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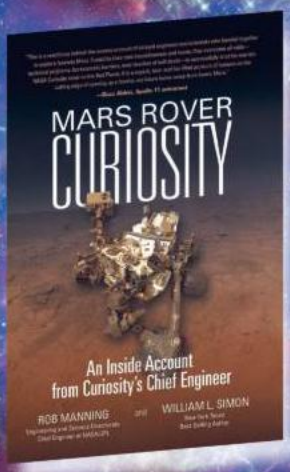

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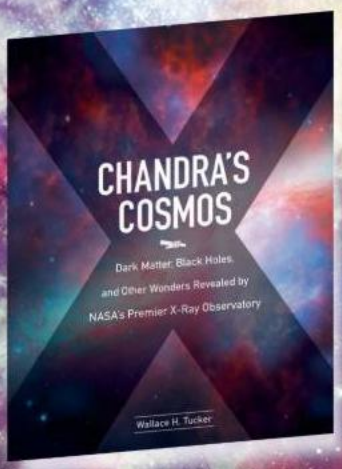

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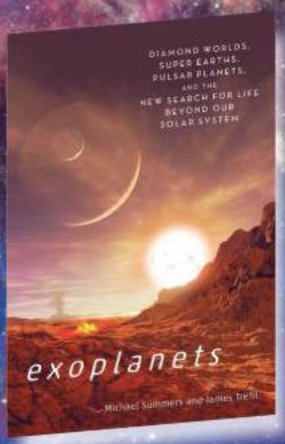

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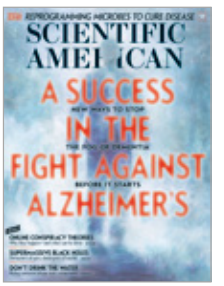

ON THE COVER

If no new treatments succeed in delaying Alzheimer's and other dementias by 2050, more than 130 million people may be afflicted. The prospect of a dementia tsunami has prompted a search for measures to prevent cognitive impairment. **Illustration by Jon Foster.**

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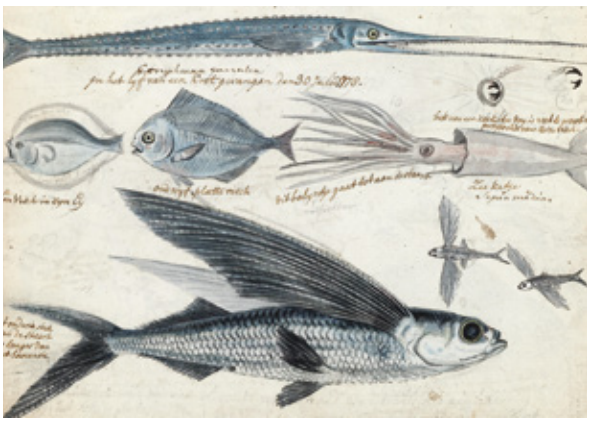

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ON THE WEB

2017 Mobile World Congress
Scientific American covers the latest in wireless gadgets, self-driving cars and the Internet of Things from the annual conference in Barcelona.
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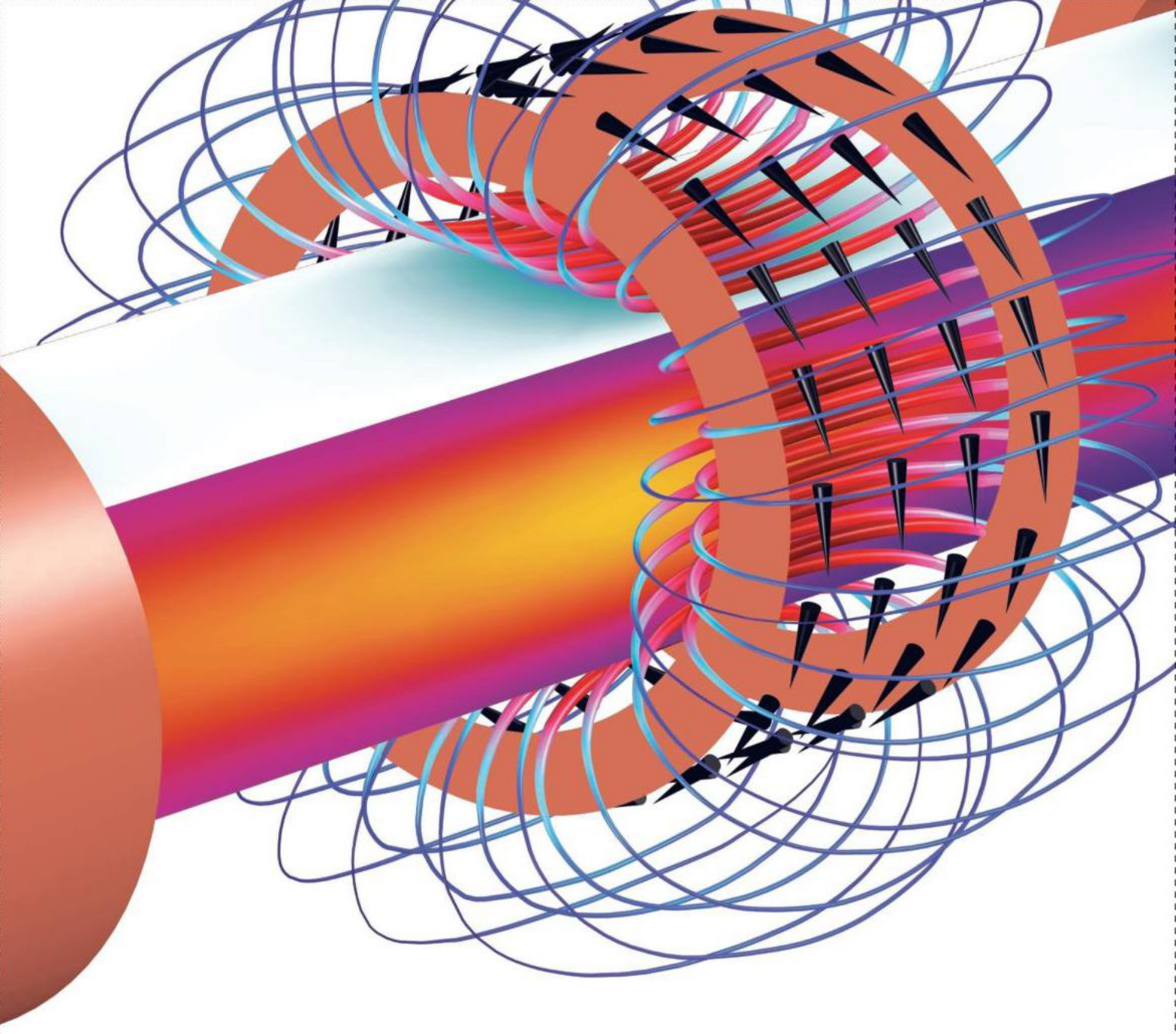

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Mariette DiChristina is editor in chief of *Scientific American*. Follow her on Twitter @mdichristina

Keeping the Future in Mind

We are often living longer—far longer—than our ancestors. But we are not always more healthy. Almost a third of all people in the U.S. who reach the age of 85, for instance, will unfortunately be diagnosed with Alzheimer's disease, often combined with other types of dementia. Some 50 million people suffer some form of mental debilitation, according to estimates—and that will worsen in the coming decades, with the global demographic shift continuing its current aging trend. Despite more than 100 current clinical trials, we have no cure.

But as you will learn from this issue's cover story, "A Rare Success against Alzheimer's," by researchers Miia Kivipelto and Krister Håkansson, the future may not be quite so grim. In fact, studies show that reducing the risk of Alzheimer's and other forms of dementia may include factors as simple as "good diet, exercise, an active social life and the achievement of higher educational levels." The story begins on page 32.

In addition to a sound mind in our autumn years, we'll want a sound body, of course. Starting on page 46, we present our annual special report on the Future of Medicine. This year the theme is "Transformers," by journalist Michael Waldholz: microbes whose genetic circuitry has been reshaped by biologists to turn them into medical treatments capable of switching on and off under certain conditions. The modified bacteria can treat genetic diseases, attack tumors and detect antibiotics. It is also just one of the many ways that science can help humanity in solving its most challenging problems. SA

A Farewell

Scientists are both the subjects and authors of *Scientific American*'s articles, the heart of this 171-year-old magazine. We are sad to report that an author of a feature in this issue, the distinguished NASA scientist Neil Gehrels, passed away after a battle with pancreatic cancer, just as the story was about to go to press. Gehrels, with S. Bradley Cenko, wrote "How to Swallow a Sun," about supermassive black holes, starting on page 38.

During his career, Gehrels was perhaps best known for his transformative studies of gamma-ray bursts, the most powerful and luminous explosions in the cosmos, and the subject of a 2002 article he co-wrote for us; he and colleagues penned a feature, in 1993, about discoveries from the Compton Gamma Ray Observatory. We are truly grateful to him for generously sharing his insights over the years. —*M.D.*

Illustration by Nick Higgins

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December 2016

"While much has changed with respect to gender equity in the sciences, there is still much more that can be done."
JOHN MORGAN *READING, PA.*

TRACKING MYTHS

In Julien d'Huy's "The Evolution of Myths," the sidebar delineating a family tree of Cosmic Hunt myths brackets ancient Greek and Roman writings with the oral traditions of North American tribes such as the Ojibwa. This striking similarity then serves to support d'Huy's claim for a link between such myths coming from settlers crossing from Siberia into the Americas 15,000 years ago.

But a more direct source for the observed similarity would be the influx of European priests and missionaries throughout the Americas in the centuries after 1492. They would have received an education that included the Greek and Latin classics, and one way for them to engage with local peoples would be through the sharing of stories and myths about the natural world.

JOHN R. HALE
Director, Liberal Studies
University of Louisville

How can you resist studying the greatest myths of all? Adam and Eve? The Garden of Eden? Noah and the Flood?

EDWARD CHIASSON
via e-mail

D'Huy assumes that parallels between myths are always the result of transmission rather than of independent invention. This leads him to the odd assertion that a Blackfoot Indian story is derived from the Greek myth of Polyphemus. As much as I would love to see empirical confirmation that myths and folktales are some sort of memory of the deep past, I don't think he has come up with more than a bit of attractive romantic speculation wrapped up in some statistical and algorithmic hand waving.

JOHN RICHARDSON
Edmonton, Alberta

D'Huy has done an impressive job of explaining his theories about Paleolithic (and earlier) origins of myth families. His identification of the therianthropic figure surrounded by bison in the Cave of Trois-Frères as an illustration of the Polyphemus myth certainly seems a possibility. I have also seen speculations that this figure is playing a musical bow, which would make him more of a Pied Piper of Hamelin. I wonder if d'Huy has any comment on a possible familial relationship between the Pied Piper myth and the Polyphemus myth?

PETER FARIS
Aurora, Colo.

D'HUY REPLIES: It is natural to connect the closeness among some Amerindian and European myths to the arrival of European priests and traders, as Hale suggests, but the evidence is against that idea. Statistical studies often place Siberian and Northwestern Amerindian variants of the same myth in an intermediate position between West Eurasian and other Amerindian versions, and, as shown by anthropologist Yuri Berezkin, some Northeastern versions of the Cosmic Hunt myth most likely predate the first European influx.

Regarding Chiasson's question: Studies of the variants of the Flood and Tower of Babel stories are in progress, and papers should be published soon.

To Richardson: As Berezkin has demonstrated, many Eurasian (particularly, Siberian and Central Asian) and Amerindian variants of the Cosmic Hunt show parallels at the level of minor details, a pattern that could be explained only by particular and very ancient prehistorical and historical links between the two continental traditions. For the Polyphemus motif, studies by others of its distribution around the world, the structure of the tale and other kinds of statistics show both the great antiquity of the Greek version and the prehistoric connection between the Eurasian versions and the North Amerindian one. Phylogenetic study and evidence from unrelated sources also converge to strong conclusions—very far from "romantic speculation."

In answer to Faris: Prehistorian Henri Begouën (whose sons discovered the cave) and archaeologist Henri Breuil proposed a connection between a musical bow and this therianthropic figure back in 1958! But to my knowledge, the Pied Piper of Hamelin tale type was found only in Eurasia; it also is probably very recent. Expanding the database to all the tales where a trickster took away a herd of animals might be a way to test the Paleolithic origin hypothesis.

WOMEN IN SCIENCE

In "Science Has a Gender Problem" [Forum], Hannah A. Valantine makes some great points about the forms of discrimination that women researchers face. While much has changed with respect to gender equity in the sciences, there is still much more that can be done regarding areas such as student recruitment and retention, hiring, grant distribution and compensation.

Regarding new people entering the field, I have seen a tremendous change in my years as a wildlife biologist. When I was an undergraduate student at Pennsylvania State University in the 1980s, there was only one woman among the students taking classes in the wildlife sciences program. It was an "old-boys network." The situation was better in my graduate school programs, but even when I was a doctoral candidate in the 1990s, there were many more men than women.

Today as a senior biologist for a state wildlife agency, I frequently give presentations to student groups. At several of the universities I have been to, more than half of the students are female. By far the female students show more interest, ask

more questions and are more likely to request volunteer opportunities. This bodes well for my profession, and I hope these students will follow through with their education and make a productive contribution to the research and management of wildlife species in the U.S. and abroad.

JOHN MORGAN
Reading, Pa.

FIGHTING HIV

Great scientific news about the possible way to create an HIV vaccine, as described in "HIV's Achilles' Heel," by Rogier W. Sanders, Ian A. Wilson and John P. Moore. Of course, the new research is exciting, and we need to continue it, but let's not forget the tools we have to save lives now! There are 18.2 million people receiving antiretrovirals in our world. This is only about half of the 36.7 million who are living with HIV, according to the World Health Organization. So we still have work to do to get our known medicine that leads to an almost normal life to the people who need it.

Thanks to the Global Fund to Fight AIDS, Tuberculosis and Malaria and the President's Emergency Plan for AIDS Relief (PEPFAR), this is happening. The question, as always, is funding. The U.S. recently made a pledge to the Global Fund to keep it on pace to create an AIDS-free generation by 2030. Will Congress come through with the money to back this pledge and continue PEPFAR? We should ask our representatives to fund these programs.

WILLIE DICKERSON
Snohomish, Wash.

CURRENT CONCERNS

Even before reading the body of David Pogue's article on Apple's elimination of the headphone jack, "Resistance Is Futile" [TechnoFiles], I and thousands of other engineers and assorted science geeks in your readership cried out, "No, resistance is voltage divided by current!"

That old joke aside, I'm reminded that, as with social resistance, electrical resistance can be useful but is often an impediment. In fits and starts, humans have found ways to overcome or harness both forms of resistance, which is perhaps what keeps us moving forward.

BILL WEHNER
via e-mail

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A Better Reckoning

It is time to improve our death certificates

By the Editors

Death is certain. Too often an accurate accounting of the events leading to it is not. When a person dies, a doctor, medical examiner or coroner must fill out a certificate listing the cause of death and the underlying factors that helped to bring it about. Too often, however, these forms are riddled with problems. When a drunk driver dies in a car accident, for example, the fact that alcohol was involved is frequently not noted. Neither are other factors that carry stigmas, such as suicide and medical errors. Tens of thousands of antibiotic-resistant bacterial infections similarly fly under the radar.

These problems give us a distorted picture of our nation's health. Failure to understand why we are dying may mean that our money and medical resources are not always going to the right places. And we already know why the mistakes happen, as well as ways to fix them.

The forms themselves are a major cause. States, counties and some cities have their own record-keeping systems, and even now one state—West Virginia—has not yet switched over to a standardized certificate created in 2003. Another reason is that the forms are filled out incompletely or inaccurately. A death certificate may record that a person died from, say, "lung cancer" when actually the tumor had metastasized from the ovaries, thus inflating the statistic for one type of cancer at the expense of another.

The person who fills out a death certificate can make matters worse. He or she may not be a doctor or other medical professional. For example, one review indicates that in 241 of Texas's 254 counties, covering 60 percent of the state's population, a death outside the hospital is usually handled by the elected justice of the peace—the same person who oversees traffic violations. Most justices are law-enforcement officers or educators with little mandated training about death certificates. They are supposed to consult with medical professionals, but at times they do not. Nationally, the latest published numbers suggest that 28 states have coroners instead of trained medical examiners in one or more counties.

The problems extend beyond lack of training and inconsistency in death certificates. Even on the standardized forms, there is no formal "check box" to record crucial factors such as suicide or antibiotic-resistant infection. Reuters recently worked with the Centers for Disease Control and Prevention to scan the text of death certificates for clues about deaths linked to resistant bacteria. Their findings were startling: between 2003 and 2014, there were 180,000 such deaths.

Alcohol-related deaths apparently go undocumented, too. One analysis of death certificates from 1999 to 2009 found that, officially, only about 3 percent of traffic deaths were linked to alcohol—yet national traffic safety records indicate the number was seven times greater. A recent study published in *BMJ* suggested that weak coding on death certificates allows medical errors to remain hidden when they should be recognized as the third leading cause of death in the U.S. (The CDC disputes that number and maintains that most underreporting of errors stems from litigation concerns or reluctance to admit wrongdoing.)

Better training is a proved way to attack some of these issues. About a dozen years ago New York City claimed that people died from coronary heart disease at 1.7 times the national rate. But when the city required physicians to undergo training on filling out the forms, those numbers dropped. Doctors reported more accurate details in other areas, too, including deaths caused by serious infections. Other cities and states should follow suit. Such training should start in medical schools and be offered throughout physicians' careers. Already there are efforts under way to create continuing education credits for this type of training. These efforts should be more widespread. States and counties should also better enforce regulations requiring nonmedical professionals to consult with people who are doctors when it comes to these forms.

Another fix: electronic death certificates. Adopting them would speed up the transfer of information into a national database and would also permit the creation of automatic pop-up boxes that would demand more complete information. For example, such boxes would not let "lung cancer" be entered as the cause of death unless the user listed the original site of the cancer. This practice need not compromise patient privacy: this year the CDC expects to launch a pilot project that will remove personal identifiers on death certificates so that they can be more readily studied by researchers without raising ethical concerns.

Once we have better information on the causes of death, we can make better decisions about when and how to spend our research and health care dollars. Understanding what kills us will help keep us healthier. SA

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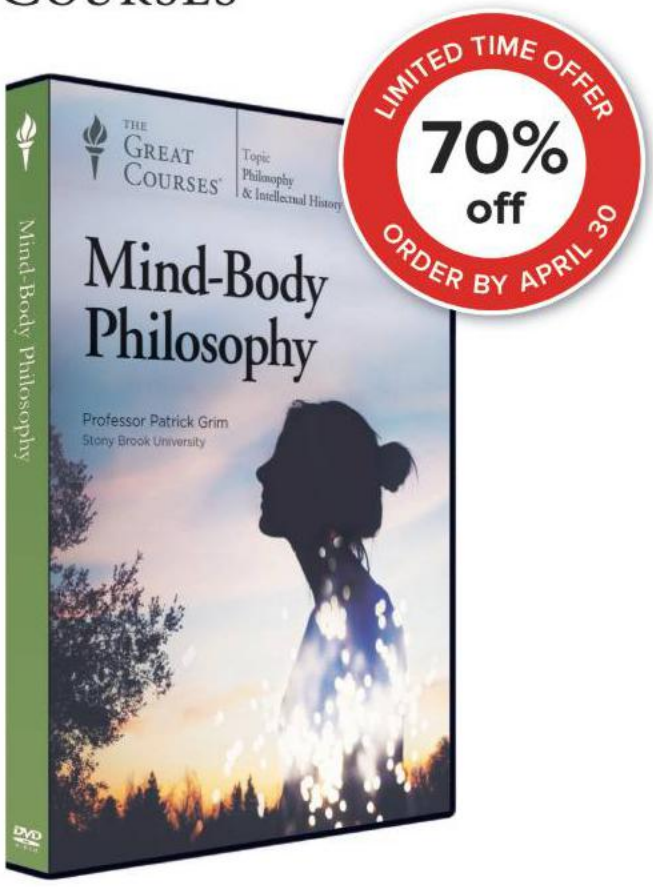

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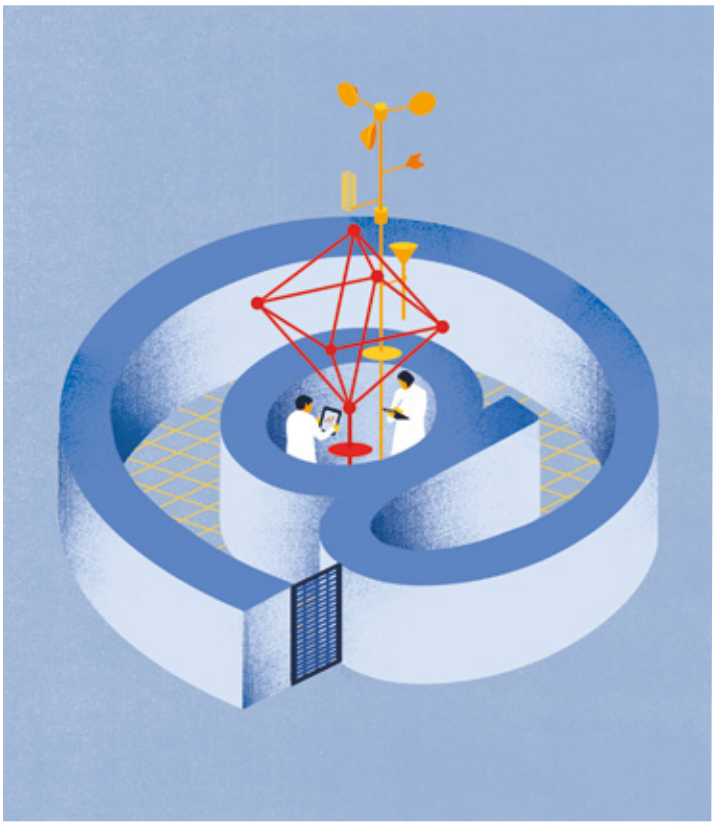

Stay Out of Scientists' E-mails

They are useless in evaluating whether research results are correct

By Kevin Cowtan and Zeke Hausfather

Last December the Trump transition team asked the Department of Energy for a list of employees who had worked on or attended meetings about how to calculate the hidden costs of carbon pollution. The DOE refused, but coming from a new administration whose leader has tweeted that global warming is a Chinese hoax, this sounded like the beginning of a political witch hunt.

If so, it wouldn't be the first. In 2009, during the so-called Climategate affair, climate "skeptics" released e-mails purporting to show that scientists were manipulating data and suppressing critics (several investigations proved that these charges were groundless). In 2010 Virginia's Republican attorney general tried to get hold of records related to the work of Michael Mann of Pennsylvania State University on the groundless assumption that he, too, had manipulated data.

And in 2015 Representative Lamar Smith of Texas claimed that scientists at the National Oceanic and Atmospheric Administration had manipulated global temperature data and instigated an investigation of them. The scientists, led by Tom Karl, had published a paper that asserted that global warming since 1998 had been underestimated. The idea of a "hiatus" in warming was therefore wrong.

Smith demanded access to the scientists' e-mail discussions and notes, hoping to find evidence of fraud. They provided the data and methods to verify their conclusions but refused to provide e-mails. Experts often argue against their own positions—this is a key part of skepticism—so e-mails offer lots of material that can be taken out of context to give a misleading impression.

The real test of a claim is to compare it with observations—to replicate it by experiment. We often have to explore many blind alleys to get to the right answer, and it frequently takes someone else to spot the errors in a study. As a result, the community generally does not fully accept a result until it has been independently verified by another group.

In a paper published in January in *Science Advances,* we set out to replicate the work of Karl and his colleagues. We evaluated their results by producing three different ocean temperature records of recent years, using data from buoys, satellites and Argo floats. Our results suggest that the new NOAA record most likely is the most accurate of the various sea-surface temperature reconstructions covering the past two decades and should help resolve some of the criticism that accompanied the original NOAA study.

These checks took a few weeks, and we did them in our spare time (although writing them up for publication took much longer). Compare this with the months of effort by Smith and his lawyers, whose hourly rates are many times those of paid scientists and funded by the taxpayer—a far less efficient process even if it had produced scientifically meaningful results, which it could not. Smith's actions send a disturbing message that experts should produce results that are convenient to political narratives rather than those that accurately reflect reality.

The balance of evidence supports the new NOAA temperature record. Does this mean that there never was a hiatus? That is a different question and one that is still being hotly debated in the scientific community. But the way to find out how fast the earth has been warming over the past two decades is through experimental replication—not a political investigation. And the best evidence we have says that NOAA got it right. SA

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Illustration by Maria Hergueta

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ADVANCES

INSIDE

COURTESY OF VIRGO COLLABORATION

The Virgo gravitational-wave detector near Pisa, Italy, is set to return online this spring, which could result in three such detectors worldwide operating together for at least a month.

ASTROPHYSICS

Sky Is the Limit

A third detector of gravitational waves could soon help pinpoint where they originate

Gravitational waves were detected for the first time a year and a half ago, when some of them throbbed through Earth. Two incredibly sensitive detectors—one in Washington State and one in Louisiana—picked up the distortions in spacetime, emanating in this case from two merging black holes. When scientists in charge of the detectors, called the Laser Interferometer Gravitational-Wave Observatory (LIGO), announced the finding five months later, it created an international sensation and became the most important physics news of 2016. Physicists had been hunting for decades for direct evidence of gravitational waves, first predicted to exist by Albert Einstein in 1916.

As impressive as the breakthrough was, it left some key questions unaddressed. Primary among them: Where was the source of the waves? If all goes as planned, scientists could soon be able to tackle this issue for future detections.

This spring physicists are gearing up to turn back on a third gravitational-wave detector, called Virgo, near the Italian city of Pisa. Virgo was offline and undergoing upgrades when LIGO received its two signals in September 2015. With a trio of these giant instruments running, scientists hope to significantly improve efforts to determine the sources of gravitational waves. A speedy response to a "triple hit"—the same waves

deforming all three detectors—could enable ground-based telescopes to focus on a triangulated area of sky constrained by the detectors and possibly spot the collisions from which the waves emanate.

A gravitational-wave detector, shaped like a giant letter L with kilometers-long "arms," picks up distortions in spacetime when the waves change the length of a detector arm by less than the diameter of a proton. But one of these ultrasensitive detectors operating solo cannot rule out vibrations caused by sources on Earth. And each detector monitors a vast chunk of the universe: the field of view covers about 40 percent of the sky surrounding Earth, which is roughly what one would see standing in a desert and twirling in a circle. Try singling out even one faint star in all of that.

LIGO's twin approach has been key for another reason. Gravitational waves travel at the speed of light, but unless they happen to hit both detectors head-on, there are milliseconds of difference between when each detector registers a disturbance. Measuring this delay allows scientists to calculate the direction of impact, trace it back to the sky and narrow the waves' origin to a smaller area—for 2015's detections, this was about 2 percent of the sky. That is still a huge slice of the universe to scan for a source event.

Virgo's two orthogonal arms (*one shown here*) each span three kilometers and house optics in a vacuum. The system is sensitive to gravitational-wave-induced distortions.

CLAUDIO GIOVANNINI *Getty Images*

Enter Advanced Virgo. Before its upgrade, Virgo lacked the sensitivity to spot even the highest-energy gravitational wave. New mirrors, vacuum pumps and lasers—used to detect and measure any length variations in the instrument's arms—

One could imagine observations of the aftermath of a supernova or of high-energy radiation bursts from near the event horizons of merging black holes.

have been installed to increase the machine's sensitivity. The electronics have been overhauled. Installation of the new hardware is complete, and adjustments are being made to remove unrelated local vibrations that might mask incoming gravitational waves. The team is working around the clock to get Virgo operational before summer, when LIGO's detectors are set to switch off for their own upgrades.

When Advanced Virgo starts running, the possible location of the waves' source in the sky should shrink by another factor of five, says Fulvio Ricci, Virgo's spokesperson and a physicist at Sapienza University of Rome. Edo Berger, an astrophysicist at Harvard University who is using telescopes to study the events LIGO and Virgo detect, has a modulated take on that gain. "By adding a third detector to the network, the positions should improve significantly, reducing the [source] problem from something horrific to just something terrible," he says.

Still, there is no denying the astrophysics opportunities on the horizon. Black hole collisions are not the only events with enough power to wrench spacetime out of shape. And unlike black holes, some of these phenomena should emit light and other electromagnetic radiation that telescopes can see. One could imagine observations of the aftermath of a supernova or of high-energy radiation bursts emitted from near the event horizons of merging black holes—or perhaps some optical evidence of two colliding neutron stars or a neutron star caught in the gravitational maw of a black hole. Gravitational-wave detectors have yet to capture the ripples from these types of events, but when they do, Berger and other astrophysicists are ready and waiting to point their telescopes at an area narrowed down by three detectors instead of two. The tighter sky location could also enable smaller telescopes to enter the fray and register the myriad radiation emissions these events should produce.

The current plan is to run all three detectors together for at least a month. Chances are good that this interval will be long enough at least to detect waves from a black hole merger, if not other, less frequent events. The collaboration could inspire LIGO and Virgo operators to consider extending their runs, says LIGO team member B. S. Sathyaprakash, a physicist at Pennsylvania State University. "The plan might change if people get excited," he says. That bodes well for the future of a new era of astrophysics.

—Katherine Wright

ADVANCES

EARTH SCIENCE

Telltale Sounds of Tsunamis

Tsunami-generating earthquakes may produce unique sound waves that could improve warning times

The aftermath on January 2, 2005, of the Indian Ocean tsunami in Sumatra, Indonesia.

PATRICK M. BONAFEDE Getty Images

Buoys operate as today's state-of-the-art tsunami-detection system. Seismic data can tell officials that an underwater earthquake has occurred, but strategically placed floating sensors often give the key warning if the earthquake has created a potentially devastating series of waves. Even so, warnings are often issued only minutes before a tsunami hits—if at all. Aiming to buy more time for evacuations, scientists have begun decoding a new aspect of the sounds that underwater earthquakes produce. Sound waves can travel at upward of 1,500 meters per second through water—more than 10 times faster than a tsunami.

Usama Kadri, an applied mathematician and engineer at Cardiff University in Wales and the Massachusetts Institute of Technology, is one these researchers. He is especially interested in the "acoustic gravity waves" that tsunami-generating earthquakes produce. These underwater sound waves have such low frequencies that gravitational forces can alter their wavelength and speed under a sudden change in pressure. In theory, these sound waves' distinctive properties could allow scientists to tease them out from oceanic background noise. "Without acoustic gravity-wave theory, you can say for sure there's an earthquake, but you can't say there's a tsunami," Kadri says.

NEUROSCIENCE

Which One Is Mom Again?

Ducklings' imprinting works in only one eye at a time

In the summer of 2015 University of Oxford zoologists Antone Martinho III and Alex Kacelnik began quite the cute experiment—one involving ducklings and blindfolds. They wanted to see how the baby birds imprinted on their mothers depending on which eye was available. Why? Because birds lack a part of the brain humans take for granted.

Suspended between the left and right hemispheres of our brains sits the corpus callosum, a thick bundle of nerves. It acts as an information bridge, allowing the left and right sides to rapidly communicate and act as a coherent whole. Although the hemispheres of a bird's brain are not entirely separated, the animals do not enjoy the benefits of this pathway. This quirk of avian neuroanatomy sets up a natural experiment. "I was in St. James's Park in London, and I saw some ducklings with their parents in the lake," Martinho says. "It occurred to me that we could look at the instantaneous transfer of information through imprinting."

The researchers covered one eye of each of 64 ducklings and then presented a fake red or blue adult duck. This colored duck became "Mom," and the ducklings followed it around. But when some of the ducklings' blindfolds were swapped so they could see out of only the other eye, they did not seem to recognize their "parent" anymore. Instead the ducklings in this situation showed equal affinity for both the red and blue ducks. It took three hours before any preferences began to emerge. Mean-

DON FARRALL Getty Images

As outlined in the *Journal of Geophysical Research,* Kadri ran a simulation with data from the December 2004 Indian Ocean tsunami, which killed hundreds of thousands of people. It took two hours for those waves to hit Sri Lanka, for example, but the island nation received no tsunami warning. According to the study's calculations, if an acoustic gravity-wave-detection station with hydrophones had been 1,000 kilometers from the earthquake epicenter, that warning time could have been more than 90 minutes.

Kadri's work is important but still theoretical—and contains simplified assumptions, says Ali Abdolali, a postdoctoral researcher at the University of Delaware's Center for Applied Coastal Research. Abdolali is also trying to decipher the underwater sound waves that emanate from a tsunami-causing quake. In fact, researchers have known for more than 60 years that underwater earthquakes give off specific sounds, but the availability of sensitive hydrophones and faster computing has sparked renewed interest in this field, says Tiago Oliveira, a postdoctoral fellow at the Woods Hole Oceanographic Institution who has worked with Kadri. Still, Oliveira cautions that it could be 10 years or more until tsunami-warning systems can rely on sound. —*Ryan F. Mandelbaum*

while ducklings with eyes that were each imprinted to a different duck did not show any parental preferences when allowed to use both eyes at once. The study was recently published in the journal *Animal Behaviour.*

The results reveal the fundamental lack of quick communication between the left and right sides of a bird's brain—and make it apparent that information received by one eye gets transmitted to only one hemisphere. It may not seem like a good strategy to have separate records of memory in different sides of the brain, but Giorgio Vallortigara, a neuroscientist at the University of Trento in Italy who was not involved in the study, suggests that there may be an advantage to living without a corpus callosum: each hemisphere may become specialized for certain kinds of memories.

Birds normally use both eyes, allowing the two halves of their brain to work in harmony. "What this means is they are engaging in tremendous behavioral adaptations to integrate two discontinuous streams of information to make decisions," Martinho says. "What it's like to be a bird is very different from how we might initially think of it." —*Jason G. Goldman*

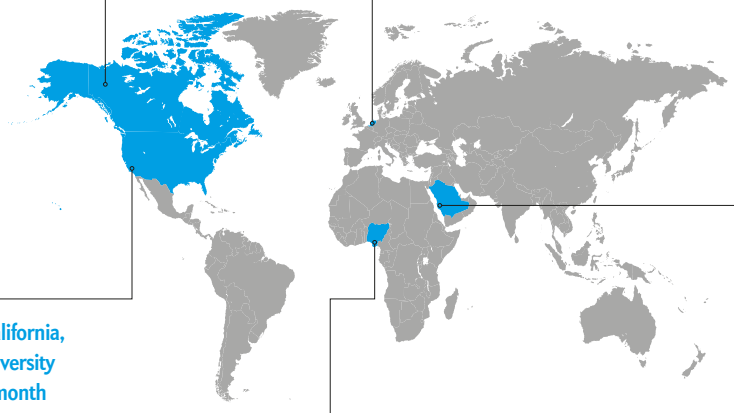
IN THE NEWS

Quick Hits

CANADA
Carbon dating of animal bone fragments in caves in the Yukon has revealed human occupation of North America 24,000 years ago—about 10,000 years earlier than previous studies suggested.

NETHERLANDS
Designers are testing loads on a new biocomposite bridge. Made of hemp and flax fibers held together by resin, the bridge spans a stream on the Eindhoven University of Technology campus.

WESTERN PACIFIC OCEAN
A series of seismometers was recently set along the steep slopes of the Mariana Trench to study whether it could trigger large earthquakes.



SAUDI ARABIA
Inventors at the King Abdullah University of Science and Technology have created a low-cost digital personal fitness tracker similar to a Fitbit, with sensors made of household items such as aluminum foil and sponges.

U.S.
Researchers at the University of California, Riverside, and San Diego State University will gather high-speed video this month or next to study kangaroo rats' acrobatic escapes from rattlesnakes.

NIGERIA
Malnutrition has nearly wiped out the population of children younger than five, reports say. Starvation has weakened the immune systems of infants and toddlers in particular, making them more susceptible to virulent cases of measles, pneumonia and malaria.

—Andrea Marks

For more details, visit
www.ScientificAmerican.com/apr2017/advances

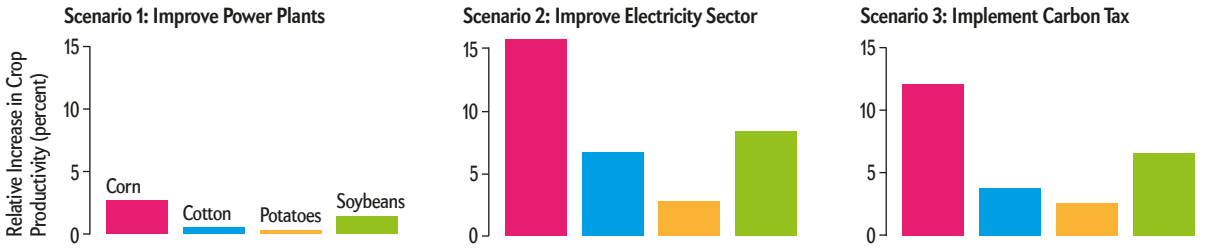
ENVIRONMENT

A Crimp on Crops

Pollution from coal plants chokes agricultural productivity

Nearly 20 U.S. states have started implementing former president Barack Obama's Clean Power Plan, which places limits on carbon dioxide emissions from power plants in an effort to reduce the impacts of climate change. The plan has been in legal limbo for the past year. Yet scientists have now calculated another outcome of the policy: harm to crop yields if the plan is scrubbed. Along with carbon pollution, coal-fired power plants spew pollutants that form ground-level ozone, or what we know as smog. The contribution of smog to increased rates of asthma and premature deaths was already known. The new research estimates the extent to which smog, under air-pollution policies in place before the Clean Power Plan, would limit production in 2020 of four major crops: corn, cotton, potatoes and soybeans.

Led by environmental engineer Shannon L. Capps, now at Drexel University, the team also sketched the extent to which those crop production losses would shrink under three nationwide counterscenarios. One improved the efficiency of individual power plants. Another modeled a policy similar to the Obama plan, setting state CO_2 emissions goals for the electricity sector. A third established a tax on carbon emissions, under which emissions fell the most. But the greatest drop in smog-forming pollutants—and greatest gains in crop yields—came from policies such as the Clean Power Plan. *—Ashley Braun*



Researchers calculated how well each scenario would mitigate the potential productivity loss (PPL) of each crop. PPL is a projected value for 2020 and indicates how much crop growth would suffer because of smog. Scenario 2 most closely aligns with results expected from the Clean Power Plan.

SOURCE: "ESTIMATING POTENTIAL PRODUCTIVITY COBENEFITS FOR CROPS AND TREES FROM REDUCED OZONE WITH U.S. COAL POWER PLANT CARBON STANDARDS," BY SHANNON L. CAPPS ET AL., IN *JOURNAL OF GEOPHYSICAL RESEARCH: ATMOSPHERES*, VOL. 121, NO. 24; DECEMBER 27, 2016

Graphic by Amanda Montañez

ECOLOGY

A Lift for Lichens

Rare species threatened by rising seas could be moved to higher ground

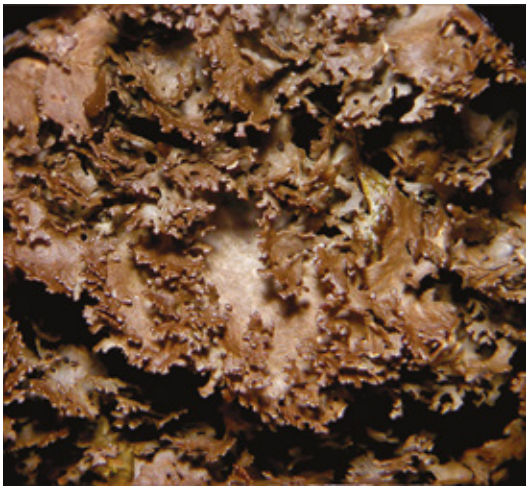
As a result of climate change, saltwater is predicted to soon swallow much of a North Carolina swamp forest and its biodiversity. But certain denizens of Alligator River National Wildlife Refuge might get a ticket out in time. Some of the lichens that embellish local tree bark there could be carefully plucked and transported to a new habitat under a plan now being developed by a team of lichenologists.

The stakes are high for some of these unusual organisms. Almost all the known living individuals of dey's moon lichen, *Sticta deyana* (*right*), are found within several square miles of the refuge, and other rare and endemic lichen species there are in jeopardy as well. Saltwater inundation eventually kills coastal forests in low-lying areas such as the swamp forests of the Alligator River region, so relocation may be the only way to save many of the resident lichens.

Without help, about half the area's lichen population will likely be lost within five decades; the rest could disappear in the five decades after that under a worst-case climate scenario. In an effort to intervene, James Lendemer, an assistant curator and lichenologist at the New York Botanical Garden, and a colleague are mapping out an ambitious plan for physically relocating entire communities of the area's lichens.

Lichens comprise a symbiotic partnership involving fungi, algae and sometimes cyanobacteria. They provide shelter for spiders, nematodes and moths, as well as food for voles, caribou and other ungulates. They also help to regulate microclimates and keep humidity levels steady by absorbing the water from fog, dew and rain, then later releasing it within a forest canopy.

From 2012 to 2016 Lendemer and Jessica Allen, a researcher at the botanical garden, documented a rich biodiversity of lichens, including dey's moon, stretching from southern New Jersey through South Carolina. The team has already mapped possible assisted migrations of lichens in the Mid-Atlantic Coastal Plain and has conducted some successful tests of transplant methodologies for a number of lichen species within the southern Appalachians. Allen used forceps to carefully remove lichens from their habitats and place them onto surfaces such as burlap, gauze and plastic mesh for transport. Now the team is studying ways to transplant lichen communities from imperiled habitats, among them the swamp forests of the Mid-Atlantic Coastal Plain, to nearby preserves or to other parts of a species' previous range. The team's results were most recently detailed in the October 2016 issue of *Biological Conservation*.



JASON HOLLINGER

Lichenologists have transplanted individual specimens in the past—but efforts to relocate entire lichen communities represent a new conservation approach for these organisms, says Christopher Ellis, a lichenologist at the Royal Botanic Garden Edinburgh. Lichens benefit collectively from each individual's work to establish ideal conditions, such as a certain humidity level. Thus, moving multiple species that belong to a community is key to their long-term survival. Progress with collective transplants in North America might inspire similar efforts along parts of Scotland's coast. Conservation biologists could move coastal lichens from shorelines to restored habitats, Ellis notes, as Scotland embarks on an ambitious "managed retreat" initiative to counter the squeeze of rising seas. —*Roger Drouin*

MATERIALS SCIENCE

Screen Grab

A nanofiber coating on window screens purifies incoming air

New window screens with pollutant-trapping nanofibers may allow residents of smog-choked cities to breathe easier. The fibers are made of nitrogen-containing polymers and are sprayed onto screens in a technique called blow-spinning, in which a stream of air stretches out droplets of polymer solution in midspray to form an extremely thin layer of nanofibers.

Scientists at Stanford University and at Tsinghua University in Beijing recently reported in *Nano Letters* that they have developed a variety of blow-spun polymers (materials commonly used in rubber gloves and tents) capable of filtering more than 90 percent of the hazardous, lung-penetrating particulate matter that typically passes through standard window screens. The pollutant-absorbing nanofibers were sprayed onto rolling flexible nylon mesh at a rate of almost one meter per minute. Researchers also deposited the fibers onto metal-coated mesh and wiped off the film with tissues after heavy absorption.

In a 12-hour field test on a window in Beijing under severely hazy air conditions, a window screen coated with the so-called polyacrylonitrile nanofibers filtered out 90 percent of harmful particulate matter, which can cause lung cancer and heart disease. Now that's a breath of fresh air.

—*Tien Nguyen*

Illustration by Thomas Fuchs

HEALTH

Is the U.S. Ready for Future Disease Threats?

The CDC lacks the authority to direct funding in response to emergencies and outbreaks

During Tom Frieden's seven and a half years as director of the U.S. Centers for Disease Control and Prevention, his agency was buffeted by crises that included government furloughs, H1N1 flu, laboratory safety issues, an earthquake in Haiti, and outbreaks of Ebola and Zika virus. To better manage emerging diseases—and to detect them before they spread globally—the agency is now working with dozens of countries to boost diagnostic and testing capabilities. Frieden spoke with SCIENTIFIC AMERICAN during his last week on the job about some of the nation's future health challenges, as well as his most memorable moments as director. An edited excerpt of that conversation follows. *—Dina Fine Maron*

SCIENTIFIC AMERICAN: What immediate health issues are facing the Trump administration?

Tom Frieden: Zika is not over. It is likely to spread in Latin America and the Caribbean for months and years to come, and we still don't fully understand the range of birth defects it causes. Antibiotic resistance in the U.S. is something that threatens to undermine modern medicine. The opioid epidemic is something that has quadrupled [overdose deaths] in the U.S. And we are always concerned about an influenza epidemic. We have also identified new pathogens and pathogens in new places—so we know that tick-borne pathogens are more widespread around the world than previously thought, including Crimean-Congo hemorrhagic fever.

How prepared is the CDC to deal with these problems?

It's a big problem that when there is an emerging threat, we are not able to surge or work as rapidly as we should, as a result of a lack of additional funding and legislative authority. When there is an earthquake, the Federal Emergency Management Agency doesn't have to go to Congress and say, 'Will you give us money for this?' But the CDC does. We have made a really good start working with 70 countries to strengthen lab systems, rapid-response and field-monitoring systems, but it is going to take a while before countries around the world are adequately prepared. A blind spot anywhere puts any of us at risk.

1

2

Fumigation for mosquitoes was undertaken in Lhokseumawe, Indonesia, in September 2016 to help prevent the spread of Zika virus (*1*). A technician packages a urine sample for Zika testing (*2*).

What was an experience that really stuck with you during your tenure at the CDC?

Certainly during the shutdown of the federal government, when we had to furlough [about] 8,500 staff and couldn't protect Americans as effectively because of that—that was a terrible time. During the Haiti earthquake, when Diane Caves, a 31-year-old public health employee at the CDC, died—when the hotel she was staying in in Haiti collapsed—I certainly will never forget sitting down with her husband and father to tell them that she had passed away and been killed there. But there have also been very encouraging moments: the moment we knew we had broken the back of the epidemic of Ebola in West Africa, the moment when we were able to see rigorously that our antismoking campaign had saved more than 10,000 lives, the moment when we were able to definitively say that Zika causes microcephaly and other birth defects, and the moment when the data came back on teen pregnancy showing that the programs we and others had run had driven it down. Teen pregnancy is really a perpetuation of poverty, and by reducing teen pregnancy we have been able to reduce poverty.

What do you consider unfinished business or a regret?

I hoped that we would be over the finish line on polio [eradication] by now. In Nigeria, we thought we were over the finish line—but [Islamic extremist group] Boko Haram is partly in control where polio is circulating, and that was an issue. So we have further to go.

BILL O'LEARY *Getty Images (Frieden);* FACHRUL REZA *Getty Images (1);* JOE RAEDLE *Getty Images (2)*

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Aircraft landing at London's Gatwick Airport.

TECHNOLOGY

NASA Fights Flight Delays

A new air traffic control system could ensure passengers spend less time flying the crowded skies

In early 2017 two large passenger planes and a smaller corporate jet practiced landing, one right after the other, without the usual constant help of an air traffic controller. Instead they relied on NASA-developed technology that lets planes automatically "talk" to one another and to control towers, simultaneously. If these flight tests—which took place at an airport near Seattle—prove convincing, the technology could eventually make its way to the Federal Aviation Administration for approval. And if all planes one day adopt the system, more aircraft could land in less time at the country's increasingly congested airports.

As planes line up for landing today, pilots maintain steady communication with air traffic controllers to ensure that all planes maintain safe distances from one another. The time spent relaying information means pilots can adjust speed only as quickly as they hear from the tower. This wait creates the need to leave an extra safety buffer of space between each arriving aircraft, limiting the number that can land within a given time.

NASA's flight deck interval management (FIM) system cuts down on the banter: it combines satellite-based location tracking and automated computer commands to keep track of planes' positions and constantly updates pilots on safe flight speeds for landing. This eliminates the padding between aircraft—which could save on fuel costs, reduce emissions and bump up the number of flights that arrive on time. "More aircraft landing per hour at airports means less delay for passengers," says William Johnson, former project manager for Air Traffic Management Technology Demonstration-1 at the NASA Langley Research Center. *—Jeremy Hsu*

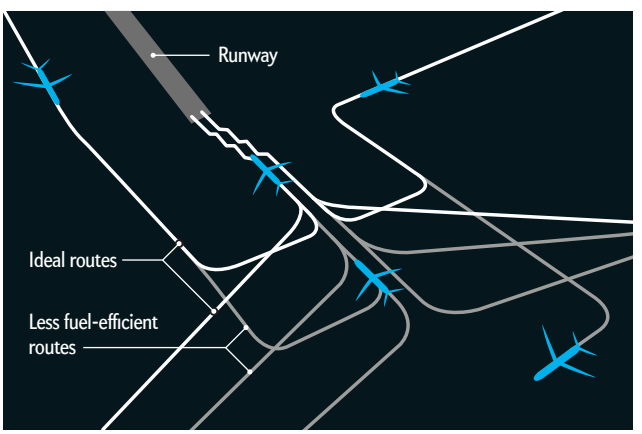
HOW IT WORKS

1 GPS signals determine each plane's location and ground speed. The plane automatically broadcasts this information to satellites and ground stations about once every second.

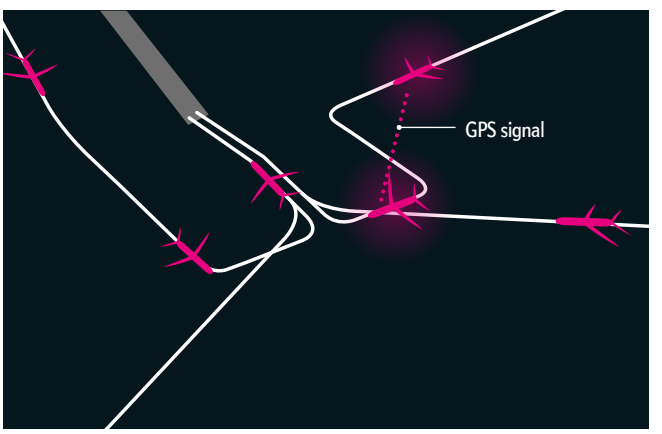
2 On the ground, a computer system uses the flight data to calculate the ideal spacing for each aircraft to maintain a fuel-efficient and continuous descent to the runway. Air traffic controllers pass that information to pilots via radio.

3 The pilots plug the spacing data into the FIM software installed in the plane's cockpit computer system. FIM also receives updates on the flight speeds of nearby aircraft, derived from GPS signals.

4 FIM processes all of that information and calculates the proper speed to maintain ideal spacing between planes preparing to land without compromising safety. That speed is displayed to the pilots in the cockpit and constantly updated until the landing gear touches the ground.



Air traffic controllers typically assign ideal routes (*white*) to each incoming aircraft. As more aircraft approach for landing, pilots are assigned longer, less fuel-efficient routes (*gray*) to ensure that a safety buffer exists between planes. The longer routes give air traffic controllers time to relay speed adjustments as necessary.



By comparison, the next-generation air traffic control system could enable incoming aircraft to continue flying the most fuel-efficient landing routes (*white*) even during heavy traffic conditions. This is because NASA's FIM technology can provide constant, automatic speed commands to pilots—no back-and-forth communication, or extra padding, needed.

DEREK CROUCHER *Getty Images (plane)*; SOURCE: NASA AVIATION SYSTEMS DIVISION www.aviationsystemsdivision.arc.nasa.gov/research/tactical/atd1.shtml *(illustrations)*

Illustration by Amanda Montañez

BRIGHT HORIZONS 33

SCIENTIFIC AMERICAN Travel

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The Epilepsy Dilemma

Current medicines fail to relieve seizures in about a third of people with epilepsy. What can be done?

By David Noonan

Like many people with epilepsy, Richard Shane, 56, has some problems with memory. But he can easily recall his first seizure, 34 years ago. "I was on the phone with my father, and I noticed that I started moaning, and I lost some level of consciousness," Shane says. After experiencing a similar episode three weeks later, he went to a doctor and learned he had epilepsy, a neurological disorder caused by abnormal electrical activity in the brain. The first medication he was prescribed, Dilantin (phenytoin), failed to stop or even reduce his seizures. So did the second and the third. His epilepsy, it turned out, was drug-resistant.

Over the next 22 years Shane suffered two to five or more seizures a week. He and his doctors tried every new antiseizure drug that came along, but none worked. Finally, in 2004, as a last resort, a neurosurgeon removed a small part of Shane's brain where his seizures originated. "It was a matter of what sucks less," Shane says, "having brain surgery or having epilepsy." Shane has been seizure-free ever since.

As many as three million people in the U.S. live with epilepsy, and more than 30 percent of them receive inadequate relief from medication, a number that persists despite the introduction of more than a dozen new antiepileptic drugs since 1990. Although surgery has helped some patients such as Shane, uncontrollable epilepsy remains a living nightmare for patients and an intractable foe for clinicians and researchers. "I hate to say it, but we do not know why" some people respond to medications and others do not, says neurologist Michael Rogawski, who studies epilepsy treatments at the University of California, Davis. And yet if the central conundrum continues, so does the determined quest for new and different approaches to treating the toughest cases.

FAULTY TREATMENTS

EPILEPSY HAS BEEN BAFFLING humans ever since it was first described in Babylonian texts more than 3,000 years ago. Over the centuries sages have attributed its seizures to everything from the presence of excess phlegm in the brain (per the ancient Greeks) to possession by evil spirits (during the Middle Ages). Past treatments included drilling holes in the skull, animal sacrifice and exorcism.

The first effective drug for epilepsy, potassium bromide, was introduced in the 1850s and works by inhibiting the excitability of neurons. The compound, since supplanted by phenobarbital and other treatments with fewer side effects, stopped seizures in about a quarter of those who took it and lessened them in another 43 percent of patients. As Rogawski points out, about 50 percent of current patients become seizure-free with the first drug they try, and another 20 percent will be able to control most of their seizures with their second or third drug. Thus, in some respects, "we have not made much of an improvement," he says.

Which leaves roughly one million people with epilepsy for whom the more than 20 available agents are about as helpful as a handful of jelly beans. Rogawski and others in the field believe that more people could benefit from surgery than are receiving it. Around 60 percent of surgery patients remain seizure-free after 10 years. Less than a quarter of drug-resistant patients, however, meet the medical criteria for the procedures, the main one being a distinct site of origin in the brain for their seizures (confirmed with brain scans and electroencephalography) that does not overlap with regions involved in essential functions, such as language. Studies have found that most surgical candidates, like Shane, typically live with their condition for 20 to 25 years before choosing to undergo the knife. Many people may delay the decision because they fear potential complications, which include infections of the brain and permanent paralysis.

For Orrin Devinsky, director of the Comprehensive Epilepsy Center at N.Y.U.'s Langone Medical Center, the ongoing mystery of intractable epilepsy carries a certain irony. "I went into epilepsy [research] 25 years ago, paradoxically, because it was one of the few things in neurology that you could treat," he says. The fact that nearly a third of his patients do not respond to medication is only made worse by the long-term effects of uncontrolled epilepsy. "People who keep having seizures, especially convulsive seizures, may suffer progressive impairment of cognitive functions [as well as personality changes]," Devinsky says. He attributes those complications to the chronic disruption of brain function by seizures and medications, among other things. Other problems include anxiety, depression, migraine and sleep disorders.

Epilepsy can also be fatal—either on its own or as the cause of an accident. "I would estimate that epilepsy kills at least 6,000 people a year in the U.S.," Devinsky says. About half those deaths occur for reasons that cannot be determined, whereas the rest are the result of seizure-related drownings, traffic accidents, falls, burns, and the like.

NEW APPROACHES

THE FIRST CHALLENGE in treating any patient with epilepsy is figuring out what kind he or she has. The disorder falls into two broad categories: generalized epilepsy, in which seizures begin simultaneously in all parts of the brain, and focal epilepsy, in which seizures begin in a particular region of the brain, such as the temporal lobe. These types are further broken down into subtypes, including a rare genetic condition, known as Dravet syndrome, which usually shows up in affected children in the first 12 months after birth. There are also many different kinds of seizures—among them tonic-clonic seizures, in which a person loses consciousness and experiences whole-body spasms, and absence seizures, brief spells in which a person spaces out for five to 10 seconds on average and is unaware of his or her surroundings.

David Noonan is a freelance writer specializing in science and medicine.

Epilepsy specialists such as Devinsky decide which of the many drugs to prescribe for patients based on the type of seizure they are experiencing, their medical history, and other details such as age, gender and body weight. The drugs act on multiple molecular targets in the brain, including specialized molecules located in neurons that help them communicate with other neurons by transferring sodium, calcium and potassium ions in and out of the cells.

Unfortunately, for people who do not respond to existing drugs, new ones that might help will not be coming soon. "There aren't any major drugs in the pipeline at the moment," Rogawski says. A 2013 joint report from epilepsy research organizations explained that "because the marketplace is already awash with [antiseizure drugs], many pharmaceutical companies now refrain from the expensive enterprise of developing new compounds."

Faced with this roadblock, many patients and families have opted to conduct their own experiments. In recent years, for example, as marijuana was approved for medical uses in Colorado and other states, parents of children with Dravet syndrome have started giving their sons and daughters doses of cannabidiol, a nonpsychoactive component of the plant, prepared as an oil. In anecdotal reports online and in the media, some families described a dramatic reduction in seizures. Since then, a few clinical studies of cannabidiol have also supported its potential as an effective treatment for some forms of epilepsy.

In 2014 GW Pharmaceuticals, a British drug company, received special permission from the U.S. Food and Drug Administration to test its pharmaceutical version of cannabidiol, called Epidiolex. In a recent trial of 225 patients, completed in September 2016, participants who took the drug (along with their other epilepsy medications) reduced their nonstop seizures by 42 percent, compared with 17 percent for those taking a placebo.

Other groups have taken a page from history to develop a nutritional approach to treating epilepsy. A so-called ketogenic diet (high in fats and low in carbohydrates) was widely used in the 1920s to lessen seizures, particularly in children. Recent studies have confirmed that it offers some antiseizure benefits, although 90 percent of children in one study found the diet so unpalatable that they eventually dropped it.

Given how long it is likely to take for new medications against epilepsy to be tested and approved, some experts argue that more patients with relentless epilepsy could benefit from recent advances in surgical techniques and various methods for stimulating neurons in ways that make them behave less erratically. Devinsky estimates that up to 20 percent of such patients are candidates for surgery because they have focal seizures that can be traced to a specific and surgically approachable site in the brain.

Another option that has been around for two decades consists of a kind of pacemaker for the brain. The idea is to prevent seizures by stimulating the vagus nerve in the neck, via electrodes attached to a battery pack implanted in the chest. A programmed pattern of mild electric current overrides and calms the abnormal activity in the brain. A 2011 meta-analysis of 74 clinical trials involving more than 3,300 subjects found that vagus nerve stimulation reduced seizures by more than half in 50 percent of the patients.

A newer device, NeuroPace's RNS System, approved by the FDA in 2013, has a neurostimulator that is implanted in the skull, under the scalp. When it detects unusual electrical activity in the brain, it sends a charge through two electrodes to stop or even prevent a seizure. According to Devinsky, 10 to 15 percent of patients with otherwise unmanageable epilepsy are potential candidates for the treatment; clinical trials have shown that the implants reduce seizures in the treated group by an average of as much as 66 percent after three to six years of follow-up.

In the laboratory, meanwhile, researchers are working with mice, fruit flies, worms and computers to develop new and better models of epilepsy in animals, in an effort to speed drug discovery. In 2016, for example, scientists at Florida Atlantic University and the Scripps Research Institute for the first time induced seizures in nematodes, microscopic worms with just 302 brain cells. They then successfully treated the creatures with existing antiepileptic drugs, suggesting the worms could potentially serve as fast and efficient tools for testing new medicines.

As for Richard Shane, who now owns his own travel company, epilepsy is still part of his life. He no longer has seizures, but there is something else that nags at him: "I wonder sometimes who I would have been if I never had all this electrical activity in my brain. How did it change who I am?"

It is a question without an answer, another unknown in the swirl of unknowns around drug-resistant epilepsy. But doctors such as Gregory Bergey, director of the Johns Hopkins Epilepsy Center, try to offer encouragement as they confront the disorder's myriad riddles: "I always tell my patients, we never give up." SA

Illustration by Nicole Xu

David Pogue is the anchor columnist for Yahoo Tech and host of several *NOVA* miniseries on PBS.

What Happened to User Manuals?

Google happened, and something important was lost

By David Pogue

In the olden days—say, the 1980s—if you bought a piece of technology, a paperback user guide came with it. It was the manufacturer's one big chance to explain its engineers' thinking to you, to communicate what the designers and marketers had in mind.

Supplying documentation seemed, at the time, like a good idea all around. Mastery made customers happy, and happy customers meant repeat sales. But there were other forces at play. Printing and binding took time and money—and customers didn't seem to be *reading* user manuals.

Over time, therefore, physical manuals began disappearing from our hardware and software boxes. Maybe you'd get a Quick Start leaflet, but the rest was online.

To take up the slack, independent publishers began creating their own books. Bookstores had huge computer-book departments. For a while there—say, in the 1990s—that was a very good business indeed.

In those days, says my own tech-book agent David Rogelberg, "almost any book published would sell 7,000 copies—even the really bad books. A computer book best seller could sell hundreds of thousands of copies. The business was practically like printing money." And then Google happened.

Online, you can search for certain terms, find topics faster and post questions for other people. Online communities and answer sites sprouted up. Mini tutorials on YouTube began *showing* you how to perform a task. And it's all free.

Meanwhile the *kind* of technologies we use has changed. "People increasingly spend time in apps and social sites that have a fairly simple interface," Tim O'Reilly told me. (He's founder of O'Reilly Media, which publishes my own how-to books.) "You don't need a book to use Facebook."

That was the beginning of the end for computer books. Small independent publishers closed their doors or got folded into bigger publishers. "Many of the old imprints [publishing brands] still exist under the big publishers, but there have been tremendous layoffs of editors. In short, the people who made the imprints unique are long gone," Rogelberg says.

According to O'Reilly's research department, computer-book sales have dropped 54 percent since 2007. In principle, the demise of professionally prepared support materials shouldn't be any cause for concern. It's just another sea change unleashed by the Internet, another in the list of casualties, such as printed encyclopedias, newspaper classified ads and music on discs.

In reality, though, *none* of the tech industry's teaching channels—manuals, computer books, online sources—is universal and effective. To this day, it's astonishing how little we know about our phones, computers and software. How many times have you heard people sheepishly admit to knowing only 10 percent of their phone's or computer's features?

A Microsoft product manager once told me, with exasperation, that most feature requests the company gets for Microsoft Office are, in fact, *already* features of Microsoft Office.

And seeking help online is often frustrating. The posts you find may not cover the right software version or product model. Or they don't quite describe your problem. Above all, they fail in teaching what O'Reilly calls "structural literacy." That's the art of knowing *what* to look for. "At the consumer level, this means that a new system may move around the knobs and levers, but you know what they do and how to look for them. You see the same thing in a car: 'Where is that damn lever to open the gas cap?'"

Hardware and software makers still operate with their traditional business model: Every year or so they sell us a new version, whose appeal is supposed to be *more features*. And so, as time goes by, our gadgets and apps become more and more complex—but access to documentation remains scattershot and incomplete.

In the fantasy version of our world, designers would make our tech products simple enough, their important features obvious enough, for the masses to figure out on their own. Until then, there will be a growing information gulf between the features we want and the engineering work that's already been done. SA

SCIENTIFIC AMERICAN ONLINE
HEAR WHAT A USER MANUAL EXPERT HAS TO SAY:
scientificamerican.com/apr2017/pogue

Illustration by Jay Bendt

NEUROLOGY

A RARE SUCCESS AGAINST ALZHEIMER'S

A gold-standard clinical trial provides evidence that diet, exercise and an active social life can help prevent cognitive decline

By Miia Kivipelto and Krister Håkansson

IN BRIEF

Two hundred experimental drugs intended to treat Alzheimer's disease have failed in the past 30 years. Without new therapies, the number of patients worldwide will increase dramatically by 2050.

A ray of hope has come recently from a clinical trial that showed that dementia's cognitive impairment might be prevented by paying close attention to various health factors.

Participants in the study who followed a regimen of health-related steps registered improvements on cognitive measures such as memory and mental-processing speed.

Results of this research suffice for health care professionals to begin making a series of recommendations to patients on diet, exercise and levels of social engagement that may help prevent dementia.

DAN SAELINGER *Trunk Archive*

Miia Kivipelto is a professor of clinical geriatrics at Sweden's Karolinska Institute. She heads "Theme Aging" at Karolinska University Hospital, an initiative to develop specialized health care for the elderly. Kivipelto is also research director in neuroepidemiology at the University of Eastern Finland.

Krister Håkansson is a researcher in the department of neurobiology, care sciences and society at the Karolinska Institute and a psychology lecturer at Linnaeus University in Sweden.

MORE PEOPLE ARE REACHING A RIPE OLD AGE THAN EVER before. Life expectancy has increased from 45 years in the early 1800s to more than 80 today in most European countries and in Japan, Canada and Australia, among other nations. In fact, if the trend continues, a majority of babies born in these countries today will live past their 100th birthday.

This greater longevity comes with some bad news. Although we manage to survive longer than preceding generations did, we often gain time without being healthier in those extra years. Studies from different parts of the world indicate that after age 60, most people have at least one chronic disorder, such as heart disease or diabetes, and a recent population-based study in Sweden found that at 80, only around one out of 10 individuals were free of chronic diseases. In fact, most people older than 80 in this population had two or more chronic illnesses.

Modern medicine has become increasingly adept at treating and controlling many of these conditions, but a few common age-related diseases have defied attempts to find preventive therapies or cures—most notably, Alzheimer's disease, the leading cause of dementia. Alzheimer's follows a merciless course that progressively deprives a person of memories and a sense of self-identity, losses that have devastating consequences for relatives and friends as well.

In the U.S., around 32 percent of people older than 85 have received an Alzheimer's diagnosis, often combined with other types of dementia, such as that caused by vascular disease. Estimates put the number worldwide with any kind of dementia at about 50 million. By 2050 if no new treatments succeed in delaying the condition, more than 130 million may suffer with some form of the disease. About 60 to 70 percent of these patients will have Alzheimer's dementia, and around 20 to 25 percent will be classified as suffering from the vascular form of the illness.

In spite of more than 100 ongoing clinical trials, no cure or drug has been able to halt the course of Alzheimer's. More than 200 experimental drugs intended to treat it have failed during the past 30 years. But all is not grim. New findings from a gold-standard clinical trial the two of us have been involved in indicate that cognitive impairment can be prevented or delayed even in the absence of new drugs by promoting changes in behavior and by managing vascular risk factors.

The study we conducted took its inspiration from epidemiological research that sought ways to reduce the risk of Alzheimer's. Such investigations, called association studies, measure, at different points, health-related variables, such as depression, high blood pressure, diet and exercise. Then, usually many years later, they investigate whether individuals go on to acquire a particular disorder. A strong correlation between a variable and the disease in question suggests that some aspect of our health history might merit being labeled as a risk factor. Also, if one of the observed variables correlates with a low risk of disease, the finding can be taken as a sign that it might be protective.

HOW WE LIVE

DURING THE PAST 10 TO 15 YEARS association studies have indicated that maintaining cardiovascular health and adopting certain measures—good diet, exercise, an active social life and the achievement of higher educational levels—may diminish the risk of both Alzheimer's and other dementias later in life, even for those who carry genes that place them at increased risk. Epidemiologists have also increasingly begun to discover specific factors that may be protective—for instance, living with a partner or consuming a Mediterranean diet (mainly based on fish, vegetables, fruit and olive oil). Some studies suggest that controlling, for example, blood pressure and diabetes may constitute primary prevention—protections against the onset of a disease. They might also afford secondary prevention, slowing memory loss and other symptoms in the earliest stages of illness.

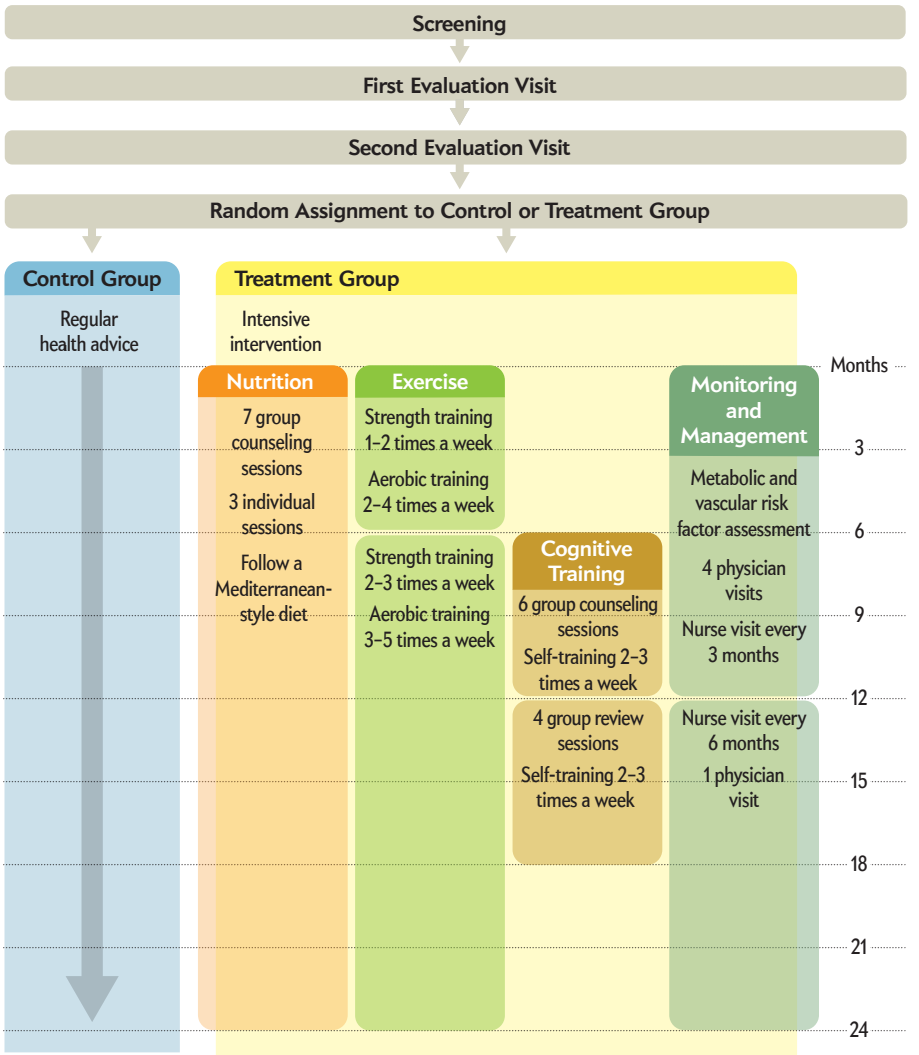
Although association studies can flag a purported protective factor, they unfortunately cannot prove that taking these steps will actually prevent dementia. People who eat a Mediterranean diet or exercise three times a week may avoid disease because of some other variable ignored by epidemiological sleuths.

Epidemiologists try to deal with this problem by making statistical adjustments, but it is virtually impossible to discount every aspect of a person's life that could confound a study's conclusions. They can never be sure that they have succeeded, and sometimes the relevant data may not even exist. Obtaining reliable data on early childhood experiences is extremely difficult, although what happens during the first years might influence development of high blood pressure or some other aspect of

TRIAL DESIGN

FINGERing Dementia

Between 2009 and 2011 a clinical trial—the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER)—enrolled 1,260 men and women between the ages of 60 and 77. Of that number, 629 were randomly assigned to a control group, and 631 were directed to a treatment group. All of those recruited in both groups had a slightly higher risk for dementia. Members of the treatment group were then directed to follow a regimen of diet, exercise and cognitive training. They received nurse visits, initially every three months, and visited physicians five times during the two-year course of the trial to check on how well they were able to follow recommendations. Control group participants, in contrast, received only basic health advice during two physician visits.



health that contributes to the development of Alzheimer's late in life. Lacking all the necessary data can produce spurious associations among variables that lead to the wrong conclusions. Statistical equations, moreover, all but collapse under their own weight if too many variables are considered at the same time.

In 2010 the problem of establishing causality from association studies prompted a U.S. National Institutes of Health conference to conclude that not enough evidence existed to make firm recommendations on whether a given factor might diminish the risk of cognitive decline. To overcome this difficulty, a systematic review article from the NIH conference suggested that Alzheimer's researchers launch randomized controlled trials—and that any study undertaken examine not one but multiple factors that might prove to be pivotal in preventing dementia.

The randomized controlled trial is the gold standard that science uses to determine whether a treatment is in fact effective—in this case, whether a true cause-and-effect relation links variables—perhaps diet and exercise—with outcomes such as avoiding cognitive decline. Participants in these trials are randomly assigned to either a treatment or a control group. To avoid biasing results, neither the researchers nor the study participants know which individuals are assigned to a particular group.

In the past investigators have undertaken relatively few long-term randomized controlled trials of whether lifestyle changes can improve health because accurately monitoring day-to-day behavior is challenging. But the NIH conference experts still recommended them as the best way to proceed because of the need for substantive data and because past randomized controlled trials looking at only a single variable had failed or produced mixed results. Moreover, Alzheimer's researchers had come to recognize the need to learn from successes in advancing prevention strategies for heart disease and diabetes, which relied on studies that looked at multiple risk factors.

THE STUDY

SINCE 2010 SEVERAL LONG-TERM, randomized controlled studies have progressed, and findings are now being reported. Our project—the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER)—was the first to publish. FINGER's goal was to assess the effect on cognitive health of improved diet, physical exercise and mental training while providing regular health advice and cardiovascular health monitoring.

Graphics by Jen Christiansen

We and our colleagues wanted to know whether, over a two-year period, overall cognitive performance would differ between the treatment group—631 men and women between the ages of 60 and 77—and the 629 members of the control group. (The control subjects received health advice, and their cardiovascular health was checked regularly. If health problems were identified, such as high blood pressure, control group members were referred to a physician.) To optimize chances that the trial would succeed, we structured the pool of subjects to consist of individuals who had an elevated risk for cognitive decline, as judged by scores on a survey that measures dementia risk (the Cardiovascular Risk Factors, Aging and Dementia risk score).

In comparison with the control group, the intervention group received a mix of nutritional guidance, cognitive training and physical exercise, and the subjects' cardiovascular status was also more intensely monitored. The nutritional guidance aimed at a healthy balance of protein, fat, carbohydrates, dietary fibers and salt and included restrictions on consumption of trans-fatty acids, refined sugar and alcohol, all in accordance with recommendations by Finland's National Nutrition Council. The main ingredients in the recommended diet were fruits, vegetables, whole grains and rapeseed oil, along with a fish meal at least twice a week. The only food supplement was vitamin D.

Physical exercise included muscle-strength training, aerobic exercise and postural balance. The exercise program was individually tailored to each participant and led by a physiotherapist during the first six months, then performed independently by the participants in group sessions. The initial recommendation was to go to the gym one to two times a week for sessions of 30 to 45 minutes to train muscle strength. After six months of gradual increases in intensity, the participants reached a maximum level of two to three gym sessions of 60 minutes a week, which they then maintained during the remaining 18 months. In addition, subjects received advice to perform aerobic training twice a week and increase their regimen gradually to three to five times a week. Based on individual preferences, they could choose to engage in Nordic walking, aqua gym, jogging or calisthenics as part of the aerobic component of the intervention.

The intervention group also used a computer program to train on different cognitive tasks to enhance executive function (planning and organizing), memory improvement and mental speed. After six introductory group lessons led by a psychologist, group members trained on their own two to three times a week in 10- to 15-minute sessions during two six-month periods. Four group reviews monitored progress along the way and discussed topics such as age-related cognitive changes.

The participants also had regular checkups of metabolic and vascular health. They met with a study nurse on six occasions to measure weight, blood pressure, and hip and waist circumference. Physicians also reviewed these and other laboratory results with subjects five times during the two-year trial period, using them as a basis to encourage changes in daily habits.

By any standard, FINGER proved to be an intensive intervention for most participants, a drastic change to their lives during the two years it lasted. That most of them adhered to the routine was regarded as a success in itself. Only 12 percent dropped out, usually citing health problems. Further, just 46 of the 631 participants in the intervention group experienced any difficulty completing the tasks—the most common adverse event was muscle pain following physical training. We concluded that a comprehensive program of changes to one's daily activities in later life is practical to implement. But the more important question was whether the goal of preserving cognition had actually been reached.

STEPS TO PREVENTION

Physical activity was a key part of the FINGER intervention.

After two years the treatment group showed clear benefits: overall cognitive performance improved on average in both the treatment and control groups, but the intervention group benefited 25 percent more than did controls. Another analysis—looking at the number of people who deteriorated in cognitive performance over the two years—showed a surprising result: the risk of waning cognitive performance turned out to be 30 percent higher in the control group. Improvement in control groups often occurs in randomized controlled trials for various reasons. People usually perform better on the same tests the second time they take them. But FINGER did not have a control group in the traditional sense. The regular meetings with health advice and cardiovascular monitoring attended by participants in the control group became a kind of mini intervention.

Many control subjects may have been inspired by these sessions to make at least some changes to benefit cognitive functioning. Even though we knew that this arrangement might narrow the differences in results between the two groups, we also had an ethical obligation to ensure that the intervention had at least some benefit for the control group. Still, after tallying our results, we did not lose confidence that it represented a real effect, because the treatment group improved by a significantly higher degree than the control group did.

Participants in the treatment group also registered significant gains in other areas as well. They improved in specific cognitive domains that help people in daily activities that often decline with aging. The intervention group logged an 83 percent improvement over the control group in executive function, a 150 percent better score in speed of processing (time required to perform mental tasks) and a 40 percent performance increase in complex memory tasks (remembering long lists, for instance).

Delving further into our data, we found that participants with a gene variant (*APOE* e4) that puts them at higher risk for Alzheimer's seemed to receive somewhat more benefit from the specified changes than others without it, more proof of the intervention's effectiveness. Those in the treatment group who carried the risk gene had a slower rate of cellular aging, as measured by biological markers called telomeres, caps at the end of a chromosome.

COURTESY OF FINNISH GERIATRIC INTERVENTION STUDY TO PREVENT COGNITIVE IMPAIRMENT AND DISABILITY

FINGER EXTENSION

WE NOW HAVE FAIRLY GOOD EVIDENCE that a combination of improved diet, physical exercise, mental and social stimulation, and management of cardiovascular problems can improve cognition even after age 60. But we still have more follow-up work to do on our original results.

Finding an improvement in mental functioning after two years implies—but does not prove—that changing one's diet and exercise habits can protect against dementia. To investigate whether it is possible to delay the onset of dementia, we have to consider the long presymptomatic period that is typical of the various forms of dementia. Alzheimer's develops over probably 15 to 20 years before cognitive problems can be diagnosed. We might therefore need to follow people over an extensive period. Of course, it will also be necessary to decide at which point this type of study becomes too expensive and impractical to complete.

Another question we needed to address was whether someone experiencing the brain changes that precede actual cognitive complaints might be helped by counteracting the physiological alterations. Could changes to one's activities of the type implemented in FINGER push back the onset of cognitive issues? Postponing symptoms by two to five years would translate into a significant improvement in public health. Such a delay would mean that many people would probably not receive a dementia diagnosis, because they would die of other causes first.

To investigate some of these questions, we have put in place an extension of FINGER for another seven years. For this next phase, we plan to use brain scans to determine whether good habits might counteract the breakdown in connections among neurons and stem atrophy in certain brain areas, both hallmarks of Alzheimer's. Blood tests may pinpoint whether adopting behaviors that appear to improve cognition lessens inflammation, cellular stress and a deficiency of the proteins that help to ensure brain health—signs of pathology that often turn up in the postmortem brains of Alzheimer's patients.

We are also working with various research teams to bring together findings from studies similar to our own conducted in other countries. The comparisons can help determine whether our discoveries generalize to different populations—combining results can also increase the statistical power of the research and enable more detailed analyses of timely interventions. We could, for instance, compare the levels of physical training among intervention groups from the various studies to identify optimal levels to preserve brain health.

What we have learned from FINGER can also serve as a model for similar studies that attempt to mine the epidemiology literature to extrapolate multiple risk factors that can then be examined in a randomized controlled trial. We are now collaborating on two such projects: the European Union's Healthy Aging through Internet Counseling in the Elderly and the Multimodal Strategies to Promote a Healthy Brain in Aging.

It will not be necessary to wait another decade for health care professionals to start making recommendations to their patients. Already FINGER has provided enough evidence to start suggesting that patients take up the health measures we investigated. If the NIH decides to convene a new conference, it might now come to a more optimistic conclusion than the one held seven years ago that was unable to endorse any preventive steps.

The agency might also take assurances from recent reports indicating a decreasing rate of Alzheimer's in the U.S. and for all forms of dementia in both the U.S. and several European countries. This decline may stem from behavioral changes people have implemented on their own after hearing about scientific studies on such changes that can benefit cognitive health.

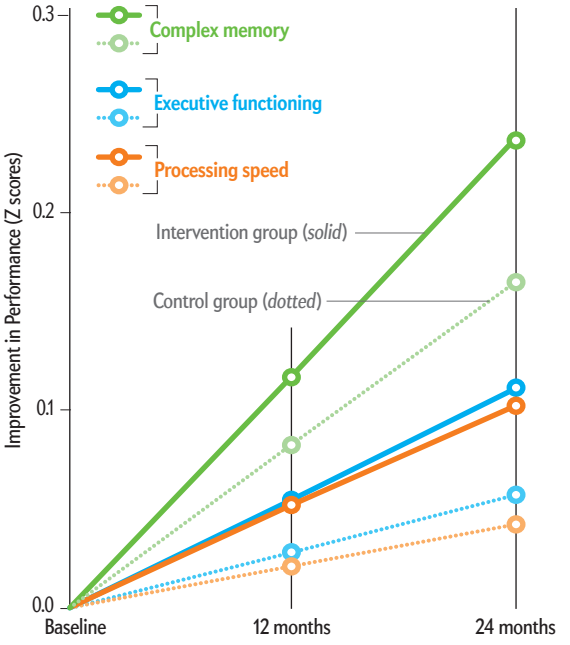
In the face of a multitude of drug failures, prevention may prove the best way to manage the dementia epidemic, as it has for many other chronic diseases. The take-home message from FINGER is that it may never be too early to take measures to prevent Alzheimer's—and fortunately, it may never be too late, either: changes to the way one lives seem to help some people even after cognitive decline has already begun. SA

SOURCE: "A 2 YEAR MULTIDOMAIN INTERVENTION OF DIET, EXERCISE, COGNITIVE TRAINING, AND VASCULAR RISK MONITORING VERSUS CONTROL TO PREVENT COGNITIVE DECLINE IN AT-RISK ELDERLY PEOPLE (FINGER): A RANDOMISED CONTROLLED TRIAL," BY TIIA NGANDU ET AL., IN *LANCET*, VOL. 385; JUNE 6, 2015

TRIAL RESULTS

Getting Better

FINGER trial participants in both the treatment and control groups improved on various cognitive measures of memory, executive functioning and mental-processing speed. But the treatment group had better scores after 24 months than the control group did.



MORE TO EXPLORE

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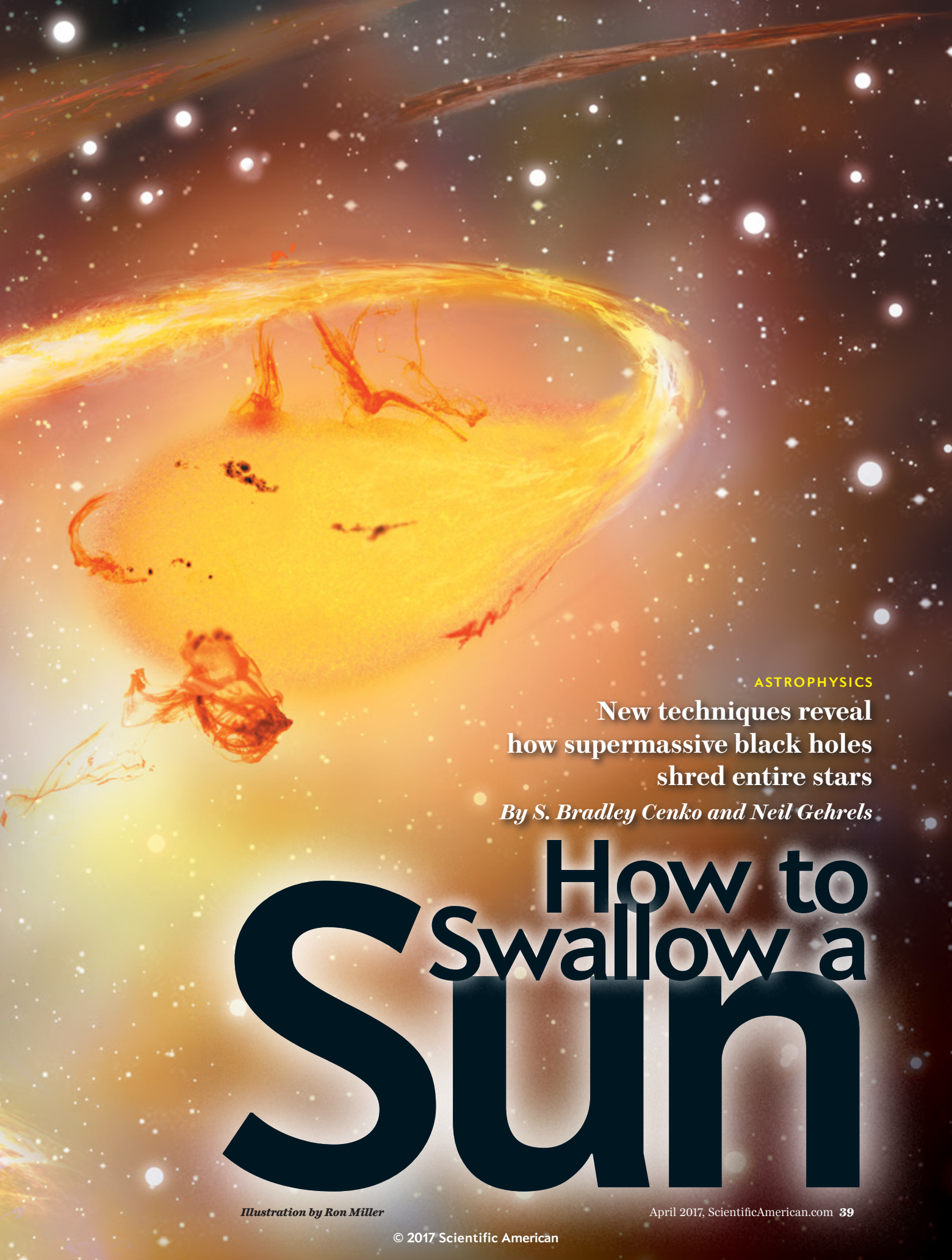


ASTROPHYSICS

New techniques reveal how supermassive black holes shred entire stars

By S. Bradley Cenko and Neil Gehrels

How to Swallow a Sun

Illustration by Ron Miller

S. Bradley Cenko is a research astrophysicist at the NASA Goddard Space Flight Center, where he serves as a deputy project scientist for the Swift mission. He works with wide-area ground- and space-based surveys to study the time-variable universe.

Neil Gehrels was chief of the Astroparticle Physics Laboratory at the NASA Goddard Space Flight Center, as well as principal investigator of the Swift mission and project scientist for the Wide-Field Infrared Survey Telescope (WFIRST) and the Fermi Gamma-ray Space Telescope. He passed away in February 2017, just before this article went to press.

AT THE HEART OF OUR MILKY WAY AND OF VIRTUALLY EVERY other large galaxy lurks a deep cosmic mystery—a supermassive black hole. Squeezing millions to billions of times more mass than our sun into regions smaller in size than our solar system, these objects are so bizarre as to seem almost mystical. No one yet understands exactly how nature has managed to compress so much matter into such small spaces. What is clear is that the hidden gravitational hands of supermassive black holes reach out to shape their surrounding galaxies in profound yet subtle ways. By studying the growth and behavior of these ghostly black holes, scientists hope to unlock the secrets of how galaxies themselves are born and evolve.

The trouble is that because they emit no light, supermassive black holes spend most of their time dormant and invisible to us. They come to life only when they feed, but their meals are surprisingly rare—most of the gas, dust and stars swirling around them reside in stable orbits and will never be consumed. Yet they are always hungry, and whenever something sizable does happen to fall in, the resulting feeding frenzies can be seen from far, far away.

For most of the past half a century, scientists have primarily observed just one variety of feasting black holes: quasars. Discovered by astronomer Maarten Schmidt in 1963, quasars are the ultraluminous centers of active galaxies that can be seen all the way to the outskirts of the visible universe, each shining brighter than billions of suns. They are thought to occur when massive clouds of gas and dust plunge onto a supermassive black hole for hundreds of thousands or millions of years, compressing, heating and glowing as they circle the black hole's maw. Quasars, however, are less than ideal objects of study. They are extreme events that are typically quite distant and relatively rare, and they constitute a small portion of any supermassive black hole's lifetime. They thus provide a limited view, leaving astronomers blind to how supermassive black holes more routinely feed and grow in the local universe. Researchers have also studied supermassive black holes by clocking the speeds of stars whizzing around them, but these measures work solely for objects very close to home—in the Milky Way or one of our immediate galactic neighbors—where current telescopes can resolve individual stars.

In 1988 astronomer Martin Rees proposed a third way to study supermassive black holes—a method that has recently begun to bear fruit. Instead of watching for the steady glow of quasars or the speeds of orbiting stars, astronomers can look for

IN BRIEF

A star passing too close to a supermassive black hole will be ripped apart by tidal forces and consumed.

New wide-field telescopes are allowing astronomers to study these cataclysmic events in fine detail.

The result is a dramatic improvement in our understanding of how black holes feed, how they can accelerate material to velocities approaching the speed of light and how their growth shapes their surrounding galaxies.

COSMIC BEACONS CALLED QUASARS are produced by supermassive black holes feasting on gas (*above*) but are too rare, distant and sluggish to wholly reveal how such giant black holes feed. More nuanced detail can come from watching black holes snack on entire stars.

ILLUSTRATION COURTESY OF NASA AND JPL/CALTECH

brief, bright flares of light from a black hole's vicinity. Called tidal disruption events (TDEs), these outbursts occur when a supermassive black hole consumes an unlucky star. Unfolding over months rather than millennia, they allow researchers to track the feeding process from beginning to end and are bright enough to be observed in galaxies both near and far.

HOW TO DESTROY A STAR

A TIDAL DISRUPTION EVENT is far more dramatic than the gentle tides that can wash your beach towels away at the seashore, but it is not all that different in principle. Earth's tides are chiefly caused by the gravitational tug of the moon, which pulls more strongly on the side of Earth closest to it. This difference between the moon's gravitational pull on the far and near sides of Earth is called a tidal force. That tidal force raises a bulge, or high tide, both on the moon-facing side of Earth and, somewhat paradoxically, on the opposite face as well, which also creates a corresponding low tide, oriented 90 degrees from the Earth-moon axis. When a star is in the vicinity of a supermassive black hole—perhaps pushed there by the gravitational nudging of another nearby star—the intense tidal forces can rip it to shreds.

The details of the star's demise depend on the sizes of both

the infalling star and the supermassive black hole. A small, dense object, such as a white dwarf star, will be far more resilient against tidal forces than a larger, puffier, sunlike star—similar to how a bowling ball would be harder to rip apart than a mass of cotton candy. The very largest supermassive black holes, those containing billions of solar masses, are too big to easily create TDEs—they swallow stars whole before the tidal force becomes large enough to tear the stars apart. The tidal forces around a black hole with millions of solar masses, in contrast, will tear apart most stars that approach within about 50 million kilometers—roughly the distance of Mercury from the sun.

As spectacular as the wholesale disassembly of a star may seem, this is just the beginning of the fireworks display. After the initial disruption, the stellar debris will spread out and gradually diverge from the star's original orbital path. Basic orbital mechanics dictates that roughly half of the debris will be expelled as long filaments of material streaming from the vicinity of the black hole, whereas the other half will loop back around to form an accretion disk—a structure of spiraling rings slowly funneling into the black hole. When the disk's material falls in, it accelerates to nearly the speed of light and glows as gravitational and frictional forces compress and heat it to temperatures approaching 250,000 degrees Celsius. Over a span of weeks or months a typical TDE will cause a previously dormant and invisible black hole to briefly outshine all the stars in its galaxy.

THE FIRST DISCOVERIES

ALTHOUGH THEORISTS first predicted TDEs decades ago, astronomers did not detect any until the 1990s and early 2000s. This delay was in part caused by the rarity of TDEs—they occur once every 100,000 years in a galaxy like the Milky Way, according to estimates. They can also be hard to see. Simple theoretical models suggested that the glow of a TDE's accretion disk should peak in the so-called soft x-ray or far ultraviolet parts of the electromagnetic spectrum—wavelengths that are difficult to access from the ground because of interference from interstellar dust and Earth's atmosphere. Those same models also suggested that astronomers could use a TDE to make relatively precise estimates for the mass of its accompanying black hole—a critical data point for learning exactly how a black hole's size alters its behavior and effects on its galactic surroundings. To measure a black hole's mass, astronomers can simply time how long an accompanying TDE takes to reach peak brightness (which reveals how fast an accretion disk forms and feeds the black hole). Because TDEs are so bright, they allow researchers to pinpoint masses for a wider range of supermassive black holes than any other known phenomenon.

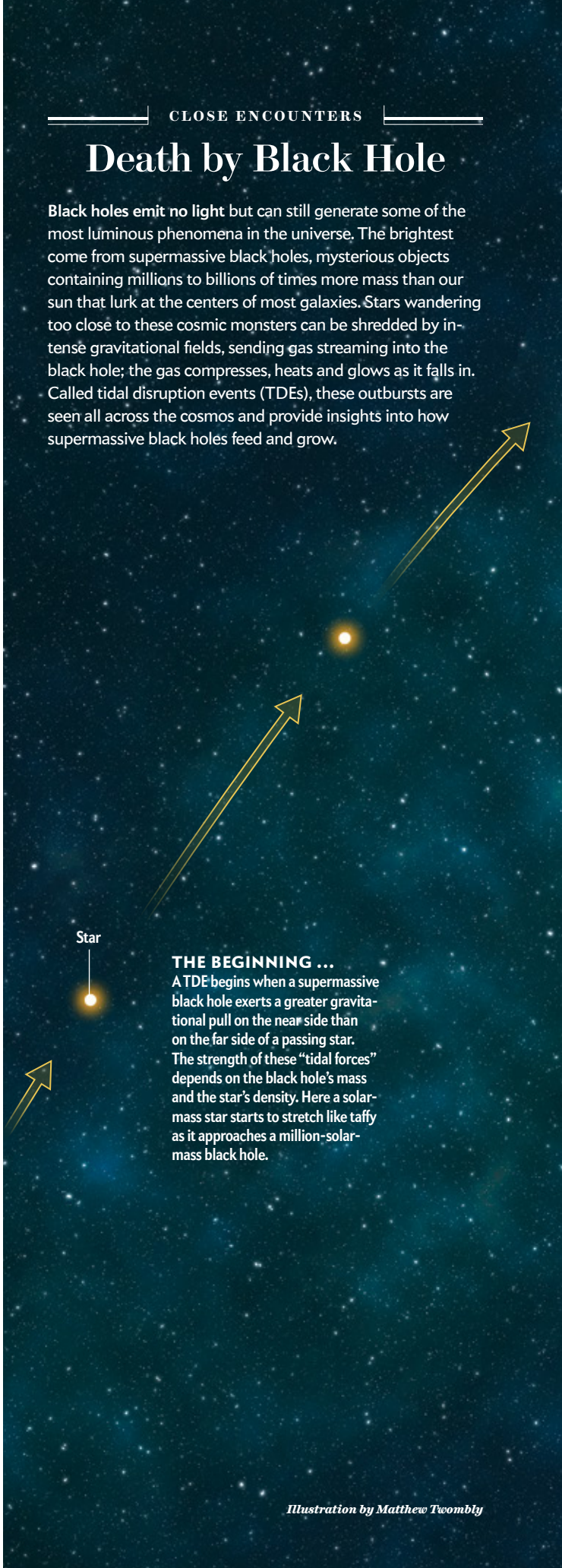
The first TDE candidates were found in data from the ROSAT x-ray and Galaxy Evolution Explorer ultraviolet space telescopes. They appeared as weeks- to months-long flaring events sourced to the centers of previously dormant galaxies. As the first manifestations of this long-predicted phenomenon, these discoveries were especially important for establishing an entirely new field of study. Because they were predominantly found in old data, however, astronomers were unable to study them across multiple wavelengths in real time to unlock their deepest secrets. To catch TDEs as they happened, astronomers would either have to be very lucky or able to continually survey mammoth swaths of sky.

As luck would have it, in the past decade steady progress in data storage and sensors has made such ambitious surveys pos-

CLOSE ENCOUNTERS

Death by Black Hole

Black holes emit no light but can still generate some of the most luminous phenomena in the universe. The brightest come from supermassive black holes, mysterious objects containing millions to billions of times more mass than our sun that lurk at the centers of most galaxies. Stars wandering too close to these cosmic monsters can be shredded by intense gravitational fields, sending gas streaming into the black hole; the gas compresses, heats and glows as it falls in. Called tidal disruption events (TDEs), these outbursts are seen all across the cosmos and provide insights into how supermassive black holes feed and grow.



THE BEGINNING ...
A TDE begins when a supermassive black hole exerts a greater gravitational pull on the near side than on the far side of a passing star. The strength of these "tidal forces" depends on the black hole's mass and the star's density. Here a solar-mass star starts to stretch like taffy as it approaches a million-solar-mass black hole.

Illustration by Matthew Twombly

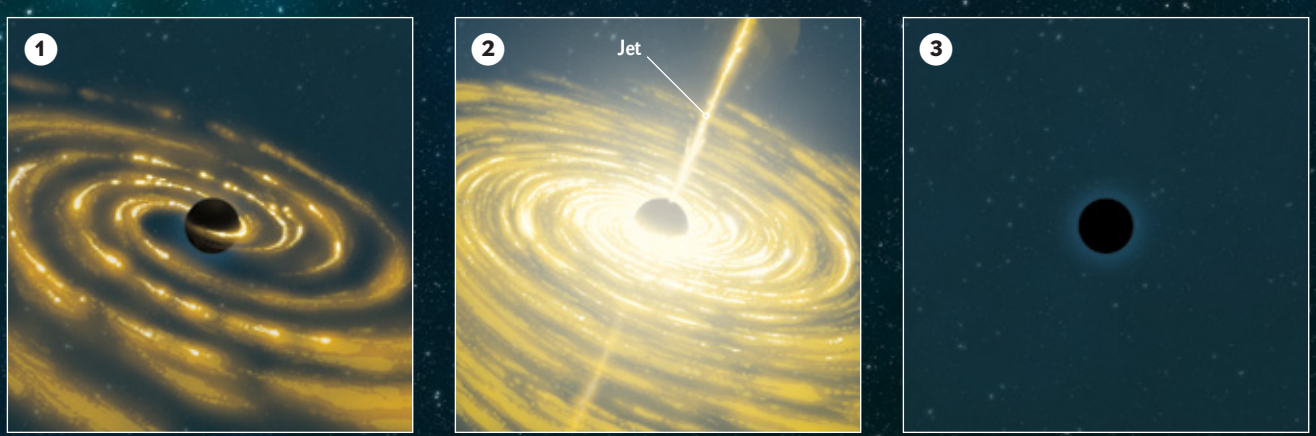
Black hole

... OF THE END

The tidal forces increase as the star gets closer to the black hole, until they overcome the star's self-gravity and rip it apart into arcing filaments of gas. Half the filaments are flung away from the black hole, never to return. The rest swirls into decaying orbits, forming a white-hot accretion disk that funnels the stellar debris into the black hole. Astronomers detect TDEs via the glowing accretion disks left in their wake.

A VIEW LIKE NO OTHER

A TDE is the only known way for astrophysicists to witness a supermassive black hole awaken, feast on a meal and return to quiescence. By tracking how long an accretion disk takes to form (1), reach peak brightness (2) and fade (3), scientists can gauge the size of the consumed star, as well as the black hole's mass and spin. As the black hole feeds, researchers can also monitor shock waves in its accretion disk, as well as the creation of relativistic jets—streams of particles launched at near light speed from a black hole's poles. No other cosmic event offers such detailed views of these extreme, dynamic processes around black holes.



sible. A high-end optical camera can now image one square degree or more of sky in a single snapshot, a situation akin to suddenly seeing the heavens with a panoramic lens after years of studying them by looking through a straw. By repeatedly surveying large areas of the sky and digitally combining the resulting images to tease out faint, temporary features, astronomers are now able to more easily discover and study TDEs and a host of other transient astrophysical phenomena. These new wide-field surveys, with names such as the Panoramic Survey Telescope and Rapid Response System (Pan-STARRS), the Palomar Transient Factory (PTF) and the All-Sky Automated Survey for Supernovae (ASAS-SN), were designed largely to identify supernovae and asteroids, but they can do much more. Because they can image millions of galaxies each night, they are also sensitive to more exotic transients such as TDEs.

By studying TDEs, astronomers are learning not only about black holes but also about stars being ripped apart billions of light-years away.

NEW QUESTIONS FOR A NEW ERA

IN 2010, SHORTLY AFTER Pan-STARRS's on-sky debut, a team led by astronomer Suvi Gezari discovered a TDE called PS1-10jh, which took place around a black hole of perhaps two million solar masses in a galaxy some 2.7 billion light-years from Earth. Because this TDE was noticed soon after the data were collected, Gezari and her colleagues were, for the first time, able to watch it unfold in subsequent optical and ultraviolet observations. What they found was shocking.

Based on careful measurements of its spectrum, this particular TDE appeared to be much too cold. At about 30,000 degrees C, it was more than eight times cooler than predicted by most basic theories of accretion disks. Moreover, rather than fading over weeks as its accretion disk cooled and dissipated, PS1-10jh maintained a constant temperature for many months after the initial discovery. Strangest of all, Pan-STARRS had detected signs of ionized helium in the afterglow—something that could be produced only by temperatures in excess of 100,000 degrees C. And although the TDE appeared to be helium-rich, it also seemed to be devoid of hydrogen, the most abundant element in the universe and the main ingredient of stars. Theorists got to work examining what could produce such confounding results.

To explain PS1-10jh's lack of hydrogen, the Pan-STARRS team suggested that the disrupted star had lost its thick envelope of hydrogen at some point in the past, possibly in a previous interaction with the black hole, leaving only the star's helium-rich core to feed the observed accretion disk. But this alone could not account for the TDE's curious thermal discrepancies—its surprisingly low temperature and, in contradiction, its abundance of helium ionized by much higher temperatures. To solve that mystery, other theorists have postulated that PS1-10jh's black hole–hugging accretion disk was not actually being directly observed. Instead astronomers must have seen a surrounding veil of gas much farther out from the black hole that absorbed the intense radiation produced by the accretion disk and reemitted it at lower temperatures. This veil would have the added bonus of clarifying the apparent absence of hydrogen without the need for an exotic, helium-rich core as the TDE's progenitor. Given the right temperature and a rather high density, such a veil could potentially mask the presence of hydrogen, hiding it in plain sight.

The only trouble was that a thick veil of gas would not be stable at the required distance from the galaxy's central black hole—over time the gas would either fall into the black hole or dissipate to invisibility. The murky origins of this material are still the subject of intense debate and study but, broadly speaking, fall into two possibilities, both related to the dynamics of a feeding black hole. As the remains of a disrupted star loop around a black hole to form a growing accretion disk, shock waves can ripple outward well away from the disk to forestall some of the outlying debris from immediately falling in, creating a temporary screen of material. Alternatively, a newborn TDE accretion disk might initially funnel so much material inward that it briefly exceeds a black hole's capacity to feed, forming transient winds or outflows just outside the black hole that push stellar debris out past the accretion disk to much larger distances.

As astronomers sorted through these muddled possibilities for PS1-10jh and other newfound TDEs that soon followed, one thing became perfectly clear: TDEs were a much more complicated phenomenon than anyone had previously appreciated. Yet the biggest surprise was still to come.

A SHOCK FROM SWIFT

THAT SURPRISE ARRIVED in the predawn hours of March 28, 2011, with an automated alert sent to the pagers and cell phones of a dedicated team of astronomers around the world. The Swift satellite had just detected a pulse of high-energy radiation from the depths of space. Built by NASA in partnership with research institutions in Italy and the U.K., Swift is an agile space telescope, designed to study all types of exploding objects across the sky. But its main targets are gamma-ray bursts, or GRBs—cataclys-

mic stellar explosions that are the most luminous astrophysical events in the universe. Whenever a torrent of gamma rays trickles into Swift's sensors, the telescope quickly reorients to observe the source in x-rays and optical light and phones home to trigger a complex chain of events on Earth. Within moments of an alert from Swift, astronomers scramble to commandeer the world's largest and most powerful telescopes to look for any emberlike afterglow associated with a GRB before it fades from view forever. Since its launch in 2004, Swift has discovered more than 1,000 GRBs, but this particular event, later dubbed Swift J1644+57, would prove to be unlike anything the satellite had seen before.

As their name suggests, GRBs tend to be brief, typically lasting anywhere between a fraction of a second and a few minutes. When we turned our telescopes to Swift J1644+57 on that early March morning, we expected to see the standard, fading afterglow of a short-lived GRB. Instead we observed bright, erratic gamma-ray flaring that lasted for a day, followed by months of intense but fading x-ray emissions. Soon we had traced the blast to a galaxy some 3.8 billion light-years away in the constellation of Draco. One of our colleagues, Joshua S. Bloom of the University of California, Berkeley, suggested we had witnessed a TDE and correctly predicted that this particular gamma-ray source would be found at the galaxy's center—the stomping ground of supermassive black holes. But whereas all previous TDEs had been detected at longer, lower-energy wavelengths where observers saw the thermal emission from the accretion disk of a shredded star, this was something wholly different.

How could a TDE produce gamma rays? The best answer we could come up with is that black holes are messy eaters. A black hole would devour most of a disrupted star's gas, locking it away forever behind an event horizon (the boundary past which the black hole's gravitational pull is so great that not even light can escape). But all black holes probably spin, and this spin can push a few percent of the disrupted star's total gas toward the black hole's poles, outside the event horizon, where the gas is accelerated and ejected as collimated beams of particles moving at nearly the speed of light. The fast-moving beams emit gamma rays and x-rays as they hurtle through the cosmos. Apparently Swift had happened to find itself in the path of Swift J1644+57's beam. It was a lucky catch—not all TDEs appear to power such relativistic outflows, and most of those that do likely miss our line of sight.

With the detection of Swift J1644+57 as inspiration, the Swift team began a concerted search for more events. As of early 2017, two more TDEs emitting gamma-ray jets have been found. These rarest and most intense death cries of stars are a novel way to study one of the foremost research topics in modern high-energy astrophysics—the creation and behavior of relativistic particle jets.

THE DEATH OF WORLDS

WHETHER THROUGH THE THERMAL EMISSIONS from accretion disks of stellar debris or rather with the gamma rays pouring off a star-devouring black hole's relativistic jets, TDEs offer a new window on the behavior and evolution of supermassive black holes and their surroundings. Most important, unlike the far larger and longer-duration jets and accretion disks of quasars, which are produced by immense clouds of gas chaotically plummeting onto a supermassive black hole across very long timescales, TDEs are brief, clean events that are more easily studied. No human being will ever live long enough to witness the complete life cycle of a single quasar, but already astronomers have found and studied more than 20 TDEs from beginning to end. And in the details of those stellar catastrophes, they have glimpsed tantalizing quirks begging for further study. By precisely measuring the fluctuating flares from TDEs, astronomers are learning not only about black holes but also about the detailed compositions and internal structures of stars being ripped apart billions of light-years away.

They may even eventually learn about a star's companions, too—planets swallowed by black holes. Each flickering flash from a faraway galactic center could signal the deaths of entire worlds. Surveys of stars in our own galaxy have found that almost every one harbors planets; planets probably accompany most, if not all, of the stars in other galaxies as well, including those that suffer TDEs. Even if they were not directly consumed, planets could still find themselves in the path of the transient relativistic jets produced by some TDEs, which extend light-years beyond their black hole sources. Life in any planetary systems unlucky enough to be struck by such a beam would be rapidly extinguished. Someday astronomers may witness a TDE right in our cosmic backyard, when the four-million-solar-mass black hole quiescently lurking at the gas-impoverished center of our very own Milky Way flares to life as it consumes some errant star. It would be very bright but also very safe because we are too far from the galactic center for the TDE's most dangerous effects to reach us here.

The advent of even more powerful surveys heralds a new era of TDE discoveries. The Large Synoptic Survey Telescope (LSST), an eight-meter telescope currently being constructed in Chile with a field of view covering 10 square degrees of sky, will by itself uncover thousands of these outbursts within a decade of its debut. In some ways, the most challenging aspect of LSST science will be sifting through the overwhelming number of transient discoveries. Planned radio observatories such as the Square Kilometer Array being built in Australia and South Africa are particularly well suited to identify relativistic jets, even if such jets are "off axis," meaning they are not beamed directly along our line of sight. In the not too distant future, astronomers may have assembled a TDE catalog with thousands on thousands of entries, more than any individual could study in a lifetime, shedding new light on the masses and behaviors of those elusive hungry ghosts, the otherwise inaccessible supermassive black holes that reside in the hearts of galaxies all across the universe. From that rich, ever growing corpus of knowledge, we can only dream of what further revolutionary discoveries may come. SA

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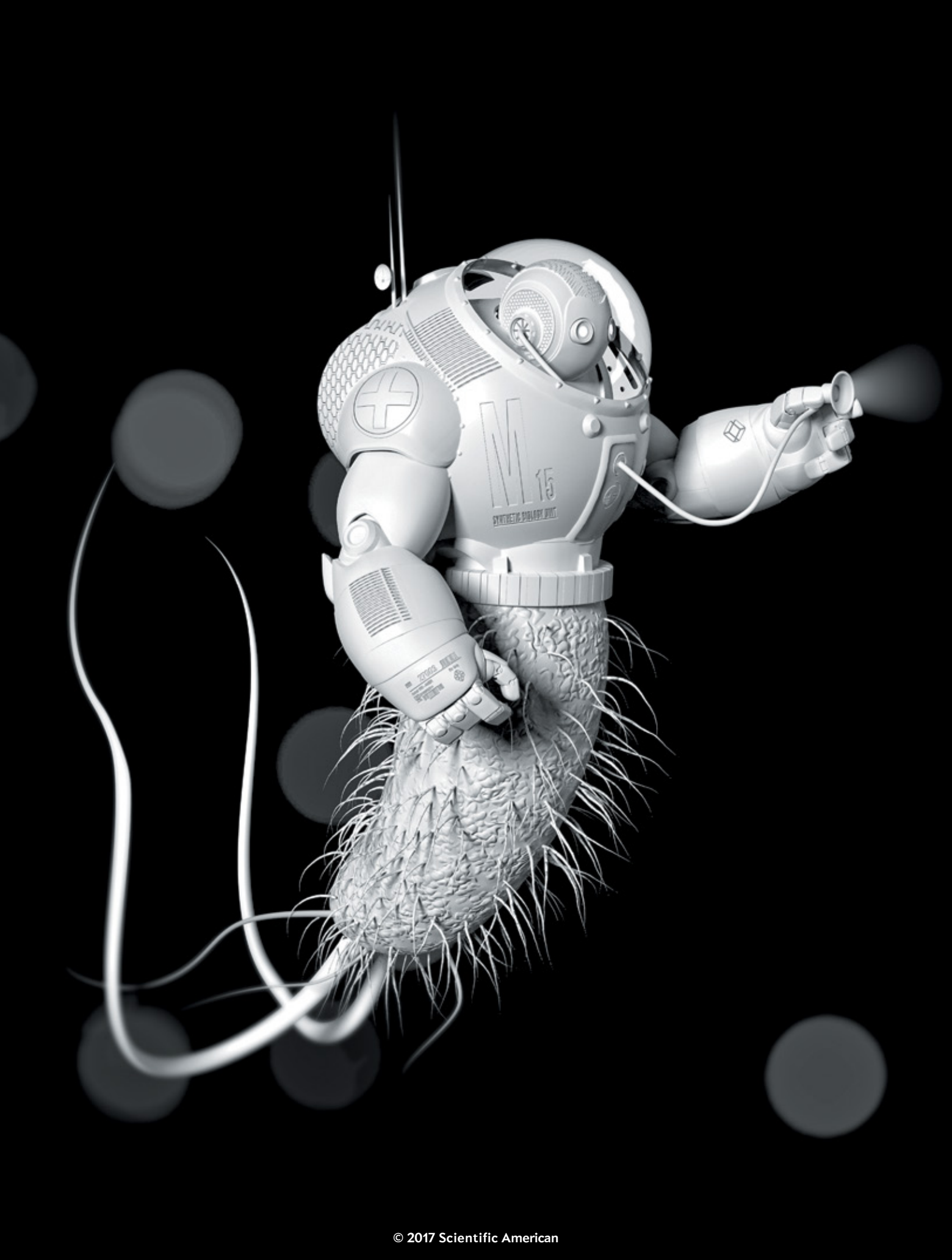


TRANSFORMERS

2017
Future of Medicine

SPECIAL REPORT

By reprogramming DNA inside harmful microbes, biologists are turning them into patient-saving drugs

By Michael Waldholz

Illustrations by GUYCO

Journalist **Michael Waldholz** led a team of reporters who were awarded a Pulitzer Prize in 1997 for their coverage of AIDS. He lives in New York State's Hudson Valley.

IN A FEW MONTHS A SMALL GROUP OF VOLUNTEERS will gulp down billions of tiny, toxin-gobbling contraptions to cure a crippling disease. The devices are not made from the usual machine parts of metal, wire or plastic. They are rebuilt organisms: bacteria, reconstructed from the inside out to perform an intricate feat of medical care.

Researchers working at Synlogic, a Cambridge, Mass., biotechnology start-up, will hand patients daily doses of a pill or a drink loaded with billions of *Escherichia coli* bacteria. These kinds of microbes typically bustle about our innards, occasionally causing infections but generally living innocuous lives. What makes these particular *E. coli* different is that scientists have revamped chunks of their DNA—genetic instructions that tell the microbes what to do—to transform these tiny cells into engines relentlessly driven to devour poisonous loads of ammonia in patients' bodies.

The patients have urea cycle disorder (UCD), a liver enzyme deficiency that can kill newborns and make adults sick. They are born with a faulty gene that produces defective enzymes unable to break down the nitrogen in high-protein foods such as meat, eggs and cheese. Normal enzymes turn excess nitrogen into a chemical called urea, which gets peed away. But for those with the genetic disorder, the excess nitrogen does not leave the body. Instead it generates toxic levels of ammonia that accumulate in circulating blood and inflict havoc when they hit the brain.

Synlogic's engineered bacteria will guzzle extra ammonia. Gut bacteria take in small amounts of ammonia already, using its nitrogen for growth. The retrofit from scientists gives the microbes a new genetic "circuit," a series of genes and regulatory bits of DNA such as volume controls and on/off toggles wired together like transistors in an electronic gadget. Wedged into the ordinary *E. coli*'s genome, the circuit replaces the bacterium's normally slow ammonia-consuming mechanism with a supercharged version, an ammonia-gobbling beast that switches on when it senses the low oxygen levels characteristic of the human gut.

If Synlogic's genetically altered bugs can gorge on ammonia in humans as they have in tests with mice, then tossing down the bacterial concoction every day for the rest of their lives may enable UCD sufferers to survive practically symptom-free. The amplified bacteria will cure a devastating genetic disease, arising in more than 100 new patients a year in the U.S., for which there is not now an adequate remedy. "We've replaced a missing physiological function with a whole new kind of therapy," says Paul Miller, Synlogic's chief scientific officer. "It's an amazingly powerful way to attack disease." Miller's company is crafting similar circuits against more common illnesses such as irritable bowel disease, inflammatory and immune disorders, and even cancer.

Transformed bacteria have a key advantage over more typical drugs, which are chemical-based pills where the only thing doctors can change is the dose. The bacterial circuits can be easily fine-tuned to increase potency or to extend or reduce the time of activity, and they can be turned down so that they become safer. Bacteria's natural ability to sense and respond to their environment also makes them target-specific: they can be programmed to release a therapeutic substance only when at the site of disease. This selective action may avoid the side effects typical of pills that act throughout the body.

IN BRIEF

By taking control of a microbe's genetic circuitry, biologists can turn it into a medical treatment that switches on and off in particular situations.

The change involves connecting protein-coding genes and switches, in the way electrical circuits link conductors, resistors and capacitors.

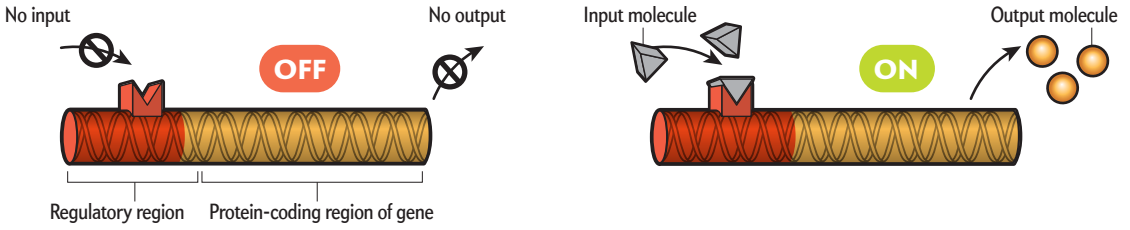
Bacteria are now being modified with new circuits that let them treat genetic diseases, attack tumors and detect antibiotics.

Living Circuits

Genes—and other segments of DNA that switch genes on and off—can be wired together in novel ways. They work like electrical circuits that run household gadgets. These DNA circuits, though, can be placed within living organisms like bacteria to control the microbes' behavior. With that control, synthetic biologists can turn the organisms into living medicine.

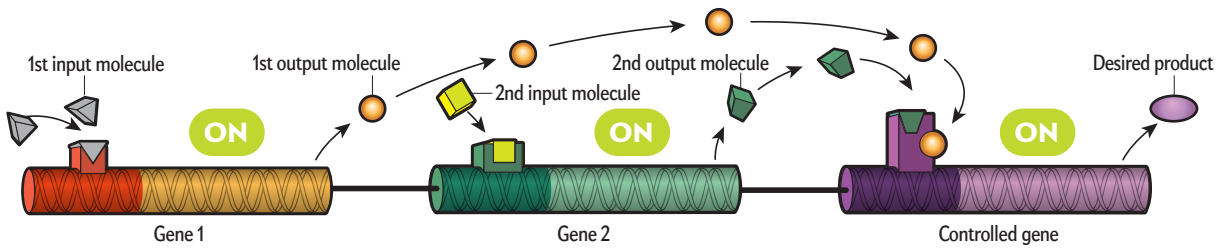
A Simple Switch

In a basic circuit, a gene can be turned on by a particular signal to produce a useful substance. The gene (*orange*) is linked to a regulatory region (*red*). When that region has no input, the circuit is off and produces nothing. But if that region is stimulated by an input molecule (*gray*), it turns the gene on and makes a desired output molecule.



Adding Complex Logic

The switch can be combined with other elements to give biologists more advanced control—logic—over what a microbe does. One example is this "AND" circuit. Gene 1 (*orange*), when switched on, sends output to the controlled gene (*purple*). Gene 2 (*green*), also switched on by an input molecule, sends output to the controlled gene as well. The controlled gene switches on only when stimulated by both gene 1 and gene 2.



Building Bacteria to Fight an Enzyme Disorder

Patients with urea cycle disorder have an enzyme deficiency that lets toxic levels of ammonia build up. Biologists are treating this by making *Escherichia coli* bacteria eat the ammonia. The microbes are engineered to produce large amounts of an amino acid, arginine, and they need to consume ammonia to make it. First a gene (*pink*) that inhibits extra arginine production is turned off. Another gene (*green*) is added, and it switches on when stimulated by a protein called FNR (*yellow*). FNR only does this in a low-oxygen environment such as the human intestines. When the entire synthetic circuit is placed in bacteria, they become arginine-producing machines only when stimulated by ammonia and low oxygen levels. The dual control ensures bacteria do this inside the body, not after they are excreted into the oxygen-rich outside world.

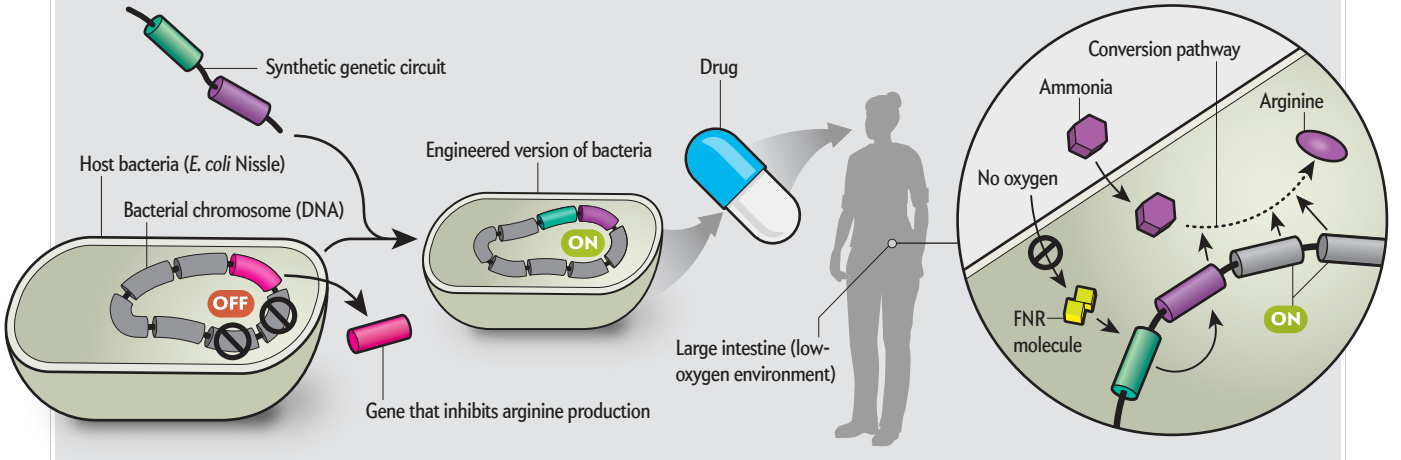


Illustration by Jen Christiansen

The bacteria also may be able to replenish themselves within the human body, something no pill can do. They must still pass safety tests, and researchers acknowledge that they must show that their genetically enhanced bugs will not get unleashed dangerously into the environment. The Food and Drug Administration has given Synlogic the go-ahead to try the therapy in people this year because the strain of *E. coli* being used in the UCD therapy has long been safely prescribed as an oral probiotic to treat inflammatory bowel disease. If the human tests pan out, the company's therapy-in-a-germ will represent the first clinical application to emerge from a relatively new branch of genetic engineering called synthetic biology.

The field rides on advances in manipulating DNA, giving scientists new laboratory tools to link stretches of DNA together and produce effects more powerful than simply changing one gene. "Synthetic biology is now producing some impressive accomplishments," says James Collins, a professor of medical engineering at the Massachusetts Institute of Technology and a leading researcher in the field. Human cells, for instance, have been fitted with enhanced DNA circuits to pump insulin into the bloodstream more precisely than daily injections for diabetics. *Salmonella*—the bacterium associated with food-poisoning outbreaks—has been rejiggered to sneak up on cancer cells and unload a cargo of toxic drugs. The DNA-circuit approach can also diagnose disease: researchers in Boston recently redesigned a microbe to alert doctors to early sepsis infections brewing in the blood of hospitalized patients. Existing tests rarely pick up the problem until patients are much sicker and hard to treat.

The new technology has the potential to be transformative not just for bacteria but for medicine itself. "Biomedicine sits on the cusp of a new revolution in medical care," says Wendell Lim, director of the Center for Systems and Synthetic Biology at the University of California, San Francisco. "Microbial and human cells are becoming versatile therapeutic engines." It was not always such a rosy picture, however.

Unnatural Responsibilities

Synthetic biology offers unusual rewards and risks

By Kevin M. Esvelt

The bold dream of synthetic biology is a world in which all living things can be reliably engineered in ways that help everyone and everything. In this dream, we can use genetics to program living organisms: "if condition A is met, then do action B." To give a near-term example, bacteria might produce a medicinal protein only in the presence of indicators of a particular disease.

Why use living systems and not a vat of chemicals? Because natural systems routinely perform complex chemistry that scientists can only envy, and they do it at room or body temperature, without the need for toxic chemicals or outside aid. Better still, living factories are far more energy-efficient than anything made of silicon and metal. Biology is fast, clean and green. And we should use such systems because people and ecosystems are alive, and the best way to repair life is with life. To fight an evolving pathogen, use an evolving cure.

There are problems, though, in bending nature to our own ends. Adopting an organism to work for us means it is using energy that could otherwise be spent replicating, so it will not reproduce as well as competitors. Evolution will constantly select for faster-reproducing mutants that no longer do what we want. Biology's greatest strength is its capacity to replicate and evolve, but that also presents the greatest challenge.

One way around this is to incorporate limits on the ability to change, particularly for those few cases where our changes might be able to spread in the wild. For example, one approach is to employ unnatural amino acid tethers: they make essential proteins within cells wholly dependent on chemicals that do not exist in nature. If the amino acids are withheld, the proteins will not function, and the bacteria cannot grow out of control. We are also better at building within the scope of evolutionary limits: microbes are now programmed to release a burst of complex molecules and then die, mostly avoiding evolutionary selection against production. Cellular pathways can be reworked to eliminate most unwanted side effects. Engineered viruses that target bacteria will kill invading pathogens, multiply until the invaders are gone and then stop, leaving the patient untouched.

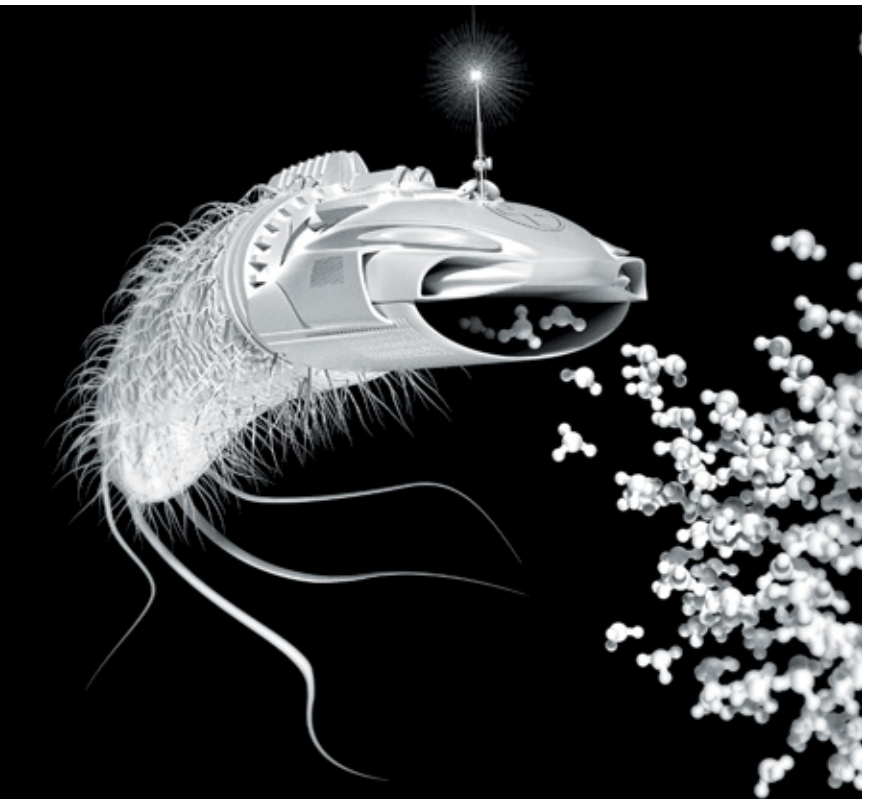
We must also be careful to make sure benefits always outweigh the risks of reworking organisms. Mistakes are inevitable. Thus, the projects have to be worth it, especially the earliest examples that must justify the technology to the world. Bacteria can be built to make a slightly cheaper flavor of vanilla, but is that a significant boon to humanity or the environment? This is likely not enough to be a pioneering example of a novel technology or to justify its use. On the other hand, building cells that can selectively destroy cancer or cure diabetes is something everyone can get behind.

The greatest biological risk to civilization stems from pandemics of infectious disease. Until now, these were inevitable, but we might soon use biotechnology to stop them. Ordinarily, a person's body confronts an invading pandemic pathogen by evolving its own defenses, creating a whole series of antibodies in the hope that one will effectively neutralize the invader. It is a

ENGINEERING BIOLOGY

FOR THE PAST 40 YEARS SCIENTISTS have used genetic engineering to discover and manipulate genes to reveal the intricate machinery that rules all life. But they were limited in their understanding of how the different parts fit together and worked in real life. Things that looked good in a test tube fell apart when tried in a real cell or animal. When synthetic biology got started, there was a lot of early hype, Collins admits. But beginning about 17 years ago, he and like-minded biologists, fueled by advances in sequencing and synthesizing DNA, have been employing the newly discovered genes and other DNA elements as interchangeable components to design and build medical applications that actually work outside a glass dish.

Part of the change has come from scientists with a bent for tinkering like engineers. "There's been a convergence of new



process of trial and error that takes time; this is why you are typically sick for three to four days before getting well. Sometimes that is just too long, and people die. A better strategy is to give the human body a head start: Take the genes for several known protective antibodies, put them into the harmless shell of a virus and inject that virus into people. The virus enters their cells, which then start to churn out already optimized protective antibodies against the invader, ending the threat.

Finally, as scientists we need to respect the fact that engineering life unsettles many people. That means we must consider social risks as well as technical ones. We cannot just explain what we are doing—that only convinces other scientists. Instead we must relate why we care, who could benefit and what the risks may be. Above all else, we should actively invite concerns and criticism from the earliest stages because no matter how great our expertise, we cannot reliably anticipate every consequence on our own. At its best, science is a fundamentally shared undertaking. If we are to engineer life, let us all decide how to do it together.

Biologist ***Kevin M. Esvelt*** *leads the Sculpting Evolution research group at the Massachusetts Institute of Technology's Media Lab.*

ideas in the past few years that's driving the field," says Jeff Hasty, who co-directs the BioCircuits Institute at the University of California, San Diego. Hasty started his science career 20 years ago with a Ph.D. in physics. Only partly joking, he describes himself now as a "hybrid computational/molecular biologist." Synthetic biology is populated with folks such as Hasty, who embrace an engineer's inclination to "make stuff," he says.

"Much as an electrical engineer uses conductors, resistors and capacitors to create new electrical devices," Collins says, "we put together the components of biology—genes, proteins, RNA, transcription factors and other DNA—to create a particular function."

Collins notes that electronic gadgets are useful models for understanding genetic circuits. Consider an air conditioner thermostat. It senses an input—warming air temperature—and responds with an output—turning on the AC. When the air is cooled, the thermostat switches the machine off. Single-cell microorganisms such as bacteria survive in a similar way. Ever alert to an input, say, the presence of a competing germ, a bacterium responds with an output, secreting a natural antibiotic to kill its enemy.

The circuit builders of synthetic biology separated from straight genetic engineers as a result of coincidental insights by Collins and another research team. In 2000 Collins's lab, which was then at Boston University, reported making a genetic "toggle switch," one of two synthetic gene networks published in *Nature* in January of that year. The twin reports (the other was from a group at Princeton University) are generally cited as launching synthetic biology because they showed that "we could take parts of cells and link them together to generate a novel circuit the way an engineer might," Collins says. (It is no coincidence that, at the time, he was surrounded by circuits. He was running a bioengineering lab that was designing mechanical limbs for the disabled. Today Collins works at synthetic biology facilities in three different institutions in the Cambridge area. And he has trained about two dozen scientists—among them Hasty—who now have their own operations.)

In the years following the first primitive DNA-based switches, the still small community of synthetic biologists entered into a can-you-top-this competition, cooking up increasingly complex circuits that harnessed cells' natural sense-and-respond behavior. "As we went along, we learned, more than we first realized, how remarkably versatile the cell is," U.C.S.F.'s Lim says. He describes the cells as adaptable automotive "chassis" into which researchers can swap different genetic engines to carry out therapeutic functions.

One of the first commercial applications emerged in 2006 from scientists led by Jay Keasling of the University of California, Berkeley. Backed with a $42.6-million grant from the Bill & Melinda Gates Foundation, Keasling's lab refashioned the metabolic pathways of ordinary baker's yeast with lab-designed circuitry that turned sugar molecules into a critical ingredient for making the malaria drug artemisinin. Previously, the precursor

molecule for manufacturing the drug was extracted by hand from sweet wormwood plants native to Asia, a costly process that made the drug too expensive for use in poor regions where malaria is rampant. "It was a breakthrough," Collins says. "It was the first time a network of genetic material, not just one gene at a time, was used to transform a microbe—the yeast—into a solution for an important real-world problem."

BROKEN CIRCUITS

BUT IT DID NOT LAUNCH a revolution. At about that time, J. Craig Venter, a famous genome scientist and co-founder of Synthetic Genomics in La Jolla, Calif., joined the synthetic biology fray, giving the technology its first public star. His highly publicized objective, which garnered a whopping $300-million investment from Exxon in 2009, was to make gasoline from algae found in pond scum. In 2010 Keasling received a $134-million grant from the Department of Energy to fund research aimed at coaxing yeast cells to synthesize diesel from chemicals in sugar plants. Earlier that decade Keasling had co-founded Amyris, a biotech company in Emeryville, Calif., to commercialize the alternative fuel technology.

Both projects wound up giving synthetic biology a bad rap. After four years, Exxon and Venter, as well as Amyris, essentially gave up the synthetic oil project. The cost of scaling up commercial production, as compared with the current low price of oil and natural gas, has forced Amyris and several other biofuel-from-microbes start-ups to put the venture on hold. These companies were disasters for investors. Amyris and different synthetic biotech companies launched between 2005 and 2010 on the promise of making oil from bugs continue to produce notable advances in biocircuitry design. But their new genetic circuits are not as widely celebrated. Instead these one-time rock stars of synthetic biology are reconstructing microbes to fabricate chemicals used in manufacturing solvents and lubricants, as well as the principal ingredients for cosmetics, fragrances, detergents and over-the-counter health products.

While Wall Street investors and the science media largely focused on the headline-grabbing dreams—and the less dreamy waking reality—of biofuels from bugs, without fanfare Collins and his colleagues spent much of the new century's first decade working out technical hurdles for what was to come next: better medicine. After years of tedious experiments, in 2010 Collins engineered a bacterium that, in lab tests, weakened drug-resistant germs enough to make them vulnerable to existing antibiotics.

At about the same time, Tim Lu, another Collins postdoctoral protégé (with a Ph.D. in electrical engineering and computer science from M.I.T., as well as a medical degree from Harvard University), embedded circuits into a different kind of microbe, a virus that infects bacteria. Certain hard-to-treat infections arise when bacterial colonies encircle themselves within a gooey, protective biofilm. These bacteria may have evolved the biofilm to fend off the marauding viruses, which are called bacteriophages. Lu designed his circuit in the virus with a gene that codes for a biofilm-degrading enzyme. Lu's circuit also programmed the bacterial viruses to sense the presence of biofilm, infiltrate its defenses and respond by off-loading the film-busting enzyme.

Lu and Collins realized it might take years to perfect their infection fighters. But they also thought their bacteria might be ready sooner for another commercial use. In a meeting in 2013, Lu and Collins told a gathering of biotech funders at Atlas Venture in Cambridge that their labs' genetically enhanced microbes could be transformed into living sentinels able to provide early detection of disease within the human body or contaminants in the air or water.

The Atlas executives, however, were taken by another, related idea. They envisioned greater profits if the bacteria could be wired not simply to act as sentinels but to sense a health problem within the human gut—and then generate a therapy to treat it. The idea for Synlogic was born. In early 2015, about six months after the company hired its first researchers, it used Collins and Lu's inventions to create an early version of the UCD therapy.

The circuit is designed to first fabricate a cancer drug inside the bacterium. It then directs the microbe to slip into the interior of a tumor, carried by the bloodstream, and self-destruct. When the microbe bursts apart, it releases its payload of drugs.

"I've been in the pharmaceutical industry a long time, and I've never seen a pharmacologic go from a scientist's idea to clinical testing in so short a time," says Bharatt Chowrira, a consultant to Synlogic.

REPURPOSED PARTS

THE TREATMENT'S COMPONENT is an especially clever circuit assembled with genetic parts that biologists uncovered during decades of *E. coli* research. The Synlogic circuit changes the bacterium's usual ammonia-to-nitrogen-to-cell growth mechanism into a factory to churn out an amino acid called arginine. The researchers chose arginine because its cellular manufacturing demands more nitrogen than other amino acids. The need to make arginine turned the bacterium into an ammonia-gulping organism because it was desperate to take in nitrogen. With the circuit embedded into its genome, the microbe winds up producing "5,000 times more arginine than the normal

strain of bacteria," says Jose-Carlos Gutiérrez-Ramos, Synlogic's chief executive.

The circuit depends on a switch, a sequence of DNA that responds to a protein called FNR. Like the thermostat in an air conditioner, FNR is sensitive to changes in the bacteria's surroundings. It enables *E. coli* to respond to an environment that lacks oxygen. When FNR senses that the bacteria are in a low-oxygen environment such as the large intestine, it turns on genes the microbes need to thrive. When the bacteria move outside the body, where there is plenty of oxygen, FNR is silent. This is a safety mechanism designed to prevent runaway organisms with high growth rates. Once the microbes exit the intestines and hit our oxygen-rich atmosphere as feces, the entire system shuts down, and the *E. coli* die.

There was one problem, though, Synlogic's Miller says. *E. coli*'s genome contains a "repressor switch," a gene called *argR,* that shuts down arginine production when it senses the bacteria have enough. So designers needed a mechanism to deactivate *argR* in their new circuit. Synlogic researchers accomplished this by knocking out the long DNA sequence that surrounds and includes *argR* with a nearly identical stretch of DNA in which the *argR* gene is deleted.

Several synthetic biologists have come up with other genetic circuitry to deliver anticancer drugs deep inside tumors. U.C.S.D.'s Hasty has armed a strain of *Salmonella* bacteria that is not harmful to humans with a special set of genetic instructions. Hasty's experimental cancer therapy takes advantage of recent research that found that some bacteria often reside inside tumors. Scientists believe but are not certain that bacteria that naturally circulate in the bloodstream are attracted to tumors "because the environment provides a safe refuge from the immune system," Hasty says.

Hasty's genetic program forces the *Salmonella* to carry out a two-step process. The circuit is designed to first fabricate a cancer drug inside the bacterium. It then directs the microbe to slip into the interior of a tumor, carried there by blood the tumor needs for nourishment. At a moment directed by the circuit, the *Salmonella* self-destructs. When the microbe bursts apart, it releases a payload of drugs. "Sort of like a kamikaze mission," Hasty says.

In another ingenious bit of designing, Hasty added several genetic components to make the therapy self-renewing. "We introduced into the bacteria a 'quorum-sensing' system that can detect when *Salmonella* reproducing inside the tumor achieve a certain population," he says. When the multiplying microbes reach a high-enough density, the quorum sensor triggers the release of a protein that slices the *Salmonella* apart from the inside, spilling out the anticancer drug. This act of suicide kills most but not all of the *Salmonella*. Those that remain begin multiplying again, driving the cycle to repeat itself over and over.

The idea of attacking a tumor cell from within is especially attractive because most chemotherapy drugs work by eating away at a cancer cell's outer walls. In a study in mice, the bacterial therapy did not work any better than standard chemotherapy when delivered alone, Hasty says. "But when we combined it with chemotherapy, we observed decreases in tumor sizes and a 50 percent increase in life expectancy in mice with a type of metastatic cancer," he notes.

SEARCHING FOR APPROVAL

THE *SALMONELLA* WORK is still being refined. Synlogic's UCD treatment is much further along, and the FDA's approval process for this first therapy to involve genetically modified microbes is being scrutinized closely. The agency has released rules to regulate the microbe-based therapies under a new category it calls "live biotherapeutic products." Unlike other medicines (with the exception of some vaccines), the new therapies are composed of organisms that are alive and have the potential to mutate as they reproduce. Because of this, the FDA wants assurance that the makeup of the therapies will not vary from one batch to another. In addition, it wants proof that the microorganisms cannot survive in the environment by themselves, as Synlogic claims. "Many of us are watching how Synlogic is handled by the regulators," Hasty says. "If they can't get their therapy approved, we may all be in trouble."

An FDA review process for cells refashioned to detect disease, not produce new compounds within the human body, most likely will be faster and less expensive than one for a medical treatment. Many emerging synthetic biology projects are aimed at repurposing bacteria to diagnose the earliest presence of an ailment. "Gut bacteria can be engineered to sense, remember and report on their experiences as they pass through the intestine," says Pamela Silver, a founding member of Harvard's department of systems biology. Silver's lab has created a proof-of-principle diagnostic tool composed of a genetic circuit that enables bacteria to identify the presence of an antibiotic in the digestive system of mice. The circuit produces a fluorescent signal that is visible in fecal waste if the antibiotic is active.

"This synthetic circuit demonstrates our ability to build a living diagnostic—in this case, exposure to antibiotic," Silver says. The eventual goal is to use the technology to detect potential disease activity within the intestines. "The human intestine is a 'dark' place—difficult to explore yet the site of much activity affecting daily health and debilitating diseases, inflammation being one of most prevalent," she says. Current diagnostics for digestive ills are invasive and costly.

A living diagnostic, Silver says, offers a cheap, potentially more sensitive approach. And if it passes muster, new functions can be added. "We also believe the diagnostic circuits can be further engineered to deliver treatment for bowel disease at the site of inflammation," she says. "The power of the new circuits is creating all manner of possibilities." SA

MORE TO EXPLORE

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FROM OUR ARCHIVES

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BIOLOGY

LUTION AT THE LIMITS

Studies of fishes that inhabit toxic sulfide springs reveal mechanisms of natural selection

By Rüdiger Riesch and Martin Plath

Illustration by Mark Ross

Rüdiger Riesch is a lecturer in evolutionary biology at Royal Holloway, University of London. His research focuses on the mechanisms that create, maintain and constrain biodiversity.

Martin Plath is a professor of basic and applied zoology at Northwest A&F University in Yangling, China. He studies behavior, behavioral evolution, local adaptation and speciation.

ON A SEPTEMBER AFTERNOON IN TABASCO IN SOUTHERN MEXICO, THE TWO of us made our way through the rain forest toward the sound of flowing water, in pursuit of a small but important fish. Iridescent blue morpho butterflies flitted by, and howler monkeys roared from the trees overhead, offering welcome distractions from the broiling heat and humidity. Soon we spotted a green kingfisher diving into the nearby creek and then returning to its perch to consume its catch. The bird had nabbed the same kind of fish we were after: an Atlantic molly (*Poecilia mexicana*), a member of a family of fishes called poeciliids, whose females give birth to live young and whose males have flashy colors that make them popular among aquarists around the world.

For a moment, we remembered with longing our fieldwork during the previous days, when we had studied Atlantic mollies at a locale only few kilometers away, a site we call Arroyo Cristal for its crystal-clear waters. Our research there had been a pleasure—we could sit on large stones and logs, dangling our legs in the water to cool off while our study species swam right between our feet.

Fieldwork on this particular day was bound to be different, however. Long before we actually reached our destination, the smell of rotten eggs filled the air, and the waters that now slowly came into view were hardly clear. Instead they were turbid and milky-white from the high concentration of sulfur particles suspended in them. Reaching the water's edge, we saw that all the submerged rocks were coated in slimy sulfur bacteria, and the many fish in the smelly waters were hanging out at the surface with their mouths agape, seeming to gasp for air.

A newcomer would have found it hard to believe we were looking at the same species we had observed in Arroyo Cristal the day before. After all, the habitat here was drastically different, and these fish had far larger heads and showed that distinctive surface-breathing behavior. But there was no doubt about it, we had finally arrived at our field site for the day: El Azufre, a small creek with naturally toxic levels of hydrogen sulfide (H_2S) and Atlantic mollies that have evolved to survive in them.

H_2S-rich environments can kill most nonadapted organisms, including humans, within minutes or seconds. Given the toxicity of sulfide waters, it should come as no surprise that scientists have long been fascinated with the organisms that inhabit them. Indeed, researchers have been studying sulfide-adapted poeciliid fishes since the 1960s. But the past 15 years have seen a surge of scientific studies on the ecology and evolution of these creatures, thanks in large part to advances in genome-sequencing technology that have enabled investigators to see, at a molecular level, how organisms adapt to environmental challenges. By combining field observations of these fishes with analyses of their DNA, we and our collaborators have gained fascinating new insights into the inner workings of natural selection, a key mechanism of evolution. In addition to pulling back the curtain on natural selection, this research is allowing scientists to explore the limits of adaptation in fishes. Armed with that information, we might one day be able to forecast the fate of species in the face of pollution and other human-mediated habitat alterations.

IN BRIEF

Several species in the family of poeciliid fishes have managed to colonize creeks and rivers containing toxic levels of hydrogen sulfide.

The fish share traits such as a large head and big offspring that aid survival in their deadly environment.

Analyses of the DNA of these species indicate that they acquired these similar adaptations via different molecular pathways.

The extreme environment may spur speciation.

EXTREME HABITATS

POECILIID FISHES are not the only organisms to adapt to seemingly inhospitable conditions. Our planet contains a variety of extreme environments—from scalding thermal springs and highly pressurized ocean depths to salt deserts and sunless subterranean caves—and all of them harbor life-forms. Still, sulfidic waters are especially hostile to life. Hydrogen sulfide is a widespread toxicant that can enter the environment naturally at freshwater sulfide springs, hydrothermal vents on the ocean floor, or coastal mudflats and salt marshes. Naturally occurring H_2S can either stem from geologic activity that releases the toxic gas from deep within the earth—as occurs in the sulfide creeks we are studying—or from the decay of large amounts of organic matter. It can also enter aquatic environments as a pollutant from human activities, such as paper milling, leather tanning, and production of natural gas and geothermal power. Even very small amounts of H_2S are acutely toxic to most animals because the compound binds freely available oxygen in the environment, which deprives them of breathable oxygen, and it blocks the activity of the hemoglobin protein, which transports oxygen in the blood. All this activity results in death by suffocation. H_2S also blocks the process by which cells extract energy from food. Compounding these dangers, it freely penetrates cell membranes in the delicate gill tissues of fish, so they do not have to consume it to suffer harm. Humans also risk harm when inhaling H_2S, thus we either try to keep our exposure time to H_2S short, or we wear protective gear when working in the vicinity of sulfide sources for extended periods. Not surprisingly, both natural and anthropogenic pulses of H_2S discharged in aquatic habitats around the world have caused mass mortalities in fishes and other organisms.

Yet various members of the teleost group of fishes—the dominant group in today's oceans and freshwater habitats and the group to which the poeciliids belong—have adapted to environmental H_2S. Some of the most intriguing of these species, including sinuous eelpouts and flounderlike flatfish, live around hydrothermal vents and cold vents on the ocean floor. Reaching these animals is difficult and expensive, however, requiring the use of robust submarines, which precludes most of the experimental work we are interested in. Our own research has therefore focused on the more readily reachable poeciliids, particularly the more than 10 different species of mollies, guppies, swordtails and mosquitofish that have independently colonized dozens of toxic sulfide springs in small creeks and rivers across the New World.

COPING MECHANISMS

SULFIDE-ADAPTED POECILIIDS have evolved a number of traits that enable them to thrive in their toxic environs. Some of these traits are behavioral. For instance, in response to the low oxygen availability in sulfidic water, the fishes spend a lot of time near the surface, where they can exploit the more highly oxygenated topmost layer of the water column. (Although the fishes practicing this so-called surface respiration look like they are gulping air, they cannot actually do that. Instead they are gulping oxygen-rich water.) The behavior has a price in that it limits the time left for other activities, such as foraging, but it helps them get the oxygen they need.

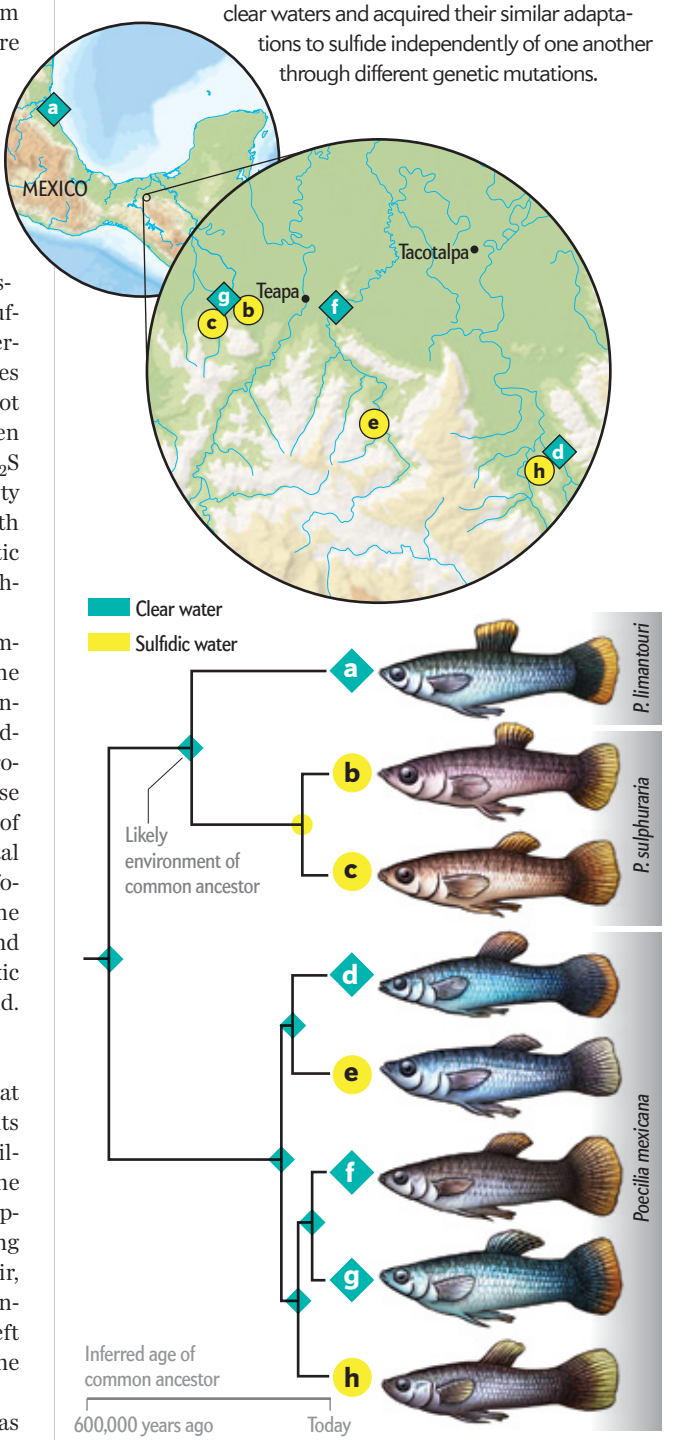
The limited availability of oxygen in these toxic waters has also shaped physical characteristics of these fishes. Most con-

SOURCE: "PARALLEL EVOLUTION OF *COX* GENES IN H_2S-TOLERANT FISH AS KEY ADAPTATION TO A TOXIC ENVIRONMENT," BY MARKUS PENNINGER ET AL., IN *NATURE COMMUNICATIONS*, VOL. 5, ARTICLE NO. 3873, PUBLISHED ONLINE MAY 12, 2014

FINDINGS

Same but Different

Various members of the family of so-called poeciliid fishes inhabit toxic sulfide springs in creeks and rivers across the New World. They have a number of features in common that help them cope with the inhospitable conditions, including proportionately larger heads and mouths. DNA analyses of these fishes indicate that they evolved from ancestors in the surrounding clear waters and acquired their similar adaptations to sulfide independently of one another through different genetic mutations.



Map by Mapping Specialists, Illustrations by Jillian Walters

spicuously, sulfide-spring populations have significantly larger heads than their counterparts from nonsulfidic habitats. This enlargement of the head stems from an expansion of the gill region, which helps the fishes take in more oxygen. One particular sulfide-adapted species, the sulfur molly (*Poecilia sulphuraria*), which is endemic to a few sulfide springs in Tabasco and Chiapas in Mexico, has also evolved odd-looking lower lip appendages to further aid oxygen intake. Similar protuberances are also found in nonpoeciliid fishes from various low-oxygen environments around the globe and are thought to facilitate the skimming of the uppermost water level for its oxygen by expanding the surface area of the mouth region.

In addition to evolving traits that enhance oxygen intake, fishes that dwell in sulfide springs have undergone adaptations that help them detoxify H_2S. All animals make an enzyme called sulfide:quinone oxidoreductase (SQR) that allows them to detoxify very low concentrations of H_2S by binding to it and forming nontoxic compounds. But once concentrations of the toxicant get too high, as occurs in sulfide springs, the enzymes cannot catch it all, and the excess starts interfering with cells' ability to produce energy. Our fishes have evolved modifications to the SQR pathway that enable detoxification at higher concentrations of H_2S.

Sulfide-adapted poeciliids also give birth to much larger babies than their counterparts that inhabit nontoxic environs. Although the larger size of the babies means that the fishes have fewer offspring, the strategy makes sense for their environmental conditions. An increase in size results in a larger increase in volume, relative to a smaller increase in surface area. Thus, slightly larger offspring will have a higher volume-to-surface-area ratio. This arrangement is beneficial because it makes more body tissue available to detoxify the incoming H_2S while only slightly increasing the body surface exposed to the toxin.

Perhaps the most striking thing about sulfide-adapted poeciliids is that they share many of the same adaptations. We have found that sulfide populations across various species and geographical regions have evolved the same novel traits when compared with their ancestors living in the surrounding sulfide-free waters.

The high degree of similarity among these separate lineages of sulfide-adapted fishes raises an intriguing question: Did the populations of poeciliids that have repeatedly and independently adapted to H_2S undergo the same DNA changes in evolving their shared adaptive traits, or did they acquire the traits via different molecular pathways? Working with Markus Pfenninger of the Biodiversity and Climate Research Center in Frankfurt, Germany, and several other colleagues, we decided to find out. We analyzed DNA from several hundred Atlantic mollies from two population pairs—each of which consisted of one sulfide-adapted group and its nonadapted ancestors—from two parallel river drainages in southern Mexico. (The same river drainage can have both sulfide-rich and sulfide-free tributaries.) Statistical methods allowed us to infer how many variants exist for any given gene throughout the genome. They also allowed us to determine which variants showed signs of being driven to high frequency in these populations by natural selection—that is, by aiding survival and reproduction—as opposed to becoming abundant by chance.

We found that the genomic changes in one sulfur-adapted population tended to be unique to that population and not shared with the other. We then ran the genes that differed between the two sulfide-adapted populations through a database

NATURALLY TOXIC creek in southern Mexico called El Azufre gets its milky appearance from suspended sulfur particles.

COURTESY OF MATTHIAS SCHULTE

that lists the functions and interactions of various genes. It turns out that even though the exact genes that have been altered differ by population, most of them are involved in the regulation of the same so-called metabolic pathways—chemical reactions that support life. (Metabolism in this sense refers not only to how fishes burn energy from food but also to the actions different proteins in the biochemical machinery take to keep them alive, which could be involved in all kinds of adaptations.) What our data suggest, then, is that there are many genetic routes to evolving similar adaptations to an environmental stressor.

A recent study by Joanna Kelley of Washington State University, Michael Tobler of Kansas State University and their colleagues further supports this notion. They found that patterns of gene expression—the use of genes to make proteins and certain other molecules—differed from population to population among the sulfide-tolerant Atlantic mollies of southern Mexico. But expressions of genes involved in regulating metabolic pathways were all elevated to roughly the same degree across the board. This pattern of gene activity mirrors what we see in the gene sequences themselves: the fish have followed different molecular paths to the same solutions to the problem of living in toxic waters.

Studies of sulfur-adapted poeciliids also bear on another fundamental question in evolutionary biology. Whereas some spe-

cialists have argued that populations exposed to the same stressors should undergo fairly similar evolutionary changes, others have contended that the exact sequence of evolution could affect the outcome. The thinking behind the latter idea is that if certain, randomly arising mutations represent key adaptations, they should spread fast in the respective sulfide-adapted population. Different initial key adaptations could then affect the subsequent evolutionary trajectory of a given population by altering the selective advantage of mutations arising at a later stage. Our results support this notion. We looked at three populations of sulfide-adapted Atlantic mollies and found that, in two of them, sulfide resistance had evolved in a gene that makes a key protein called cytochrome c-oxidase (COX) and is involved in generating the cell's main energy source. The third population did not acquire this initial key adaptation and had to come up with another evolutionary solution to protect its energy-making process from the toxic sulfide.

HOTBEDS OF EVOLUTION

THE CHALLENGES OF COLONIZING such a hellacious environment are formidable enough that one might reasonably wonder why on earth natural selection would ever favor such an undertaking. But there is a major upside: an absence of most other species, including other fish predators and competitors for food. In sulfidic creeks in southern Mexico, for example, only specialized poeciliids can be found—none of the numerous other fishes from surrounding waters are present.

In fact, as forbidding as these sulfidic waters are, they may actually foster, rather than stifle, the evolution of new life-forms. In the conventional view of speciation, prolonged separation of formerly connected populations by geographical barriers allows the populations to evolve along their own evolutionary trajectories until they become so different from one another that they qualify as different species. But biologists are uncovering increasing evidence that adaptation to divergent ecological conditions can promote speciation even in the absence of such barriers. Observations of sulfide-adapted poeciliids bolster this scenario.

We have found that adaptation to one habitat type, be it sulfidic or nonsulfidic, limits the potential for fishes to move freely into the other habitat type. This form of natural selection essentially leads to sulfide-adapted fishes occurring only in sulfidic sites, and vice versa, even when the two habitats are separated by only a few dozen to a few hundred meters.

Other factors are important in creating and maintaining reproductive isolation in these systems, such as predation (maladapted individuals fall victim more easily to predators). If migration between habitats does occur or if members of the different populations, known as ecotypes, meet in mixing zones between sulfidic and nonsulfidic habitats, the fishes will not interbreed. Mate choice experiments have revealed that females in nonsulfidic waters prefer to mate with males of their own ecotype. Whether or not (and to what degree) females exhibit such a preference seems to depend on the strength of natural selection: we found that females' preferences for their own ecotype were stronger when natural selection against migrating sulfide-adapted males was weak. It seems that when females had a higher likelihood of encountering alien males—and thus of producing unfit hybrid offspring—they evolved a stronger aversion to the outsiders. In contrast, when natural selection against migrants was strong, and the likelihood of encountering them was therefore low, the females were unlikely to evolve an aversion to the alien males.

The exact number of poeciliids that evolved new species while adapting to sulfide springs is uncertain because, in many cases, we do not yet know how far genetic differentiation has progressed or if interbreeding with neighboring populations still occurs. But some of the sulfide-adapted lineages that show all these adaptations are approximately 100,000 years old—quite young in evolutionary terms. That they have evolved their distinguishing characteristics and achieved a certain degree of reproductive isolation from their neighbors in nontoxic waters in a relatively short time hints that the extreme conditions of the sulfidic waters may actually hasten speciation. A recent study of ours supports this notion. We found that the degree of reproductive isolation across sulfide-adapted poeciliids directly correlates with the concentration of H_2S toxicity in each ecosystem.

If the poeciliids have been able to quickly evolve adaptations to a natural toxicant, are they equipped to adapt to toxic pollution from human activities? A study published last year in *Science* by Noah Reid, now at the University of Connecticut, and his colleagues found that killifish (which belong to a different family of fishes than the poeciliids, albeit a related one) from polluted sites in North America were capable of repeated rapid evolutionary adaptation to toxic pollution from industrial complexes. The authors suggest this might be the result of a large amount of genetic variation in killifish, which gave them a lot of preexisting genetic tools to "choose" from in adapting to new selective pressures from pollution. Whether or not the poeciliids are similarly equipped is not yet fully understood, although our research suggests that new DNA mutations are more important to these fishes than standing genetic variation is. But, taken together, the killifish research and our own findings do seem to indicate that at least a few relatively small and fast-lived fishes that produce several generations a year might, under certain conditions, be able to adapt even to some of the drastic environmental change stemming from human activities.

Many questions remain. For example, we do not yet understand why the presence of H_2S has led to predictable adaptations and reproductive isolation in some ecosystems but not others. But techniques for DNA sequencing are rapidly improving, and costs are steadily decreasing. Given these trends, along with the recent publications of the genomes of several poeciliid species, we expect to soon make great gains in our understanding of the genetic mechanisms governing the shared and unique patterns of evolution in these deadly waters. SA

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SOCIAL SCIENCE

INSIDE THE ECHO CHAMBER

COMPUTATIONAL SOCIAL SCIENTISTS ARE STUDYING HOW CONSPIRACY THEORIES SPREAD ONLINE—AND WHAT, IF ANYTHING, CAN BE DONE TO STOP THEM

By Walter Quattrociocchi

IN BRIEF

Despite optimistic talk about "collective intelligence," the Web has helped create an echo chamber where misinformation thrives. Indeed, the viral spread of hoaxes, conspiracy theories, and other false or baseless information online is one of the most disturbing social trends of the early 21st century.

Social scientists are studying this echo chamber by applying computational methods to the traces people leave on Facebook, Twitter and other such outlets. Through this work, they have established that users happily embrace false information as long as it reinforces their preexisting beliefs.

Faced with complex global issues, people of all educational levels choose to believe compact—but false—explanations that clearly identify an object of blame. Unfortunately, attempts to debunk false beliefs seem only to reinforce them. Stopping the spread of misinformation is thus a problem with no apparent simple solutions.

Illustration by Chris Malbon

Walter Quattrociocchi coordinates the Laboratory of Computational Social Science at the IMT School for Advanced Studies Lucca in Italy. His research focuses on the quantitative characteristics of social dynamics, from how opinions are formed to the way information spreads. Quattrociocchi is particularly interested in the origin, production, and spread of online narratives and social contagion.

In the summer of 2015 Governor Greg Abbott gave the Texas State Guard an unusual order: keep an eye on the Jade Helm 15 exercise, just in case the online rumors are true. In reality, Jade Helm 15 was a routine eight-week military exercise conducted in Texas and six other states. In the online echo chamber, however, it was something more sinister: the beginning of a coup ordered by President Barack Obama.

Conspiracy theories are nothing new, but in an age of rampant populism and digital activism, they have acquired new power to influence real-world events—usually for the worse. In a 2013 report on global risks, the World Economic Forum named the viral spread of baseless or false information as one of the most dangerous social trends of the age, on an equal footing with terrorism. With antidemocratic politicians on the rise throughout the West, we are now seeing the danger of viral misinformation become manifest. People are surprisingly bad at distinguishing credible information from hoaxes. In my country, according to the Organisation for Economic Co-operation and Development, more than half of Italians between the ages of 15 and 65 have poor literacy. And social media have made it easy for ideas—even false ones—to spread around the globe almost instantaneously.

Social scientists have recently made significant progress in understanding the spread and consumption of information, its effect on opinion formation, and the ways people influence one another. Advances in technology have made it possible to exploit the deluge of data from social media—the traces that people use as they choose, share and comment online—to study social dynamics at a high level of resolution. The approach, called computational social science, unites mathematics, statistics, physics, sociology and computer science, with the aim of studying social phenomena in a quantitative manner.

By applying the methods of computational social science to the traces that people leave on Facebook, Twitter, YouTube and other such outlets, scientists can study the spread of conspiracy theories in great detail. Thanks to these studies, we know that humans are not, as has long been assumed, rational. Presented with unfiltered information, people will appropriate that which conforms to their own thinking. This effect, known as confirmation bias, fuels the spread of demonstrably false arguments—theories about global mega conspiracies, connections between vaccines and autism, and other nonsense. And unfortunately, there seems to be no easy way to break this cycle.

THE ECHO CHAMBER

AT THE IMT SCHOOL for Advanced Studies Lucca, my colleagues and I have spent the past five years investigating the spread of information and misinformation on social networks. The research group comprises two physicists (Guido Caldarelli and Antonio Scala), a statistician (Alessandro Bessi, now at the University of Southern California's Information Sciences Institute), a mathematician (Michela Del Vicario), and two computer scientists (Fabiana Zollo and me). We are especially interested in learning how information goes viral and how opinions are formed and reinforced in cyberspace.

One of our first studies on the subject, which we began in 2012 and published in 2015, was designed to learn how social media users treat three different types of information: mainstream news, alternative news and online political activism. The first category is self-explanatory: it refers to the media outlets that provide nationwide news coverage in Italy. The second category includes outlets that claim to report information that the mainstream media have "hidden." The final category refers to content published by activist groups that use the Web as a tool for political mobilization.

Gathering information for our study, especially from alternative sources, was time-consuming and painstaking. We collected and manually verified various indicators from Facebook users and groups active in hoax busting (*Protesi di complotto, Bufale un tanto al chilo, La menzogna diventa verità e passa alla storia*). From the 50 Facebook pages that we investigated, we analyzed the online behavior of more than two million Italian users who interacted with those pages between September 2012 and February 2013. We found that posts on qualitatively different topics behaved very similarly online: the same number of users tended to interact with them, to share them on social media and to debate them. In other words, information from major daily newspapers, alternative news sources and political activist sites all reverberate in the same way.

Two different hypotheses could explain this result. The first possibility was that *all* users treat *all* information equally, regardless of its veracity. The other was that members of certain interest groups treat all information equally, whether it is true or not, *if it reinforces their preexisting beliefs*. The second hypothesis

SCIENTIFIC AMERICAN ONLINE For more on the spread of misinformation, go to ScientificAmerican.com/apr2017/misinformation

was, to us, more interesting. It suggested that confirmation bias plays an important role in the spread of misinformation. It also suggested that, despite optimistic talk about "collective intelligence" and the wisdom of crowds, the Web has in fact driven the creation of the echo chamber.

THE MANAGER AND THE MESSAGE

THE NEXT STEP was to test these two hypotheses. We decided to compare the online behavior of people who read science news with that of people who usually follow alternative news and conspiracy theories. We chose these two types of content because of a very specific difference—whether they have a sender, a manager of the message. Science news is about studies published in scientific journals: work by authors and institutions that are known quantities. Conspiracy theories, in contrast, have no sender: they are formulated to amplify uncertainty. The subject is always a secret plan or truth that someone is deliberately concealing from the public.

There is another major difference between science news and conspiracy theories. Whether true or not, science news belongs to a tradition of rational thinking based on empirical evidence. Conspiracy thinking, on the other hand, arises when people find themselves unable to determine simple causes for complex, adverse circumstances. The very complexity of issues such as multiculturalism, the growing intricacy of the global financial system and technological progress can lead people, regardless of educational level, to choose to believe compact explanations that clearly identify an object of blame. Martin Bauer, a social psychologist at the London School of Economics and a scholar of conspiracy dynamics, describes conspiracy thinking as a "quasireligious mentality." It is a little bit like the dawn of humanity, when people attributed divinity to storms.

For this study, which we called "Science vs Conspiracy: Collective Narratives in the Age of Misinformation" and published in *PLOS ONE,* we investigated 73 Facebook pages, 39 of which trafficked in conspiracy and 34 of which published science news. Altogether, these pages had more than a million Italian users between 2010 and 2014. We found that both sets of pages attracted very attentive audiences—users who rarely leave their echo chambers. People who read science news rarely read conspiracy news, and vice versa. But the conspiracy pages attracted three times more users.

The tendency of Facebook to create echo chambers plays an important role in the spread of false rumors. When we investigated 4,709 posts that satirized conspiracy theories (example: "Airplane chemtrails contain Viagra"), we found that consumers of "real" conspiracy news were much more likely to read these satirical pieces than readers of legitimate science news. We also found that users who focus primarily on conspiracy news tend to share content more widely.

When we reconstructed the social networks of our two groups (science news readers and fans of conspiracy theories), we discovered a surprising statistical regularity: as the number of likes for a specific type of narrative increased, the probability of having a virtual social network composed *solely* of users with the same profile also increased. In other words, the more you are exposed to a certain type of narrative, the greater the probability that *all* your Facebook friends will have the same news preferences. The division of social networks into homogeneous groups is crucial to understanding the viral nature of the phenomena. These groups tend to exclude anything that does not fit with their worldview.

A WICKED PROBLEM

IN 2014 WE DECIDED to start investigating efforts to correct the spread of unsubstantiated claims in social media. Does debunking work? To find out, we measured the "persistence"—the tendency of a person to continue engaging with a specific type of content over time—of conspiracy news readers who had been exposed to debunking campaigns. The results, currently pending for publication, were not encouraging. People who were exposed to debunking campaigns were 30 percent more likely to keep reading conspiracy news. In other words, for a certain type of user, debunking actually reinforces belief in the conspiracy.

Conspiracy thinking arises when people find themselves unable to determine simple causes for complex, adverse circumstances.

We observed the same dynamics in a study of 55 million Facebook users in the U.S. Users avoid cognitive discord by consuming information that supports their preexisting beliefs, and they share that information widely. Moreover, we found that over time people who embrace conspiracy theories in one domain—say, the (nonexistent) connection between vaccines and autism—will seek out such theories in other domains. Once inside the echo chamber, they tend to embrace the entire conspiracy corpus.

These dynamics suggest that the spread of online misinformation will be very hard to stop. Any attempt at reasoned discussion usually degenerates into a fight between extremists, which ends in polarization. In this context, it is quite difficult to accurately inform people and almost impossible to stop a baseless report.

In all probability, social media will continue to teem with debates on the latest global mega conspiracy. The important thing is to share what is being hidden from us; whether it is true or false hardly matters. Perhaps we should stop calling this the Information Age and start calling it the Age of Credulity. SA

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DON'T DRINK THE WATER

IN BRIEF

More communities are finding high levels of perfluorochemicals (PFCs) in drinking water. The EPA recommends concentrations stay below 70 parts per trillion.
PFCs, used to manufacture many consumer products, are everywhere because they do not readily break down. They accumulate in the human bloodstream.
Studies show possible correlations between high PFC levels and weakened immune systems, enlarged livers, and more, but no direct causation has been shown.
Scientists are having a difficult time determining what levels may be dangerous because potential health effects vary among species in animal studies and are hard to isolate in human studies. No "unsafe" limits have been declared, leaving residents and municipalities uncertain whether to take corrective actions.

Photographs by Jesse Burke

HEALTH

More communities are emerging as hotspots for drinking water tainted with PFCs, but scientists and regulators are struggling to determine how much is unsafe

By Charles Schmidt

SPRAWLING OVER A MANICURED SUBURBAN LANDSCAPE

Charles Schmidt is a freelance journalist based in Portland, Me., covering global health and the environment. He wrote our June 2016 article about the lasting legacy of Agent Orange.

in Portsmouth, N.H., the Pease International Tradeport office park encompasses 250 companies, a golf course and a pair of day care centers. Nearly 10,000 people arrive here for work every day. But belowground lies a toxic legacy. Until 1988, the site was a U.S. Air Force base, where fire crews, during routine training exercises, would torch old planes in a field, then douse the flames with chemical foam. At the time, it did not seem to matter that the foam sank into the soil. But it contaminated groundwater Pease workers and their children have been drinking for decades.

Three years ago scientists sampled the drinking water at Pease and detected perfluorochemicals, or PFCs—compounds in the foam that could snuff out fuel fires. The concentrations were up to 35 times higher than what the U.S. Environmental Protection Agency says is okay to drink. PFCs have been used for decades in hundreds of products, and they are now widely dispersed in soils and groundwater around the planet. Virtually everyone in the industrial world has some of the particles in their blood from drinking water or eating crops, meat and fish. Of even more concern, the chemicals can accumulate at high levels in local environments where they were manufactured or used to make products. People who live in these hotspots can have concentrations in their bodies that are much higher than average.

The number of hotspots is rising. In May 2016, citing emerging evidence that the compounds are especially toxic to children developing in the womb and to breastfeeding infants, the EPA dropped its health advisory level for PFCs in drinking water to a new low: 70 parts per trillion, or a little more than half a teaspoon in 20 Olympic-sized swimming pools. Communities in more than two dozen states have since reported PFCs exceeding the new threshold. With all this attention, more towns are looking and finding they have a problem.

The discoveries are fueling fears that the nation's drinking water, already threatened in many places by lead and other chemicals, is not adequately protected. PFCs are a rising concern because they are still being discovered widely and because the amounts ingested in drinking water add to the accumulated exposures from other sources, such as food and consumer products. Between 2013 and 2015 the EPA looked for PFCs in every water utility around the country that served more than 10,000 people, along with a sample of 800 water systems that served fewer. Sixty-six utilities serving a combined six million Americans had on at least one occasion detected PFCs in their water at levels over the EPA's new threshold.

Many states are taking action. This past summer health officials advised 100,000 residents in northern Alabama to avoid PFC-contaminated tap water until a temporary supply was brought online. In Bucks and Montgomery counties in Pennsylvania, officials had as of October closed 22 public and 150 private drinking-water wells serving 100,000 people. In Ohio and West Virginia, 3,500 people have sued DuPont, a major PFC manufacturer, claiming that releases from its Washington Works chemical plant on the states' common border drove up rates of cancer and other illnesses. More than a year ago state officials told residents in Hoosick Falls, N.Y., not to drink the water but have not yet fully resolved the problem. "We think we're just scratching the surface in terms of how many communities are affected by PFCs," says David Andrews, a senior scientist at the Environmental Working Group in Washington, D.C. "We expect the numbers are enormous."

High PFC levels in blood raise health fears not just for cancer but also for immune system suppression and reproductive problems. But precisely how particular levels affect human health is not clear, and that is driving pitched debates over the amounts that people can consume safely.

INDESTRUCTIBLE MOLECULES

MANUFACTURED FOR DECADES in large quantities, PFCs were developed commercially in the 1940s by the Minnesota Mining and Manufacturing Company, now 3M. PFC molecules look like a zipper, with a backbone of carbon atoms interlaced with fluorine atoms, and they form durable and impenetrable films. When applied as a coating, say, on rain jackets, carpets and even computer microchips, the hard but slick films helped water, oils and dirt slide off. They were also used as manufacturing aids in making products for cooking and food storage, such as nonstick pans, pizza box liners and popcorn bags. The chemicals allowed other coatings, such as Teflon, for instance, to spread evenly over surfaces that would come into contact with food. Companies tried to remove PFCs after the coatings were applied, but studies disagree over whether the removal processes were successful, meaning PFCs could have remained in coatings of nonstick pans, for example, and been released when the pans were heated on home stoves.

Over time many companies made and used the chemicals. More than 3,000 varieties remain on world markets today. But the structural stability that makes PFC-based coatings so useful to industry also has a health and environmental downside. Carbon-fluorine bonds—which are wholly unnatural—are not read-

ANDREA AMICO'S husband and children have elevated PFCs in their blood. He worked at the Pease International Tradeport, where the compounds were found in drinking water; the kids went to day care there.

ily digested by microbes, broken down by the sun, or metabolized to anything else in soils, plants, or the bodies of humans or animals. Most PFC molecules ever made still linger somewhere on the earth. Scientists have detected PFCs in polar bears, whales, fish and the produce that winds up on American dinner plates. "Nothing in the environment can degrade them," says Ian Cousins, a chemist and professor at Sweden's Stockholm University. "PFCs can only be diluted and dispersed."

For years PFC production was dominated by long-chain compounds that had backbones of eight carbon atoms or more. The two most widely manufactured compounds were perfluorooctanoic acid (PFOA), also called C8, which had been used to make Teflon and Gore-Tex, and perfluorooctane sulfonic acid (PFOS), formerly a key ingredient in Scotchgard fabric protector and many firefighting foams. Unlike other widespread chemical pollutants that build up in fatty tissue—think dioxin or DDT—PFCs accumulate in blood and then pass from the body in urine. But long-chain PFCs are reabsorbed in the kidneys, allowing them to circulate in the blood for years.

That is why, by the early 2000s, most of the major PFC manufacturers in the U.S., Europe and Japan joined in EPA-coordinated efforts to voluntarily phase the long-chain PFCs out of production; 95 percent were to be gone by 2010 and the rest by 2015. Certainly older products hanging around homes may contain the chemicals. Some companies not in the voluntary program continue to produce or import and use long-chain PFCs. Chinese companies still make up to 500 tons of PFOA and PFOS a year. The firms that have stopped using the long-chain molecules have adopted alternatives, including short-chain PFCs that flush out of the body. Because they do not linger in blood, short-chain PFCs are arguably less harmful to people, but they persist in the environment. In May 2015 more than 200 scientists signed a warning called the Madrid Statement, cautioning that there is little public information about the chemical structures, properties, uses or biological effects of the short-chain PFCs now on the market, which are used in making treated upholsteries and other products.

Cousins says that before the voluntary phase out of the long-chain PFCs, food packaging and treated fabrics accounted for most PFOS and PFOA exposure. Now most of the general public's exposure comes from fish or produce contaminated by PFCs. With the decline in commercial sources, levels in blood have fallen accordingly. In 1999, when the Centers for Disease Control and Prevention first began to look, PFOA amounts in American blood averaged just over five nanograms per milliliter (ng/mL). By 2012, according to the CDC's most recently published data, those levels had been cut by more than half. The average PFOS levels in blood fell even more dramatically, from 30 ng/mL to just over 6 ng/mL during the same period in the U.S.

Those averages are little solace, however, for people who live in the growing list of hotspots with PFC-contaminated drinking water. There blood levels can spike off the charts. In June, New Hampshire officials reported results from a study at Pease showing that the nearly 1,600 people tested—a quarter of them children who attended the on-site day care centers—had average PFC levels far higher than current national averages. Extraordinarily high blood levels were measured in people living near DuPont's chemical plant in Wood County, West Virginia. PFOA levels among the 70,000 local residents there averaged 28 ng/mL, but half had levels of 82 ng/mL or more, "and the most highly exposed people had PFOA levels greater than 1,000 ng/mL," says Kyle Steenland, an epidemiologist and professor at Emory University's Rollins School of Public Health. Most likely hundreds of thousands of U.S. residents live in PFC hotspots near military installations, chemical plants and wastewater-treatment facilities, not to mention millions more outside the country.

TOXIC UNCERTAINTIES

DETERMINING WHETHER such levels are dangerous is tricky. "I'm always asked, 'How are PFCs going to affect me?'" says Patrick Breysse, director of the CDC's National Center for Environmental Health in Atlanta. "But there's no easy answer. Our ability to measure them outstrips our ability to interpret what they do to the human body."

One reason for the uncertainty is that the data on PFC toxicity are all over the map. PFCs cause myriad effects in animals, but species also vary from one to the next in their toxic susceptibility to the chemicals. Certain levels cause harm in certain species yet do not in others. Likewise, the evidence on humans diverges from study to study. Some show harms that others do not, "making it very inconsistent," says Benjamin Chan, state epidemiologist in the New Hampshire Department of Health and Human Services. "People want to compare their own blood levels with those causing effects in a particular human study, but the quality of each

study individually isn't very high," he says. "We need to look at the weight of the evidence in the literature as a whole to gauge what the science says about health effects from PFCs, and that gets confusing quickly."

Scientists have known since at least 2000 that PFCs cause liver, testicular and pancreatic cancer in exposed rats, although those cancers do not appear in monkeys. Enlarged livers, suppressed immune systems, neurological changes, obesity and delays in mammary gland development have been documented in different kinds of animals. The EPA based its new health advisory on evidence that mice born to PFC-exposed mothers are prone to low birth weights, skeletal problems and accelerated puberty.

Whereas researchers can feed PFCs to animals under controlled conditions in the laboratory, they cannot do so with people. Instead they have to study them epidemiologically, which means trying to determine if communities with higher levels of exposure also have higher rates of disease. Epidemiology also requires that researchers contend with potentially complicating factors—smoking, poor diets, other chemical exposures—that can obscure any PFC effects. Steenland says the best opportunities come from studying large groups of highly exposed people, among whom changes in the frequency of certain diseases, such as cancer, can be more easily detected. One example is the population next to DuPont's chemical plant in West Virginia, which discharged PFOA into the Ohio River for over 50 years and polluted groundwater for miles around to levels reaching 3,000 parts per trillion or more.

Under settlement terms from a 2004 class action lawsuit against the company, DuPont agreed to fund a $35-million investigation into the potential health consequences. The ensuing C8 Science Panel enrolled 69,000 local residents and ultimately revealed "probable links" between PFOA exposures in drinking water and six different diseases: kidney and testicular cancers, ulcerative colitis, thyroid disease, hypercholesterolemia and pregnancy-induced hypertension.

Steenland, who co-directed the study, says the odds are better than 50–50 that PFOA exposure and those illnesses are related. "But that's a far cry from saying that PFOA actually *causes* any of those conditions," he adds. "Our data are fairly strong, but one large study isn't definitive. We need to establish the links in other populations to reach more convincing conclusions."

More study may also be needed to determine harmful effects of even low exposure to children's developing immune systems. When a child is inoculated with a vaccine intended to fight a disease such as measles, the body reacts by producing antibodies—foot soldiers that learn to recognize the pathogen. If, later, the child contracts the actual pathogen, his or her immune system is already prepared to fight it and can rapidly build up a counterattack. Evidence suggests that PFCs might impede the body's response to vaccines, rendering them less effective. In 2012 Harvard University scientists reported in a high-profile study that antibody levels mobilized by diphtheria and tetanus vaccines dropped off steadily with increasing PFC exposures. They conducted the study in the Faroe Islands, where the population gets most of its PFCs from a marine diet that includes whale meat. Children and pregnant women had PFC levels similar to those of the general U.S. population. Philippe Grandjean, a professor at the Harvard T. H. Chan School of Public Health who led the study, says it suggests that those levels could make it harder for youngsters to resist infectious diseases.

Andrew Rooney, acting director of the Office of Health Assessment and Translation at the National Institutes of Health, says studies with mice show the same thing: both PFOA and PFOS suppress antibodies in the animals. "We're talking apples to apples," he says. "And the fact that we see similar immune effects in animals and humans increases confidence in the results. We expect a less effective response to vaccines among people who have more PFCs in their bodies."

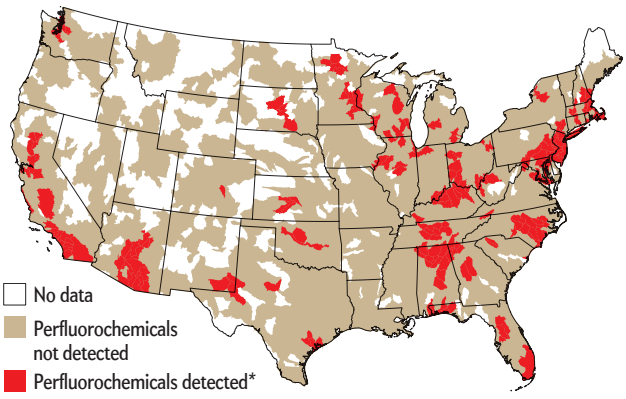
Still, the animal evidence on antibody suppression is so far limited to mice; neither rats nor monkeys experience that effect when dosed with PFCs. Scientists from the C8 study looked for evidence of antibody suppression in the highly exposed communities in Ohio and West Virginia and found that antibody levels were slightly suppressed for one of three flu strains that were evaluated, but they could not detect any evidence of increased colds or flu in the population. Tony Fletcher, an epidemiologist at the London School of Hygiene & Tropical Medicine and a C8 study co-director, says it is unclear why the C8 and Grandjean studies produced such divergent findings. "You would expect a greater response when the exposure levels are high," he says.

Epidemiology is a slow process. Steenland says results trickling in from other studies around the world will lend clarity. But health officials trying to set exposure levels can work only with the data they have, and they often disagree over interpretation. New Jersey officials, for instance, recently undercut the EPA by proposing a much lower drinking-water standard for PFOA of 14 rather than 70 parts per trillion. They argued that the lower stan-

FIELDWORK

Hotspots Abound

More than six million U.S. residents are exposed to perfluorochemicals in their public drinking-water supplies that exceed recommended levels, according to EPA test data, analyzed by Xindi Hu of Harvard University and her colleagues. Data for municipalities under 10,000 people and for private wells have not yet been taken, so the numbers could rise.



**Zip codes where the chemicals were detected in one or more water samples that were at or above the minimum reporting levels required by the EPA (2013–2015). Not all drinking-water sources within a zip code necessarily have high levels.*

SOURCE: "DETECTION OF POLY- AND PERFLUOROALKYL SUBSTANCES (PFASS) IN U.S. DRINKING WATER LINKED TO INDUSTRIAL SITES, MILITARY FIRE TRAINING AREAS, AND WASTEWATER TREATMENT PLANTS," BY XINDI C. HU ET AL., IN *ENVIRONMENTAL SCIENCE & TECHNOLOGY LETTERS*, VOL. 3, NO. 10; OCTOBER 11, 2016

Map by Mapping Specialists

SCIENTIFIC AMERICAN ONLINE For more on possible PFC links to infertility, go to ScientificAmerican.com/apr2017/schmidt

dard would protect against enlarged livers and delays in mammary gland development, which are the most sensitive effects seen at the lowest doses in mice. When I asked the EPA why it did not do the same, a spokesperson replied by e-mail that the agency does not consider changes in rodent liver weights to be adverse and that, moreover, liver enlargement might result from a biological response that humans do not share. The spokesperson also wrote that delays in mammary gland development do not prevent the animals from lactating normally or from adequately feeding pups. Yet Grandjean is advocating for an even lower drinking-water standard of one part per trillion, which he says is necessary to protect against immunological effects in children.

REGULATORY DYSFUNCTION

THESE ARE THE TYPES OF TENSIONS that the EPA confronts daily. Add insufficient funding and staffing shortages, a frequently hostile Congress, and competing interests of environmental groups and industry, and the EPA's attempts to set enforceable standards for drinking-water contaminants can grind nearly to a halt. "Chemical health assessments are often delayed indefinitely without being completed," says Andrews of the Environmental Working Group. "And the EPA has to finish those assessments before it can set regulatory standards under the Safe Drinking Water Act (SDWA)." In fact, the EPA has not set an enforceable standard for any contaminant under the act for 20 years. Its health advisory for PFCs—which are still unregulated by the agency—amounts to little more than a cautionary threshold. Water utilities do not actually have to sample for PFCs, although with the growing publicity, many are now doing so.

Other unregulated drinking-water contaminants are also drawing mounting scrutiny, including 1,4 dioxane, chromium 6 and perchlorate, an oxidizer in rocket propellants that the EPA was supposed to be regulating under the SDWA by August 11, 2014. Plagued by internal disputes over the chemical's toxicity, the EPA missed that deadline and was subsequently sued by the Natural Resources Defense Council. Erik Olson, an attorney with the council, complains that the studies imposed on the EPA by the SDWA consume too many resources and provide too many opportunities for industry meddling. "The EPA just gets boxed in," he says. In an e-mail, EPA officials said they were "evaluating PFOA and PFOS as in accordance with processes required under the SDWA," but they would not comment on whether a standard was imminent.

For decades the EPA was hamstrung by the very law that allows it to regulate—and ban—industrial chemicals at the point of production. When the Toxic Substances Control Act (TSCA) was enacted in 1976, it grandfathered every one of the more than 60,000 industrial chemicals that were in commerce at the time—including PFCs. The TSCA instead directed the EPA to focus on new chemicals. Charlie Auer, currently an attorney in Washington, D.C., directed the EPA office that administers the TSCA. He says he bypassed the law when coordinating voluntary efforts to pull PFOA and PFOS off the market: "The fact that long-chain PFCs are largely out of commerce and that human blood levels have fallen from levels seen before the EPA got involved shows that a lot of progress was achieved despite the manifest weaknesses in the TSCA at the time. The problem of PFC production and use was largely solved within about 15 years—which is pretty fast for any regulatory scheme, given how hard it is get things done these days."

Last June, Congress finally amended the TSCA to give the EPA more authority over existing chemicals. In an e-mail, EPA officials stated that they would "consider PFCs for risk evaluations" under the amended law. But they also said they would not prioritize PFCs for evaluation, because the EPA had already spearheaded efforts to remove long-chain PFCs from the market.

The regulatory and scientific uncertainties mean residents in towns across the U.S. remain unclear about what levels of PFCs in drinking water may be safe or not and whether they need to take corrective action or not. Andrea Amico just wants to know what PFCs are doing to her family's health—especially her children's. An occupational therapist, Amico lives in Portsmouth, N.H. Her husband worked at Pease for seven years before the contamination was discovered there, and her two children attended the local day care. Her husband and children all have elevated PFCs in their blood. In 2015 Amico launched a community action group called Testing for Pease, which is urging CDC officials to launch a long-term health study with roughly 350 children exposed to PFCs at Tradeport. "Some of these children started drinking PFC-contaminated tap water with powdered formula when they were just six weeks old," Amico says. "We don't know what's going to happen to them. We need a plan to get answers."

That plan, Amico says, should include what is called a longitudinal study with blood sampling and medical monitoring until the children become adults. There are too little pediatric data on PFC effects, Amico emphasizes, and too few long-term studies. She and others from the Pease community say they want to contribute to research by being tracked over time because no one can tell them if their exposures will eventually be harmful.

But at a September meeting with the Pease community, officials from the Department of Health and Human Services' Agency for Toxic Substances and Disease Registry (ASTDR) balked. Breysse, who is also director of ASTDR, explained that although his organization would consider a cross-sectional study to investigate health effects at a single time point, a longitudinal study was not practical, because the group of exposed children at Pease is too small to identify health changes with statistical confidence. The better approach, Breysse says, would be to incorporate the Pease children into a larger national study of exposed communities from around the country. "Right now we're trying to figure out what that study would look like," Breysse says. "At the same time, we're trying to address individual community concerns."

What troubles Amico most is not knowing: "This is affecting us all personally. I lose sleep at night wondering how these exposures are going to affect my kids." SA

MORE TO EXPLORE

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FROM OUR ARCHIVES

Gauging the Effects of Lead. Ellen Ruppel Shell; July 2016.

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BIOLOGICAL WARFARE

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USSR: Biological Warfare (BW) Accident [redacted]
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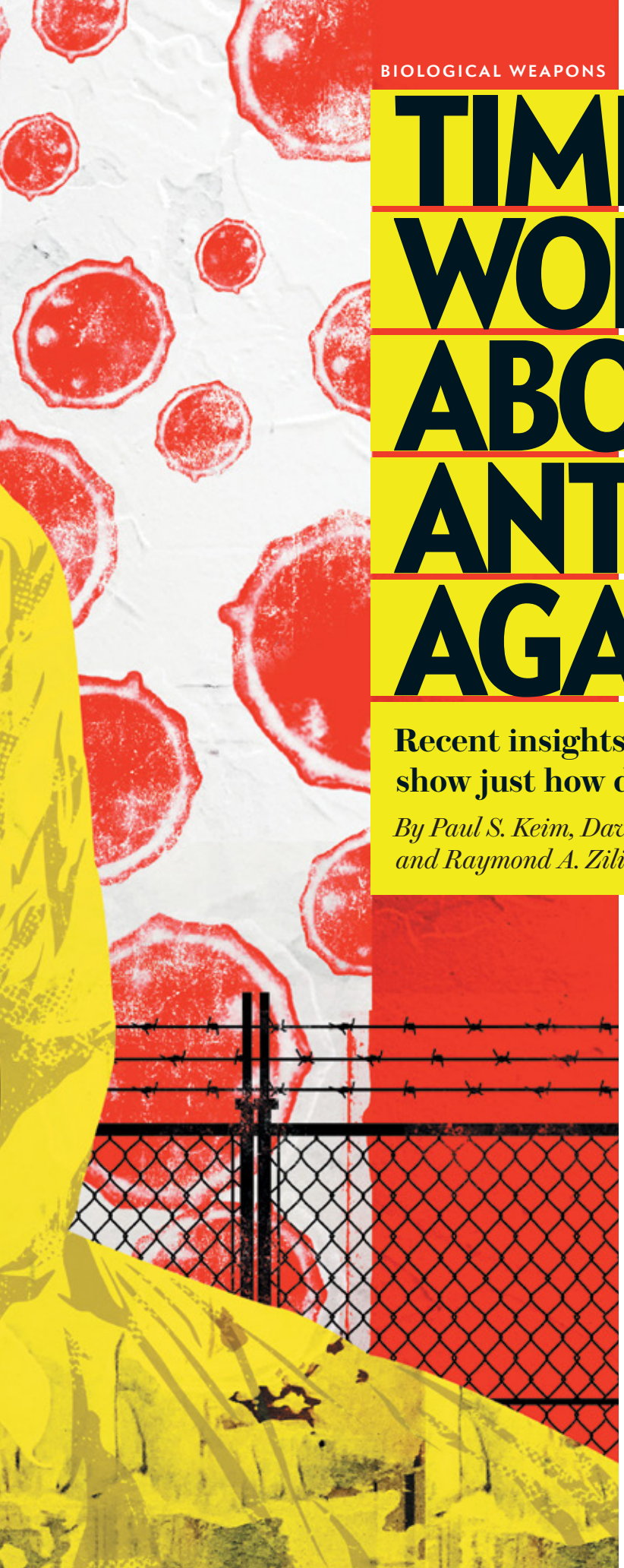
Illustration By Taylor Callery



BIOLOGICAL WEAPONS

TIME TO WORRY ABOUT ANTHRAX AGAIN

Recent insights into a long-ago accident show just how deadly bioweapons can be

By Paul S. Keim, David H. Walker and Raymond A. Zilinskas

On April 2, 1979, a mysterious powder wafted unseen into the air from a chimney that rose 25 meters above a Soviet military camp some 1,400 kilometers east of Moscow.

Over the course of the next few weeks, at least 80 residents in the surrounding Central Asian city of Sverdlovsk, now known as Yekaterinburg, fell ill with what at first seemed like flu. After a few days, however, they developed massive internal bleeding, among other problems, and 68 or more of them died.

A few people inside the base, known as Compound 19, knew at the time what had happened: missing air filters had allowed the release of an unknown quantity of bacterial spores from a secret military research and production facility located within the confines of the site. The spores emerged from a strain of bacteria, known as *Bacillus anthracis,* which causes the disease known as anthrax and is naturally found in many regions around the world. But

these particular spores had been milled to just the right size so that they could be easily inhaled into the lungs of animals or people, where they could do the most damage and cause the most deaths.

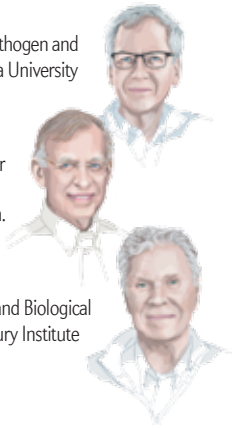
Once inside the body, the spores germinated, adopting their original rod-shaped appearance. Then they began multiplying, spreading in the bloodstream and attacking various tissues. Indeed, inhalational anthrax usually kills within a matter of days unless patients are promptly treated with the proper antibiotics. The Soviet military did not, however, reveal the nature of the outbreak to anyone—including local health authorities, who might have saved more lives if they had understood what they were up against.

Despite the KGB's strenuous attempts to keep the event a secret, news of the accident eventually leaked to the outside world in the fall of 1979, stunning Western intelligence analysts, among others. They had completely missed any clue that the Soviet Union was manufacturing material for bioweapons—an action that placed it in direct violation of a treaty banning their development, production, stockpiling or use. More than 100 countries—including the Soviet Union and the U.S.—had signed the treaty, commonly known as the Biological Weapons Convention, in 1972. Even so, the U.S. declined to launch a formal complaint against the U.S.S.R., as provided under the terms of the agreement.

Because the genetic engineering revolution had already begun in several other countries in the 1970s, Western intelligence analysts speculated at the time that Soviet researchers might have modified the *B. anthracis* at Sverdlovsk to be more deadly than normal. It took 37 years to disprove that mistaken supposition. The only enhancements were the addition of a few chemicals and other refinements to make the spores easier to disperse.

The Soviet Union, for its part, eventually admitted that a number of people had died of anthrax in and around Sverdlovsk but denied that anything unusual had occurred. The true cause of the tragedy, they said, was gastrointestinal anthrax, caused by the butchering and consumption of animals infected with naturally occurring spores—a contention that was later disproved after international experts were able to examine autopsy samples that had been saved by local pathologists.

Finally, in 1992, then Russian president Boris Yeltsin admitted that the former Soviet Union had in fact built and maintained a large program for researching and manufacturing agents for biological weapons. Although he said he had ordered the program's immediate shutdown, declassified material has since made clear that the Russian military merely concealed what remained of the effort from the civilian leadership. At any rate, official policy changed again after Vladimir Putin was appointed president in 1999. Neither the Soviet Union nor the subsequent Russian government had ever undertaken an offensive bioweapons program, the new leadership maintained. Whatever research had taken place or continued to occur was purely for defensive purposes—to protect against an attack rather than to launch one—an activity that was allowed by the bioweapons treaty.



Paul Keim is executive director of the Pathogen and Microbiome Institute at Northern Arizona University in Flagstaff.

David H. Walker is executive director of the Center for Biodefense and Emerging Infectious Diseases at the University of Texas Medical Branch at Galveston.

Raymond A. Zilinskas is director of the Chemical and Biological Weapons Nonproliferation Program at the Middlebury Institute of International Studies at Monterey in California.

Today, as a newly resurgent Russia asserts its power on the global stage, the lessons of the long-ago Sverdlovsk incident become increasingly important to appreciate and understand. Further investigations by us and others over the intervening decades have shown that it is not that difficult for a country (or terror organization) with a modicum of bioindustrial capability to build or conceal a bioweapons program. And yet the U.S., which had dismantled its own bioweapons program by the early 1970s, continues to drag its feet in making sure that others have done the same.

DEADLY SPORES

UNDER NATURAL CONDITIONS, anthrax has historically been more of a problem for herders, wool sorters and tanners. But soon after researchers in the 19th century discovered the bacterium that causes the ailment, military strategists realized that the pathogen could be used to create incredibly deadly new weapons.

In the late 1800s German scientist Robert Koch (who is often called the father of bacteriology for his work on pathogens) was the first to prove that a particular germ (*B. anthracis*) caused a particular illness (anthrax), based on experiments he conducted in his apartment lab. A few years later French researcher Louis Pasteur (the father of germ theory) developed an effective vaccine for it.

Koch showed that the bacteria adopt long, rodlike shapes when they find themselves in an environment conducive to rapid growth—such as the moist, nutrient-rich insides of an animal. Under arid conditions, however, the microbes create hard, nearly indestructible spores that can lie dormant for a long time. When Koch injected these spores into healthy mice, they turned back into bacilli, triggering the disease and killing the animals.

Early recognition and treatment of anthrax are key to survival. The death rate from untreated infections depends on where the germs first sneak into the body: inhaling even a few spores

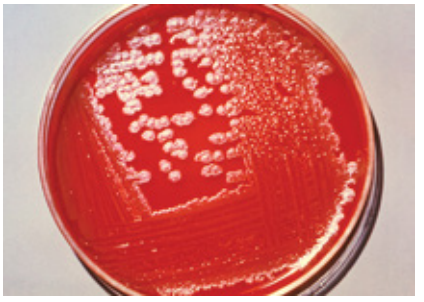
IN BRIEF

Dozens of people died of anthrax in a Central Asian city in 1979. Only later did it become clear that the outbreak had occurred because of an accident in a secret Soviet bioweapons facility. **The bacterium** that causes anthrax, known as *Bacillus anthracis*, is particularly well suited for arming unconventional weapons. Some parts of the former Soviet program were verifiably dismantled in the 1990s. **Recent revelations** underscore new concerns that the Russian government may be relaunching its bioweapons program, which would be a violation of an international treaty first signed in 1972.

into the lungs can be fatal without proper medication. Mortality from untreated skin infections is about 10 percent, and the rate for gastrointestinal anthrax is unknown but thought to range from 25 to 60 percent.

The advantages for unconventional warfare are obvious. Dried and kept in cold storage, the spores that cause anthrax will survive for years, allowing for industrial-scale production and stockpiling of the material long before it is used against soldiers on the battlefield. In addition, any soils seeded with spores will be contaminated for decades, seriously hampering an enemy's ability to raise cattle, sheep or other livestock in the affected fields.

Inhalational anthrax also offers the added edge—for anyone who wants to rain terror in addition to death on a civilian population—of being easily mischaracterized at first. The initial signs are often mild, with fever, fatigue and muscle aches reminiscent of influenza or pneumonia. Several days later infected patients suddenly develop shortness of breath, their lips turn blue, and fluid begins to accumulate in their chest, at which point death is generally unavoidable. Autopsies show characteristic patterns of internal bleeding in lymph nodes adjacent to the lungs and in tissues surrounding the brain.



KILLER MICROBES: Colonies of *Bacillus anthracis* grown on an agar plate in a lab.

THE ACCIDENT

NO FOREIGNER HAS EVER been allowed inside the gates of Compound 19—let alone the Scientific Research Institute of Microbiology located within it, where the accident occurred. Over the course of the past several decades, however, and particularly after the dissolution of the Soviet Union in 1991, we and others have pieced together a timeline of the accident. We conducted many interviews with scientists, physicians and technicians who worked in the city of Sverdlovsk or who were colleagues with others who had been inside the institute. Many of the facts that follow have been published previously by us as well as by Soviet defectors.

Based on this information, we believe the Soviet bioweapons scheme started in 1928. At its height, in the late 1980s it employed about 60,000 people. *Bacillus anthracis* quickly became one of the most important pathogens in the program. Research showed it could easily be "weaponized," meaning it could be produced in a stable manner that would allow it to be widely dispersed.

When a military lab was first established in 1949 at the site of an old infantry school near Sverdlovsk, the facility was well outside the city limits. Fifteen years later, however, the city had grown and spread around the secret installation. Despite the proximity of the civilian population, the Ministry of Defense decided to upgrade the setting in the 1960s so that it could produce the tons of *B. anthracis* spores necessary to fuel a robust bioweapons program. (Similar production facilities—later dismantled—we now know, had been established in Arkansas in the U.S. in the mid-1950s.)

The Soviets equipped a four-story building at Sverdlovsk with fermenting vats for growing *B. anthracis* and drying equipment to force the bacteria to generate spores—pretty standard steps for any industrial facility dedicated to the production of living organisms. The real innovation lay in the next few stages. Certain chemicals (we still do not know which ones) were added to the spores so that they would not clump together, making them too large to inhale into the airspaces of the lungs. Then the resulting formulation was dried yet again and ground to a fine powder, capable of penetrating deep into the lungs. Eventually the finished product was stored in stainless steel tanks.

Inevitably all that drying and grinding caused deadly spores to spread throughout the building. The workers wore bulky hazmat suits for their own protection, but the air inside the facility also had to be scrubbed before it could be vented to the outside world. The solution was fairly straightforward. Each dryer's stream of contaminated exhaust, for example, was conveyed through a series of filters to remove large particles, such as regular dust, and small ones, such as the anthrax spores.

At some point on April 2, 1979, while the dryers were off, the production unit's day crew removed two filters to check on how well they were working. This crew later claimed that it had notified the operations center that that particular dryer was not to be used until the filters had been replaced. But for some reason, the night crew did not get the message, and the crew members started up the usual manufacturing and drying cycle when their shift began. Because some of the filters in the series were missing, another one became clogged and burst, causing a sudden increase of air pressure in the air-handling system. A worker immediately noticed the change, and the 30 or 40 members of the night crew raced to shut down the system. But the production process was complex and could not be immediately halted; it took three hours to wind down—three hours in which an unknown number of spores spewed unhindered out of the chimney.

After the night crew realized what had happened, its leader told Compound 19's commander, General V. V. Mikhaylov, of the accident. He informed the Ministry of Defense headquarters in Moscow and was told to keep quiet. Afterward, the KGB confiscated all the medical records and autopsy reports of victims.

Although no one knows how many spores escaped Compound 19 during the incident, some experts later estimated that between 0.5 and one kilogram of contaminated material (containing between a few milligrams to about a gram of spores) was involved. Assuming the spores were fully viable and widely dispersed, they could have potentially sickened several hundred thousand of Sverdlovsk's unsuspecting population, which then numbered about 1.2 million. Fortunately, the prevailing winds were blowing away from the urban center and over more sparsely populated neighborhoods.

AFTERMATH

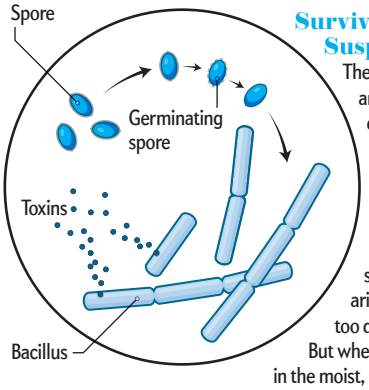
LITTLE BY LITTLE, we have learned more about the underlying biology of the specific *B. anthracis* strain responsible for the Sverdlovsk tragedy. In the 1990s, for example, Harvard University researcher Matthew Meselson led a team of experts on two different medical and epidemiological investigations to Sverdlovsk.

Advances in biotechnology have also allowed researchers to more fully analyze autopsy samples that Russian physicians

SCOTT CAMAZINE *Science Source*

Three Kinds of Anthrax

The bacterium known as *Bacillus anthracis* causes illness in different ways depending on where it enters the body (*right*). Anytime that the infection spreads to the bloodstream, however, it can quickly become fatal. Naturally distributed throughout the world, *B. anthracis* possesses several characteristics that potentially make it highly effective as a biological weapons agent: among them, it produces long-lasting spores that can be chemically treated and milled to a size that allows them to penetrate deep into the lungs, where they can trigger the most deadly form of anthrax.

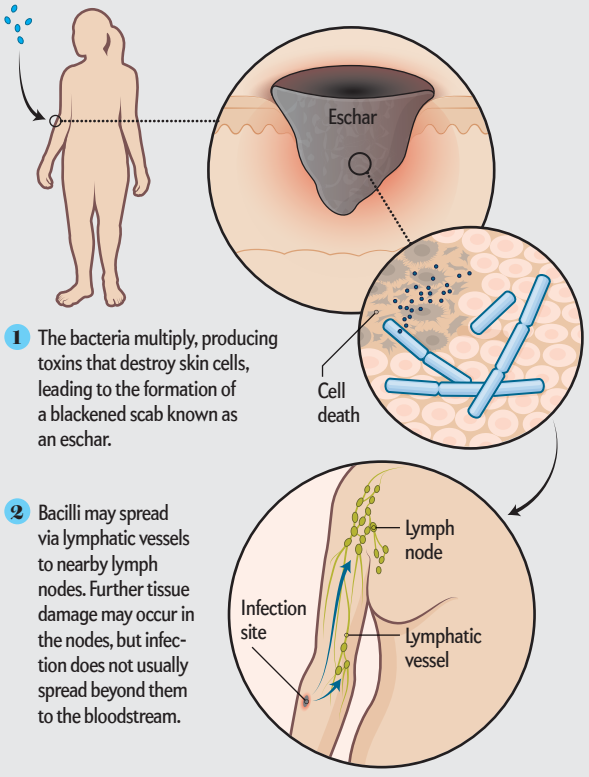


Survival Trick: Suspended Animation

The pathogen that causes anthrax can exist in two different forms—as either a rod-shaped bacillus, which can multiply and release tissue-damaging toxins, or a hardy spore that exists in a state of suspended animation. Spores arise whenever conditions are too dry for the bacilli to survive. But when conditions are right—as in the moist, nutrient-dense interior of the body—spores may germinate, giving rise to many infective bacilli.

Cutaneous Anthrax

For centuries down to the present day, the most common and least deadly form of anthrax begins when *B. anthracis* infects the skin, forming a lesion that at first resembles a spider bite.



1 The bacteria multiply, producing toxins that destroy skin cells, leading to the formation of a blackened scab known as an eschar.

2 Bacilli may spread via lymphatic vessels to nearby lymph nodes. Further tissue damage may occur in the nodes, but infection does not usually spread beyond them to the bloodstream.

shared with international teams during the more cooperative 1990s.

One of us (Walker) accompanied Meselson on the first trip and met with local pathologists to better understand the event. Later one of them, Lev Grinberg, brought autopsy samples (safely fixed in formalin and embedded in paraffin) from the victims to the U.S. for further study. Another of us (Keim) worked with Paul Jackson, then at Los Alamos National Laboratory, to extract DNA from the samples, which confirmed that the patients had died of anthrax. Later research by other scientists revealed a unique genetic signature for the Sverdlovsk strain, also known as *B. anthracis* 836.

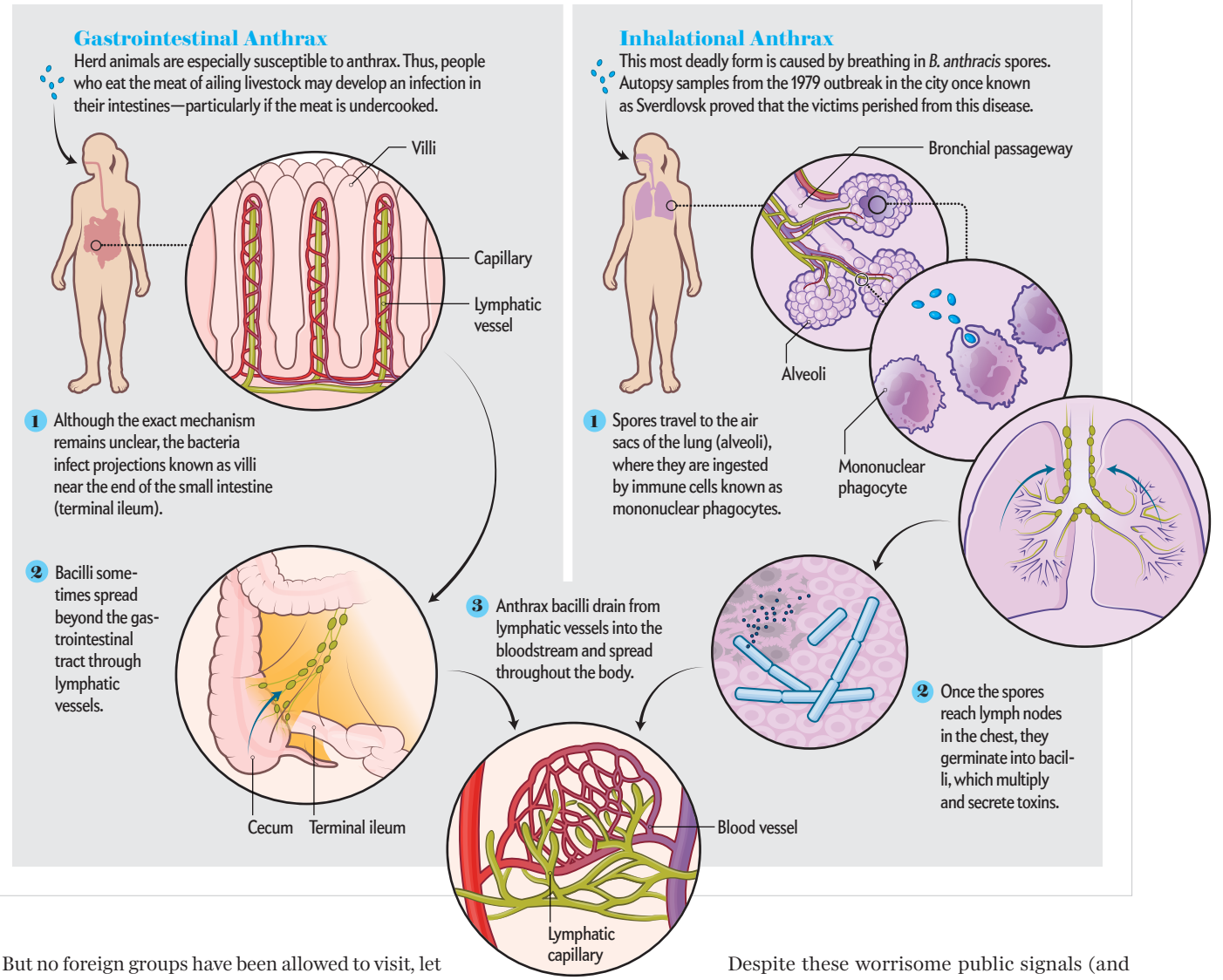
With this molecular fingerprint in hand, scientists can now track the strain on a global basis. Critically, in 2001 researchers (including Keim) determined that the anthrax letter attacks in the U.S., which killed five people, did not use the Sverdlovsk strain. But still, only small portions of the accident genome were known, and many questions remained.

Finally, in 2015, technology had advanced to the point that Keim and others were able to re-create the entire genetic sequence of the *B. anthracis* in the autopsy samples of two Sverdlovsk anthrax victims. Both bacteria samples proved to be identical to each other and to *B. anthracis* 836; the genetic analysis, which was published in 2016, showed that the strain was a member of the well-known "Trans Eurasia" group. In addition, the authors found no evidence of genetic engineering to enhance virulence, resist antibiotics or foil vaccine protection. In other words, Soviet military scientists had found and developed a highly suitable bacterium that was already lethal enough in its natural state to be used as a weapon.

Everything we have learned about the Sverdlovsk matter also serves as a sobering reminder that the best way to minimize the casualties from an anthrax attack is to act before the spores have been dispersed. Despite spending billions of dollars on biodefense research, the U.S. government still struggles to coordinate and prioritize its activities across multiple agencies with different missions and goals. The only vaccine available in the U.S., which tests show can prevent illness after exposure to *B. anthracis,* requires multiple shots over several months, followed by regular boosters.

No one knows whether any of the *B. anthracis* produced by the former Soviet Union still exist. Under agreements between the U.S., Uzbekistan and Kazakhstan, many tons of spore-containing material were rendered inert and some production facilities were converted to civilian use in these former Soviet republics in the 1990s—and under the watchful eye of international scientists.

SCIENTIFIC AMERICAN ONLINE Learn about anthrax and antibiotics at ScientificAmerican.com/apr2017/anthrax



But no foreign groups have been allowed to visit, let alone inspect, the three Ministry of Defense or five civilian "antiplague" institutes in Russia that played a role in researching and producing the agents for bioweapons.

Since 2003 the U.S. Department of State has issued nine arms-control reports, and all contain statements that Russia might be supporting activities that violate the bioweapons treaty of 1972. The reports offer no details to support these allegations (presumably, the information is classified). But there are plenty of known reasons for concern. Among them, public satellite photographs show that certain buildings in Compound 19 have been upgraded with new equipment, which appear to be ventilation units, and that new buildings have been added. In addition, in 2012 Putin wrote an essay in a Russian newspaper saying that "weapon systems based on new principles (beam, geophysical, wave, genetic, psychophysical and other technology)" were likely to appear in the future; the minister of defense later proclaimed his department was making progress on these goals. Finally, in a related move, Putin allowed a nearly 25-year-old partnership between the U.S. and Russia to actively dismantle some of their nuclear stockpiles to lapse in 2015.

Despite these worrisome public signals (and whatever top-secret information is possessed by Western governments), recent administrations, as far as can be discerned, have not confronted the Russian government on possible violations of the bioweapons treaty. Nor does the current administration appear likely to do so. By its inactivity, however, the U.S. government may be, in effect, giving Russia a green light to develop advanced biological weapons against which other countries would be ill prepared to defend themselves. SA

MORE TO EXPLORE

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Assessing the Bioweapons Threat. Crystal Boddie et al. in *Science*, Vol. 349, pages 792–793; August 21, 2015.

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scientificamerican.com/magazine/sa

Illustration by Tami Tolpa

RECOMMENDED

By Clara Moskowitz

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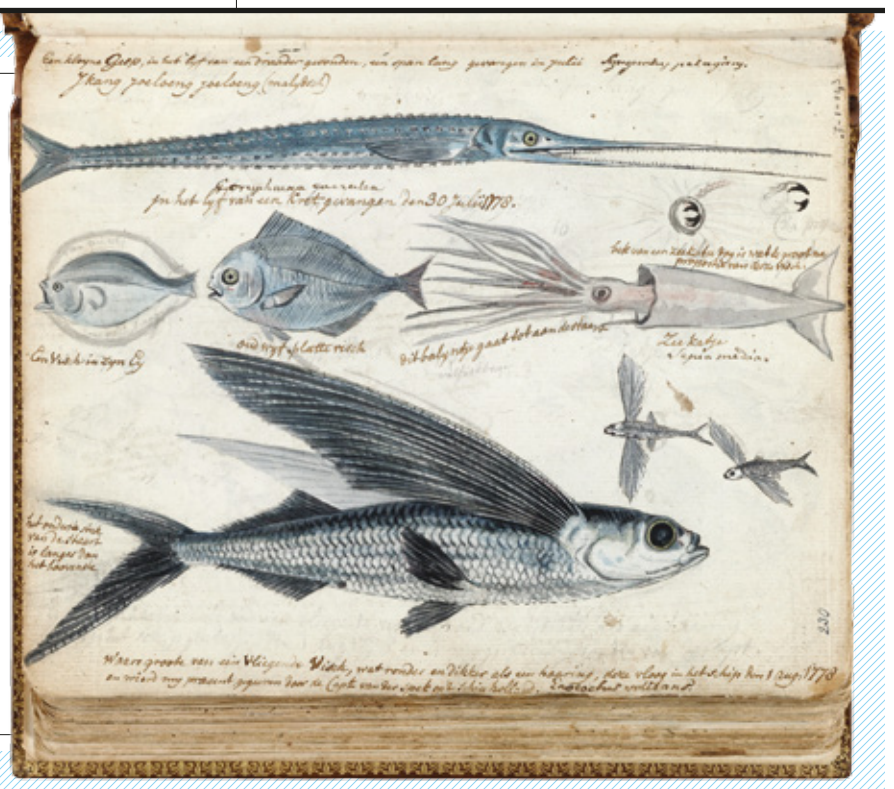
Explorers' Sketchbooks: The Art of Discovery & Adventure

by Huw Lewis-Jones and Kari Herbert. Chronicle Books, 2017 ($40)



DUTCH SCHOLAR and pastor Jan Brandes traveled throughout Asia and South Africa, sketching everything he saw, from parakeets to marine life (*right*).

Alexander von Humboldt, one of the founding fathers of the natural sciences, traveled the world in the late 18th and early 19th centuries, recording his observations as sketches of everything from the stars to plant distribution on a mountainside—some of which appear in this collection of adventurers' drawings, compiled by writers and explorers Lewis-Jones and Herbert. Also here are drawings by Charles Darwin, father of modern taxonomy Carl Linnaeus and fearless flower hunter Margaret Mee. Each braved the unknown to discover the world at large. As 20th-century travel writer Freya Stark (whose work is featured in the collection) quoted a man she met on one of her journeys as saying, "I have no reason to go, except that I have never been, and knowledge is better than ignorance."

—Andrea Gawrylewski

The Greatest Story Ever Told—So Far: Why Are We Here?

by Lawrence M. Krauss. Atria Books, 2017 ($27)

The story of the past 50 years of physics has been a slow realization that symmetry rules the particles and forces that make up our universe. Symmetry, in this case, refers to properties of nature that do not change when our perspective or mathematical descriptions of them alter—for instance, rotating a sphere does not modify its shape. Theoretical physicist (and *Scientific American* advisory board member) Krauss makes the concept of scientific symmetry accessible and shows how it allowed physicists to put together a coherent description of the fundamental particles and forces of nature. One type of symmetry, he writes, called gauge symmetry, "has allowed us to discover more about the nature of reality at its smallest scales than any other idea in science."

Not a Scientist: How Politicians Mistake, Misrepresent, and Utterly Mangle Science

by Dave Levitan. W. W. Norton, 2017 ($15.95)

"I'm not a scientist" is a line officials love to use to avoid having to acknowledge that what actual scientists say is true—for example, that human-caused climate change is ravaging the planet. "It is a dodge," journalist Levitan writes, "a bit of down-home hucksterism designed to marginalize those eggheads over there who actually *are* scientists as somehow out of touch or silly." He identifies several ways politicians misrepresent science, such as "the certain uncertainty," in which they argue that "since we don't know it all, we don't know anything." This well-argued guide should help readers see through such smoke screens and encourage lawmakers to be more accountable and accurate when it comes to science.

How to Tame a Fox (and Build a Dog): Visionary Scientists and a Siberian Tale of Jump-Started Evolution

by Lee Alan Dugatkin and Lyudmila Trut. University of Chicago Press, 2017 ($26)

Our furry companions evidently descended from wild wolves—resulting from thousands of years of human selection. Nearly 60 years ago Russian researchers Trut and Dmitri Belyaev decided to domesticate wild foxes to learn in detail how the journey from wild beast to household pet happens. They set up their experiment on a farm in Siberia and over the following decades mated the tamest animals from each successive generation. In this book, biologist and science writer Dugatkin and Trut recount this grand experiment. The result: a host of docile foxes and the identification of the genetic underpinnings for their domestication. *—A.G.*

JAN BRANDES FROM *EXPLORERS' SKETCHBOOKS*

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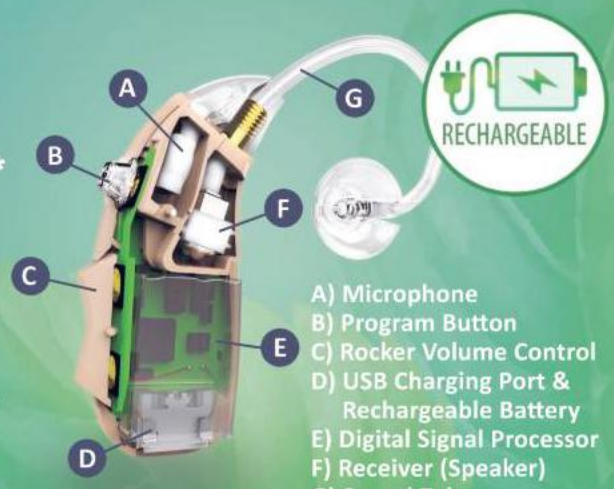

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Michael Shermer is publisher of *Skeptic* magazine (www.skeptic.com). His book *The Moral Arc* (Henry Holt, 2015) is out in paperback. Follow him on Twitter @michaelshermer

What Is Truth, Anyway?

How to think about claims, even the Resurrection

By Michael Shermer

According to the *Oxford English Dictionary*'s first definition, a "skeptic" is "one who holds that there are no adequate grounds for certainty as to the truth of any proposition whatever." This is too nihilistic. There are many propositions for which we have adequate grounds for certainty as to their truth:

There are 84 pages in this issue of *Scientific American*. True by observation.

Dinosaurs went extinct around 65 million years ago. True by verification and replication of radiometric dating techniques for volcanic eruptions above and below dinosaur fossils.

The universe began with a big bang. True by a convergence of evidence from a wide range of phenomena, such as the cosmic microwave background, the abundance of light elements (such as hydrogen and helium), the distribution of galaxies, the large-scale structure of the cosmos, the redshift of most galaxies and the expansion of space.

These propositions are "true" in the sense that the evidence is so substantial that it would be unreasonable to withhold one's provisional assent. It is not impossible that the dinosaurs died a few thousand years ago (with the universe itself having been created 10,000 years ago), as Young Earth creationists believe, but it is so unlikely we need not waste our time considering it.

Then there are negative truths, such as the null hypothesis in science, which asserts that particular associations do not exist unless proved otherwise. For example, it is telling that among the tens of thousands of government e-mails, documents and files leaked in recent years, there is not one indication of a UFO cover-up or faked moon landing or allegation that 9/11 was an inside job by the Bush administration. Here the absence of evidence is evidence of absence.

Other propositions are true by internal validation only: dark chocolate is better than milk chocolate; Led Zeppelin's "Stairway to Heaven" is the greatest rock song; the meaning of life hinges on the number 42. These types of truth are purely personal and thus unverifiable by others. In science, we need external validation.

What about religious truths? The proposition that Jesus was crucified may be true by historical validation, inasmuch as a man whom we refer to as Jesus of Nazareth probably existed, the Romans routinely crucified people for even petty crimes, and most biblical scholars—even those who are atheists or agnostics, such as renowned religious studies professor Bart Ehrman of the University of North Carolina at Chapel Hill—assent to this fact. The proposition that Jesus died for our sins, in contrast, is a faith-based claim with no purchase on valid knowledge. In between these is Jesus's Resurrection, which is not impossible but would be a miracle if it were true. Is it?

The principle of proportionality demands extraordinary evidence for extraordinary claims. Of the approximately 100 billion people who have lived before us, all have died and none have returned, so the claim that one (or more) of them rose from the dead is about as extraordinary as one will ever find. Is the evidence commensurate with the conviction? According to philosopher Larry Shapiro of the University of Wisconsin–Madison in his 2016 book *The Miracle Myth* (Columbia University Press), "evidence for the resurrection is nowhere near as complete or convincing as the evidence on which historians rely to justify belief in other historical events such as the destruction of Pompeii." Because miracles are far less probable than ordinary historical occurrences, such as volcanic eruptions, "the evidence necessary to justify beliefs about them must be many times better than that which would justify our beliefs in run-of-the-mill historical events. *But it isn't.*"

What about the eyewitnesses? Maybe they "were superstitious or credulous" and saw what they wanted to see, Shapiro suggests. "Maybe they reported only feeling Jesus 'in spirit,' and over the decades their testimony was altered to suggest that they saw Jesus in the flesh. Maybe accounts of the resurrection never appeared in the original gospels and were added in later centuries. Any of these explanations for the gospel descriptions of Jesus's resurrection are far more likely than the possibility that Jesus actually returned to life after being dead for three days." The principle of proportionality also means we should prefer the more probable explanation over less probable ones, which these alternatives surely are.

Perhaps this is why Jesus was silent when Pontius Pilate asked him (John 18:38), "What is truth?" SA

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Illustration by Izhar Cohen

Steve Mirsky loves fact-checking in the age of Twitter, through which Elayne Boosler personally verified her quote. He also hosts the *Scientific American* podcast Science Talk.

Floor Plan

Let's take a time-out to review the five-second rule

By Steve Mirsky

Comedian Elayne Boosler touched on a great deal of the human experience thusly: "My mother was so proud of her housecleaning. She always said, 'You could eat off my floor.' You can eat off my floor, too. There're thousands of things down there." Homer Simpson, spotting a piece of pie on the floor, said, "Mmmm, floor pie!" And then there was the episode of *Friends* where Rachel and Chandler are picking at a slab of cheesecake that's fallen on the hallway floor when Joey walks in—and sits down, pulls a fork out of his pocket and says, "Alright, what are we having?"

As these three popular culture examples clearly show, people often eat food that has fallen on the floor. Of course, most people try to pick the food up as quickly as possible after it has hit the deck. That practice has been codified as the five-second rule: it's safe to eat any comestibles retrieved from the floor within five seconds. Actually, I remember it from when I was a kid as the 15-second rule, but we were on a budget.

Back in March 2014, my *Scientific American* colleague Larry Greenemeier wrote a Web story about research at Aston University in England that appeared to confirm the five-second rule. (The study results were announced by the institution but were not published in any peer-reviewed journal.) "Food retrieved just a few seconds after being dropped is less likely to contain bacteria than if it is left for longer periods of time," Greenemeier summarized. "The Aston team also noted that the type of surface on which the food has been dropped has an effect, with bacteria least likely to transfer from carpeted surfaces. Bacteria is much more likely to linger if moist foods make contact for more than five seconds with wood laminate or tiled surfaces."

At this point, I'm reminded of the famous story of the old Jewish man perturbed by the fact that when he dropped a piece of buttered bread, it landed with the buttered side up. Now, the sticky butter avoiding the floor might seem like good luck. But as life is a vale of tears, the man was troubled that the universe did not appear to be functioning in accordance with the Creator's vast, eternal plan. So he consulted his rabbi. And the rabbi, after days of study and reflection, arrived at a scientific explanation: the bread was buttered on the wrong side.

Again, the Aston University work, which found contamination by *Escherichia coli* and *Staphylococcus aureus* bacteria to be a function of food's time spent on the floor, was interpreted as supportive of the five-second rule. But not so another study that came out online in September 2016 in the journal *Applied and Environmental Microbiology*.

That work, by scientists at Rutgers University, tracked *Enterobacter aerogenes* transfer from various surfaces to different foods. And the researchers state: "Although we show that longer contact times result in more transfer, we also show that other factors, including the nature of the food and the surface, are of equal or greater importance. Some transfer takes place 'instantaneously' at times [less than one second], disproving the 'five second rule.'"

And that's how the Rutgers study was reported by numerous news outlets—as the debunking of the five-second rule. But what is fascinating to this observer is that both studies basically found the same thing: the degree of bacterial contamination is dependent on contact time, surface type and what we'll call food Elmeritude, or glueyness. The coverage echoed the different ways the two studies' conclusions were couched. (Don't drop food on the couch.)

But what's truly bothering me is, When did the five-second rule come to pertain to bacterial transfer? Unless I'm misremembering my misspent youth, the key factor in edibility of fallen food was whether it had schmutz all over it. If you picked it up and it was free of dust bunnies or cat hair, bombs away for your stomach acid and immune system to deal with. Anyway, that's the side my bread is buttered on. SA

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Illustration by Matt Collins

APRIL

1967 Race Relations

"The concept of 'black power' is an inflammatory one. It was introduced in an atmosphere of militancy (during James Meredith's march through Mississippi last June) and in many quarters it has been equated with violence and riots. The fact is that a form of black power may be absolutely essential. The experience of Negro Americans, supported by numerous historical and psychological studies, suggests that the profound needs of the poorest and most alienated Negroes cannot be met—and that there can therefore be no end to racial unrest—except through the influence of a unified, organized Negro community with genuine political and economic power. The traumatic effects of separation from Africa, slavery and the denial of political and economic opportunities after the abolition of slavery created divisive psychological and social forces in the Negro community.
—James P. Comer"

Comer has been a full professor of psychiatry at Yale University since 1975.

1917 War Declared

"Occasionally in the great crises of human history it has happened that the whole world, of whatever race, creed or tongue, by common consent, has given ear to the voice of one man. Conspicuous among such occasions will ever be reckoned the joint session of the two branches of Congress, which gathered on the night of April 2nd to learn from the lips of the President of the United States [Woodrow Wilson] why it was that the great republic, of which he is the executive head, was compelled to declare that a state of war existed between itself and the greatest military autocracy of all time. Particularly acceptable to the American people is that portion of the President's address in which he makes it clear that we enter, not as a struggle against the German people, but against that military clique which has led them, deluded and unsuspecting, into a war of aggression and attempted world conquest."

Opinion in the U.S. about participation in the war can be sampled in editorials and readers' letters at www.ScientificAmerican.com/apr2017/war-opinions

1967

1917

1867

Reader's Complaint

"For over ten years I have been reading your papers. Especially welcome was your impartiality in all matters, scientific and political alike—until the outbreak of the European war. Unfortunately you appear to believe that your articles must be tinged with sympathy for the Allies, since the greater part of your readers presumably consist of persons born in these countries. Or is it to be inferred that Wall Street and the munitions makers exercise, through your patent department, an influence upon the color of your pages?"

Scientific American*'s editors replied in 1917: "The above communication comes from Mexico, and was written in faultless German. As a sample of Teutonic thought and argument it should take a leading rank."*

Improved tractor tread, 1917: better for navigating hillsides and muddy fields and ditches.

Tractor Treads

"It was over four years ago that the first attempt was made to apply the principle of the ball bearing to the endless tread of a tractor. For some three years the ball-tread tractor has been made commercially—ample evidence of the practicability of the invention. The advantage of a track of this kind consists in reduction of friction. Experiments were conducted by the College of Agriculture of the University of California [*see illustration*]."

1867 Cause of Milk Sickness

"This pernicious affection of domestic animals is sufficiently mysterious and important to have induced the Legislature of Illinois, some years since, to vote a handsome reward to anyone who should discover its cause. The *Medical and Surgical Reporter* gives information from three separate observers (one quoted from the *Missouri Republican*) tending to throw the responsibility upon a common and hitherto unsuspected plant, *Eupatorium Ageratoidis* (white snake root). Mr. Wm. Jerry, of Edwardsville, Ill., in June of 1860, gathered the plant by mistake for the nettle, and (alone) partook of it as boiled greens. On the next day he was suddenly seized with the usual symptoms of milk sickness, violent trembling, prostration and faintness, and a fevered state of the stomach. When in bloom, animals are said to like it."

The toxin tremetol from the white snakeroot plant (now called Ageratina altissima*)—largely responsible for milk sickness—was not formally identified in a laboratory until 1928.*

SCIENTIFIC AMERICAN, VOL. CXVI, NO. 16; APRIL 21, 1917

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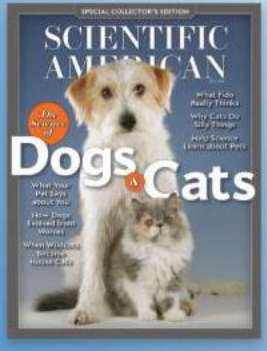

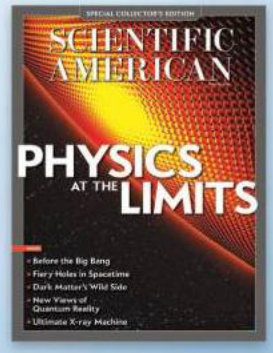

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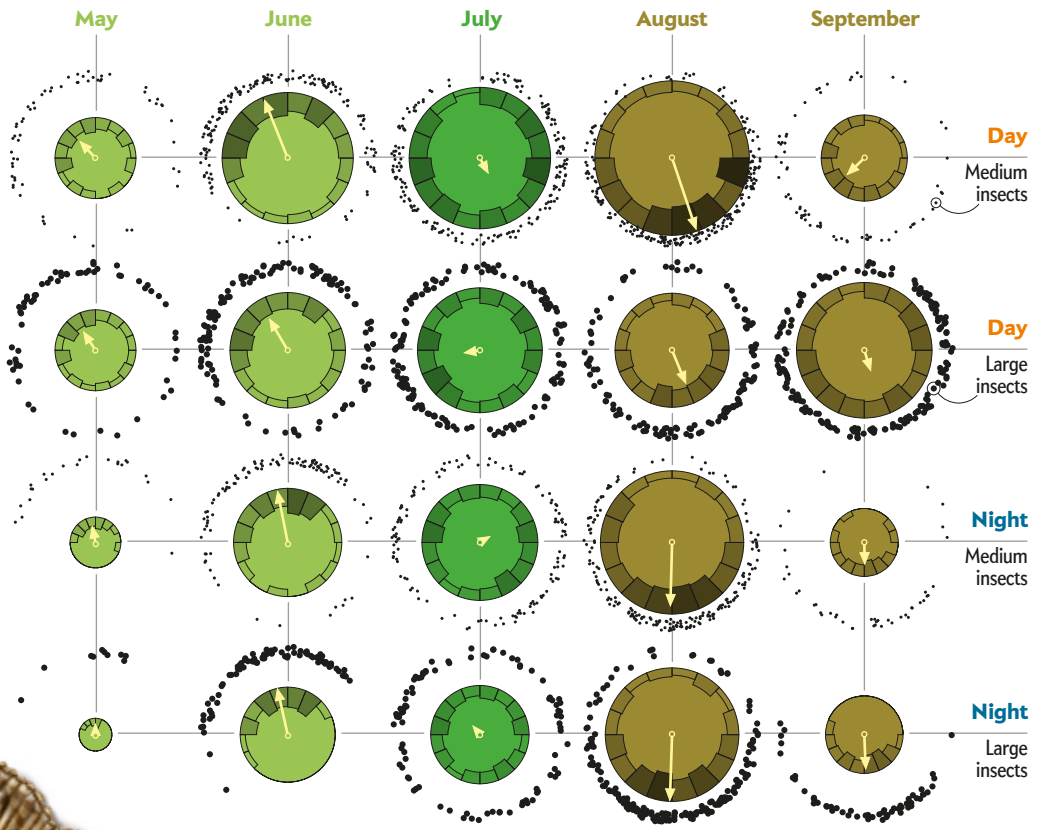
Flight Patterns

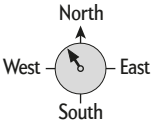
Over southern Britain, the most bug movement occurs in late May and June toward the northwest and in late August and September toward the southeast (*arrows*). Many insects do not live long and struggle to survive the cold, so it may take up to six generations for one family, flying in slightly different directions from one breeding area to the next, to complete an annual migration.



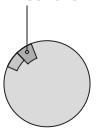
How to Read This Graphic

More than 70 percent of migrations occur during daytime (*top two rows*); fewer are at night (*bottom two rows*).

Migration Direction
Arrows depict the overall direction of insect flight. A longer arrow means more insects stick close to that path.



Darker, larger shapes inside a circle show the more heavily traveled directions.



Relative Number of Insects
Larger circle means more insects are airborne. Black dots indicate episodes when many insects are flying in a given direction.

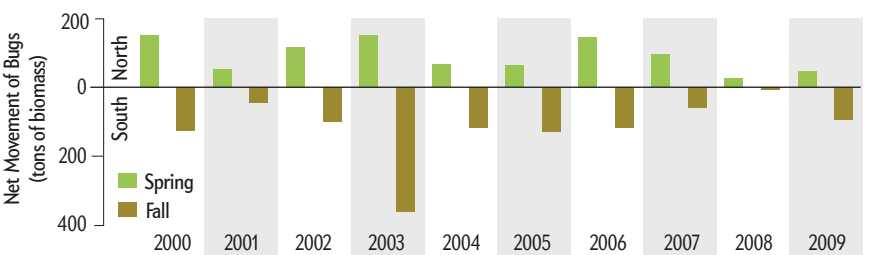
Trillions of Insects Migrate

Surprising data show many species make annual treks

Some butterflies migrate thousands of miles a year, yet scientists have conjectured that most other insects spend their lives pretty much in one place. Not so. A 10-year study found that more than 3.3 trillion insects migrate high above southern Britain every year, especially in spring and fall (*graphic below*). "People thought insects were passive and just got accidentally blown about," says researcher Jason W. Chapman of the University of Exeter in England. "That is absolutely not the case. Insects make active choices about when to migrate and how to use the winds, often moving fast and over long distances, in beneficial directions" (*above*). What they are looking for, he surmises, is greener vegetation and better weather for breeding. Initial studies in Texas, India and China are showing similar patterns. Insect migration, Chapman says, "is starting to look universal." —*Mark Fischetti*

Seasonal Travel

Radars looking skyward from the ground show that, on average, 3,200 tons of bugs a year travel overhead at heights greater than about 500 feet (which disregards random movement close to the ground). In years with harsher weather, more bugs than usual move south in autumn and north in spring.



SOURCE: "MASS SEASONAL BIOFLOWS OF HIGH-FLYING INSECT MIGRANTS," BY GAO HU, KA S. LIM, NIR HORVITZ, SUZANNE J. CLARK, DON R. REYNOLDS, NIR SAPIR AND JASON W. CHAPMAN, IN *SCIENCE*, VOL. 354; DECEMBER 23, 2016

Graphic by Jan Willem Tulp, Illustrations by Jessica Huppi

Digital tools have evolved some techniques farmers use to help protect natural resources. Advancements in data allow them to look at water, land and energy in new ways—all in an effort to positively affect farming and have less impact on the environment. Learn how innovations are shaping agriculture at **ModernAg.org**

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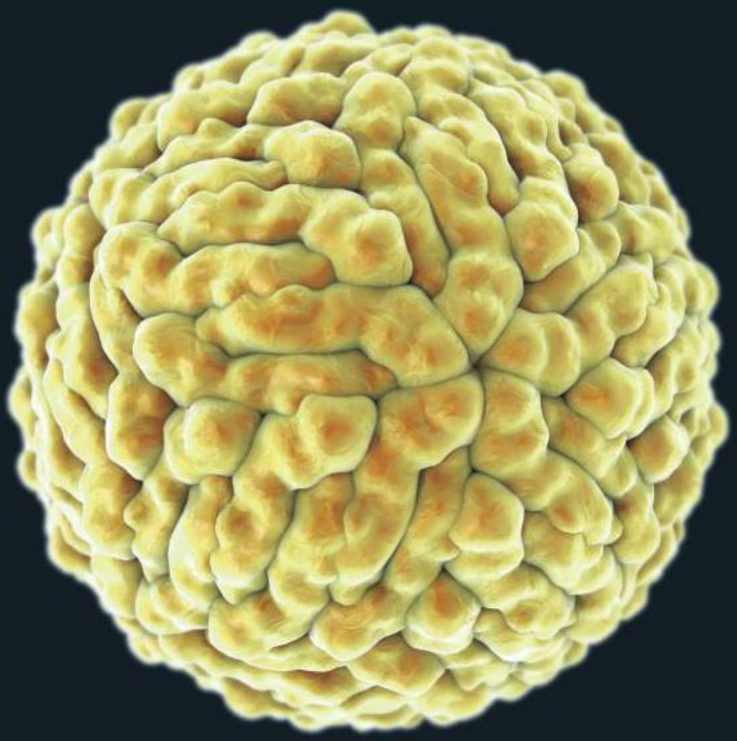

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