. As a direct consequence, effectiveness has been variable across different age groups, driven by the immunological imprint or exposure of an individual (Fig. 2). Studies have shown, despite original antigenic sin, current vaccines can effectively recall immunity to previously seen strains often resulting in breadth, a phenomenon described as immunological 'back-boosting'[14]. Today's technologies allow us to study immunity in subjects with different immune histories at the cellular level, helping us better understand this phenomenon and ultimately assess performance of improved vaccines. Factoring this information into vaccine design to maximize immunity to key determinants across all age groups is a goal for 'next-generation' influenza vaccines.

The fifth pillar looks at the impact of using modern influenza vaccine manufacturing technology, inherently designed to preserve the fidelity of the vaccine sequence and address issues of reduced vaccine effectiveness from adaptation of the virus during passage in eggs or culture cells. Technologies that rely upon production of subunit proteins may have an inherent advantage as they are less prone to change and can be a better match to circulating viruses. Equally, messenger RNA (mRNA)-based technologies hold promise, given its ability to preserve sequence fidelity and deliver a multivalent vaccine formulation that could address the need to cover co-circulating virus drift variants.

Critical to the advancement of influenza vaccine science is the development of tools, models and working platforms to ensure their success. This includes the development of pre-clinical models translatable to the human immune response to influenza and vaccines, optimal selection of vaccine strains, identification of predictive biomarkers beyond the traditional HAI assay, and new immunological assays to evaluate the impact of these approaches on increasing vaccine effectiveness and reducing severe outcomes. When testing novel vaccines in clinical trials, we may have to defer from classical and costly efficacy studies to more adaptive trial designs that will have the benefit of assessing the impact of key variables and their contribution to efficacy, as will a global perspective that embraces the role of real-world evidence.

THE JOURNEY TO TOMORROW

The quest for a 'universal' influenza vaccine — one vaccination that protects against all human influenza for life —

continues to be the highest goal for our work and the global public-health community. However, the technical challenges of developing this type of vaccine are difficult and will likely take decades to overcome. At Sanofi Pasteur, we believe a more achievable, and increasingly impactful, approach is an iterative stepwise development pathway.

As a first step, we aim to build on available influenza vaccines by developing a multi-component vaccine that provides greater effectiveness by limiting the impact of vaccine mismatch through inducing broader 'strain-specific' immunity. Such vaccines could reduce low effectiveness seen in some years by providing protection to cover the majority of circulating strains within the four circulating subtypes: influenza A virus subtypes H3N2 and H1N1, and influenza B virus subtypes Yamagata and Victoria. This would build on learnings from current vaccines and seek to engage new mechanisms of protection, antigenic targets, adjuvants and structural biology for antigen design. Such a 'forward-looking' vaccine would cover future strains likely to circulate in subsequent seasons.

As a second step, we will look to develop a vaccine targeting conserved regions of each subtype, or lineage, and thus potentially providing long-lasting protection against novel subtypes and lineages with pandemic potential. This approach, which would necessitate multi-components, might provide sufficient protection against the majority of influenza epidemics and potential pandemics.

Our goal is for these two steps to provide iterative information on protective mechanisms to develop a 'universal' influenza vaccine that covers both influenza A and influenza B types including those of pandemic potential. This would be particularly important for infants where vaccination would enable 'imprinting' of the immune response early in life and could potentially direct the immune response to the highly conserved regions of the virus targeted by the universal influenza vaccine.

In this stepwise approach, a number of challenging questions remain to be answered. Do we expect the same vaccine to work equally well for naive infants, imprinted adults and older immunosenescent populations? How often would the vaccine need to be administered to maintain long-lasting protection — annually versus a booster every five years?

At Sanofi Pasteur, we will continue to ask those questions and aim to enhance the science of influenza immunization through innovative research, development, and delivery of differentiated and proven vaccines. We are committed to raising the public awareness of the serious and far-reaching impact of influenza on human health, and the positive benefits of today's vaccines, while spearheading efforts to reduce human suffering through our next-generation influenza vaccines.

REFERENCES

1. World Health Organization. Influenza (Seasonal). *Newsroom Fact Sheets* https://www.who.int/en/news-room/fact-sheets/detail/influenza-(seasonal) (2018).

2. Cassini, A. *et al.* Impact of infectious diseases on population health using incidence-based disability-adjusted life years (DALYs): results from the Burden of Communicable Diseases in Europe study, European Union and European Economic Area countries, 2009 to 2013. *Eurosurveillance* **23**, 17-00454 (2018).

3. Gurfinkel, E. P. Influenza vaccine pilot study in acute coronary syndromes and planned percutaneous coronary interventions: the FLU Vaccination Acute Coronary Syndromes (FLUVACS) Study. *Circulation* **105**, 2143–2147 (2002).

4. Naghavi, M. *et al.* Association of influenza vaccination and reduced risk of recurrent myocardial infarction. *Circulation* **102**, 3039–3045 (2000).

5. MacIntyre, C. R. *et al.* Influenza vaccine as a coronary intervention for prevention of myocardial infarction. *Heart* **102**, 1953–1956 (2016).

6. Centers for Disease Control and Prevention, National Center for Immunization and Respiratory Diseases (NCIRD). CDC seasonal flu vaccine effectiveness. *Influenza (Flu)* https://www.cdc.gov/flu/vaccines-work/effectiveness-studies.htm (2019).

7. Rolfes, M. A. *et al.* Effects of influenza vaccination in the United States during the 2017–2018 influenza season. *Clin. Infect. Dis.* doi:10.1093/cid/ciz075 (2019).

8. Vattia, A. *et al.* Original antigenic sin: A comprehensive review. *J. Autoimmun.* **83**, 12–21 (2017).

9. Fonville, J. M. *et al.* Antibody landscapes after influenza virus infection or vaccination. *Science* **346**, 996 (2014).

10. Cobey, S. & Hensley, S. Immune history and influenza virus susceptibility. *Curr. Opin. Virol.* **22**, 105–111 (2017).

11. Mysliwska, J. *et al.* Immunomodulating effect of influenza vaccination in the elderly differing in health status. *Exp. Gerontol.* **39**, 1447–1458 (2004).

12. Monto, A. S. *et al.* Antibody to influenza virus neuraminidase: An independent correlate of protection. *J. Infect. Dis.* **212**, 1191–1199 (2015).

13. Dormitzer, P. R. *et al.* Influenza vaccine immunology. *Immunol. Rev.* **239**, 167–177 (2011).

14. Nuñez, I. A. *et al.* Impact of age and pre-existing influenza immune responses in humans receiving split inactivated vaccine on the induction of the breadth of antibodies to influenza A strains. *PLoS One* **12**, e0185666 (2017).

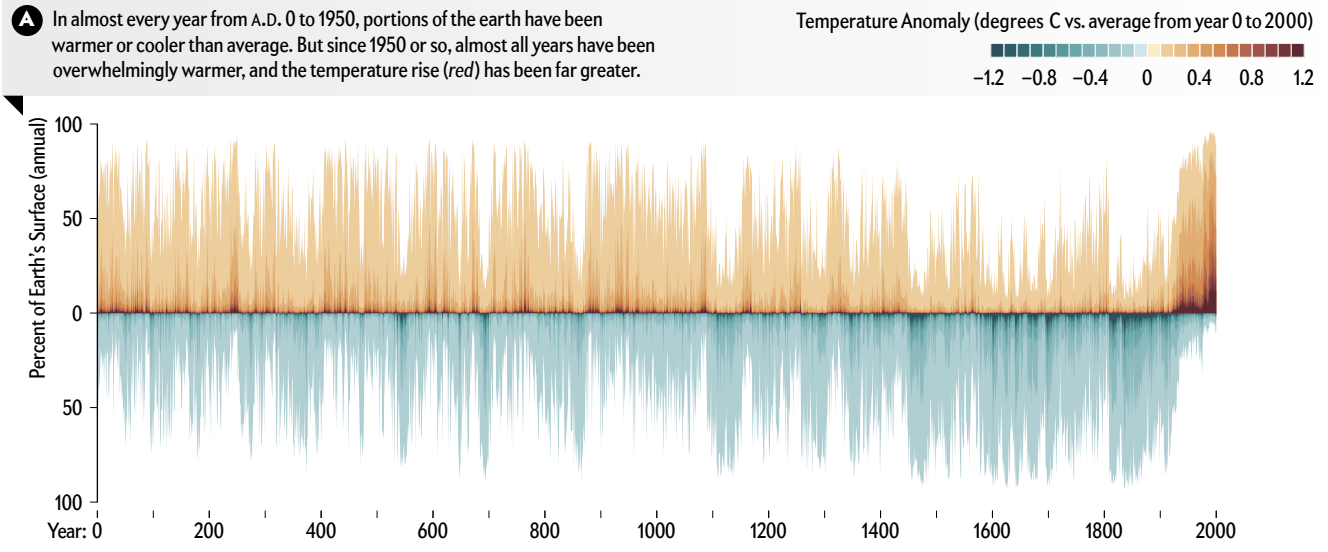
Text by Mark Fischetti | Graphic by Pitch Interactive

Climate Clincher

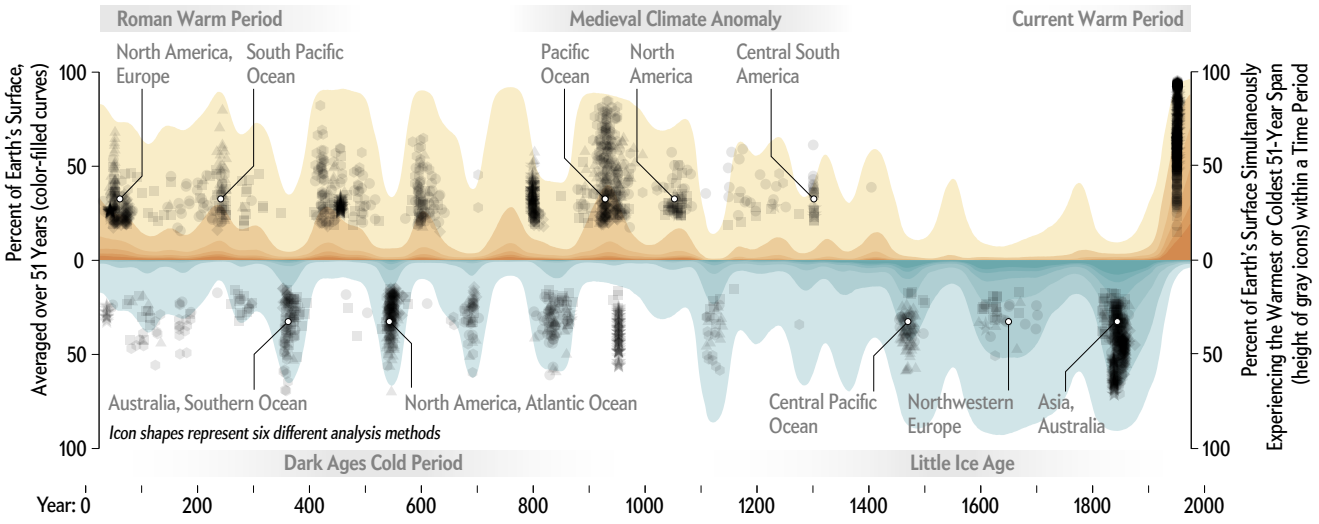
The argument that global warming is part of a natural cycle is dead

People who dismiss climate change often claim that the earth's warm-up is simply part of "natural climate variability." A paper published in July in *Nature* puts that argument to rest. The authors show that warm and cold years were regularly interspersed during the past 2,000 years **A** and that even the warmest and coldest periods were experienced only by isolated regions at a given time—never across the entire globe simultaneously **B**. For example, the so-called Little Ice Age occurred in the 1400s across the central Pacific Ocean, in the 1600s across northwestern Europe and in the mid-1800s in other places. The warm Medieval Climate Anomaly occurred in the Pacific in the 900s, in North America in the 1000s and in central South America in the 1200s. But the current warm-up has taken place across 98 percent of the globe at the same time, from about 1900 through today. "It's completely different," states lead researcher Raphael Neukom of the University of Bern in Switzerland. All regions have heated up relentlessly, in unison.

A In almost every year from A.D. 0 to 1950, portions of the earth have been warmer or cooler than average. But since 1950 or so, almost all years have been overwhelmingly warmer, and the temperature rise (*red*) has been far greater.



B Six hundred analyses of 210 data sets from corals, glacier ice, lake sediments and other temperature markers worldwide are shown by icons. Only some coalesce during any time period from A.D. 0 to 1950; at most, 70 percent of the earth warmed or cooled. Since 1950, however, all 600 reconstructions have lined up; 98 percent of the planet has warmed at once—an unnatural variation.



SOURCE: "NO EVIDENCE FOR GLOBALLY COHERENT WARM AND COLD PERIODS OVER THE PREINDUSTRIAL COMMON ERA," BY RAPHAEL NEUKOM ET AL., IN NATURE, VOL. 571; JULY 25, 2019

a nature conference

Weizmann Institute of Science, *Nature Medicine*, and *Nature* are pleased to present:

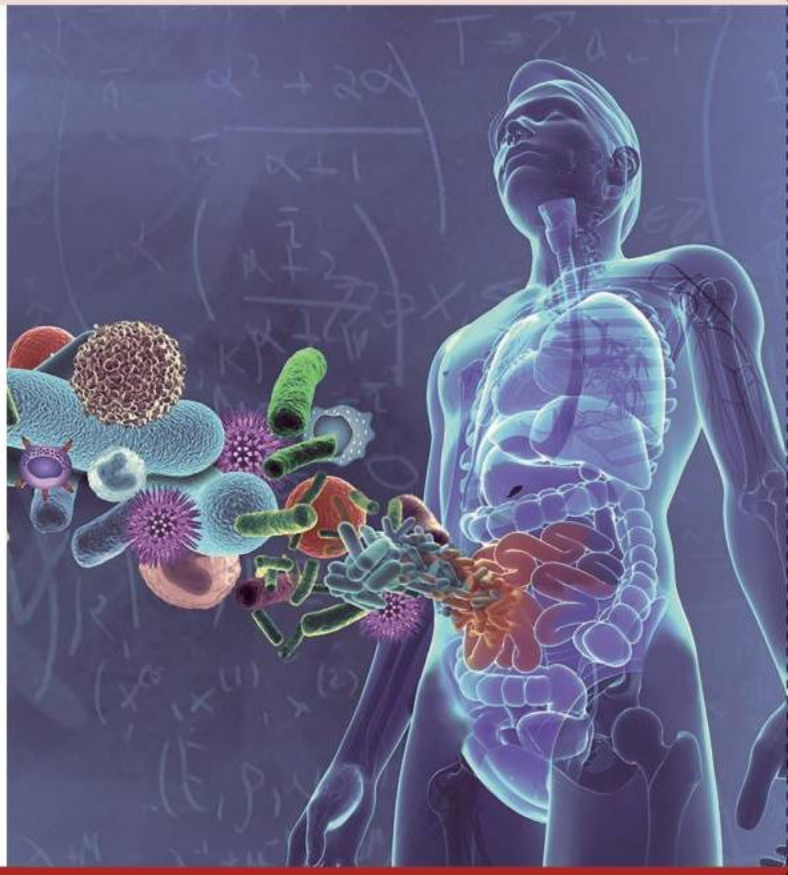
Next Gen Immunology 2020

February 2-5, 2020 | Weizmann Institute of Science, Rehovot, Israel

Next Gen Immunology is a unique interdisciplinary think tank putting forward discussions on frontier areas of immunology, involving world leaders from science, medicine, microbiome and biomedical industry. As in previous NextGen Immunology meetings, this will be a closed meeting with only the most exciting unpublished work being presented and discussed by the leaders of the field, thereby pushing the community into the next frontiers of Immunology in years to come. This year, the meeting will be focused on understanding immunity in the context of health and disease – including the nervous system, cancer, metabolic tissue and mucosal barrier sites – as well as our meta-organismal partners: the microbiome.

SCIENTIFIC SESSIONS INCLUDE:

- Systems Immunology
- Host-microbe Interactions
- Microbiome in Health & Disease
- Neuroimmunology
- Immuno-metabolism
- Immune-cancer
- Immune Gut Health



TO REGISTER VISIT:
weizmann.ac.il/conferences/NGI2020

מכון ויצמן למדע
WEIZMANN INSTITUTE OF SCIENCE

nature medicine nature

A72821

is

CHANGING MEDICINE AS WE KNOW IT.

Uncommon is daring to question the established way.
At UPMC, we're transforming health care, one fearless idea at a time.
Welcome to change.

UPMC
LIFE CHANGING MEDICINE

UPMCNext.com

nature OUTLOOK

Produced with support from:

SANOFI PASTEUR

Science targets an evasive virus

nature podcast

The week's best science,
from the world's leading science journal.

NATURE.COM/NATURE/PODCAST

nature

nature OUTLOOK

INFLUENZA

Cover art: Antoine Doré

For a disease that can resemble the common cold, influenza packs a powerful — and sometimes lethal — punch. As many as half-a-million people around the world die annually from flu. The culprit is a virus that mutates to evade our immune systems, leaving vaccines and therapies scrambling to keep up. In some years, a mutation creates a pathogen that is particularly nasty, resulting in pandemic flu. Last year marked 100 years since the 1918 'Spanish flu' pandemic, which killed at least 50 million people worldwide. In 2009, another pandemic swept across the world at frightening speed, and in 2017–18 so-called seasonal flu (not considered a pandemic) hit hard in the United States.

Vaccines are the first line of defence against flu. Researchers have made it a top priority to develop a vaccine that protects against as many strains of the virus as possible (see page S4). And because speed is of the essence in mounting a response to flu, new methods are being pursued to speed up vaccine production (S14). If prevention fails, there is only a limited arsenal of antiviral drugs to treat flu, although researchers are working to develop more (S8). But it is a never-ending battle, as the wily virus mutates its way to resistance (S7).

Treatment, of course, depends on diagnosis. For individual patients, molecular tests can now give conclusive results more quickly than older methods, but adoption of the new tests has been slow, partly because of their high cost (S10). On a public-health level, it is important to know when and where an outbreak is under way — a task made easier by information technology (S12). And because some of the most dangerous flu viruses make the leap from animals to humans, researchers are studying how to monitor the disease on farms and in wild bird populations (S16).

We are pleased to acknowledge the financial support of Sanofi Pasteur in producing this Outlook. As always, *Nature* retains sole responsibility for all editorial content.

Herb Brody
Chief supplements editor

CONTENTS

Nature Outlooks are sponsored supplements that aim to stimulate interest and debate around a subject of interest to the sponsor, while satisfying the editorial values of *Nature* and our readers' expectations. The boundaries of sponsor involvement are clearly delineated in the Nature Outlook Editorial guidelines available at go.nature.com/e4dwzw

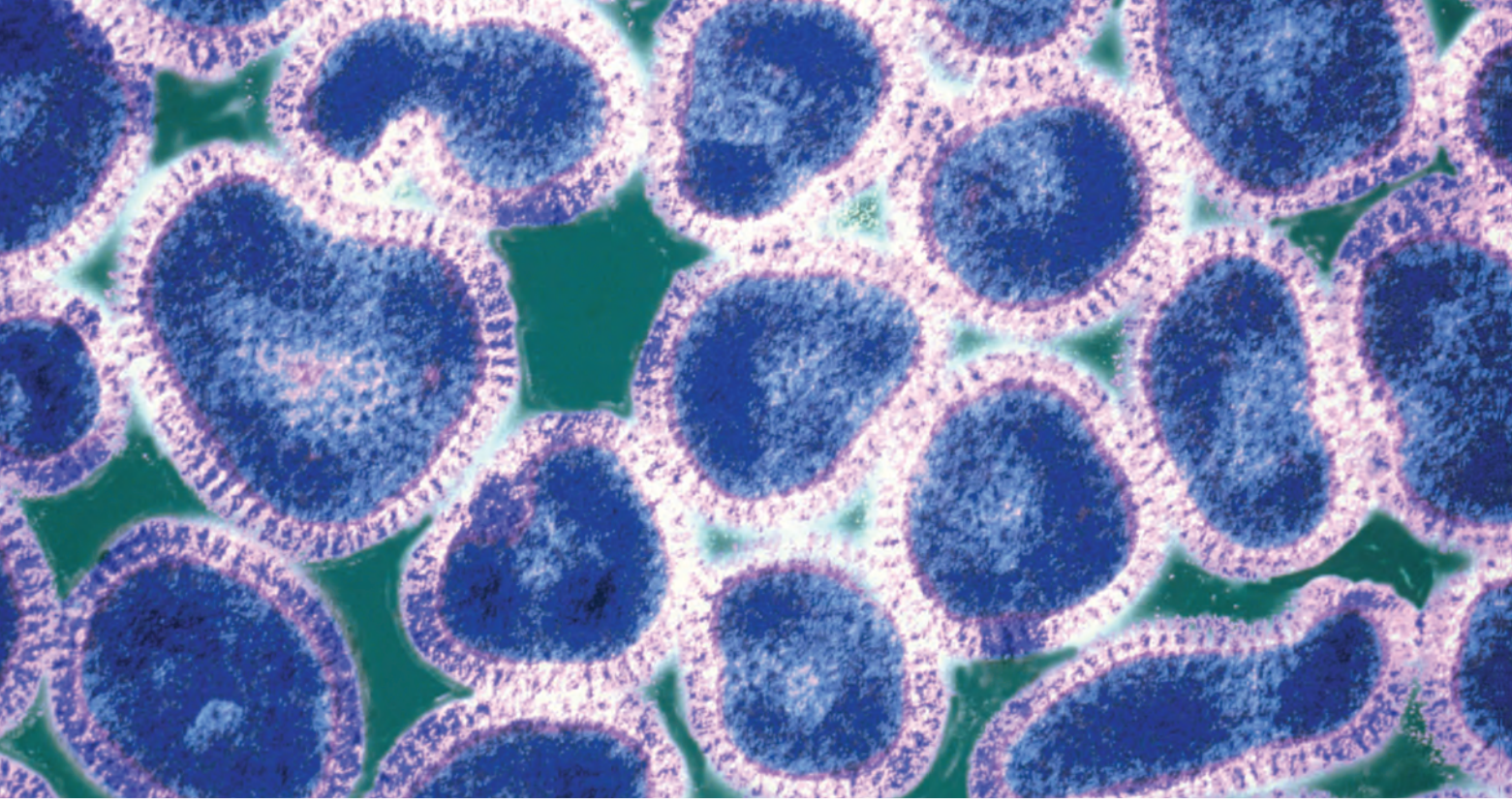
CITING THE OUTLOOK
Cite as a supplement to *Nature*, for example, *Nature* **Vol. XXX**, No. XXXX, Suppl., Sxx–Sxx (2019).

VISIT THE OUTLOOK ONLINE
The *Nature Outlook Influenza* supplement can be found at www.nature.com/collections/influenza-outlook
It features all newly commissioned content as well as a selection of relevant previously published material that is made freely available for 6 months.

SUBSCRIPTIONS AND CUSTOMER SERVICES
Site licences (www.nature.com/libraries/site_licences): Americas, institutions@natureny.com; Asia-Pacific, http://nature.asia/jp-contact; Australia/New Zealand, nature@macmillan.com.au; Europe/ROW, institutions@nature.com; India, npgindia@nature.com. Personal subscriptions: UK/Europe/ROW, subscriptions@nature.com; USA/Canada/Latin America, subscriptions@us.nature.com; Japan, http://nature.asia/jp-contact; China, http://nature.asia/china-subscribe; Korea, www.natureasia.com/ko-kr/subscribe.

CUSTOMER SERVICES
Feedback@nature.com

This special report first appeared in *Nature* [26 September 2019 | Vol. 573 | Issue No. 7775]. Internal references may vary from original version.



Transmission electron micrograph of influenza viruses, which can cause seasonal or pandemic flu.

PREVENTION

A shot for all seasons

A better understanding of the immune response to influenza is driving progress towards vaccines that protect against both seasonal and pandemic flu strains.

BY MICHAEL EISENSTEIN

Flu shots can be hard to sell to the public. Even a run-of-the-mill influenza infection can be debilitating to otherwise healthy people, and lethal to those who are elderly or frail, so vaccinations are important. The problem is that flu vaccines deliver inconsistent performance. "In a good season, we're up to 60% effectiveness, but in bad, mismatched years it can be as low as 10% or 20%," says Barney Graham, deputy director of the Vaccine Research Center at the US National Institute of Allergy and Infectious Diseases (NIAID) in Bethesda, Maryland.

Current flu vaccines provide protection only against the strains they have been matched to, so a 'universal' flu vaccine that provides broader protection against most influenza viruses has been a long-standing dream. The 2009 swine-flu pandemic, which caught the public-health community off guard and claimed the lives of as many as half-a-million people worldwide, gave the issue new urgency.

"The 2009 pandemic made it obvious and clear that we didn't have good enough solutions for influenza vaccines," says Graham. "We knew the virus, but we weren't able to make enough vaccine quickly enough." More-effective manufacturing is one solution (see page S14) but a single inoculation that protects against both seasonal and emerging strains would have much greater impact.

Fortunately, the timing of the pandemic coincided with great progress in the development of technologies for investigating the human response to influenza. "Around 2008 or 2009, people started finding a few broadly neutralizing antibodies against the influenza virus," says Ian Wilson, a structural biologist specializing in vaccine development at Scripps Research Institute in La Jolla, California. "Once people started looking, many more were discovered."

Now, around 100 years after the 'Spanish flu' pandemic of 1918 that killed about 50 million people, multiple universal-vaccine programmes are demonstrating promise in both preclinical and clinical testing. But it remains to be seen whether any will ultimately deliver the broad protection that clinicians seek.

A VARIABLE VIRUS

Peter Palese, a microbiologist at the Icahn School of Medicine at Mount Sinai in New York City, believes that today's flu vaccines come in for too much criticism. "They are fairly good vaccines but they're not perfect," he says. The main problem, he adds, is that they elicit a focused immune response against a moving target.

Humans are affected by two main types of influenza. Influenza A and B can both contribute to seasonal flu, but some influenza A subtypes preferentially infect animal hosts. Sometimes these subtypes abruptly acquire the ability to infect humans, leading to pandemics such as the one in 2009. Each year the seasonal flu vaccine is designed to cover two strains each of influenza A and B, based on the public-health community's best informed guess about which strains will be dominant that year.

Every influenza virus is studded with hundreds of molecular structures formed by a multifunctional protein called haemagglutinin. Haemagglutinin helps the virus to bind and penetrate host cells. It comprises a bulky head attached to the virus by a slender stalk. Most of the immune response is targeted at the head because it is highly exposed, but there is also evidence that the head contains features that preferentially elicit a strong antibody response. "There are structured loops, and antibodies easily recognize loops that stick out like that," explains James Crowe, director of the Vanderbilt Vaccine Center in Nashville, Tennessee. Unfortunately, these immunodominant elements are also highly variable between strains.

GOPAL MURTI/SCIENCE PHOTO LIBRARY

Influenza A viruses are particularly diverse. They are classified by numbers based on the subtype of haemagglutinin (H) protein and a second viral protein known as neuraminidase (N), with even greater strain variation observed among those subtypes. For example, the 2009 pandemic arose from a new strain of the H1N1 subtype. The extent of haemagglutinin variability means that poor strain selection can leave recipients largely unprotected — and even a good vaccine offers limited protection against future strains. "In two years, the virus can change again so we can get re-infected and get disease," says Palese.

Further complicating the quest for a universal flu vaccine is the fact that our immune system is strongly biased by its earliest encounters with influenza through a phenomenon called imprinting — or, as it has been dubbed, 'original antigenic sin'. This means that individuals have a strong antibody response to viruses with molecular features shared by the strain encountered during their first exposure, but they essentially start from scratch when exposed to distantly related strains for the first time. "It's not that you cannot see the second virus — it's just like you're a baby and you're seeing it for the first time," says Crowe.

Imprinting is a double-edged sword because early exposure to the right strain could theoretically produce far-reaching and vigorous protection in response to vaccination. But if a child's first influenza encounter is with a relatively unusual or atypical strain, vaccination might prove less effective in terms of rousing broadly protective immunity.

STALKING STABILITY

A vaccine that focuses the immune response on a more stable target on the virus could overcome the problem of viral diversity. Researchers have known that such targets existed for decades. In 1983, Palese and his colleagues determined that the haemagglutinin stalk domain is so similar between strains that antibodies can recognize specific physical features, known as epitopes, of haemagglutinin proteins from multiple influenza subtypes. Unfortunately, the stalk is something of an immunological wallflower, overshadowed by the influence of the head. "We have engineered epitopes into the stalk and the same epitopes into the head, and we get a much better response to epitopes in the head," says Palese. But immunity can still emerge naturally in some cases, and a series of stalk-specific antibodies were isolated from human donors in 2008 and 2009.

More recently, several research groups have devised multiple vaccine strategies for selectively provoking a stem-specific response. Graham's team at NIAID, for example, undertook a painstaking process of protein engineering a standalone version of the stem from an H1 influenza virus. "It took us about seven or eight years to engineer it and stabilize it enough to maintain the right surfaces and structures," says Graham. The researchers subsequently generated nanoparticles displaying multiple copies of these engineered stems and showed[1] that these could generate strong protection against entirely different subtypes of influenza A, such as H5 — at least in animal models. This vaccine design is now undergoing a phase I clinical trial and could in principle confer protection against many of the most prominent pandemic virus subtypes. A newer haemagglutinin stem construct developed by NIAID could lead to even broader protection against the remaining subtypes.

Palese and Florian Krammer, a virologist who is also at Mount Sinai, have developed an alternative approach to stimulating stem-specific immunity. They have generated multiple influenza viruses with chimaeric haemagglutinin proteins in which the same stalk domain is paired with various exotic head domains from virus subtypes that primarily infect birds and are therefore unlikely to trigger an imprinting-biased response in humans. "If you then revaccinate with a vaccine that has the same stalk but a completely different head, the immune memory against the stalk could be boosted," explains Krammer.

"This trimer interface is a whole new universal flu epitope, and everybody's going crazy about it."

This approach uses the entire virus particle, creating the potential to elicit parallel immune recognition of other influenza antigens. On the basis of promising evidence of cross-protection against diverse influenza A subtypes in animals, the Mount Sinai team is now conducting phase I trials to explore the vaccine's safety and effectiveness in humans.

HIDDEN WEAKNESSES

Inspired by the discovery of cross-protective stalk antibodies in the wild, several research groups have been casting the net wider to find more such molecules. "We use all kinds of donors — people who are actively sick, people who have recovered from avian influenza, or we'll go to other countries to find donors with exposure to unusual strains," says Crowe. After isolating the antibody-producing B cells from these individuals, researchers can comprehensively profile the specific influenza targets that elicit a natural immune response and identify antibodies that might have broad infection-neutralizing capabilities.

These studies have revealed that even in the variable head domain of haemagglutinin there are structural elements that are consistent across influenza subtypes. In 2012, researchers at Scripps and Janssen's Crucell Vaccine Institute in Leiden, the Netherlands, identified[2] an antibody called CR9114, which exhibited unprecedented breadth of recognition. "That could actually bind to both influenza A and influenza B," says Wilson, who helped characterize the antibody. This antibody is now being used to identify target epitopes on haemagglutinin that can be exploited to achieve far-reaching virus neutralization for both prevention and treatment.

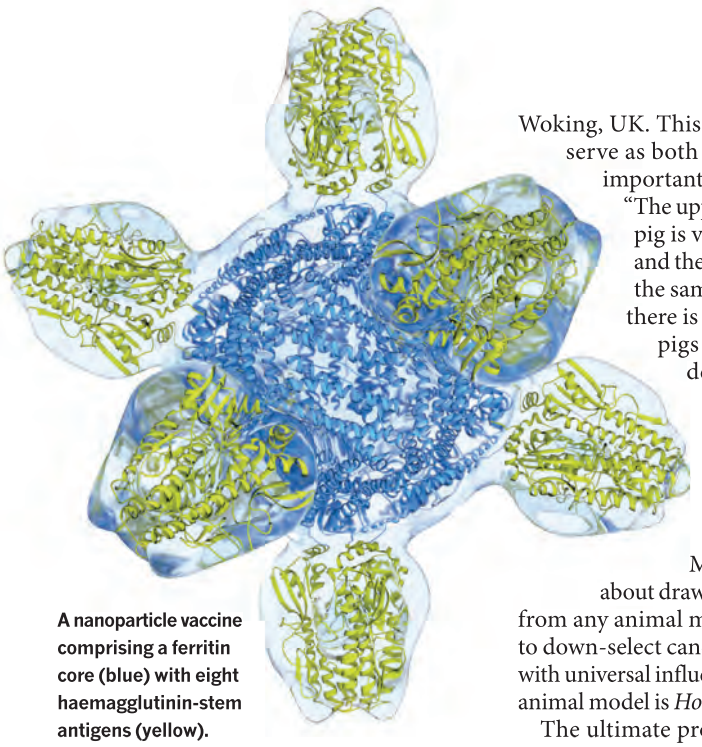
In some cases these searches have revealed unexpected vulnerabilities in the virus. Haemagglutinin normally assembles into highly stable complexes of three closely coupled molecules, but Crowe and Wilson discovered[3] this year that these trimers occasionally open up to expose a weak point to which antibodies can bind, potentially thwarting infection by a wide range of influenza A viruses. "This trimer interface is a whole new universal flu epitope, and everybody's going crazy about it," says Crowe. "It's not even clear how it works, but it clearly works in animals."

Much of the variability between influenza viruses is only skin deep. Probe more deeply within the virus particle and you find greater similarity in the essential proteins. These are beyond the reach of antibodies but they can be recognized by T cells — an element of the immune system that can target and eliminate influenza-infected cells, which present peptide signatures of their viral intruders.

So far, antibodies have been the primary focus of the vaccine community because they represent a crucial first line of defence against circulating virus particles, but T cells provide critical protection by containing infection once it is under way. "People get exposed and infected every two or three years on average," says Sarah Gilbert, who heads vaccine development at the University of Oxford's Jenner Institute, UK. "The vast majority of these infections

ANNE RAYNER, VANDERBILT UNIV.

Research at the Vanderbilt Vaccine Center studies the immune response to the influenza virus.



A nanoparticle vaccine comprising a ferritin core (blue) with eight haemagglutinin-stem antigens (yellow).

NIAID/NIH; VACCINE DESIGNED BY J. BOYINGTON & B. GRAHAM AT NIAID VACCINE RESEARCH CENTER; STRUCTURE DERIVED BY A. HARRIS & J. GALLAGHER AT NIH LABORATORY OF INFECTIOUS DISEASES

are either asymptomatic or mild," she says, "and the reason is that people have a T-cell response that's strong enough to protect them."

In general, eliciting a truly protective T-cell response entails reawakening memory T cells that were formed in the aftermath of a previous exposure. Gilbert's team uses a crippled vaccinia virus that can infect human cells and that synthesizes two different immunity-stimulating influenza proteins but is incapable of further replication. "With a single dose, we saw a boost in pre-existing T-cell responses of between eight- and tenfold in humans," says Gilbert. She adds that the target proteins are 90% identical across influenza A viruses, offering the potential for broad protection against pandemic strains.

Gilbert's vaccine is undergoing two phase II trials under the guidance of Vaccitech, a company she co-founded in Oxford. A potent T-cell response also seems to contribute to the apparent cross-protection offered by a replication-defective flu vaccine from FluGen, based in Madison, Wisconsin, which has reported success in a recent phase II clinical trial.

TRIALS AND TRIBULATIONS

Even with several promising series of human trials under way, the road to the clinic remains fraught with difficulties. Mice are often used for early studies of vaccine preclinical development but Palese points out that they are not a natural reservoir for the influenza virus. Many researchers therefore quickly switch to using ferrets to test their vaccine candidates, because they are broadly susceptible to influenza and are physiologically more like humans in that ferrets have a longer respiratory tract than mice. Both species are short-lived, however, making it difficult to study the effects of a vaccine over many rounds of influenza exposure.

Gilbert has started working on pigs in collaboration with the Pirbright Institute near Woking, UK. This long-lived species could serve as both a useful test case and an important beneficiary for vaccines. "The upper respiratory tract of the pig is very similar to the human and they tend to get infected with the same viruses," she says. "And there is a need for flu vaccines in pigs — the 2009 H1N1 pandemic virus is thought to have come from pigs."

Krammer has also used pigs as a model but says their large size makes them difficult to use routinely in research. Moreover, he is hesitant about drawing too many conclusions from any animal model: "You can use them to down-select candidates and for safety, but with universal influenza vaccines, the ultimate animal model is *Homo sapiens*."

The ultimate proof for any flu vaccine is protection against disease in clinical trials. But for a putative universal vaccine, such testing is more complicated. A growing number of groups are using 'human challenge' trials, in which healthy volunteers are deliberately exposed to a particular influenza strain after vaccination. This approach allows for faster trials with smaller cohorts and defined exposure conditions — lowering the trial cost — and it also allows researchers to hand-pick the viruses they wish to protect against.

But challenge trials also have their critics. "It's not a natural infection. You have to inoculate people with a million or even ten million virus particles," says Krammer, "and it doesn't seem to work like a natural infection." These trials also leave out very young and very old people, which are the groups most vulnerable to flu.

***"With universal influenza vaccines, the ultimate animal model is* Homo sapiens."**

Another problem is that the US Food and Drug Administration still requires a real-world trial before giving approval, and these are difficult and costly. They require thousands of participants to ensure that a sufficient number of people are exposed to flu, and they must span several seasons to demonstrate efficacy against multiple virus strains or subtypes.

Many academic researchers say that even embarking on a clinical trial can pose a nearly insurmountable challenge, because it requires access to sophisticated production facilities that meet the high bar of good manufacturing standards. "Even if it's a simple construct, we're talking about at least a year to make it and a cost of approximately US$1 million to $2 million," says Krammer. A few major companies such as GlaxoSmithKline and Janssen have made these investments, but obtaining that much funding from either public or private bodies is far from easy. Gilbert struggled for five years to obtain funding before launching her company, which raised the capital needed to bring her lab's vaccine programme into phase II trials.

More investment may be on the way. In the past few years, both NIAID and the US Biomedical Advanced Research and Development Authority have prioritized the development of a universal vaccine, and the Bill & Melinda Gates Foundation has joined forces with governmental and non-governmental organizations to form the Global Funders Consortium for Universal Influenza Vaccine Development.

RAISING THE BAR

The vaccines now being developed promise much broader protection than current seasonal shots but fall well short of being truly universal. The World Health Organization (WHO) still sees considerable value in such vaccines, and has called for a vaccine that prevents severe disease from all forms of influenza A by 2027, which would prevent pandemics. But Krammer points out that seasonal influenza B infections can also inflict a serious death toll, and both he and Palese have focused their sites on true universality. "I think the WHO is making the bar too low," says Palese. "We really should be trying to aim high."

Universal protection need not entail eliminating all traces of influenza virus but simply providing sufficient immunity to minimize the symptoms of infection. Even achieving that more modest goal will probably require a multipronged attack. "Stem antibodies contribute to protection but are probably not sufficient for very potent protection," says Crowe. "They would be just part of the scheme."

Indeed, Gilbert is exploring the potential of a broader immunological assault that melds the Mount Sinai group's chimaeric stem vaccine with her team's vaccinia technique. "At least in mice," she says, "combining these two approaches was better than either alone."

A greater understanding of the human immune system and its response to infection could inform smarter vaccination strategies. In May 2019, the US National Institutes of Health awarded $35 million to an international team of researchers to profile the immunity of young children in the years after their initial exposure to influenza, providing the deepest insights yet into the imprinting process.

Their findings could help vaccine designers figure out the best way to rewire the immune system while it remains malleable. And that, says Crowe, could be a game-changer. "You could envision doing a universal vaccination as your first exposure, with beneficial imprinting for the rest of your life," he says. ■

Michael Eisenstein *is a science writer in Philadelphia.*

1. Yassine, H. M. *et al. Nature Med.* **21**, 1065–1070 (2015).
2. Dreyfus, C. *et al. Science* **337**, 1343–1348 (2012).
3. Bangaru, S. *et al. Cell* **177**, 1136–1152 (2019).

Q&A: Josef Järhult
Resistance in the wild

Like all microorganisms, viruses can develop resistance to the drugs meant to treat them, and not only in clinical situations. The rise of environmental resistance to antiviral drugs is a potential disaster we can avert, argues Josef Järhult at Uppsala University in Sweden, especially when it comes to influenza A, the virus that can lead to a human flu pandemic.

MIKAEL WALLERSTEDT

How could influenza A develop resistance to antiviral medicines?

The influenza A virus has high genetic variability and mutates rapidly. It needs only one point mutation to develop resistance to certain antiviral drugs, and such mutations happen all the time.

For H1N1, the virus subtype that caused the most recent influenza A pandemic in humans, the point mutation H274Y affected the shape of the pocket where the antiviral drug oseltamivir (Tamiflu) binds to the protein neuraminidase. Neuraminidase inhibitors such as oseltamivir stop this protein cutting the virus loose from a cell and so stop the virus spreading to other cells. But the drug cannot do that if a mutation stops it binding. Such mutations rob us of a cornerstone of our defence against pandemics.

Where in the environment is it most likely that influenza A will pick up resistance to antiviral drugs?

You have to consider where the virus is going to meet the antiviral in the environment. One place that happens is in rivers. Mallard ducks are natural reservoirs for influenza, and drug residues can enter the rivers in which they live. We have seen in our experiments that low levels of the drug in water can lead to oseltamivir-resistant influenza A viruses (J. D. Järhult *et al. PLoS ONE* **6**, e24742; 2011), which can then be passed on through several generations of mallards, even if the drug is removed from the water (A. Gillman *et al. Appl. Environ. Microbiol.* **81**, 2378–2383; 2015).

For some antivirals, rivers downstream of sewage treatment plants are likely breeding grounds of resistance. Humans pass the active ingredient of these drugs out of their bodies in their urine. Sewage treatment plants do not have the technology to remove antivirals, or pharmaceuticals in general, so these drugs end up in rivers and other natural waters.

MAURIBO/GETTY

Mallards act as reservoirs in which the influenza virus can develop drug resistance.

Are antivirals reaching rivers in sufficient quantities to bring about resistance?

The highest recorded levels of oseltamivir in river water, 865 ng l^{-1}, were found in Japan during the 2004–05 influenza season (R. Takanami *et al. J. Water Environ. Technol.* **8**, 363–372; 2010). In our work with ducks, we found that the lowest levels at which viruses developed resistance was 950 ng l^{-1}. That's a little higher than the levels measured in the environment but it's the same order of magnitude.

Japan is one of the top consumers of oseltamivir, which is why it has such high levels of the drug in its river water. But several other countries, including the United States, have a liberal policy for oseltamivir. Environmental levels in those nations could be just as high, but no one seems to be checking.

Have viruses that are resistant to antiviral medicines been found in the wild?

There have been a few reports of viruses in wild birds that have an antiviral-resistance mutation. It's uncommon but it's there. Whether this is due to drug pressure or just natural variation, I can't say. Examples from humans have demonstrated that in some circumstances the oseltamivir-resistant flu virus can outcompete all other flu strains, even in the absence of drug pressure. It's rare, but it happens. And if a resistant virus is circulating in wild birds, there is a risk that it will form the basis of a new pandemic or highly pathogenic flu.

Are some drugs more likely than others to give rise to resistant viruses?

Our experiments have shown that zanamivir (Relenza) is less likely than oseltamivir to give rise to genetic resistance in influenza A viruses in wild ducks. But it's still possible.

For any new class of drugs, such as the polymerase inhibitors recently approved in the United States and Japan, we need to study the mechanisms of environmental resistance as soon as possible, before they are used at high levels. If they are not chemically stable, or do not pass through sewage treatment plants intact, resistance may not be a problem. The sooner we know the better, so we have the opportunity to use them prudently or propose sewage treatment techniques to destroy the drugs before they get into the environment.

What can we do to prevent antiviral resistance arising?

There is no simple solution. It's good to keep a broad mindset and take a multidisciplinary approach. The network One Health Sweden, which I chair, brings together doctors, veterinarians, epidemiologists, virologists and others — everyone working on some aspect of problems that include humans, animals and the environment.

In the same way we think about cutting antibiotics use to reduce antimicrobial resistance, we also need to use antiviral drugs more prudently. For example, we should not use oseltamivir for uncomplicated seasonal influenza in otherwise healthy people.

We need effective treatment at sewage treatment plants to reduce the levels of antivirals in rivers. Ozonation treatment works but is expensive and has practical problems. And we need drug manufacturers to not release antivirals and their precursors into natural waters. Researchers in Germany have found oseltamivir's parent compound in the Rhine, probably from a pharmaceutical manufacturer (C. Prasse *et al. Environ. Sci. Technol.* **44**, 1728–1735; 2010).

We also need more monitoring of both the levels of drug residues in the environment and the flu viruses themselves, particularly in wild ducks. Our research shows that it is possible for resistance to develop in the environment. Now it is time to go and find it in nature. ■

INTERVIEW BY NAOMI LUBICK

This interview has been edited for length and clarity.

ANTOINE DORÉ

THERAPEUTICS

A bigger arsenal

Understanding how the influenza virus replicates inside the body is helping researchers develop a wider range of antiviral drugs.

BY NEIL SAVAGE

In 2004, Rick Bright was looking for a new project. As an immunologist then at the US Centers for Disease Control and Prevention (CDC) in Atlanta, Georgia, he had learned about a new, faster method of sequencing viral genomes. He decided to use it to test whether the influenza A virus was developing resistance to adamantanes, which at the time were the main antiviral drugs used to treat flu.

Bright collected samples of the flu virus and tested them for an altered amino-acid sequence known to confer resistance. To his surprise, every virus in his sample had the mutation. Bright took his results to the CDC's director, Julie Gerberding, who was sure he must be mistaken and told him to run the tests again.

Some 25,000 samples later, Bright came to a sobering conclusion. Nearly all the viruses in circulation around the globe had a mutation that rendered amantadine and rimantadine — the two adamantanes used to treat flu, which work by blocking a particular step in viral replication — completely useless. In January 2006, Bright and Gerberding held a press conference to issue new guidelines: do not use adamantanes to treat flu because they will not work.

Fortunately, by that time a second class of flu antivirals had been introduced that attack a different mechanism used by the virus to reproduce. These drugs — oseltamivir, zanamivir and, more recently, peramivir — remained the only drugs for treating flu until 2018 when the United States and Japan approved baloxavir, which targets a third part of the viral life cycle. But the arsenal of drugs to combat flu remains limited and there has been evidence of resistance to all of them, although it is not yet widespread. To be effective, each drug must be given within two days of symptoms appearing.

Researchers around the globe are working to develop further antiviral therapies for flu. They are searching for drugs that attack different parts of the virus's reproductive cycle, and are exploring whether the combination of two or more drugs might lead to faster recovery, reduce the development of resistance, or both. They hope that by the time the next pandemic comes around, they will have better weapons to fight this deadly disease.

VITAL ANTIVIRALS

Much of the attention paid to fighting flu is aimed at vaccination (see pages S4 and S14) but antiviral drugs such as baloxavir have a crucial role in reducing illness and death from flu, says Bright, who now directs the Biomedical Advanced Research and Development Authority (BARDA). BARDA funds research into treatments for various diseases and health threats, including flu. "Vaccines get all the marquee lights," Bright says, "but we can't vaccinate everyone, and the vaccines don't offer full protection to everyone. So there's a lot of room for effective therapeutics."

The first antiviral drug, amantadine, was approved by the US Food and Drug Administration (FDA) back in 1966. It works — or rather, it used to until viruses developed resistance — by blocking the virus's M2 proton channels, which the virus uses to release its RNA for replication by a host cell.

M2 blockers were the only way to interfere with the flu virus until 1999, when the oral drug oseltamivir and the inhaled drug zanamivir won FDA approval. These drugs inhibit neuraminidase, an enzyme that allows viruses to escape from one cell and spread to others. Oseltamivir, marketed as Tamiflu, has become the standard flu treatment in most countries. Another neuraminidase inhibitor, peramivir, which is administered intravenously, has been

approved for use in the United States, Japan and South Korea.

The latest addition to the antiviral arsenal, baloxavir, targets a third component of viral reproduction: the enzyme polymerase, which controls the transcription and replication of viral RNA. Baloxavir inhibits transcription by preventing the virus from commandeering the host cell's manufacturing facilities. Normally, in a process known as cap snatching, the virus steals a short string of the host cell's RNA and attaches it to its own RNA, tricking the cell into duplicating it. Baloxavir blocks the part of the polymerase that assists in this cap snatching.

Although baloxavir is available in Japan and the United States, it has yet to be approved by the European Medicines Agency. One appealing aspect of baloxavir is that it requires just one oral dose compared with ten doses over a five-day period for oseltamivir.

FRESH TARGETS

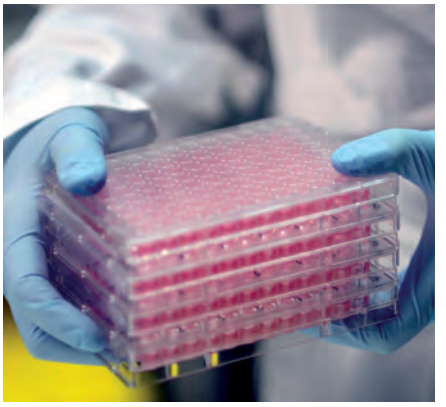
To expand the treatment options, researchers are broadening their search to find a range of different targets. Jun Wang, a pharmacologist at the University of Arizona in Tucson, has his eyes on several. His main approach has been to target the mutation in the M2 channel that created resistance to amantadine and rimantadine. One particular mutation, dubbed AM2-S31N, confers resistance in more than 95% of influenza A viruses. Amantadine blocks the process by which viral RNA is released into the host cell, and the mutation provides a new channel through which the virus can release its RNA.

"We know the mutation," Wang says. The question now is whether new drugs can be developed to target it. "If we can do that then we can treat current viral infections," he adds. So far, Wang has found a molecule that blocks the new channel in cells in his laboratory. He now aims to study it in mice.

Another one of Wang's projects, which is still at an early stage, also focuses on viral polymerase but has a different target to baloxavir. Polymerase consists of three parts that must work together. Wang has found several compounds that seem to block the assembly of the enzyme, rendering it useless and stopping the virus in its tracks. The beauty of this approach, he says, is that the virus is unlikely to get around the blockage with a single mutation.

Wang's drug candidates bind to one component of the polymerase, PA_C, and prevent it from binding to a second component, $PB1_N$. A single mutation could be enough to stop the drug binding to the target, Wang explains, but that mutation would probably mean that the enzyme's components would no longer fit together. "It still will not be able to assemble," he says, because there would need to be a second mutation to allow the reshaped piece of the enzyme to bind to the other parts.

The polymerase complex is an attractive target for antivirals because it is highly conserved — it does not change much as the virus evolves. Being highly conserved is usually a clue that something is vital to the functioning of an organism, as it is less likely to successfully mutate. In addition, Wang's compounds and baloxavir target different parts of the polymerase complex, so together they might be able to cripple the virus more effectively than either could alone.



MATTHIEU YVER, EQUIPE VIRPATH, UNIV. CLAUDE BERNARD

Plates of cells infected with the influenza virus are used to test antiviral drugs.

A third project in Wang's lab that is at an early stage focuses on haemagglutinin, a surface protein that allows the virus to bind to a cell. "It's an easy target, but it's also a really difficult one," Wang says, because its main part, the head, mutates readily, letting it evade attackers. As a result, drugs targeting haemagglutinin might be most effective when used in combination with other drugs.

Different groups of researchers have tried to target the stem of haemagglutinin, as this is more conserved than the head. Scientists at Scripps Research Institute in La Jolla, California, and the pharmaceutical company Janssen Research and Development, based in Raritan, New Jersey, found a small molecule that, like an antibody, could bind to the stem of haemagglutinin. When they gave it to mice that had been infected with 25 times the lethal dose of flu, all of them survived. But Jason Chien, who leads Janssen's research and development team for respiratory infections, says that although the project was scientifically useful, the molecule was effective only against type A influenza, not type B, so the company will not be pursuing it.

"At least in theory it's a very interesting and very quick strategy to propose new drugs."

Chien says that teams at Janssen are studying other potential antivirals in the lab but he declined to disclose details. The company is, however, conducting two phase III clinical trials on pimodivir — one using hospitalized patients and one involving outpatients at high risk of complications. Pimodivir inhibits yet another aspect of the polymerase complex, and if approved it will expand the class of drugs now dominated by baloxavir.

CHECKING THE MEDICINE CABINET

Instead of developing new drugs to target flu, researchers in France are scouring databases of known compounds to see whether any might make effective treatments. "At least in theory it's a very interesting and very quick strategy to propose new drugs," says Olivier Terrier, a virologist at the International Centre for Infectiology Research in Lyon.

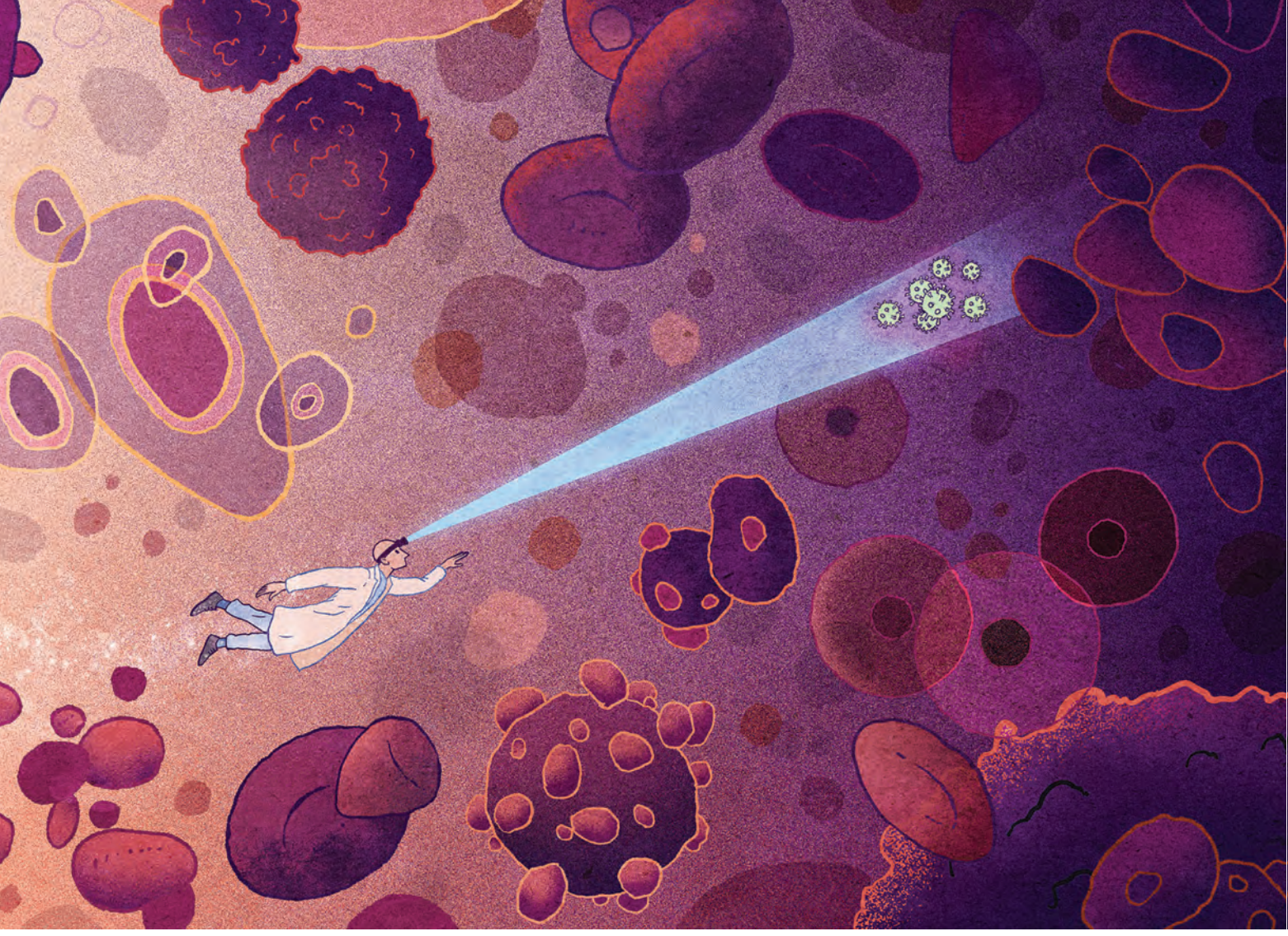
Terrier and his colleagues used a database known as the Connectivity Map (CMap), developed by the Broad Institute of Massachusetts Institute of Technology and Harvard University in Cambridge, Massachusetts. The CMap contains gene-expression profiles that are produced when cells are exposed to various drugs. First, the Lyon team developed a profile of how a cell's gene expression is affected by a flu virus — "a fingerprint of infection", as Terrier calls it. Then they combed through CMap looking for drugs that produce a mirror image of that fingerprint. If, for example, the virus causes a particular gene to express less of a certain protein, they looked for a drug that leads it to express more. They hope that a drug that produces an effect opposite to that of the virus could potentially be used to counteract the flu.

The team screened 1,309 FDA-approved molecules and found 35 that looked promising. Of these, 31 showed antiviral activity in viruses swabbed from the nasal passages of people with flu. Studies in mice narrowed the search to just one candidate, the calcium-channel blocker diltiazem, which is normally used to treat hypertension. The researchers founded a company in Lyon, Signia Therapeutics, which is running a phase II clinical trial on the drug. The drugs are already FDA approved, Terrier says, which could shave years off the process for getting them to flu patients.

Other researchers are trying to use antibodies to fight flu. A group at the Liverpool School of Tropical Medicine (LSTM), UK, and Imperial College London attached extra sialic acids to part of an antibody. The flu virus normally infects cells in the lungs by binding through its haemagglutinin and neuraminidase proteins to sialic acid on the surface of lung cells. But when the virus encounters antibodies covered in sialic acids, it binds to those instead, stopping it attaching to the lung cells. Richard Pleass, a virologist at LSTM, says that a treatment based on these antibodies could act as a prophylactic for hospital staff, slowing the spread of flu.

Despite the number of approaches to new flu treatments, it can take years to take a drug from the lab to the clinic. But Wang is confident that an expanded array of antivirals is on the horizon. "We're getting there," he says. "Within the next few years we will definitely see a few other new flu drugs on the market." ■

Neil Savage *is a science and technology journalist in Lowell, Massachusetts.*



ANTOINE DORÉ

DIAGNOSTICS

A sticking point for rapid flu tests?

Rapid molecular tests for influenza are as quick as older on-the-spot tests and much more accurate. But that might not be enough to drive widespread adoption.

BY ELIZABETH SVOBODA

It begins like many other tests at the doctor's surgery: a quick swipe inside the nostrils with what looks like a giant cotton bud, which is then plunged into medium designed to keep the sample fresh.

But it is what happens next that makes the Xpert Xpress molecular influenza test different. A technician places the sample into the machine, which then makes copies of any genetic information it contains. Fluorescence detectors scan for the presence of specific genes. In less than half an hour, the doctor knows with near certainty which influenza virus — if any — is present in the patient's respiratory tract.

The developer of the Xpert Xpress, Cepheid based in Sunnyvale, California, thinks that rapid molecular tests like this will transform flu diagnosis. And other pharmaceutical companies such as Abbott, based in Chicago, Illinois, and Roche of Basel, Switzerland, have created similar diagnostic tools. Since these tests were launched in the United States several years ago, medical providers have raved about their speed and accuracy, which they say makes treatment decisions easy and reduces the burden of disease. But a few problems, including high costs and the risk of sample contamination, make it hard to predict whether these tests will become the standard diagnostic tool.

INCONSISTENT RESULTS

Influenza cuts a seasonal swath of destruction around the world, leading to more than 200,000 hospitalizations and 30,000 deaths each year in the United States alone. The virus is highly contagious but treatable, so it is important to identify it as quickly and as accurately as possible. Today, many people who visit a clinic with flu symptoms receive a rapid influenza diagnostic test (RIDT). Unlike molecular tests, such as the Xpert Xpress, RIDTs contain an antibody that sticks

ABBOTT LABORATORIES

to an antigen protein on the flu virus, typically changing colour to show a positive result.

The main advantage of RIDTs is their speed — they produce a result in less than 30 minutes. But they sometimes deliver poor results. "You need a lot of flu to be there, and if there's not enough, you'll get a negative result," says Neil Anderson, who studies infectious diseases at the Washington University School of Medicine in St Louis, Missouri. Children tend to shed a lot of virus particles, he adds, but some adults do not produce enough to give a positive test result even if they have severe symptoms.

False-negative results are therefore a big problem. In one clinical study[1] involving 600 people, 77% of those with influenza initially received an incorrect negative result from a RIDT. Newer RIDTs have been developed to address such accuracy issues but several researchers say that even these are still not sensitive enough to be reliable. Another type of quick influenza test known as an immunofluorescence assay has similar reliability problems.

Rapid molecular tests, however, use a different approach. Rather than relying on finding sufficient quantities of antigen, they instead copy long stretches of viral genetic code contained in the sample. Flu viruses have RNA so the tests first immerse the sample in lab-made nucleotides, creating a matching strand of DNA. Multiple rounds of heating and cooling then create many more strands of DNA. This process, called amplification, makes it easy to detect even small quantities of virus. Abbott's rapid molecular test, called ID Now, amplifies the DNA at a constant temperature.

After amplification, fluorescence detectors test whether the genetic sequences match those of known flu viruses. In Cepheid's test, much of this sample processing takes place inside a maze of plastic channels no wider than a poker chip. Within 20–30 minutes, the machine reveals not just whether a person has flu, but which strain and subtype of the influenza virus is causing the illness.

A DEFINITIVE RESULT

There is widespread consensus that rapid molecular tests for influenza are much more accurate than RIDTs. A 2017 meta-analysis[2] that pitted RIDTs against rapid molecular tests found that both were more than 98% accurate in identifying people who did not have flu; the big difference was in people who did. Using RIDTs, more than 45% of people with flu received false negatives, compared with just 8% using rapid molecular tests.

Greater accuracy also improves the speed of diagnosis because it eliminates the need for further lab tests, says Esther Babady, a microbiologist at the Memorial Sloan Kettering Cancer Center in New York City. A negative result from an RIDT is treated as merely advisory, she says: "They would still send the sample to the clinical lab." The molecular tests change that protocol. "With the molecular tests it's done," she says. "It doesn't require additional testing."

A rapid, accurate diagnosis allows doctors to prescribe treatment faster, which brings noticeable benefits to patients. In a study[3] of more than 1,400 people with flu, those who took antiviral medication within 12 hours of the onset of fever had three fewer sick days than those who started medication after 48 hours. "Getting treatment earlier is going to lessen symptoms," Anderson says.

A 2019 study[4] compared the outcomes of pregnant women with flu-like symptoms at two time points: before rapid molecular flu tests were introduced and afterwards. In women with flu, hospitalization rates were 83% before the tests were introduced but only 38% in those given the rapid molecular tests, largely because these women were given effective treatment sooner. Women given the new tests also received fewer than half as many antibiotic prescriptions as those who did not, because there is no benefit in prescribing antibiotics for viral diseases such as flu once they are diagnosed.

As well as streamlining treatment, rapid molecular tests could also reduce the rate of flu transmission, says Ritu Banerjee, who studies antimicrobial drugs at the Mayo Clinic in Rochester, Minnesota. "If patients are diagnosed with influenza quickly using an accurate test, they will spend less time in health-care settings waiting for test results," Banerjee says, reducing the opportunity for the virus to spread in busy waiting rooms. People given a quick, definitive diagnosis might also be more likely to avoid going to work or school, she adds, lowering the odds of transmission even further.

SLOW UPTAKE

Despite the benefits of rapid molecular tests, hospitals and health systems have been slow to buy them. In 2016, the World Health Organization found that only 15% of hospitals were using rapid molecular tests to diagnose flu. One of the biggest problems is the cost, Babady says. Whereas RIDTs cost about US$15 per test, rapid molecular tests can cost up to $45 — a financial burden that many health-care providers, both public and private, would struggle to bear. Rapid molecular testing also requires a hefty initial investment in a testing platform, such as Cepheid's GeneXpert Xpress or Abbott's ID Now. "Right now, everyone has to make the case to their hospital system because of the added costs," Anderson says.

"With the molecular tests it's done. It doesn't require additional testing."

Some researchers argue that the cost of rapid molecular testing would be paid for by reductions in flu complications and the resulting unnecessary treatments. A team at Newcastle University, UK, concluded[5] that adopting rapid molecular tests would save the UK National Health Service about £240,000 ($295,000) each year for every 1,000 people with flu-like symptoms, largely because patients who are quickly and correctly diagnosed consume fewer hospital resources. When improved patient outcomes and reduced resource use are considered, "the cost savings almost come to the point of balancing out", Anderson says, and could result in a cost benefit over time.

Rapid molecular tests, such as Abbott's ID Now, quickly and accurately identify viruses in a sample.

Another problem that has slowed the adoption of rapid molecular testing is the risk of contamination. Rapid molecular tests are designed to detect and magnify snippets of viral RNA but their high sensitivity means they can post an inaccurate result if a lab technician has flu, for example, or if a sample is mishandled. "Monitoring that is something we do consistently in the clinical lab," Babady says. "In a busy emergency room, it becomes much more complicated."

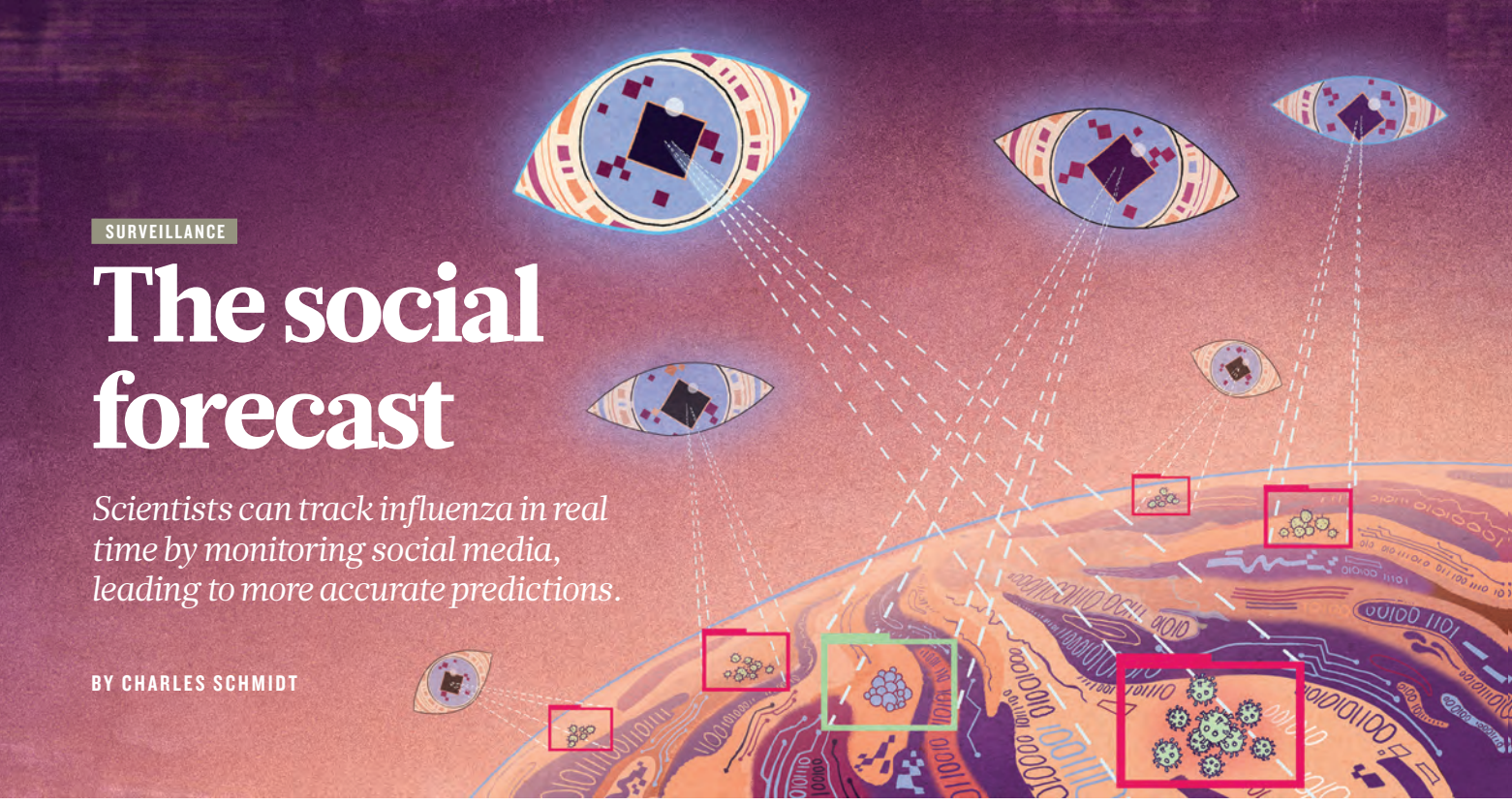
Babady is not sure whether rapid molecular tests will ever become commonplace. But Anderson thinks that early institutional adopters — such as his own medical centre at Washington University — could encourage other health providers to try the tests, as they pile up more and more data illustrating how the test results affect patient outcomes and hospitals' bottom lines.

And conventional health systems are not the only potential customers. As the tests become more widely accepted, Anderson says, "you're going to see them used outside hospital settings — at pharmacies, potentially even at a nurse's room in a high school."

The unpredictability of the influenza virus's evolution could ultimately be what nudges fine-tuned rapid diagnostics into routine use. If a virulent flu strain lays waste to schools and workplaces in a few years, a nearly instant test that offers accurate results might just be too compelling a prospect to ignore. ■

Elizabeth Svoboda *is a science writer in San Jose, California.*

1. Koul, P. A. *et al. Indian J. Med. Microbiol.* **33** (suppl.), 26–31 (2016).
2. Merckx, J. *et al. Ann. Intern. Med.* **167**, 394–409 (2017).
3. Aoki, F. Y. *et al. J. Antimicrob. Chemother.* **51**, 123–129 (2003).
4. Anselem, O. *et al. PLoS ONE* **14**, e0217651 (2019).
5. Allen, A. J. *et al. Diagnost. Prognost. Res.* **2**, 15 (2018).



SURVEILLANCE

The social forecast

Scientists can track influenza in real time by monitoring social media, leading to more accurate predictions.

BY CHARLES SCHMIDT

ANTOINE DORÉ

Conventional influenza surveillance describes outbreaks of flu that have already happened. It is based on reports from doctors, and produces data that take weeks to process — often leaving the health authorities to chase the virus around, rather than get on top of it.

But every day, thousands of unwell people pour details of their symptoms and, perhaps unknowingly, locations into search engines and social media, creating a trove of real-time flu data. If such data could be used to monitor flu outbreaks as they happen and to make accurate predictions about its spread, that could transform public-health surveillance.

Powerful computational tools such as machine learning and a growing diversity of data streams — not just search queries and social media, but also cloud-based electronic health records and human mobility patterns inferred from census information — are making it increasingly possible to monitor the spread of flu through the population by following its digital signal. Now, models that track flu in real time and forecast flu trends are making inroads into public-health practice.

"We're becoming much more comfortable with how these models perform," says Matthew Biggerstaff, an epidemiologist who works on flu preparedness at the US Centers for Disease Control and Prevention (CDC) in Atlanta, Georgia.

In 2013–14, the CDC launched the FluSight Network, a website informed by digital modelling that predicts the timing, peak and short-term intensity of the flu season in ten regions of the United States and across the whole country. According to Biggerstaff, flu forecasting helps responders to plan ahead, so they can be ready with vaccinations and communication strategies to limit the effects of the virus. Encouraged by progress in the field, the CDC announced in January 2019 that it will spend US$17.5 million to create a network of influenza-forecasting centres of excellence, each tasked with improving the accuracy and communication of real-time forecasts.

The CDC is leading the way on digital flu surveillance, but health agencies elsewhere are following suit. "We've been working to develop and apply these models with collaborators using a range of data sources," says Richard Pebody, a consultant epidemiologist at Public Health England in London. The capacity to predict flu trajectories two to three weeks in advance, Pebody says, "will be very valuable for health-service planning."

SPREAD BETTING

Digital flu surveillance was transformed when Google turned its attention to flu forecasting in 2008. The company's surveillance platform, called Google Flu Trends, used machine learning to fit flu-related searches together with time-series data gathered by the CDC's US Outpatient Influenza-like Illness Surveillance Network (ILINet). With 3,500 participating clinics — each counting how many people show up with sore throats, coughs and fevers higher than 37.8 °C with no cause other than influenza — ILINet is the benchmark for flu monitoring in the United States. The aim of Google Flu Trends was to estimate flu prevalence sooner than the ILINet data could.

But two high-profile failures belied the media fanfare of its launch. First, Google Flu Trends missed a spring pandemic of H1N1 flu in 2009. Then it overestimated the magnitude of the 2012–13 flu season by 140%.

According to Mauricio Santillana, a computational scientist at Harvard Medical School in Boston, Massachusetts, the system failed because many of the selected search terms were only seasonal, with limited relevance to flu activity, making the predictions noisy and inaccurate. After the H1N1 debacle, Google revised its flu-tracking algorithm. But the algorithm was not routinely recalibrated when the company's search-engine software was upgraded, and that created additional problems. In 2015, Google dropped the platform altogether, although it still makes some of its anonymized data available for flu tracking by researchers.

The demise of Google Flu Trends raised concerns about the role of big data in tracking diseases. But according to Vasileios Lampos, a computer scientist at University College London, the accuracy of flu forecasting is improving. "We have a lot more data and the computational tools have improved," he says. "We've had a lot of time to work on them."

Santillana points out that machine learning has markedly improved in the years since Google Flu Trends folded. "With more sophisticated approaches, it's possible to automatically ignore spuriously correlated terms, so the predictions are more robust," he says.

COMPETITIVE ADVANTAGE

The proving ground for new approaches to modelling is an annual forecasting challenge hosted by the CDC. About 20 teams participate every year, and the winners are those that perform best relative to the ILINet benchmark. In the absence of these models, the CDC's approach has been to estimate future trends based on what ILINet data gathered from previous flu seasons would predict for each region and for the United States as a whole. But during

CARNEGIE MELLON UNIV.

the 2017–18 flu season, most of the models in the challenge generated predictions more accurate than those using ILINet's historical baseline. The CDC now incorporates several of the challenge's top-performing models into its FluSight system.

For the past four years, the winner of the CDC's challenge has been a team led by computer scientist Roni Rosenfeld of Carnegie Mellon University in Pittsburgh, Pennsylvania. Rosenfeld's team, called the Delphi Research Group, bases its predictions on two complementary systems. One is an online crowdsourcing website called Epicast that allows people to express their opinions about how the current flu season might play out. "Epicast exploits the wisdom of the crowds," Rosenfeld says. "The opinion of any one person who responds isn't as accurate as the aggregated opinions of all the responders together."

The team's second system relies on machine-learning algorithms that repeatedly compare trends observed during the current flu season with those seen in previous decades. The algorithm draws on historical ILINet data as well as data from search engines and social media to assemble a distribution of all possible seasonal trajectories. It then models how the current season differs at the moment, and how it is likely to differ as it continues.

As well as machine learning, researchers also rely on mechanistic models that work in a fundamentally different way. Machine learning merely looks for patterns in data, whereas mechanistic approaches depend on specific assumptions about how a flu virus moves through the population. "This often requires biological and sociological understanding about the way disease transmission really works," says Nicholas Reich, a biostatistician at the School of Public Health and Health Sciences at the University of Massachusetts Amherst. "For instance, mechanistic models take into account the susceptible fraction of the population, the transmissibility of a particular virus, and social-mixing patterns among infected and non-infected people."

"This is something we've learned from the challenges. Combinations work better."

At Northeastern University in Boston, Massachusetts, Alessandro Vespignani, a computational scientist who models epidemics, has been forecasting flu by using agent-based approaches that he describes as "mechanistic modelling on steroids". Agents are simply interacting entities, including people, and Vespignani has modelled 300 million individuals, representing the US population, in various settings, and simulated how the flu virus moves among them in workplaces, homes and schools. The agent-based approach allows researchers to zoom in on disease transmission patterns with high spatial resolution. The downside is that these models require high-performance computing, Vespignani says, "and they're also data-hungry, in that they require very detailed societal descriptions."

The Delphi research group at Carnegie Mellon University forecasts the spread of influenza.

Vespignani and Santillana are now collaborating on ways to combine machine learning with the agent-based approach to create what they claim would be an even stronger flu-forecasting model.

STRENGTH IN NUMBERS

Researchers have started to combine models into 'ensembles' that have more forecasting power than the constituent models alone. "This is something we've learned from the challenges," Biggerstaff says. "Combinations work better." That has certainly been the experience of the FluSight Network, which is a consortium of four independent research teams that collaborate on a multimodel ensemble. The ensemble links 21 models — some that use machine learning and others that are mechanistic — into a single composite model that took second place in the latest CDC flu-forecasting challenge, just behind Rosenfeld's team.

The models in this case are combined using a method called stacking, which weighs their contributions based on how well they each performed during previous flu seasons. According to Reich, who directs one of the FluSight Network's four participating teams, the ensemble approaches make optimal use of the component models' idiosyncrasies. The stacking approach, he says "is like conducting them in a symphony. You want each model at its appropriate volume."

Modelled flu forecasts, however, face a series of hurdles before they can be factored routinely into public-health preparedness in the way that, for instance, weather forecasts are used to plan for storms. To be truly effective, even the best model needs to be paired with policy measures that take into account the trends revealed by the software. But Vespignani says it is not entirely clear how confident policymakers and health officials are when it comes to using modelled flu forecasts in real-world settings. Many of these individuals have a poor understanding of how the computational models work, he says, and the models are most accurate at forecasting flu two to four weeks in advance, which does not really provide enough time to allocate resources where they are most needed. Vespignani says that models that could reliably predict the peak and intensity of the flu season six to eight weeks in advance would be more useful.

Santillana says that more research is needed into how social behaviour, vaccination programmes, strain composition, population immunity and other factors affect the models' accuracy. But researchers also need to understand how spatial scales factor into forecasting. For example, the CDC's forecasts are limited to national and regional levels but investigators have begun to consider the prospects for city-scale forecasts, as well as forecasting across global hemispheres.

Meanwhile, work is under way to provide machine-learning-enabled forecasting in developing countries that lack surveillance data. Lampos trained a model using surveillance data from the United States, and reported that it was accurate at forecasting flu in France, Spain and Australia without drawing on historical data from any of those countries. He says this approach could work in poorer locations that lack comparable surveillance infrastructure by analysing the frequency of search queries for flu on mobile phones and other devices. Lampos now plans to test his model in countries in Africa.

There is still a long way to go before flu forecasting becomes as routine and widely accepted as weather forecasting. But Santillana says that progress is advancing rapidly. "The predictions," he says, "are getting better and better." ■

Charles Schmidt *is a freelance science writer in Portland, Maine.*

Moderna Therapeutics produces mRNA vaccines at its factory in Norwood, Massachusetts.

MODERNA

VACCINES

Breaking out of the egg

Can the latest techniques speed up the dangerously slow production of flu vaccines?

BY ERIC BENDER

There is always a race against the clock to tackle influenza outbreaks, both the seasonal global waves of disease and the occasional pandemic. "Somewhere in the world right now, influenza is causing a horrible problem and killing lots of people," says Rick Bright, director of the US Biomedical Advanced Research and Development Authority (BARDA).

Better responses to flu outbreaks demand not just more-effective flu vaccines, but quicker ways to produce them. This is because catching the outbreak in time is crucial and the volumes of vaccines required are huge. In the United States, for instance, manufacturers are expected to make more than 160 million doses for the coming flu season. And to stem a pandemic, BARDA might need 600 million doses.

Most flu vaccines are made in chicken eggs in a process little changed for decades. "Just over 90% of the vaccines supplied for influenza come from eggs," says Martin Friede, coordinator of the Initiative for Vaccine Research at the World Health Organization (WHO) in Geneva. Production takes six months — an eternity when there is a potentially deadly virus constantly mutating around the world.

But alternative manufacturing methods are emerging. Cell-based flu vaccines have been approved that can be made more quickly, and in some seasons these are more effective than egg-based vaccines because they can match more closely with target flu strains. More-radical production techniques are also approaching approval, such as growing vaccines in plants or delivering them using messenger RNA. But the road to commercial manufacturing is long and expensive, as each platform must show that the vaccines it produces can outperform conventional drugs and are cheaper to produce than egg-based vaccines.

NOT-SO-RAPID RESPONSE

Academic and industry researchers around the world are searching for a universal flu vaccine — one that works for several years at least, and ideally one that permanently guards against certain types of flu or protects particular populations (see page S4). The Center for Infectious Disease Research and Policy at the University of Minnesota in Minneapolis is tracking about 80 flu-vaccine research efforts. "We are seeing the emergence of a renaissance around influenza vaccines," says its director, Michael Osterholm. "And it's not just cosmetic improvement in the current vaccines."

Many research efforts are targeting manufacturing technologies that do not require eggs and so avoid the limitations of this decades-old technique. The biggest problem is time. It takes weeks to optimize viruses to grow well in eggs while ensuring that they remain effective and safe. Egg-based vaccine production also requires a massive number of eggs to grow the virus — a particular headache when a pandemic is looming. "Egg production is a huge bottleneck," Friede says. "You can't just call your local egg farm and say tomorrow I need 10 million more eggs."

In the 2009 H1N1 swine-flu pandemic, most vaccines did not arrive in the United States and Canada until after the pandemic had peaked. The United States stockpiles vaccines in advance of the most worrisome pandemic threats. BARDA sometimes spends hundreds of millions of dollars on stockpiles that could treat 20 million people. But that is an expensive gamble, as became clear in 2016 when the agency learned that its vaccine stockpile for the H7N9 flu family would no longer be effective against the latest H7N9 strains, so it had to create a second stockpile.

Whether or not a flu pandemic seems to be imminent, "we're continually identifying viruses that are emerging, characterizing them and making vaccine virus preparations," says Daniel Jernigan, director of the influenza division at the US Centers for Disease Control and Prevention (CDC) in Atlanta, Georgia.

The vaccines made available in the Northern Hemisphere each October are usually based on strains picked by the WHO and partner organizations worldwide the previous February, when seasonal flu remains active. This leaves

MEDICAGO

months in which viruses can evolve fresh tricks to dodge the vaccines.

"We would love it if the production time of the vaccine was shorter," says David Wentworth, chief of virology, surveillance and diagnosis at the CDC's influenza division. "If we could push vaccine strain selection forward to the end of the influenza season in the Northern Hemisphere, we would have a much more complete picture of all the different viruses that are circulating."

"Timing is still everything when it comes to responding to changes in the influenza virus and ensuring that the vaccine is performing as well as possible," says Danuta Skowronski, epidemiology lead for influenza and emerging respiratory pathogens at the BC Centre for Disease Control in Vancouver, Canada. "Looking at that historic reliance on egg-based production is at the top of many lists."

CELLS BEAT EGGS

The best-established alternative to egg-based production is to make vaccines in other types of cell. For example, the four-strain (quadrivalent) Flucelvax from Seqirus in Maidenhead, UK, is generated in mammalian cells and has been approved for seasonal flu in both Europe and the United States. Such vaccines might be a closer match to circulating human flu viruses than egg-based vaccines, making them more effective, says Bright. This is because during vaccine development, candidate viruses are passed through many generations, looking for one that grows quickly and lacks bad traits. During this process, egg-based vaccines evolve away from human flu strains towards ones that work well in chickens, something that is less likely to happen in mammalian cells.

Cell-based manufacturing might have a slight speed advantage too, he adds: "We're not relying on 900,000 eggs coming in from a bunch of different farms and waiting 11 days to inoculate those eggs." However, even vaccines produced in mammalian cells are based on candidates developed in eggs before they are repeatedly groomed for growth.

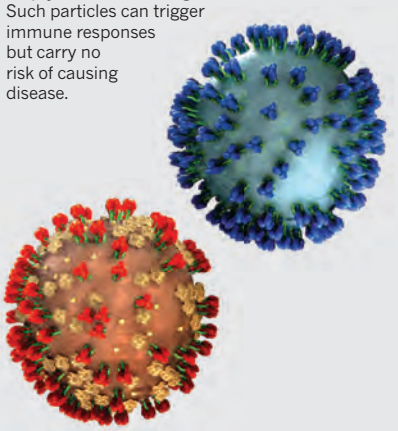
An alternative method of production that does away with chicken eggs altogether involves recombinant technology. The quadrivalent FluBlok vaccine developed by Sanofi Pasteur in Lyon, France, is manufactured in this way. To generate FluBlok, genetically modified baculoviruses are used to insert tailored RNA into insect cells, where the vaccine proteins are subsequently grown.

In a pivotal clinical study (L. M. Dunkle *et al. N. Engl. J. Med.* **376**, 2427–2436; 2017) that led to its approval by the US Food and Drug Administration in 2016, FluBlok was at least 30% more efficacious than a standard flu vaccine in adults over the age of 50, who are generally more vulnerable than younger people, says John Shiver, senior vice-president of global vaccine research and development at Sanofi Pasteur in Swiftwater, Pennsylvania.

Because recombinant-protein platforms do not rely on chicken eggs at any point, manufacturers can take the genetic sequence of the target virus strain and begin to produce vaccines almost immediately, shaving weeks off the production time, Bright says.

LIKE A VIRUS

Some vaccines use virus-like particles (right), which mimic influenza viruses (left) but are empty shells containing no RNA. Such particles can trigger immune responses but carry no risk of causing disease.



PLANT PARENTHOOD

Many flu vaccines are designed as virus-like particles (VLPs). Under an electron microscope, VLPs look like viruses, and they can trigger similar immune reactions. But they are empty shells, lacking the RNA of an actual virus and posing no risk of infection.

VLPs can be generated in yeast or insect cells, but Medicago in Quebec City, Canada, takes a distinctive approach — growing the vaccines in tobacco leaves. "Plants are very complex systems and are capable of making very complex proteins," says Nathalie Landry, the company's executive vice-president for scientific and medical affairs.

Medicago produces its VLP vaccines by a process known as transient expression. Each plant is dipped into liquid that contains bacteria carrying recombinant DNA engineered to encode the desired proteins. A vacuum forces the bacteria into the leaves. The recombinant DNA enters the nucleus of leaf cells, where the protein is transcribed for a period of days.

"We are generating the vaccine inside the body."

"This is a very quick process," says Landry. Getting the recombinant DNA into the leaves takes just three to four minutes, and then the plants are incubated for five to seven days. "If we know which virus strain we need, we could start producing material five to six weeks after a declaration of a pandemic," Landry says.

The results of phase II trials were positive and Medicago expects to complete its third phase III trial for flu this year. The company is preparing applications for regulatory approval in the United States and Canada, and is building a factory that would use its process to produce 30 million doses of quadrivalent vaccine each year.

KILLING BY MESSENGER

Another way to precisely match the target flu strains and have rapid, high-volume production is to use mRNA vaccines, but these are some way from regulatory approval. With mRNA, the final manufacturing steps occur not in a factory but in the person receiving the vaccine.

"The flu virus infects you and uses your body as a bioreactor to make itself," says Hari Pujar, vice-president for technical development and manufacturing at Moderna Therapeutics in Cambridge, Massachusetts. "We are mimicking that path with an mRNA that encodes for flu proteins, so we are generating the vaccine inside the body."

At its factory in Norwood, Massachusetts, Moderna can produce mRNA drugs on a pilot scale from raw materials. These vaccines do not require cells or proteins at all. Instead, workers make a DNA template to churn out the desired mRNAs in a bioreactor the size of a domestic water heater, rather than the giant tanks that are normally used to produce vaccines and other biological drugs. The mRNAs are then embedded in lipid nanoparticles. After injection into the recipient, the nanoparticles enter cells and deliver their mRNA cargos, which generate the proteins that constitute the vaccine.

As reported in May 2019, phase I clinical trials tested two first-generation Moderna mRNA vaccine candidates against two dangerous flu strains that lack approved vaccines. The studies found that the Moderna vaccines were safe and ought to be effective. Moderna is talking to potential industry and government partners about moving to commercial production.

Over at Sanofi Pasteur, Shiver sees several potential advantages of mRNA vaccines, which his company is investigating in collaboration with Translate Bio of Lexington, Massachusetts. He says that "mRNA probably has a good potential to scale up to very large scales, and frankly the same manufacturing facility could be used for more than one type of vaccine". But he emphasizes that, given the huge investment required to turn vaccines into commercial products for seasonal flu, new manufacturing platforms such as mRNA must deliver improvements in the efficacy of vaccines.

The threat posed by pandemics is so great that government agencies such as BARDA might provide assistance for emerging vaccine platforms. "We've spent over US$6 billion on optimizing influenza vaccines, diversifying and augmenting the national supply chain," says Bright. "We don't think there is any pathogen on the planet that can devastate public health, lives, national security and our economic situation faster than a pandemic influenza virus." ■

Eric Bender *is a science writer in Newton, Massachusetts.*

Pigs were the source of the 2009 H1N1 influenza pandemic.

AGNORMARK/GETTY

AGRICULTURE

Flu on the farm

Farms help to spread influenza but they might be an early warning system for the next human pandemic.

BY CASSANDRA WILLYARD

In December 2014, virologist Hon Ip received a shipment from a biologist in Washington state. It was a package containing nine dead birds.

Ip's job at the US Geological Survey's National Wildlife Health Center in Madison, Wisconsin, was to work out what had killed the birds. He was worried that it might be avian influenza. There had been an outbreak in South Korea earlier that year, and in December a novel version of avian influenza was detected in Canada, just 70 kilometres north of where the birds now in Ip's possession had been found. He feared that these waterfowl might also have been infected.

The cause of death was indeed avian flu. Whole-genome sequencing revealed[1] the presence of a highly pathogenic strain of the influenza virus. Such viruses do occasionally arise in the United States but this strain differed from all those that had been detected previously: it came from Asia.

For more than a decade, Ip had been monitoring wild birds for signs of Asian bird flu but had never found the virus. Now, less than a year after the virus emerged in China and South Korea, it had made the leap across the Bering Strait into the United States. "It is the scenario we'd been watching for since 2005," Ip says.

Over the next six months, the virus evolved in a variety of ways, jumped from wild birds to turkeys and chickens, and wreaked unprecedented havoc on the US poultry industry. More than 50 million chickens and turkeys in the United States were killed, either by the virus or by efforts to stop its spread, making this the largest and most expensive avian influenza outbreak in the United States.

Modern farms are particularly vulnerable to devastation from influenza. A large farm might hold tens of thousands of chickens or thousands of pigs in the name of efficient protein production, and this creates an opportunity for viruses such as influenza to mutate and spread.

But there is an even greater fear: that these ever-changing viruses will give rise to the next human pandemic. Last year marked the 100-year anniversary of a pandemic that killed as many as 50 million people worldwide. "We're worried," says Ip, "about another Spanish flu." To prevent that from happening, researchers need to bolster surveillance efforts and curb the spread of flu in animals.

THE BIRD FLU

There are four types of influenza. The most common, influenza A, can infect both humans and animals. Virologists classify these viruses into subtypes based on two proteins on their surface, haemagglutinin (H) and neuraminidase (N). There are 18 recognized haemagglutinin types and 11 neuraminidase types. The dead birds that Ip examined were infected with the H5N8 virus.

But viruses do not stay neatly in their assigned categories. "Flu viruses have an infinite capacity to mutate," Ip says. "They mutate at some of the fastest known rates" of any virus. They also change through a process called reassortment. The influenza A virus has eight RNA segments, and if more than one virus infects a single cell, the viruses can swap some of those RNA segments. This could give rise to an entirely new virus for which no human or animal has immunity, Ip says, and it is this

constant shuffling that makes influenza so difficult to treat — and so dangerous.

The concern around avian influenza began in the late 1990s when a highly pathogenic strain of H5N1 began infecting people in Hong Kong. Until then, avian influenza had caused only mild disease in humans. But H5N1 was different. The first 18 cases in Hong Kong resulted in 6 deaths. On that occasion, there was no pandemic — no more human cases emerged. But in 2004, the World Health Organization (WHO) warned that the next pandemic could result in the deaths of up to 7 million people worldwide.

Health officials feared that deadly Asian viruses such as H5N1 might make the leap to North America, so Ip and others began monitoring wild birds for signs of such viruses. For nearly a decade, every search came up clean.

Then, in 2014, those nine dead birds arrived at Ip's lab. The moment the H5N8 virus crossed the Bering Strait and entered North America represented the dawn of a new reality. "Not only was it an exchange of an avian influenza virus, it was an exchange of a deadly form — a highly pathogenic virus," says David Swayne, laboratory director of the Southeast Poultry Research Laboratory of the US Department of Agriculture (USDA) in Athens, Georgia.

Another concern is that avian influenza viruses of Asian origin often have higher morbidity and mortality rates in humans than other avian flu strains, says James Kile, an influenza specialist at the US Centers for Disease Control and Prevention (CDC) in Atlanta, Georgia.

The H5N8 strain has not yet caused disease in humans but other avian virus strains have. In 2013, a new strain of avian influenza emerged in China: H7N9. Unlike the virus that caused the US outbreak, H7N9 did not typically kill poultry, at least not initially. Indeed, it caused such mild illness that it was not detected until it began infecting people.

To combat the spread of the virus, the authorities in China began closing live poultry markets in provinces where human infections had occurred. But these measures to curb the spread of influenza may not always have had the intended effect[2]. Rather than shutting all the markets at once, the closures happened at different times in different provinces. In Jiangsu, for example, the policy took effect in December 2013, whereas the neighbouring province of Anhui took no action until February 2014. This meant that although the measure seemed to work initially, poultry farmers in infected areas were able to send their birds to markets in neighbouring provinces that had not yet been affected, thereby spreading the virus.

The CDC currently ranks H7N9 as the influenza virus with the highest potential pandemic risk. The virus has made more than 1,500 people ill and killed at least 615 since 2013. But the threat seems to have abated, at least for the moment. During the winter of 2016–17, H7N9 evolved into a highly pathogenic strain. The Chinese government responded by mandating that poultry producers immunize their birds with a vaccine targeting both the H5 and H7 strains. The strategy worked. By June 2018, the vaccine had been linked[3] to a 92% decrease in H7 detection rates in poultry and a 98% reduction in human cases.

A CAULDRON OF VIRUSES

Some researchers are more worried about pigs than poultry. Gregory Gray, an epidemiologist at Duke University in Durham, North Carolina, considers pigs to be ideal mixing vessels for influenza viruses because the animals are susceptible to not only swine flu, but also avian and human influenza. Even so, flu viruses in swine often go undetected and unreported. "Influenza A viruses are largely tolerated because they don't cause a big problem, at least not in the pigs," Gray says.

The World Organisation for Animal Health, the Paris-based intergovernmental body that sets standards for reporting animal disease, requires that certain strains of avian influenza be declared. But pork producers do not need to report swine flu to the authorities.

In April 2009, officials in the United States detected a new strain of influenza in humans known as H1N1. The virus became known as swine flu and seemed to be the product of a reassortment between three viruses circulating in pigs. The virus spread quickly around the world, and two months later the WHO declared that the outbreak had reached pandemic status. In the wake of this pandemic, the USDA launched a programme in concert with industry and the CDC to conduct voluntary surveillance for swine flu. The goal is to keep tabs on the viruses that are circulating in pigs.

> ***"The picture we have of the types of viruses that are circulating is very superficial."***

Despite this, "the picture we have of the types of viruses that are circulating is very superficial," says Gray. That is true not only for the United States but also China, which is the world's largest producer of pork.

"There's a massive transition in China from small and medium-sized farms towards large industrialized farms, but we still see rather poor biosecurity," Gray says. When he and his colleagues toured farms in China, they noticed that personal protective equipment is used only sporadically, barriers to stop rodents entering are rare, and pigs are sometimes housed near ducks, geese or chickens. "It's a cauldron of virus mixing," Gray says.

In 2015, Gray and his colleagues launched a five-year study to examine the transmission of swine influenza in large pig farms in China. Results from the first year of that study[4] suggest that swine flu is fairly common in pigs and that farm workers are also being infected. The team found similar H1N1 viruses in pigs, workers and on surfaces in the barns.

Gray and other researchers are hopeful that improvements in technology will allow them to keep better tabs on influenza in animals and curb the spread of the virus.

STOPPING THE SPREAD

China has been vaccinating poultry against avian influenza but the practice is not common in the United States. No birds at all were vaccinated during the 2014–15 outbreak. According to Joelle Hayden, a spokesperson for the USDA's Animal and Plant Health Inspection Service, vaccination would be used only as part of an eradication effort for highly pathogenic strains of avian influenza, not as a replacement for eradication.

But vaccination can be problematic. Any virus that is not wholly eradicated could still mutate enough to render the vaccine against it ineffective. Even when an effective vaccine is available, its use is not guaranteed. A 2018 study[5] found that some H7N9 viruses had become lethal in ducks, yet only about 30% of China's duck population had been vaccinated.

Jürgen Richt, a veterinary microbiologist at Kansas State University in Manhattan, says that producers need something they can easily apply *en masse*, rather than injecting each bird individually. Richt and his colleagues are developing a sprayable live vaccine that protects against both avian influenza and the virus that causes Newcastle disease — another serious infection that affects poultry. So far, they have tested versions aimed at eradicating the H5, H7 and H9 strains of influenza. Richt is also working on a universal vaccine for humans that might eventually be used for animals too.

Richt and his colleagues have also created a pig that is genetically resistant to swine flu. This might protect not only the pigs, but also humans. Even if the pig can still be infected, its resistance to influenza could mean that it spreads less readily. But whether the US Food and Drug Administration (FDA) will allow such pigs into the food supply chain is not yet clear. "This is the biggest question at the moment," Richt says. So far the FDA has approved only one genetically engineered animal for food use: a salmon that has been modified to grow faster.

Even if these strategies are widely adopted, Ip emphasizes that we must stay vigilant. Another influenza pandemic is inevitable and no one knows exactly what it will look like.

"We always hone a strategy towards the last outbreak that we experienced," Ip says. But strategies used during the last outbreak may not work next time. "Never be dogmatic," he says. "The flu virus changes all the time." ■

Cassandra Willyard *is a science journalist in Madison, Wisconsin.*

1. Ip, H. S. *et al. Emerg. Infect. Dis.* **21**, 886–890 (2015).
2. Li, Y. *et al. PLoS ONE* **13**, e0208884 (2018).
3. Wu, J. *et al. Emerg. Infect. Dis.* **25**, 116–118 (2019).
4. Anderson, B. D. *et al. Emerg. Microbes Infect.* **7**, 87 (2018).
5. Shi, J. *et al. Cell Host Microbe* **24**, 558–568 (2018).

nature

www.nature.com/collections/influenza-outlook