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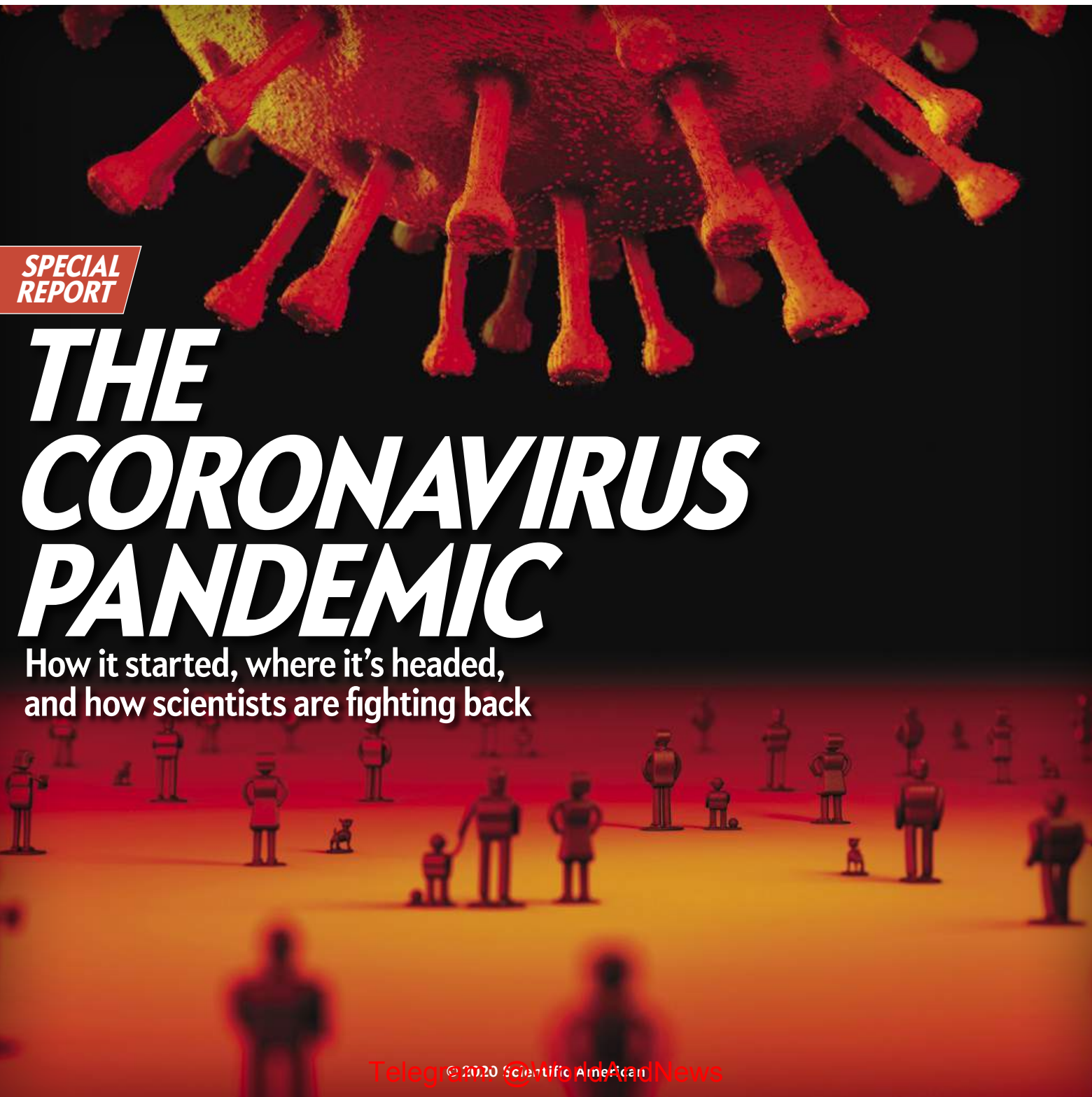

SPECIAL REPORT

THE CORONAVIRUS PANDEMIC

How it started, where it's headed, and how scientists are fighting back

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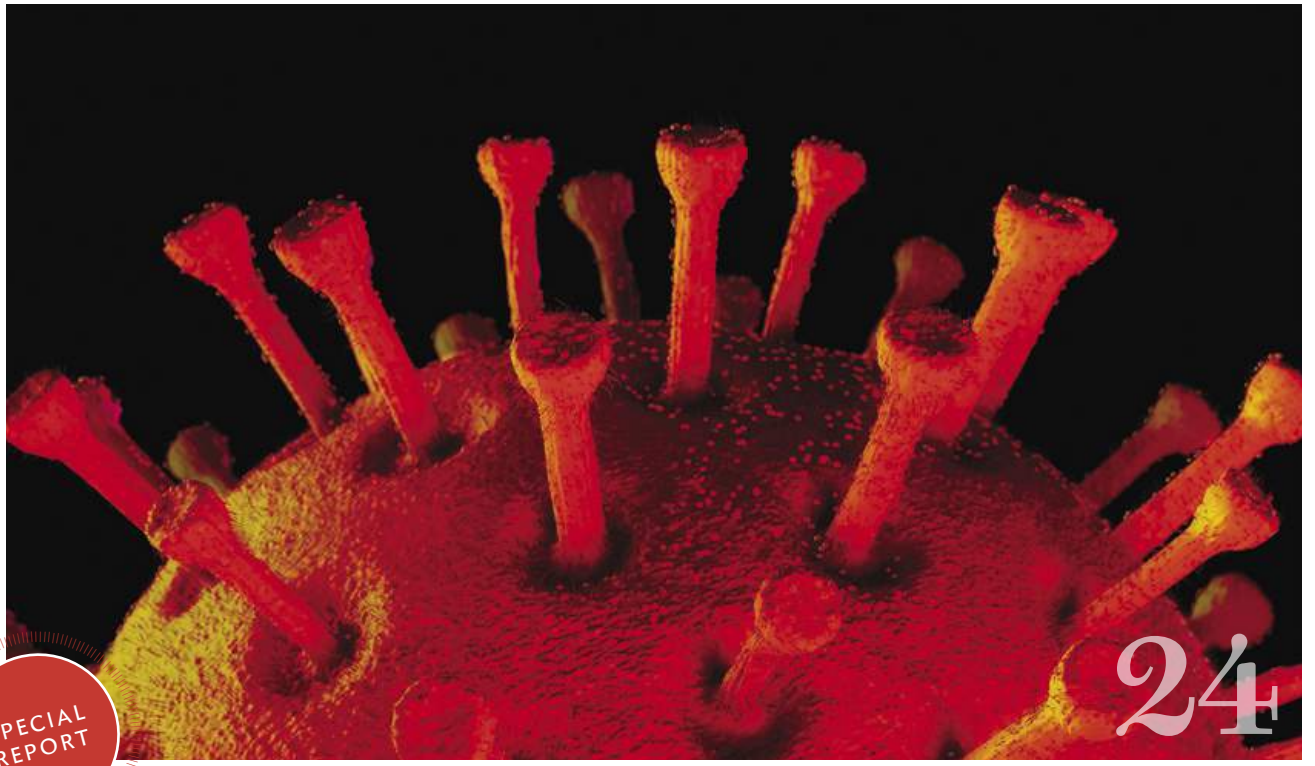

SPECIAL REPORT

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ON THE COVER
In a matter of weeks the SARS-CoV-2 virus infected millions, killing thousands and bringing the global economy to a halt. Read our special report on the origins of the plague, the human toll, and the search for treatments and a vaccine. **Illustration by Richard Borge.**

Illustration by Richard Borge

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

Covering Coronavirus

Since I last sat down to write From the Editor a few short weeks ago, the toll of the coronavirus pandemic has been staggering: at press time, more than 180,000 deaths globally and countless lives upended. Most of the planet is still on lockdown. At times it seems unreal, although it shouldn't. Many public health experts warned for a long time that something like this would happen without our taking precautionary measures.

The crisis reminds us that knowledge matters and throws into stark relief the ways that science works slowly and assiduously, over decades of painstaking research in epidemiology and virology, as well as urgently and frenetically, in the midst of tragedy and disaster, to help the world prepare for and respond to epidemics. That work is by no means perfect or complete, but it is our only hope to stop the suffering.

This month we lead with a special report that traces years of study of coronaviruses to current efforts in biomedicine to halt the pandemic. Beijing-based science writer Jane Qiu profiles the Chinese virologist who tracked down dozens of deadly SARS-like viruses in bat caves (*page 26*). Reporters Michael Waldholz and Charles Schmidt cover the race for COVID-19 treatments and a vaccine (*page 32* and *page 40,* respectively). And journalists Jillian Mock and Lydia Denworth write about the lasting impacts on frontline health workers and what comes next (*page 36* and *page 44,* respectively).

Other columns and departments in the issue focus on the pandemic as well. Our editorial calls for ending deforestation to reduce our exposure to the zoonotic viruses behind some of the world's worst outbreaks (*page 8*). Graphic Science presents a stunning data visualization of the SARS-CoV-2 virus's genetic evolution as it spread around the globe (*page 80*). There's more, and all of our coronavirus coverage is freely available online at sciam.com/coronavirusoutbreak.

If you need relief from the plague beat (and we all do), turn to the back half of the features section for a series of articles that will carry you away to a land of awe and wonder. Astronomer Meredith A. MacGregor describes how Chile's ALMA telescope has helped reveal detailed patterns in the debris disks around stars where planets are forming (*page 54*). Paleontologist John A. Long and evolutionary biologist Richard Cloutier explain how the discovery of an extraordinary 375-million-year-old fossil overturned the conventional wisdom about when and how the elements of human hands evolved in lobe-finned fishes (*page 46*). And neuroscientist Christof Koch explores the biologically mysterious commonality of near-death experiences and how researchers might uncover what is happening in the mind when we see that bright light (*page 70*).

I want to thank the *Scientific American* team for its hard work on this issue—it's not easy to cover such an epic and rapidly evolving situation in a monthly print magazine. I also want to thank all the health care workers, researchers and experts who took the time to share their stories. It's been a painful month, and we owe a debt to everyone trying to bring this pandemic to an end. SA

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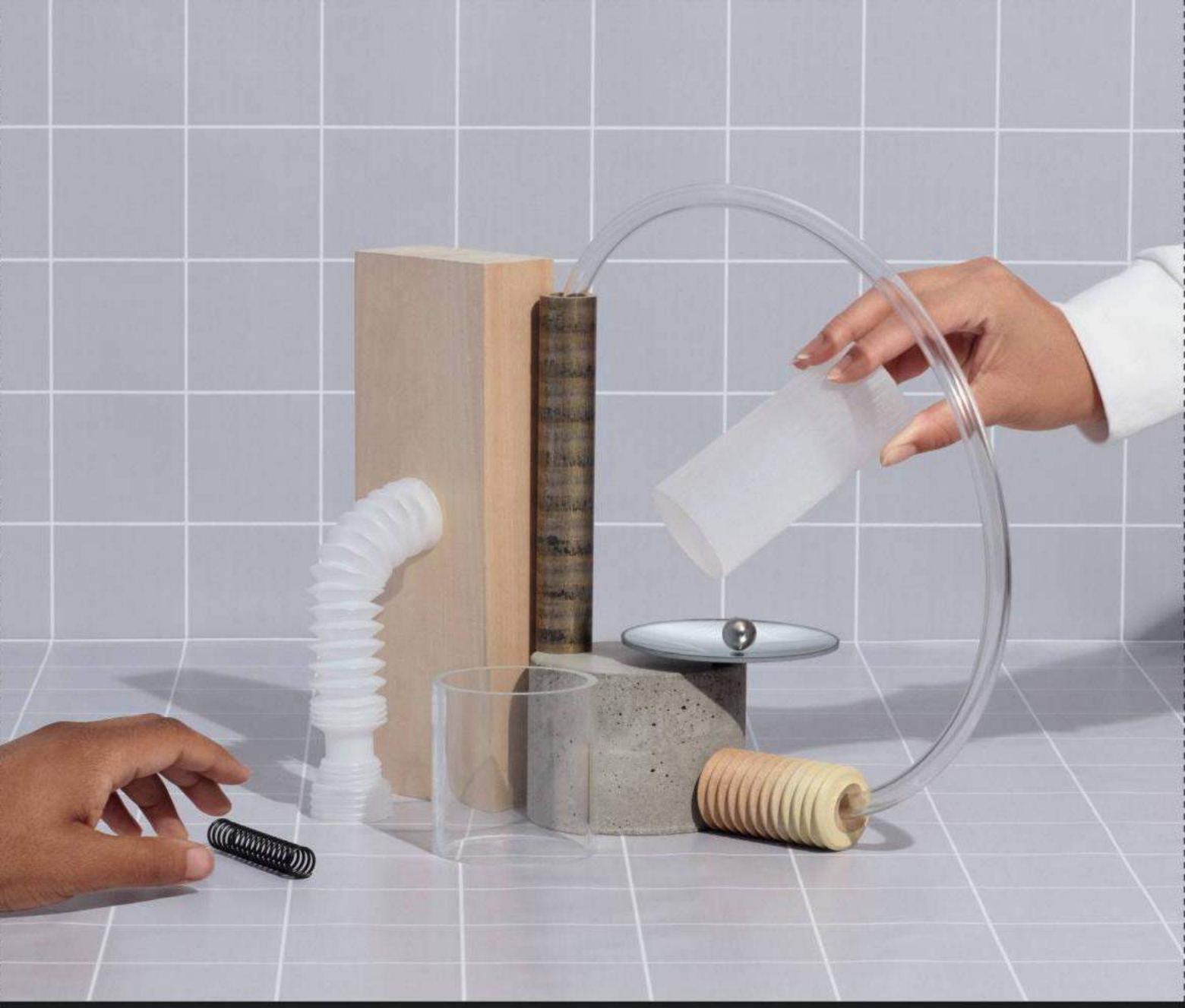

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SURGICAL DISCRETION

As an M.D., I'd like to applaud Claudia Wallis's review of the ISCHEMIA and CABANA trials of treatments for particular heart conditions in "The Case for Less Heart Surgery" [The Science of Health]. As she says, those trials conclude that stenting or bypass surgery for stable coronary artery disease—in which coronary arteries are narrowed—and ablation for atrial fibrillation—in which the heart beats irregularly—may help patients feel better, but they won't live longer.

In fact, we physicians have been aware of this concept for quite some time. A difficulty we have is imparting it to our patients. I can attest that they don't feel comfortable with the idea of treating a blockage with medication alone. If they know there is an 80 percent narrowing in one of their heart arteries, they will feel better if it's "fixed" by stenting. But by cracking open a stable narrowing, we would actually increase the risk of an abrupt closure and would have to give those patients more potent antiplatelet medications than aspirin while the lesion heals after the procedure.

The times that stents and bypasses *are* going to prevent death is when patients have unstable lesions that are at risk of occlusion. That's why these procedures do prevent catastrophes in high-risk patients but not in stable ones, for whom the risk of abrupt artery closure is very low.

There have been many cases in the past where those in the media have helped promote the fallacy that after finding a narrowing in someone who is stable, even someone without symptoms, we can prevent a heart attack simply by stenting it. I'm glad that *Scientific American* holds itself to a much higher standard.

"Legislative action is required to help scientists who are highly vulnerable to repressive actions by state politicians beholden to local (or national) interests."

JOHN P. MOORE *WEILL CORNELL MEDICINE*

Bradley J. Dibble
PACE Cardiology, Ontario

HYDROGEN POWER

In "The H_2 Solution," Peter Fairley discusses how hydrogen could be utilized as part of efforts to fully adopt renewable power. He writes that "solar and wind energy would split a limitless resource—water—to create hydrogen for electricity." But I question the term "limitless," in view of freshwater shortages around the globe. Could the electrolyzers he describes use seawater?

Additionally, I wonder if scientists have speculated whether or not the widespread production of renewable hydrogen would significantly increase the amount of oxygen in the atmosphere.

Edwinna Bernat *Shepherdstown, W.Va.*

FAIRLEY REPLIES: Readers are right to watch out for any new technology's unintended consequences. Researchers' calculations, however, indicate that a shift to wind and solar power—plus the electrolyzers required to convert some of their renewable energy to hydrogen—would use far less water than today's fossil-fuel power plants. And some of the water used would be regenerated by fuel cells or turbines that turn hydrogen back into electricity.

The reactions in both devices produce one molecule of water for every molecule of hydrogen consumed. Those reactions also consume oxygen, so even though oxygen is released by electrolyzers during hydrogen production, the system overall is unlikely to raise levels in the atmosphere.

SOCIAL BRAIN MAPS

In "The Brain's Social Road Maps," Matthew Schafer and Daniela Schiller describe exciting observations that the hippocampus, traditionally thought to be specialized for memory alone, may have cells used for social dynamics. We suggest that this arrangement would explain why many people with synesthesia, in which senses are mixed up, may make remarks such as "December is a fat, stupid man with a limp, and he is in love with February, who is a jolly and mothering presence." Curiously, in such cases, if names for two nonsequential months are placed next to each other, then two sets of emotions start blending or clashing unless a line is drawn between them, which stops the interaction. The sensory barrier becomes a conceptual-metaphorical one.

Calendar synesthesia, seen in 1 to 2 percent of the population, may involve the neural circuitry the authors describe. The calendar envisioned by people with this condition can take idiosyncratic shapes, with months set in specific fonts. Our mental calendar involves circuits in the left angular gyrus, important for sequence discrimination and connected to the same hippocampal place cell or grid cell via a band of fibers: the inferior longitudinal fasciculus.

We suggest that in calendar synesthesia, these connections are strengthened to the point of resembling real images. For example, if a calendar is projected on vertical stripes, subjects see moiré interference at the fringes. If the stripes are tilted, they see the calendar as tilted in the opposite direction. If they turn their head to the right, memories of the calendar's left side become inaccessible to them. Musical scales in the Indian *melakarta* system, which are classified into a spatial grid of 72 ragas, evoke highly distinctive and elaborate emotions and may also utilize the same map.

Vilayanur S. Ramachandran
Zeve Marcus
University of California, San Diego

I am mildly on the autistic spectrum, and the article by Schafer and Schiller spoke to me. I am fairly certain that people with autism have different social maps (and not

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just interactions) from those who do not. I wonder if anyone is doing research on how the neural circuitry that the authors discuss could also play a role in autism—that is, whether we not only build different maps but have a completely different way to "analyze" social relationships.

Alexander Duffy *via e-mail*

When Schafer and Schiller mention that "the brain has a knack for finding alternative routes," I am reminded of construction scheduling, in which those routes are the many possible paths through the activities that have to be completed to finish a project. They can be shown on a diagram connected by arrows indicating which tasks can be performed after one is finished. Arriving at a "critical path" in such a diagram requires calculating the duration of every possible path and choosing the one that gets the job done quickest. Before computers, a good engineer, or a team of them, could finish complicated projects under budget and on schedule with a hand-drawn diagram.

Terry Herlihy *Chicago*

SCIENCE SUPPRESSION

Chuck Hagel's January 2020 article "Stop Suppressing Science" [Forum] was a welcome read at a time when evidence-based policy making is indeed under sustained assault. Former secretary of defense Hagel outlines federal legislation to protect national government employees and the scientific process from politically motivated interference by the executive branch and its friends. Let's hope that new laws in this area are indeed enacted by a future, wiser administration.

Legislative action is also required, however, to help scientists who are highly vulnerable to repressive actions by state politicians beholden to local (or national) interests. Employees of public universities or agencies are particularly at risk. One needs only to recall climate scientist Michael Mann's experiences at the hands of Virginia's attorney general when Mann was employed at the University of Virginia and the harassment of seismologist Austin Holland by the University of Oklahoma's administration when he headed the state's Geological Survey.

John P. Moore
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To Stop Pandemics, Stop Deforestation

Viruses are less likely to kill humans if we leave wild animal habitats intact

By the Editors

SARS, Ebola and now SARS-CoV-2: all three of these highly infectious viruses have caused global panic since 2002—and all three of them jumped to humans from wild animals that live in dense tropical forests.

Three quarters of the emerging pathogens that infect humans leaped from animals, many of them creatures in the forest habitats that we are slashing and burning to create land for crops, including biofuel plants, and for mining and housing. The more we clear, the more we come into contact with wildlife that carries microbes well suited to kill us—and the more we concentrate those animals in smaller areas where they can swap infectious microbes, raising the chances of novel strains. Clearing land also reduces biodiversity, and the species that survive are more likely to host illnesses that can be transferred to humans. All these factors will lead to more spillover of animal pathogens into people.

Stopping deforestation will not only reduce our exposure to new disasters but also tamp down the spread of a long list of other vicious diseases that have come from rain forest habitats—Zika, Nipah, malaria, cholera and HIV among them. A 2019 study found that a 10 percent increase in deforestation would raise malaria cases by 3.3 percent; that would be 7.4 million people worldwide. Yet despite years of global outcry, deforestation still runs rampant. An average of 28 million hectares of forest have been cut down annually since 2016, and there is no sign of a slowdown.

Societies can take numerous steps to prevent the destruction. Eating less meat, which physicians say will improve our health anyway, will lessen demand for crops and pastures. Eating fewer processed foods will reduce the demand for palm oil—also a major feedstock for biofuels—much of which is grown on land clear-cut from tropical rain forests. The need for land also will ease if nations slow population growth—something that can happen in developing nations only if women are given better education, equal social status with men and easy access to affordable contraceptives.

Producing more food per hectare can boost supply without the need to clear more land. Developing crops that better resist drought will help, especially as climate change brings longer, deeper droughts. In dry regions of Africa and elsewhere, agroforestry techniques such as planting trees among farm fields can increase crop yields. Reducing food waste could also vastly lessen the pressure to grow more; 30 to 40 percent of all food produced is wasted.

As we implement these solutions, we can also find new outbreaks earlier. Epidemiologists want to tiptoe into wild habitats and test mammals known to carry coronaviruses—bats, rodents, badgers, civets, pangolins and monkeys—to map how the germs are moving. Public health officials could then test nearby humans. To be effective, though, this surveillance must be widespread and well funded. In September 2019, just months before the COVID-19 pandemic began, the U.S. Agency for International Development announced it would end funding for PREDICT, a 10-year effort to hunt for threatening microbes that found more than 1,100 unique viruses. USAID says it will launch a new surveillance program; we urge it to supply enough money this time to cast a wider and stronger net.

In the meantime, governments should prohibit the sale of live wild animals in so-called wet markets, where pathogens have repeatedly crossed over into humans. The markets may be culturally important, but the risk is too great. Governments must also crack down on illegal wildlife trade, which can spread infectious agents far and wide. In addition, we have to examine factory farms that pack thousands of animals together—the source of the 2009 swine flu outbreak that killed more than 10,000 people in the U.S. and multitudes worldwide.

Ending deforestation and thwarting pandemics would address six of the United Nations' 17 Sustainable Development Goals: the guarantee of healthy lives, zero hunger, gender equality, responsible consumption and production, sustainably managed land, and climate action (intact tropical forests absorb carbon dioxide, whereas burning them sends more CO_2 into the atmosphere).

The COVID-19 pandemic is a catastrophe, but it can rivet our attention on the enormous payoffs that humanity can achieve by not overexploiting the natural world. Pandemic solutions are sustainability solutions. SA

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Illustration by Taylor Callery

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Ben Santer is an atmospheric scientist and a member of the U.S. National Academy of Sciences.

Failure to Lead

A U.S. president who belittles science during a pandemic is a danger to us all

By Ben Santer

I was listening to the comforting background hum of the old refrigerator in my rented apartment. The noise stopped suddenly; the only sound left was the tinnitus ringing in my ears. From my chair, I looked out through the sliding glass door. Wind and rain animated the bright-yellow flannel bushes on the hillside. California had just had the driest February on record, and the flowered branches seemed to be stretching like fingers to catch the life-giving rainwater.

I had been self-quarantined at home for a week. After returning from a climate change workshop in Washington, D.C., I came down with a low-grade fever and a dry, hacking cough. On day five I was tested for the novel coronavirus and other microbes. After several anxious days I learned that I had a different infection—a serious influenza strain—and as I write this, I am slowly recovering.

While sequestered, I thought a lot about how complex systems respond to big perturbations. That is part of my job. As a climate scientist, I study the atmospheric and oceanic responses to things such as massive volcanic eruptions, large changes in the sun's energy output and a doubling of atmospheric carbon dioxide levels. The novel coronavirus is a major shock to complex human systems of governance. Here are a few personal thoughts on lessons learned from the current situation.

LESSON 1: Scientific ignorance can be fatal—particularly if it starts with the U.S. president and trickles down from there. It was scientifically incorrect for Donald Trump to dismiss the coronavirus as no worse than the seasonal flu, as he did on February 26. It was incorrect to advise U.S. citizens to engage in business as usual, which he did as late as March 10. It was incorrect to imply, as he did in a press briefing on March 19, that the malaria drugs hydroxychloroquine and chloroquine are promising remedies for COVID-19—something that has not been verified. Dissemination of such inaccurate information helped to spread the novel coronavirus in America faster by delaying the adoption of social distancing. Ignorance served as a potent disease vector.

LESSON 2: A leader tells hard truths in times of crisis, not falsehoods such as "Anybody that wants a test can get a test," as Trump said on March 6 at the Centers for Disease Control and Prevention. A leader does not assume the mantle of expertise in areas where he or she has none. A leader accepts responsibility for personal and organizational failures. A leader cares more about saving lives than about winning reelection.

LESSON 3: "America first" is a singularly poor survival strategy in the middle of a global pandemic. No nation is safe from a microscopic agent that can hitch a ride on any airplane, ship, train or car. Building effective international organizations and alliances is a far better way of surviving a global health crisis than going it alone.

The phrase "an abundance of caution" has become commonplace in the past few months. People use it when explaining their decision to self-quarantine. But an abundance of caution should have been exercised at the beginning of the pandemic. Detailed plans for scientifically accurate messaging should have been ready, along with strategies for national and international coordination of response efforts.

They were not ready. The capability to test tens of thousands of citizens a day and to give hospital staffers basic safety gear should have been in place. It was not. Members of the Trump administration should have corrected the president's misstatements on the seriousness of the coronavirus. Instead they largely remained silent. After years of belittling and neglecting science—most notably the science of climate change—Trump is suddenly discovering that science is imperative for human survival and perhaps even for his own political survival. Through science, a vaccine will be developed for the novel coronavirus. If this country invests in science now—and if we invest in the maintenance of strong global health systems—we will be better prepared for the next novel virus waiting out there. SA

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ADVANCES

Sputnik Planitia, the left lobe of Pluto's "heart," is one half of the evidence for a massive collision.

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INSIDE

PLANETARY SCIENCE

Collision Terrain

New simulation delves into potential for a buried ocean on Pluto

Pluto's heart-shaped Tombaugh Regio could be considered the dwarf planet's aesthetic highlight. This colossal, highly reflective geologic feature was captured with beautiful clarity by NASA's New Horizons spacecraft during its 2015 flyby. The feature's elliptical western lobe, Sputnik Planitia, which by recent estimates is more than 1,200 miles long, caught researchers' attention: It appears to be a "bowl" carved out by a monumental ancient impact. And today it is filled with young floes of churning nitrogen ice.

New Horizons did not get quite as good a look at the other side of Pluto. But when it had a peek, it did manage to spot an area on the part of the globe exactly opposite Sputnik Planitia that looked like a jumbled jigsaw of crevasses, mounds and pits. With no clearly apparent formation mechanism, scientists speculated on its origin.

Now research suggests the impact that carved out Sputnik Planitia is to blame. According to simulations replicating that cataclysm, it sent powerful seismic waves around and through Pluto, tearing up the surface on the opposite side. Crucially, the transmission of those potent seismic waves—and the resulting creation of that chaotic terrain's specific dimensions—would depend on Pluto having a 93-mile-thick subsurface ocean of liquid water, an idea scientists have been considering for a while.

The work was presented virtually at the Lunar and Planetary Science Conference in March. This modeling is still in its early days, and it has yet to be peer-reviewed. But con-

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necting impacts to distant geologic features to infer Pluto's interior structure is "a really novel idea," says James Tuttle Keane, a planetary scientist at NASA's Jet Propulsion Laboratory, who was not involved with the study.

If this method of simulated planetary seismology holds water, Pluto's secrets may not be the only ones extracted from afar, says Paul Byrne, a planetary geologist at North Carolina State University, who was also not involved in the research. The concept could be extended to all kinds of icy worlds and satellites, from the moons of the solar system's ice giants to the frigid behemoths hiding out in the Kuiper Belt. This research is a reminder of the incalculable value of New Horizons's meet-and-greet with Pluto, says Jani Radebaugh, a planetary scientist at Brigham Young University, who was not involved with the work. "It's amazing how we squeeze every little bit out of it," she adds.

Sputnik Planitia's location hints at a buried ocean on Pluto, but more evidence is needed to confirm its existence. Scientists use robots to detect seismic waves traveling through Earth, the moon and Mars. These waves reflect, deflect and contort, depending on what material they pass through—and they paint a picture of a world's subterranean layers. But this is not possible on far-flung Pluto, which lacks robotic explorers.

Help, as it happens, was hiding billions of miles away on Mercury. Its Caloris Basin, a roughly 950-mile-wide impact crater, lies on the planet's exact opposite side, or antipode, to a geologic pandemonium of shattered rock and maddeningly undulating topography. "There's nothing like it anywhere else on the body," Radebaugh says. Researchers long thought this rough terrain came from Caloris's violent creation—just as the undulating land opposite Sputnik Planitia may have come from a similar impact on Pluto.

So, scientists wondered, why not recreate Pluto's seismology to find out? They turned to the model iSALE, which simulates planetary-scale impacts and replicates the physics of impact shocks. Adeene Denton, a planetary geologist at Purdue University and lead author of the new work, says she has "blown up Pluto countless times."

The simulation that best replicates the dimensions of Sputnik Planitia and Pluto's mangled antipodal terrain involves a 250-mile-wide projectile moving at 4,500 miles per hour and crashing into the dwarf planet. In the model, as Sputnik Planitia is carved out, a massive shock wave travels through Pluto, followed by a deformation-causing stress wave whose movement depends on the speed of sound in the material in which it travels. The stress wave traverses Pluto's rocky core relatively quickly and moves slowly through the body's icy shell. It travels even more slowly through the 93-mile-thick liquid-water ocean sandwiched in between.

In the simulation that best fits the data, Pluto's core is made of serpentine, a rock that transmits stress waves more slowly than other likely candidates. The difference in sound speed between the core and ocean would be low—a quirk of physics that allows more seismic energy to move through the ocean toward the other side than it otherwise could. This means that overall, a gargantuan amount of that energy is trained on Sputnik Planitia's antipode, enough to make the mangled features seen by New Horizons.

Still, the spacecraft's images of that half of Pluto have poor resolution compared with those of the Sputnik Planitia side, Byrne says, so it is not easy to work out precisely what they are showing. "There's a lot of weird stuff on that far side of Pluto," Keane says. "And there are a lot of different ways that you can imagine creating some of those odd patterns that we see." One such possibility involves volatile ices of methane, carbon dioxide and nitrogen that chew up Pluto's landscape as they fluctuate between gases and solids. They could also be responsible for unusual terrain, including the mess opposite Sputnik Planitia. (A recent, unrelated study also blames volatiles for creating the chaotic terrain antipodal to Mercury's Caloris Basin.)

But if the new model is correct, it adds credence to the idea that Pluto and its icy cousins elsewhere could have substantial subsurface oceans. Far from being merely frozen-through snowballs, Denton says, "they could all host such incredible, rich geologic histories." —*Robin George Andrews*

CONSERVATION

Extinguishing Extinction

Calculations suggest how to slash risk for tropical species by half

Climate change and habitat loss are two huge threats to animal and plant survival, but a new study shows how managing both factors could help prevent extinctions. Cutting greenhouse gas emissions and protecting more tropical land could reduce the probability of species blinking out, called extinction risk, by more than half, the research found.

Scientists had not previously calculated the combined benefits that limiting climate change and saving swaths of land could have for so many species, says co-author Patrick Roehrdanz, a researcher with the nonprofit organization Conservation International.

Climate change is expected to continue altering existing habitats, forcing more organisms to relocate or adapt. For this study, published in February in *Ecography,* the researchers looked at existing and future habitat ranges for 104,059 plants and animals in South America, Africa and Asia and existing ranges for 185,160 more—the largest-ever compilation of such data. They then modeled future extinction risk for those species if certain percentages of the planet's tropical land were placed under protection (around 17 percent is protected now).

The scientists calculated that with 30 percent protected, if greenhouse gases were also curtailed—consistent with the aim of keeping global temperature rise below two degrees Celsius above preindustrial levels—the species' extinction risk could fall by more than 50 percent.

These results could help inform United Nations officials scheduled to meet this year. Focused on conserving the world's flora and fauna, the U.N. Convention on Biological Diversity has proposed conserving 30 percent of Earth's land and oceans by 2030. Formal protection from development could save vulnerable ecosystems and mitigate the effects of climate change.

The model does not, however, take into account how different species interact with one another and with the landscape. A hummingbird may move to a new location, but the plants it depends on may not, for example. Still, says Rachael Gallagher, a biologist at Australia's Macquarie University in New South Wales, who was not involved in the study, the paper "provides an evidence base for those advocating to expand the world's protected areas." —*Susan Cosier*

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TECH

Water Wand

Cheap, simple device detects heavy metals in water

MELANIE GONICK *Massachusetts Institute of Technology*

Municipal water can be contaminated by electronic waste and other sources of heavy metals—but collecting, chemically preserving and transporting samples to laboratories for testing is challenging for remote communities.

To streamline the process, Emily Hanhauser, a mechanical engineer at the Massachusetts Institute of Technology, and her colleagues created a low-tech sample-collection device that costs less than two dollars to make. It consists of a plastic handle tipped by propellerlike attachments made from polymer mesh, which contain small packets of absorbent resin beads that attract heavy metal ions. Users stir the device in water and then blot or air-dry it. Dunking the attachments in an acid solution releases the absorbed ions, which can then be measured.

Unlike possibly contaminated water samples, which are considered hazardous, the device can be safely mailed to testing facilities. It can also yield results after two years of storage, its creators say. In experiments, the tool accurately reflected the amounts of copper, nickel, lead and cadmium added to a variety of water samples, the researchers reported in March in *Environmental Science and Technology.*

A detailed analysis of water quality ideally would be performed near the source, eliminating the need for sample shipping entirely, Hanhauser notes. But existing tools designed for that purpose cannot measure small enough amounts of contaminants, and they often have too much variation in measurement to be useful, she says. Her group's device might be able to provide remote communities and well owners—who in the U.S. are responsible for their own water-quality monitoring—with a feasible alternative to transporting high-volume liquid samples over long distances. A more advanced version of the device could potentially measure large clumps of contaminating metals as well, the researchers add.

"I think this could be a good diagnostic tool because of the low cost, good metal-recovery numbers and superiority over presence/absence tests," says Siddhartha Roy, an environmental engineer at Virginia Tech, who studies the notorious drinking water in Flint, Mich., and who was not involved with the new study. "I can see superior versions of the device being used following contamination events for specific metals." —*Rachel Crowell*

MEDICINE

Vaccine Transport

A flexible film could deliver crucial medication

Vaccines may soon make their film debut. Led by pharmaceutics expert Maria A. Croyle, researchers at the University of Texas at Austin have developed a thin sheet that preserves vaccines and other biological medicines for long periods without refrigeration. This means the carefully cooled vials now used to ship vaccines could potentially be replaced by lightweight, peelable films that can be mailed in an envelope and stored on a shelf.

Croyle's laboratory began developing the technology in 2007. Inspired by amber's ability to preserve the DNA of insects and other living things, the researchers set out to create their own version of the substance by mixing together "a lot of sugar and a little bit of salt, much like hard candy," Croyle explains. The vaccine-containing film is administered by mouth—sweet news for many who dislike needles.

The film's components are tailored to suit each specific vaccine candidate and provide a protective coating. "We've learned over time that the key to really stabilizing whatever the film holds is to have it intermixed with all the ingredients," Croyle says, adding that the process is quick and uses affordable, standard benchtop equipment. "We really wanted to come up with something that would be transferable to developing countries."

Immunization programs depend heavily on keeping vaccines cold (two to eight degrees Celsius) as they are transported, sometimes over thousands of kilometers to remote locations. Delivery can be difficult and costly, and transport disruptions can render the vaccines ineffective.

But this new formulation can store live viruses, bacteria and antibodies for several months at ambient temperatures (20 degrees C). In a new paper, published in March in *Science Advances,* the scientists show that the live viruses in one vaccine were preserved in the film even after 36 months. They also find that a flu vaccine suspended in their film compares favorably with a traditional flu shot. "The study demonstrates early proof of concept for an exciting platform for vaccine product development," says Lisa Rohan, a pharmacologist at the University of Pittsburgh,

who was not involved in the study. She notes that each vaccine type would need a custom formulation for future stages of development.

Finding partners to scale up manufacturing for clinical trials is the researchers' most pressing hurdle, Croyle says. They are also exploring packaging methods to keep their films stable up to 40 degrees C.

Size is a major advantage of this platform—a letter-sized sheet of the film can carry more than 500 doses of vaccine, about 1/900 the weight of equivalent traditional doses. By making it easier and cheaper to ship and store vaccines efficiently, Croyle says, the technology could vastly improve immunization rates the world over, particularly in middle- to low-income countries. —*Harini Barath*

Illustration by Thomas Fuchs

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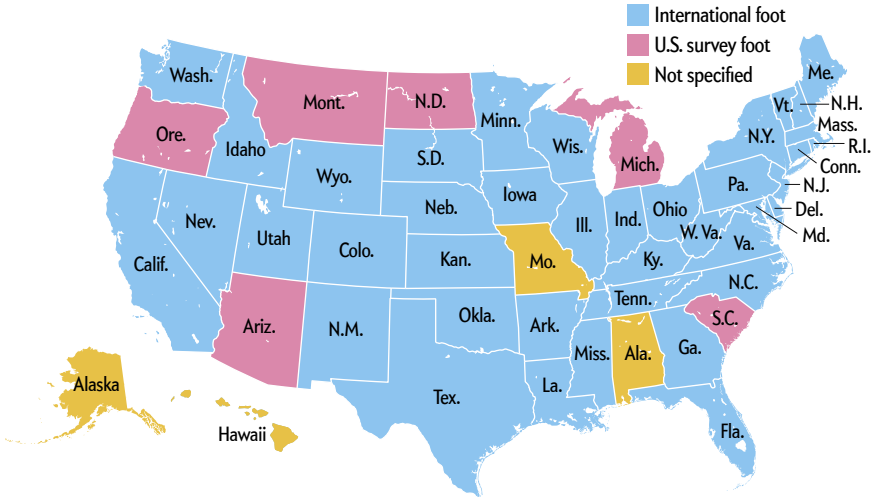
GEOMATICS

Landing on the Right Foot

Federal agencies are eliminating a multistate disagreement over a basic measurement unit's length



In 2023 every U.S. land surveyor will finally be on equal footing. One kind of foot, specifically: the "international foot." These engineers have long measured land with two versions of the unit, depending on which state they are in and whom they work for. To eliminate the resulting confusion, surveyors will soon stop using what is called the "U.S. survey foot" and use only the international version.

The two are nearly identical—dividing one by the other provides a ratio of 0.999998. But over long distances, such minuscule differences add up and can cause big problems. Every building in the U.S. sits on specific GPS coordinates, which are typically rendered and documented in meters. When mapping property or construction plans, surveyors convert those meters to feet. If they use an unexpected type of foot, future engineers referencing those maps might install or look for infrastructure in the wrong place.

"It's kind of a mess," says Michael Dennis, the National Geodetic Survey project manager overseeing the transition. Most engineering projects in the U.S. have used the international foot since 1959, but land surveys—which map boundaries and infrastructure locations—use whichever foot an organization or state wants. (The international foot is exactly 0.3048 of a meter, whereas the U.S. survey foot, 1200/3937 of a meter, has an unending decimal.) This means that anyone working in multiple U.S. locations or with different agencies must keep careful track of which foot is in use. A recent poll of 530 attendees of a National Geodetic Survey Webinar, who were mostly surveyors, found that 62 percent blamed confusion between the two feet for problems in their work.

Bungled math is common in trying to interpret others' measurements, says Brian Fisher, a registered land surveyor in Arizona: "I've seen it dozens or hundreds of times in my career." Fortunately, he adds, "it's not an error until you build it." But Dennis notes that this does happen, citing an engineer's account of a building that was constructed near a landing strip—and had to lose its top floor at the last minute to avoid obscuring the planes' glide path, which had been calculated with a differing type of foot.

The official announcement of the impending change is slated for the end of June, and the public has been given a chance to weigh in on the mandate. Some people have expressed support; others warn it may cause even more confusion, and a few suggest U.S. surveyors just embrace the metric system. "We really wanted people to go metric," Dennis says, "but that's a different kind of battle."

—Leslie Nemo

SOURCE: NOAA'S NATIONAL GEODETIC SURVEY

Graphic by Amanda Montañez

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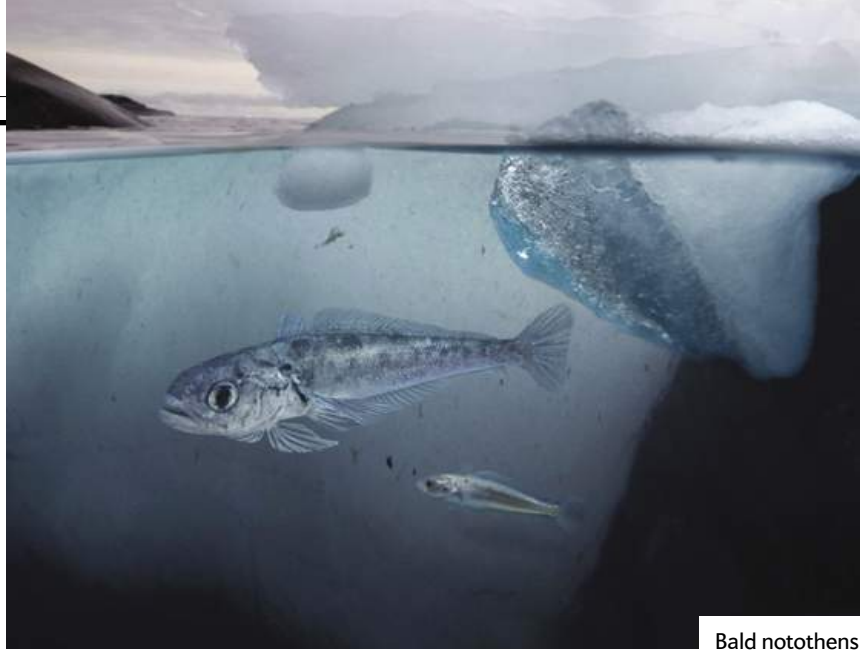

Bald notothens

ANIMAL BEHAVIOR

Blood-Doping Champion

To remain active in frigid waters, an Antarctic fish drastically adjusts blood oxygen

Blood doping to heighten performance is forbidden in professional sports. Athletes can use this technique to fuel their muscles with more oxygen-carrying red blood cells—for example, by receiving a transfusion. But many animals dope naturally: sheep, marine fishes and horses can boost their blood's capacity to carry oxygen by 16 to 74 percent in physically demanding situations. Now a study shows that an Antarctic fish called the bald notothen can ramp up its carrying capacity by more than 200 percent to pursue an active life in frigid waters.

Like most fishes native to Antarctica, the bald notothen's blood contains antifreeze proteins that help it withstand extreme cold. But these proteins, along with red blood cells (RBCs), can make blood viscous and hard to circulate. Some Antarctic fishes adapt by eliminating RBCs altogether, absorbing oxygen directly from the water via gills and skin as they passively await prey. Bald notothens, however, actively swim below surface ice to chase krill and other crustaceans while dodging predators such as penguins and seals. For this behavior, "you need to supply [more] oxygen to the muscles," says Michael Axelsson, a cardiovascular physiologist at the University of Gothenburg in Sweden and co-author of the new study, which was published in January in the *Journal of Experimental Biology*.

The scientists compared RBC levels in samples collected from bald notothens relaxing in glass tanks with those in samples drawn from fish they "chased" using a plastic tube. RBC levels were at 9 percent in the resting animals but 27 percent in the exercised ones, showing a 207 percent spike in the latter's blood oxygen-carrying capacity. "No [other] fish we've seen can more than double their RBCs or drop their numbers to such a low level when resting," Axelsson says. This low level reduces strain on the bald notothens' heart, he adds. The fish's spleen stores RBCs, and the researchers found that to eject more into the bloodstream, the organ contracts to weigh 41 percent less.

The enormous changes in RBC levels initially surprised Gerald Kooyman, a marine biologist at the Scripps Institution of Oceanography, who was not involved in the study. He notes, however, that these animals have fewer blood cells to begin with, so maintaining circulation with a tripled RBC count is less difficult. If a diving Weddell seal pushed its RBC levels from 40 to 90 percent, for instance, its blood would be dangerously hard to pump.

Yet bald notothens do face trade-offs for their ability. By attaching a probe to each fish's aorta, the scientists found blood pressure was 12 percent higher and the heart worked 30 percent harder in active individuals. The heart can rest during quiet times, but when bald notothens need to exert themselves, Axelsson says, "these fish have to live with the slightly higher consequences of [more] RBCs because they need more oxygen." —*Priyanka Runwal*

PAULO OLIVEIRA *Alamy*

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ANTHROPOLOGY

Tastes Like Pheasant

New analysis ruffles the story of poultry domestication

Modern pheasant

J MROCEK *Getty Images*

Chickens are by far the most numerous birds on the planet, with a population of around 23 billion. But new research suggests that another species was once a strong contender to become the world's favorite poultry: ancient bird remains in China have turned out to be not from the first domesticated chickens, as researchers long assumed, but from pheasants. The study further indicates that wild pheasants lived side by side with people, shedding light on the early domestication process.

"It's uncommon for us to have evidence of deer, for example, living with hunter-gatherers," says Loukas Barton, an archaeologist at California-based environmental consulting firm Dudek. "But in this case, we see what otherwise is considered a wild animal living in the human biome." Barton is lead author on the study, published in February in *Scientific Reports.*

Most archaeologists had assumed that bird bones found with those of pigs and dogs, along with agricultural tools, at 8,000-year-old sites in northern China were the earliest evidence of chicken domestication. But many wondered how red jungle fowl—known to be chickens' wild ancestors—could suddenly appear more than 1,000 miles from their native range in Southeast Asia. In 2015 researchers raised the possibility that the bones belonged to pheasants, which are native to northern China.

For a definitive answer, Barton and his colleagues analyzed the bones of eight birds found at Gansu Province's 7,500-year-old Neolithic Dadiwan site that were previously identified as chickens. Researchers at the University of Oklahoma used two different methods, including sequencing the full mitochondrial genome, to genetically confirm that the bones belonged to pheasants.

Biochemistry tests revealed that these pheasants subsisted on a diet heavy in millet, a human-grown crop, suggesting that the birds lived alongside people year-round—a first step toward domestication. Barton says the process likely paralleled early chicken domestication: wild birds started interacting closely with humans and eventually formed lasting, interdependent relationships with them. True domestication, however, entails physical or genetic change brought about by artificial human selection; the ancient pheasant genomes match modern ones, so these birds were still technically "wild."

Yu Dong, a geneticist at Shandong University in China, who was not involved in the research, says these "very important" findings provide significant insight into the history of domestication. She wonders, though, whether Neolithic people would have been likely to welcome pheasants. "In many places nowadays," Dong notes, "a net is put up in fields to prevent birds from eating up crops."

Barton says humans probably considered pheasants a good meat source. But he suspects that pheasants' intermittent egg laying may be why the more consistent chicken was ultimately domesticated instead—perhaps explaining, he says, "why today we don't eat Kentucky Fried Pheasant." —*Rachel Nuwer*

EPIDEMIOLOGY

All in One

Scientists track malaria-causing parasites in individual blood cells

Malaria struck an estimated 228 million people worldwide in 2018. Yet questions remain about how the mosquito-borne malaria parasite, *Plasmodium,* infects humans—and how antimalarial-drug-resistance genes spread. Different strains of the parasite can exchange genes with one another when they reproduce sexually inside an individual mosquito, and the resulting mixed strains infect humans through the mosquito's bite. A new study paints a detailed picture of how *Plasmodium* trades genes, and it finds that all the genetic diversity within an actively infected human host—up to 17 parasite strains—can come from just one bite. The work was published in January in *Cell Host and Microbe.*

Plasmodium spends part of its life cycle in humans and part in mosquitoes. In the mosquito, it reproduces, mixing and matching genes. Until now, the most efficient way to study *Plasmodium*'s genetic diversity was to grind up whole mosquitoes and sequence the mix. The new technique lets scientists determine whether a patient's particular parasites were the product of reproduction within a single mosquito or were introduced separately by different ones.

The researchers collected blood from patients at a hospital serving different villages in Malawi, then sequenced genomes of the parasites found in infected blood cells. Based on the parasites' intermingled genomes, the researchers found that nearly all the infections studied likely came from an individual bite.

"Using single-cell sequencing of parasites from whole populations of infected individuals, we could really start to see for the first time how people are getting infected with malaria," says Ian Cheeseman, a parasitologist at Texas Biomedical Research Institute and senior author of the new study. "Sometimes absolutely staggering amounts of genetic diversity are being transmitted in a single mosquito bite."

The findings are consistent with what Dyann Wirth, an infectious disease researcher at Harvard University specializing in parasites, who was not involved in the new study, had suspected based on earlier research. She calls the work "an important technical breakthrough that will allow a much deeper understanding of malaria transmission and recombination."

This technique can also indicate where infections are coming from. When eradication efforts reduce malaria cases in a given area, analyzing blood cells from those who still get sick can reveal if the infected mosquitoes came from afar or if local elimination was incomplete, explains Edward Wenger, director of global health research at the Institute for Disease Modeling in Bellevue, Wash., who was not involved in the study. The method could also help researchers track the proliferation of drug-resistance mutations. Finding these mutations—and containing their spread—is a critical public health strategy for preserving drugs' effectiveness. —*Viviane Callier*

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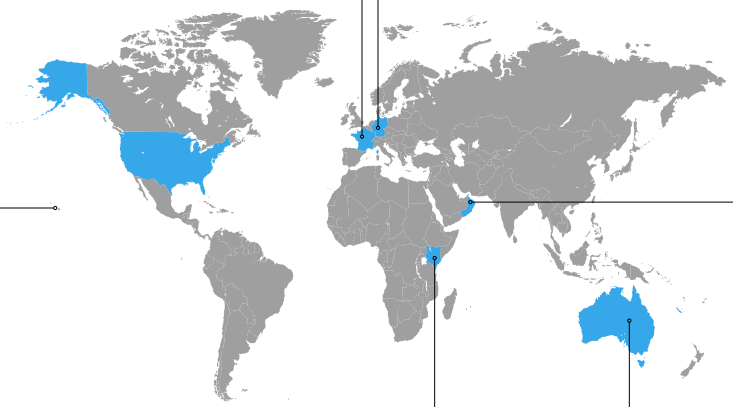
IN THE NEWS

Quick Hits

By Sarah Lewin Frasier

FRANCE
Researchers report dinosaur footprints up to 1.25 meters long on the roof of a cave in France, likely coming from a type of titanosaur. Geologic processes buried and shifted the shoreline footprints to the cave's roof, 500 meters deep.

GERMANY
In a Leipzig waste site, scientists found a soil bacterium that can break down components of polyurethane—and survive the toxic chemicals released in the process.



U.S.
A hiker found two rusted, unexploded bombs from 1935 on the Mauna Loa volcano on Hawaii's Big Island. The bombs had been intended to help divert lava flow during an eruption.

OMAN
Daily growth rings on a 70-million-year-old fossilized mollusk indicate that Earth turned faster at the time, squeezing 372 days into each year. The creature's former habitat, a shallow seabed, is now on a mountain in Oman.

KENYA
A 20-year experiment revealed that cattle-grazing areas frequented by elephants store almost twice as much carbon as areas that bar the animals; soil in these areas also has higher nutrient levels.

AUSTRALIA
Seven new peacock spider species—including one with a van Gogh *Starry Night*–like design—were discovered among crowd-sourced photographs from across the continent. The spiders are known for their vividly colored abdomens.

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PUBLIC HEALTH

Drug Tested

A new model shows opioid deaths may be significantly underreported

Opioids have been blamed for the deaths of at least 400,000 U.S. residents in the past two decades—but research now shows that number could be much higher.

Researchers looked at data from the Centers for Disease Control and Prevention on about 630,000 people who died of drug overdoses between 1999 and 2016. They separated the deaths into two categories: those with and without a specific drug indicated.

For the first category, they analyzed how contributing causes of death (such as injuries and heart problems) and personal characteristics (such as age and gender) correlated with opioid involvement. They then used these analyses to calculate the probability of opioid involvement for each unidentified drug overdose, and they found that the number of opioid deaths is likely 28 percent higher than generally reported.

The researchers also noticed that in five states—Alabama, Indiana, Louisiana, Mississippi and Pennsylvania—the number of apparent opioid deaths over the seven-year period more than doubles after taking into account their adjustments.

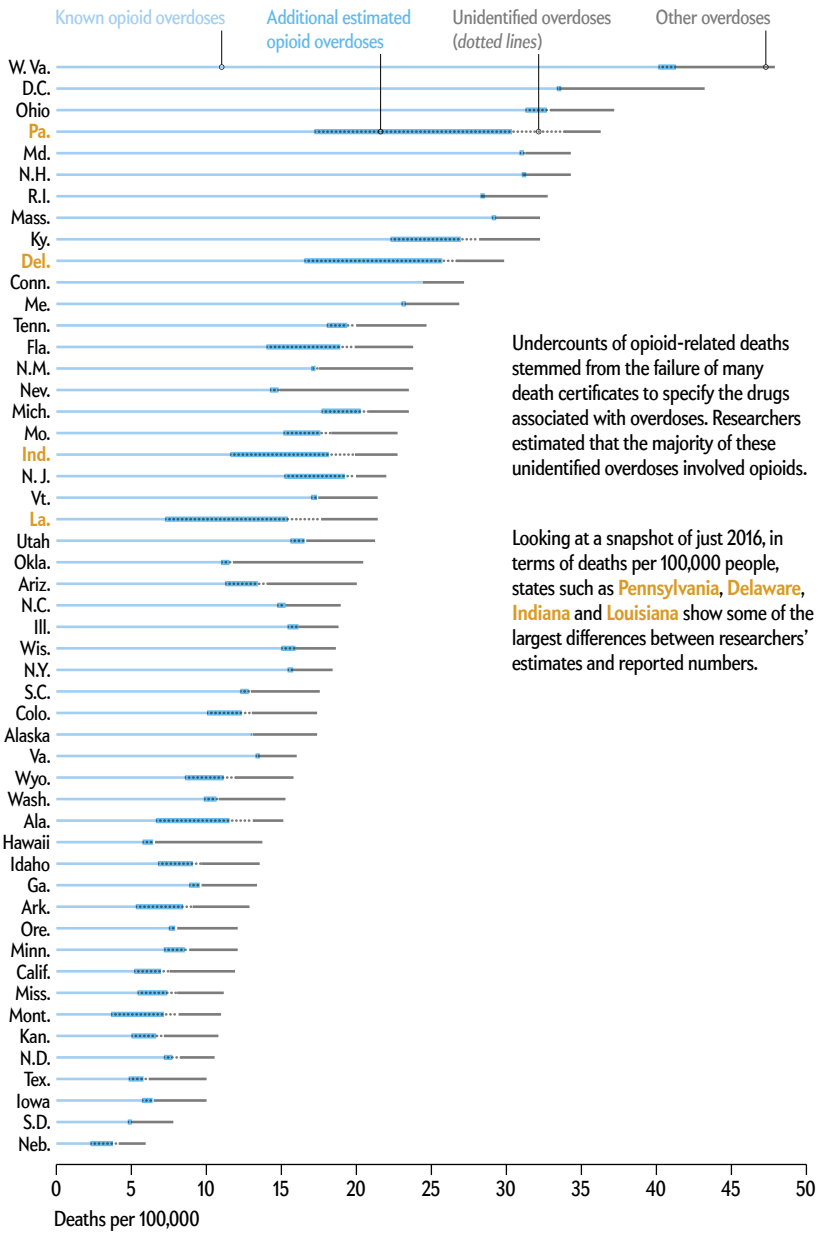
"Opioid deaths serve as one of the main measures of the opioid crisis, and if opioid deaths are not counted accurately, the extent of the crisis can be severely misrepresented," says Elaine L. Hill, an applied microeconomist at the University of Rochester Medical Center and study co-author. The findings appeared online in February in *Addiction*.

Hill says this research highlights "the potential role of state-level medical examination systems and other policies in driving high rates of underreporting." For instance, a lack of detail in death certificates could relate to whether counties have a coroner or medical examiner, the study authors say. Either can declare cause of death, notes Alina Denham, study co-author and Ph.D. candidate at the University of Rochester. But not all coroners conduct autopsies—so Denham says coroner-based jurisdictions may be more likely to have missing information on particular drugs' involvement in overdoses. Most counties in the five states with the highest discrepancies have coroners.

Robert Anderson, chief of the mortality statistics branch of the National Center for Health Statistics, who was not involved in the study, says the research highlights what his department has known for some time: drugs are often not clearly identified in drug-related deaths, and "there is substantial variability by state and by county in the level of specificity." Because of that, he adds, overdose mortality statistics for opioids—and other drugs—can be misleading. Using calculations like the ones in this study, he says, should help capture more accurate and geographically comparable opioid death estimates.

The researchers say they hope government officials and other researchers will use their new prediction model to calculate estimates for future deaths and to reexamine past data. *—Jillian Kramer*

Estimated Opioid Overdose Undercounts by State, 2016



Undercounts of opioid-related deaths stemmed from the failure of many death certificates to specify the drugs associated with overdoses. Researchers estimated that the majority of these unidentified overdoses involved opioids.

Looking at a snapshot of just 2016, in terms of deaths per 100,000 people, states such as Pennsylvania, Delaware, Indiana and Louisiana show some of the largest differences between researchers' estimates and reported numbers.

SOURCE: "USING CONTRIBUTING CAUSES OF DEATH IMPROVES PREDICTION OF OPIOID INVOLVEMENT IN UNCLASSIFIED DRUG OVERDOSES IN U.S. DEATH RECORDS," BY ANDREW J. BOSLETT ET AL., IN *ADDICTION*; FEBRUARY 27, 2020

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Jessica Goodfellow, a teacher and editor living in Japan, is author of the poetry collections *Mendeleev's Mandala, The Insomniac's Weather Report, A Pilgrim's Guide to Chaos in the Heartland* and, most recently, *Whiteout.* Her work has appeared in *Best American Poetry* and other anthologies.

North of the Drunken Forest

Absent of taproot, the black spruce leans madly
where permafrost slumps into thermokarst. Who
wouldn't fall down soused when the ground beneath
began to melt, to buckle and sink? Who wouldn't drink?

In the boreal forests, in a landscape staggered
with lurching birches, ice is a memory, while farther
north, where glaciers begin to thin, ice *is* memory,
or the keeper of memories, a kind of collective mind

in which buried deep are layers of ancient volcanic ash,
soot from fires primeval, banked bubbles of archaic air—
stories stored, frozen, in cerulean cerebral cortex, a vortex
stilled, which soon may spill. The polar ice, in stripes, remembers

what we weren't here to recall, but as with all memory,
what is buried in the blue yonder—if it escapes the icescape—
could kill us. Deep memory is a danger zone. Ice is another
nether. No wonder it numbs. No wonder it burns.

RAY BULSON *Getty Images*

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Viruses Can Be Saviors, Too

As superbugs spread, researchers are turning to viruses that kill bacteria

By Claudia Wallis

This year the world awakened to the fact that the most powerful and sophisticated species on earth is tragically vulnerable to the tiniest and most basic of creatures. Infectious disease specialists have been warning about this for decades. And the threat comes not only from novel viruses, such as the one causing COVID-19, that jump from animals to humans but also from microbial monsters that we have helped to create through our cavalier use of antibiotics: treatment-resistant bacteria such as MRSA (methicillin-resistant *Staphylococcus aureus*) and multidrug-resistant *Acinetobacter baumannii,* sometimes dubbed "Iraqibacter" because so many soldiers returning from Iraq were infected with it. The World Health Organization has predicted that deaths from resistant "superbugs" will rise from roughly 700,000 a year today to nearly 10 million by 2050.

But in a splendid irony, it may turn out that viruses, so often seen as nemeses, could be our saviors in fighting a host of killer infections. As the threat from drug-resistant bacteria has grown and the development of new antibiotics has stalled, researchers have turned their attention to bacteriophages—literally, bacteria eaters. Viruses in this class are believed to be the oldest and most numerous organisms on earth. And like guided missiles, each type has evolved to seek and destroy a specific type of bacteria. Phage therapy has long been used in eastern Europe to battle infections, but after modern antibiotics arrived in the 1940s, it was largely ignored. Interest began to pick up in this century "because the resistance issue was getting worse and worse," says Vincent Fischetti, who heads the laboratory of bacterial pathogenesis and immunology at the Rockefeller University. With modern techniques, virologists can precisely match just the right phages to a specific strain of superbug—with sometimes astonishing results.

Tom Patterson, for example, was resurrected from an overwhelming Iraqibacter infection after his wife, Steffanie Strathdee, an infectious disease epidemiologist, scoured the world for phages that might save him. The couple, both professors at the University of California, San Diego, tell his story in their 2019 book *The Perfect Predator.* Strathdee has since co-founded U.C.S.D.'s Center for Innovative Phage Applications and Therapeutics.

For now phage therapy remains experimental. In most cases, it involves making custom cocktails of several phages shown to be active in vitro against an individual patient's bug. In Patterson's case, nine different phages were used in various cocktails injected into his bloodstream multiple times a day over 18 weeks. Strathdee envisions creating a library "with tens of thousands of phages, already purified, characterized and sequenced," for medical mixologists to draw on. Researchers are also developing premixed phage cocktails for some of the more common superbug strains.

The effort that is furthest along, however, relies on a phage enzyme called a lysin rather than on whole phages. After multiplying inside a bacterium, phages use lysins to break through the cell wall of their host, instantly killing it. A purified lysin made from a phage gene isolated in Fischetti's lab was tested in a phase 2 trial with 116 patients suffering from staph infections of the blood or heart, including 43 with MRSA strains. The results led the FDA to designate the lysin, known as exebacase, a "breakthrough therapy," meaning it will be fast-tracked for approval if a phase 3 trial, now underway, bears out the findings.

The full phase 2 results have not been published, but "what really grabbed a lot of attention was what we saw in the subgroup with MRSA," says Cara Cassino, chief medical officer at ContraFect, the biotech firm developing exebacase. The infection was cleared in 74 percent of MRSA patients given the lysin plus standard antibiotics but in only 31 percent of those who got antibiotics plus a placebo. The respective mortality rates after 30 days were 3.7 and 25 percent, Cassino says. Other lysin drugs are in the pipeline at ContraFect and elsewhere.

Lysins work synergistically with standard antibiotics, Fischetti says; they can pierce the walls of superbugs, enabling the drugs to do their job. Lysins also clear up biofilms—slimy layers of bacteria, carbohydrates and gunk—that cause lasting infections not readily cured by antibiotics. Another advantage is specificity: lysins kill their target without collateral damage to the microbiome.

Phage and lysin therapies still have a ways to go, but at a time when much of the world is besieged by a virus, it's good to know that these tiny invaders may someday save us. SA

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

Illustration by Fatinha Ramos

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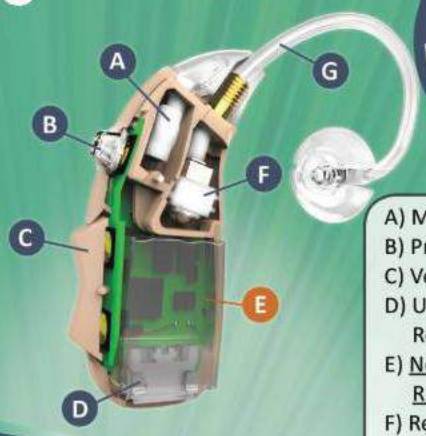

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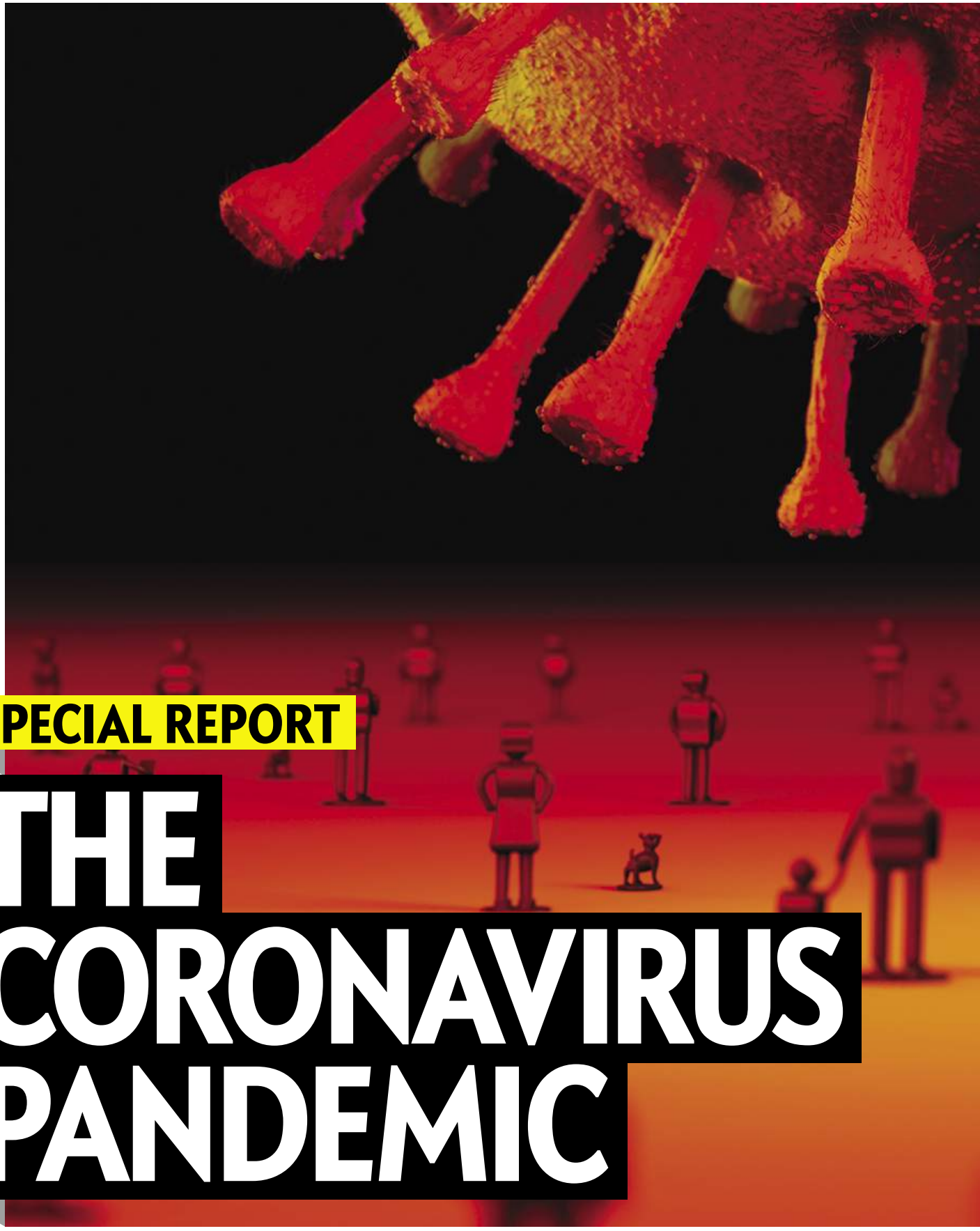

SPECIAL REPORT

THE CORONAVIRUS PANDEMIC

Illustrations by Richard Borge

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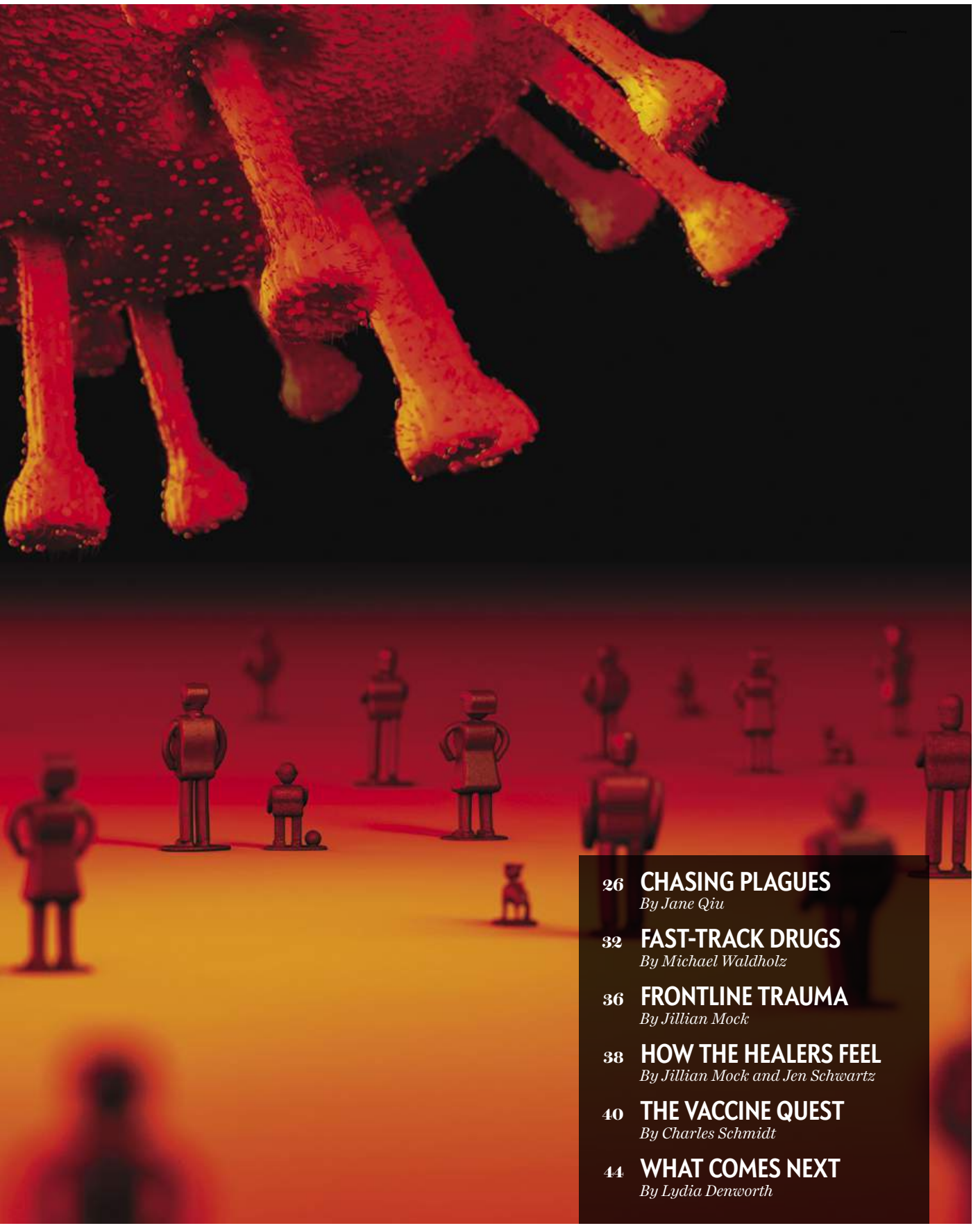

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SPECIAL REPORT

CHASING PLAGUES

VIROLOGIST SHI ZHENGLI CRAWLED THROUGH BAT CAVES IN CHINA TO TRACK THE ORIGINS OF THE FIRST SARS VIRUS AND THE CURRENT PANDEMIC

IN BRIEF

In 2004 Shi Zhengli found a natural reservoir of coronaviruses in bat caves in southern China. **Genetic analyses** show they have leaped to people several times, causing deadly diseases such as COVID-19. **Increasing contact** between people and wild animals makes more outbreaks likely.

By Jane Qiu

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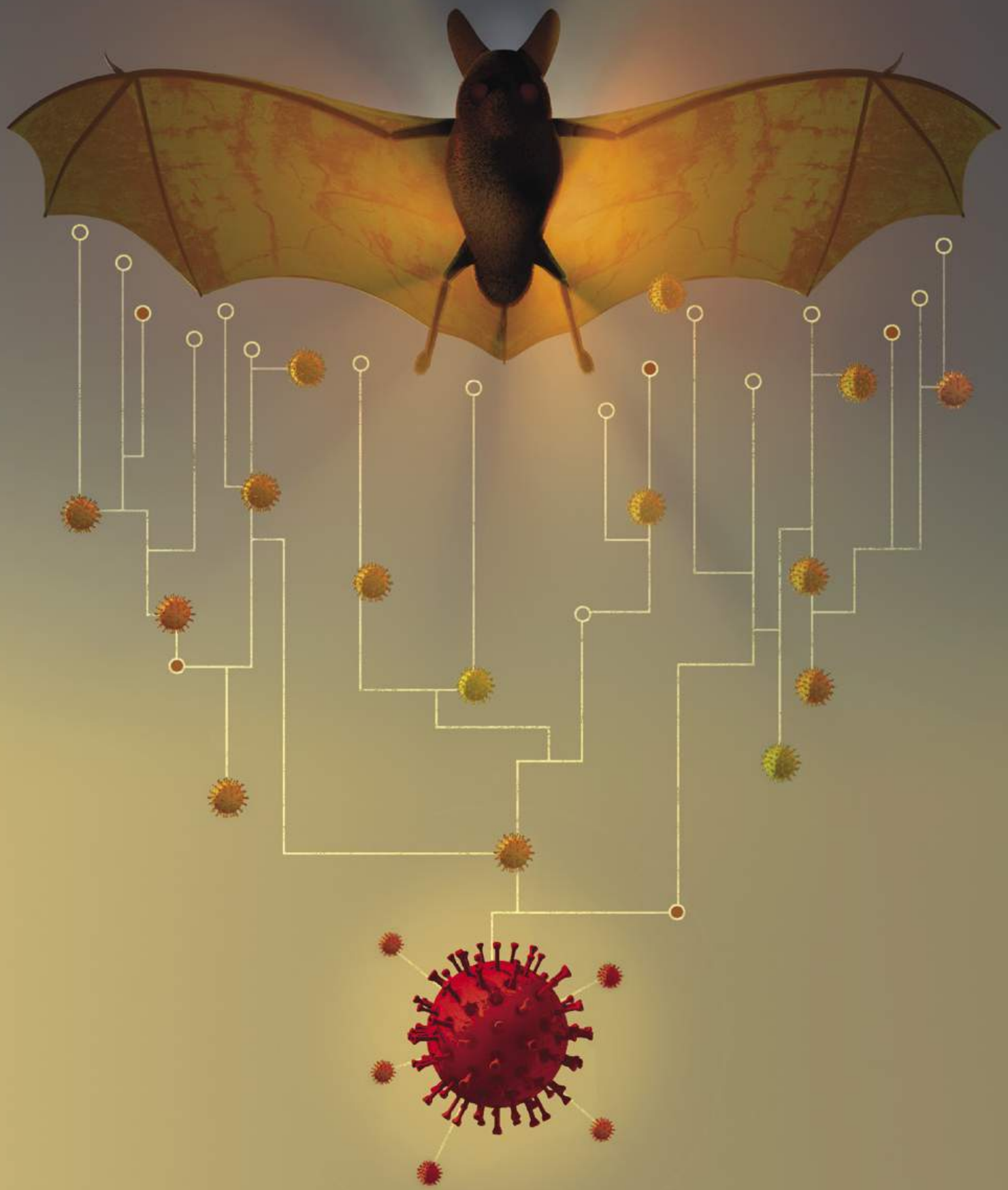

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THE MYSTERIOUS PATIENT SAMPLES ARRIVED AT THE WUHAN INSTITUTE OF Virology at 7 P.M. on December 30, 2019. Moments later Shi Zhengli's cell phone rang. It was her boss, the institute's director. The Wuhan Center for Disease Control and Prevention had detected a novel coronavirus in two hospital patients with atypical pneumonia, and it wanted Shi's renowned laboratory to investigate. If the finding was confirmed, the new pathogen could pose a serious public health threat—because it belonged to the same family of viruses as the one that caused severe acute respiratory syndrome (SARS), a disease that plagued 8,100 people and killed nearly 800 of them between 2002 and 2003. "Drop whatever you are doing and deal with it now," she recalls the director saying.

Shi, a virologist who is often called China's "bat woman" by her colleagues because of her virus-hunting expeditions in bat caves over the past 16 years, walked out of the conference she was attending in Shanghai and hopped on the next train back to Wuhan. "I wondered if [the municipal health authority] got it wrong," she says. "I had never expected this kind of thing to happen in Wuhan, in central China." Her studies had shown that the southern, subtropical provinces of Guangdong, Guangxi and Yunnan have the greatest risk of coronaviruses jumping to humans from animals—particularly bats, a known reservoir. If coronaviruses were the culprit, she remembers thinking, "Could they have come from our lab?"

While Shi's team at the Wuhan institute, an affiliate of the Chinese Academy of Sciences, raced to uncover the identity of the contagion—over the following week they connected the illness to the novel coronavirus that become known as SARS-CoV-2—the disease spread like wildfire. By April 20 more than 84,000 people in China had been infected. About 80 percent of them lived in the province of Hubei, of which Wuhan is the capital, and more than 4,600 had died. Outside of China, about 2.4 million people across 210 or so countries and territories had caught the virus, and more than 169,000 had perished from the disease it caused, COVID-19.

Scientists have long warned that the rate of emergence of new infectious diseases is accelerating—especially in developing countries where high densities of people and animals increasingly mingle and move about. "It's incredibly important to pinpoint the source of infection and the chain of cross-species transmission," says disease ecologist Peter Daszak, president of EcoHealth Alliance, a New York City–based nonprofit research organization that collaborates with researchers, such as Shi, in 30 countries in Asia, Africa and the Middle East to discover new viruses in wildlife. An equally important task, he adds, is to hunt down other pathogens to "prevent similar incidents from happening again."

Jane Qiu is an award-winning science writer based in Beijing.

THE CAVES

TO SHI, HER FIRST VIRUS-DISCOVERY expedition felt like a vacation. On a breezy, sunny spring day in 2004, she joined an international team of researchers to collect samples from bat colonies in caves near Nanning, the capital of Guangxi. Her inaugural cave was typical of the region: large, rich in limestone columns and—as a popular tourist destination—easily accessible. "It was spellbinding," Shi recalls. Milky-white stalactites hung from the ceiling like icicles, glistening with moisture.

But the holidaylike atmosphere soon dissipated. Many bats—including several insect-eating species of horseshoe bats that are abundant in southern Asia—roost in deep, narrow caves on steep terrain. Often guided by tips from local villagers, Shi and her colleagues had to hike for hours to potential sites and inch through tight rock crevasses on their stomachs. And the flying mammals can be elusive. In one frustrating week, the team explored more than 30 caves and saw only a dozen bats.

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These expeditions were part of the effort to catch the culprit in the SARS outbreak, the first major epidemic of the 21st century. A Hong Kong team had reported that wildlife traders in Guangdong first caught the SARS coronavirus from civets, mongooselike mammals that are native to tropical and subtropical Asia and Africa.

Before SARS, the world had only an inkling of coronaviruses—so named because their spiky surface resembles a crown when seen under a microscope, says Linfa Wang, who directs the emerging infectious diseases program at Singapore's Duke-NUS Medical School. Coronaviruses were mostly known for causing common colds. "The SARS outbreak was a game changer," Wang says. It was the first emergence of a deadly coronavirus with pandemic potential. The incident helped to jump-start a global search for animal viruses that could find their way into humans. Shi was an early recruit of that effort, and both Daszak and Wang have been her long-term collaborators.

With the SARS virus, just how the civets got it remained a mystery. Two previous incidents were telling: Australia's 1994 Hendra virus infections, in which the contagion jumped from horses to humans, and Malaysia's 1998 Nipah virus outbreak, in which it moved from pigs to people. Wang found that both diseases were caused by pathogens that originated in fruit-eating bats. Horses and pigs were merely the intermediate hosts. Bats in the Guangdong market also contained traces of the SARS virus, but many scientists dismissed this as contamination. Wang, however, thought bats might be the source.

In those first virus-hunting months in 2004, whenever Shi's team located a bat cave, it would put a net at the opening before dusk and then wait for the nocturnal creatures to venture out to feed for the night. Once the bats were trapped, the researchers took blood and saliva samples, as well as fecal swabs, often working into the small hours. After catching up on some sleep, they would return to the cave in the morning to collect urine and fecal pellets.

But sample after sample turned up no trace of genetic material from coronaviruses. It was a heavy blow. "Eight months of hard work seemed to have gone down the drain," Shi says. "We thought maybe bats had nothing to do with SARS." The scientists were about to give up when a research group in a neighboring lab handed them a diagnostic kit for testing antibodies produced by people with SARS.

There was no guarantee that the test would work for bat antibodies, but Shi gave it a go anyway. "What did we have to lose?" she says. The results exceeded her expectations. Samples from three horseshoe bat species contained antibodies to the SARS virus. "It was a turning point for the project," Shi says. The researchers learned that the presence of the coronavirus in bats was ephemeral and seasonal—but an antibody reaction could last from weeks to years. The diagnostic kit, therefore, offered a valuable pointer as to how to hunt down viral genomic sequences.

OUTSIDE A BAT CAVE in China's Guangxi province in 2004, Shi Zhengli releases a fruit bat after taking a blood sample (*1*). On the same trip, a group of researchers prepare bat blood samples that they will screen for viruses and other pathogens (*2*).

Shi's team used the antibody test to narrow down the list of locations and bat species to pursue in the quest for genomic clues. After roaming mountainous terrain in most of China's dozens of provinces, the researchers turned their attention to one spot: Shitou Cave, on the outskirts of Kunming, the capital of Yunnan, where they conducted intense sampling during different seasons over five consecutive years.

The efforts paid off. The pathogen hunters discovered hundreds of bat-borne coronaviruses with incredible genetic diversity. "The majority of them are harmless," Shi says. But dozens belong to the same group as SARS. They can infect human lung cells in a petri dish and cause SARS-like diseases in mice.

In Shitou Cave—where painstaking scrutiny has yielded a natural genetic library of bat-borne viruses—the team discovered a coronavirus strain that came from horseshoe bats with a genomic sequence nearly 97 percent identical to the one found in civets in Guangdong. The finding concluded a decade-long search for the natural reservoir of the SARS coronavirus.

SHUYI ZHANG (1 and 2)

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A DANGEROUS MIX

IN MANY BAT DWELLINGS Shi has sampled, including Shitou Cave, "constant mixing of different viruses creates a great opportunity for dangerous new pathogens to emerge," says Ralph Baric, a virologist at the University of North Carolina at Chapel Hill. In the vicinity of such viral melting pots, Shi says, "you don't need to be a wildlife trader to be infected."

Near Shitou Cave, for example, many villages sprawl among the lush hillsides in a region known for its roses, oranges, walnuts and hawthorn berries. In October 2015 Shi's team collected blood samples from more than 200 residents in four of those villages. It found that six people, or nearly 3 percent, carried antibodies against SARS-like coronaviruses from bats—even though none of them had handled wildlife or reported SARS-like or other pneumonialike symptoms. Only one had traveled outside of Yunnan prior to the sampling, and all said they had seen bats flying in their village.

Three years earlier Shi's team had been called in to investigate the virus profile of a mine shaft in Yunnan's mountainous Mojiang County—famous for its fermented Pu'er tea—where six miners suffered from pneumonialike diseases and two died. After sampling the cave for a year, the researchers discovered a diverse group of coronaviruses in six bat species. In many cases, multiple viral strains had infected a single animal, turning it into a flying factory for new viruses.

"The mine shaft stunk like hell," says Shi, who, like her colleagues, went in wearing a protective mask and clothing. "Bat guano, covered in fungus, littered the cave." Although the fungus turned out to be the pathogen that had sickened the miners, she says it would have been only a matter of time before they caught the coronaviruses if the mine had not been promptly shut.

With growing human populations increasingly encroaching on wildlife habitats, with unprecedented changes in land use, with wildlife and livestock transported across countries and their products around the world, and with sharp increases in both domestic and international travel, pandemics of new diseases are a mathematical near certainty. This had been keeping Shi and many other researchers awake at night long before the mysterious samples landed at the Wuhan Institute of Virology on that ominous evening last December.

More than a year ago Shi's team published two comprehensive reviews about coronaviruses in *Viruses* and *Nature Reviews Microbiology*. Drawing evidence from her own studies—many of which were published in top academic journals—and from others, Shi and her co-authors warned of the risk of future outbreaks of bat-borne coronaviruses.

NIGHTMARE SCENARIO

ON THE TRAIN BACK to Wuhan on December 30 last year, Shi and her colleagues discussed ways to immediately start testing the patients' samples. In the following weeks—the most intense and the most stressful time of her life—China's bat woman felt she was fighting a battle in her worst nightmare, even though it was one she had been preparing for over the past 16 years. Using a technique called polymerase chain reaction, which can detect a virus by amplifying its genetic material, the team found that samples from five of seven patients had genetic sequences present in all coronaviruses.

Shi instructed her group to repeat the tests and, at the same time, sent the samples to another facility to sequence the full viral genomes. Meanwhile she frantically went through her own lab's records from the past few years to check for any mishandling of experimental materials, especially during disposal. Shi breathed a sigh of relief when the results came back: none of the sequences matched those of the viruses her team had sampled from bat caves. "That really took a load off my mind," she says. "I had not slept a wink for days."

By January 7 the Wuhan team had determined that the new virus had indeed caused the disease those patients suffered—a conclusion based on results from analyses using polymerase chain reaction, full genome sequencing, antibody tests of blood samples and the virus's ability to infect human lung cells in a petri dish.

IN YUNNAN PROVINCE, CHINA, scientists from EcoHealth Alliance, an international group that searches for diseases that can jump from animals to people, hunt for pathogens in a bat cave.

ECOHEALTH ALLIANCE

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The genomic sequence of the virus, eventually named SARS-CoV-2, was 96 percent identical to that of a coronavirus the researchers had identified in horseshoe bats in Yunnan. Their results appeared in a paper published online on February 3 in *Nature*. "It's crystal clear that bats, once again, are the natural reservoir," says Daszak, who was not involved in the study.

Since then, researchers have published more than 4,500 genomic sequences of the virus, showing that samples around the world appear to "share a common ancestor," Baric says. The data also point to a single introduction into humans followed by sustained human-to-human transmission, researchers say.

Given that the virus seems fairly stable initially and that many infected individuals appear to have mild symptoms, scientists suspect that the pathogen might have been around for weeks or even months before severe cases raised the alarm. "There might have been mini outbreaks, but the viruses either burned out or maintained low-level transmission before causing havoc," Baric says. Most animal-borne viruses reemerge periodically, he adds, so "the Wuhan outbreak is by no means incidental."

"Constant mixing of different viruses creates a great opportunity for dangerous new pathogens to emerge."
—Ralph Baric *University of North Carolina at Chapel Hill*

MARKET FORCES

TO MANY, THE REGION'S burgeoning wildlife markets—which sell a wide range of animals such as bats, civets, pangolins, badgers and crocodiles—are perfect viral melting pots. Although humans could have caught the deadly virus from bats directly (according to several studies, including those by Shi and her colleagues), independent teams have suggested that pangolins may have been an intermediate host. These teams have reportedly uncovered SARS-CoV-2-like coronaviruses in pangolins that were seized in antismuggling operations in southern China.

On February 24 China announced a permanent ban on wildlife consumption and trade except for research, medicinal or display purposes—which will stamp out an industry worth $76 billion and put approximately 14 million people out of jobs, according to a 2017 report commissioned by the Chinese Academy of Engineering. Some welcome the initiative, whereas others, such as Daszak, worry that without efforts to change people's traditional beliefs or to provide alternative livelihoods, a blanket ban may simply push the business underground. This could make disease detection even more challenging. "Eating wildlife has been part of the cultural tradition" in China for thousands of years, Daszak says. "It won't change overnight."

In any case, Shi says, "wildlife trade and consumption are only part of problem." In late 2016 pigs across four farms in Qingyuan County in Guangdong—60 miles from the site where the SARS outbreak originated—suffered from acute vomiting and diarrhea, and nearly 25,000 of the animals died. Local veterinarians could not detect any known pathogen and called Shi for help. The cause of the illness—swine acute diarrhea syndrome (SADS)—turned out to be a virus whose genomic sequence was 98 percent identical to that of a coronavirus found in horseshoe bats in a nearby cave.

"This is a serious cause for concern," says Gregory Gray, an infectious disease epidemiologist at Duke University. Pigs and humans have very similar immune systems, making it easy for viruses to cross between the two species. Moreover, a team at Zhejiang University in the Chinese city of Hangzhou found that the SADS virus could infect cells from many organisms in a petri dish, including rodents, chickens, nonhuman primates and humans. Given the scale of swine farming in many countries, such as China and the U.S., Gray says, looking for novel coronaviruses in pigs should be a top priority.

The current outbreak follows several others during the past three decades that have been caused by six different bat-borne viruses: Hendra, Nipah, Marburg, SARS-CoV, MERS-CoV (Middle East respiratory syndrome) and Ebola. But "the animals [themselves] are not the problem," Wang says. In fact, bats promote biodiversity and ecosystem health by eating insects and pollinating plants. "The problem arises when we get in contact with them," he says.

TOWARD PREVENTION

WHEN I SPOKE TO SHI in late February—two months into the epidemic and one month after the government imposed severe movement restrictions in Wuhan, a megacity of 11 million—she said, laughing, that life felt almost normal. "Maybe we are getting used to it. The worst days are certainly over." The institute staffers had a special pass to travel from home to their lab, but they could not go anywhere else. They had to subsist on instant noodles during their long hours at work because the institute's canteen was closed.

New revelations about the coronavirus kept coming to light. The researchers discovered, for instance, that the pathogen enters human lung cells by using a receptor called angiotensin-converting enzyme 2, and they and other groups have since been screening for drugs that can block it. Scientists are also racing to develop vaccines. In the long run, the Wuhan team plans to develop broad-spectrum vaccines and drugs against coronaviruses deemed risky to humans. "The Wuhan outbreak is a wake-up call," Shi says.

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Many scientists say the world should move beyond merely responding to deadly pathogens when they arise. "The best way forward is prevention," Daszak says. Because 70 percent of emerging infectious diseases of animal origins come from wildlife, a top priority should be identifying them and developing better diagnostic tests, he adds. Doing so would essentially mean continuing on a much larger scale what researchers such as Daszak and Shi had been doing before their funding ended this year.

Such efforts should focus on high-risk viral groups in mammals prone to coronavirus infections, such as bats, rodents, badgers, civets, pangolins and nonhuman primates, Daszak says. He adds that developing countries in the tropics, where wildlife diversity is greatest, should be the front line of this battle against viruses.

Daszak and his colleagues have analyzed approximately 500 human infectious diseases from the past century. They found that the emergence of new pathogens tends to happen in places where a dense population has been changing the landscape—by building roads and mines, cutting down forests and intensifying agriculture. "China is not the only hotspot," he says, noting that other major emerging economies, such as India, Nigeria and Brazil, are also at great risk.

Once potential pathogens are mapped out, scientists and public health officials can regularly check for possible infections by analyzing blood and swab samples from livestock, from wild animals that are farmed and traded, and from high-risk human populations such as farmers, miners, villagers who live near bats, and people who hunt or handle wildlife, Gray says. This approach, known as "One Health," aims to integrate the health management of wildlife, livestock and people. "Only then can we catch an outbreak before it turns into an epidemic," he says, adding that the strategy could potentially save the hundreds of billions of dollars such an epidemic can cost.

Back in Wuhan, where the lockdown was finally lifted on April 8, China's bat woman is not in a celebratory mood. She is distressed because stories from the Internet and major media have repeated a tenuous suggestion that SARS-CoV-2 accidentally leaked from her lab—despite the fact that its genetic sequence does not match any her lab had previously studied. Other scientists are quick to dismiss the allegation. "Shi leads a world-class lab of the highest standards," Daszak says.

Despite the disturbance, Shi is determined to continue her work. "The mission must go on," she says. "What we have uncovered is just the tip of an iceberg." She is planning to lead a national project to systematically sample viruses in bat caves, with much wider scope and intensity than previous attempts. Daszak's team has estimated that there are more than 5,000 coronavirus strains waiting to be discovered in bats globally.

"Bat-borne coronaviruses will cause more outbreaks," Shi says with a tone of brooding certainty. "We must find them before they find us." SA

SPECIAL REPORT

FAST-TRACK DRUGS

WITH NO TIME TO MAKE TREATMENTS FROM SCRATCH, RESEARCHERS FIND EXISTING COMPOUNDS THAT DEFLECT HARM

By Michael Waldholz

MARK DENISON BEGAN HUNTING for a drug to treat COVID-19 almost a decade before the contagion, driven by a novel coronavirus, devastated the world this year. Denison is not a prophet, but he is a virologist and an expert on the often deadly coronavirus family, members of which also caused the SARS outbreak in 2002 and the MERS eruption in 2012. It is a big viral group, and "we were pretty certain another one would

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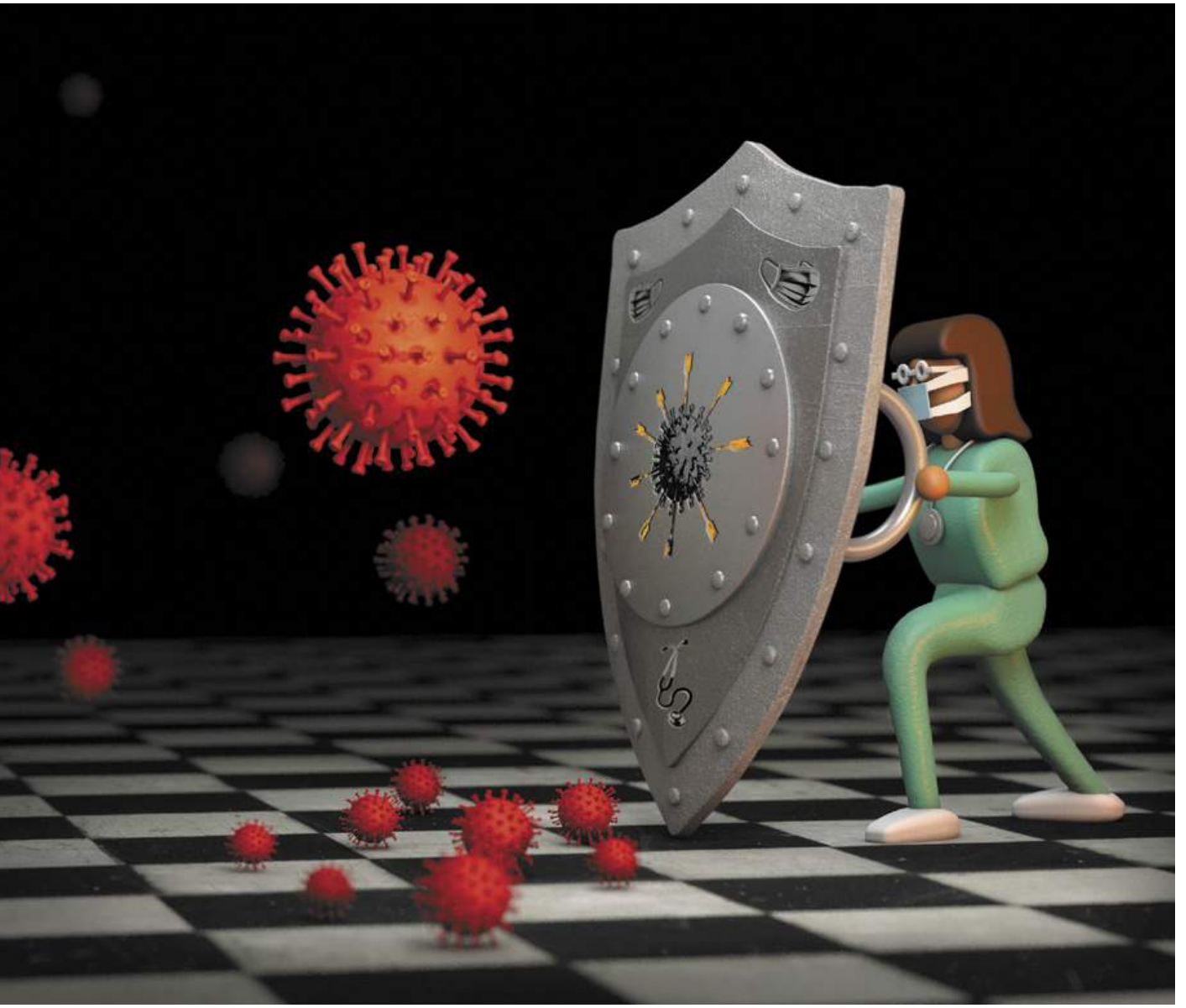

soon emerge," says Denison, who directs the division of pediatric infectious diseases at Vanderbilt University Medical Center.

A virus is an unusual beast. Essentially it is a cluster of genetic material that integrates itself into a cell and takes over some of the cell's molecular machinery, using it to assemble an army of viral copies. Those clones burst out of the cell, destroying it, and go on to infect nearby cells. Viruses are hard to kill off completely because of their cellular integration—they hide within their hosts. And they have explosive reproductive rates. Because total eradication is so hard, antiviral drugs instead aim to limit replication to low levels that cannot hurt the body.

In 2013 Denison and Ralph Baric, a coronavirus researcher at the University of North Carolina at Chapel Hill, identified a vulnerable site on a protein common to all coronaviruses they had examined, a spot that is key to the microbe's ability to make copies of itself. If that ability is hindered, a coronavirus cannot cause widespread infection. Four years later researchers in the two laboratories spotted a compound that acted on this protein site. It was sitting, unused, in a large library of antiviral compounds created by the biotech giant Gilead Biosciences. The scientists got a sample and, in test tube and animal experiments, showed that the drug, called remdesivir, shut down the replicating machinery of several coronavirus variants.

So in early January, when the alarms rang about SARS-CoV-2, Denison and Baric alerted colleagues at Gilead that they were sitting on a potential treatment. Largely because of its activity against other coronavirus strains in Denison and Baric's animal studies, remdesivir was made available to patients for "com-

IN BRIEF

Drug developers are working on three strategies to treat COVID-19, the disease caused by the novel coronavirus. **One way** is to keep SARS-CoV-2 from entering a cell; another is to gum up the virus's reproductive efforts if it does enter. **Finally, researchers aim** to put a stop to an immune system overreaction that causes the most severe symptoms.

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THREE WAYS TO TREAT COVID-19

Some of the drugs being developed to attack the disease and the SARS-CoV-2 virus that causes it

Block Viral Replication

DRUG	ACTION	COMPANY/LAB	STATUS
Remdesivir	Disrupt viral RNA synthesis	• U. of North Carolina • Vanderbilt University • Gilead Sciences	Clinical trials
EIDD-2801	Disrupt viral RNA synthesis	• Emory University • U. of North Carolina • Vanderbilt University • Ridgeback Biotherapeutics	Clinical trials
Danoprevir-Ritonavir	Inhibit viral protease enzyme	• Ascletis Pharma	Clinical trials
RNAi Experimental Compounds	Block viral RNA synthesis	• Alnylam Pharmaceuticals • Vir Biotechnology	Early research

Prevent Entry into Cells

DRUG	ACTION	COMPANY/LAB	STATUS
APN01	Decoy cell receptor	• Apeiron Biologics	Clinical trials
Multiple Human Antibody Cocktail	Antibodies neutralize virus	• Regeneron	Clinical trials planned for summer
Monoclonal Antibody Candidates	Antibodies neutralize virus	• Vir Biotechnology • Biogen • WuXi Biologics	Clinical trials planned
TAK-888	Modified antibodies against virus	• Takeda	Preclinical

Reduce Hyperimmune Response and Acute Respiratory Distress

DRUG	ACTION	COMPANY/LAB	STATUS
Kevzara (sarilumab)	Antibodies block IL-6 immune cell signal	• Regeneron • Sanofi	Clinical trials
Actemra (tocilizumab)	Antibodies block IL-6 immune cell signal	• Genentech • BARDA*	Clinical trials
Remestemcel-L	Stem cells modulate immune system	• Mesoblast • NIH†	Clinical trials
Xeljanz (tofacitinib)	Inhibit inflammatory cells	• Pfizer	Clinical trials

*U.S. Biomedical Advanced Research and Development Authority
†National Institutes of Health

passionate use" in January. By March, Gilead had rushed the compound into two human trials, planning to test the drug's safety and most effective doses on about 1,000 ill patients over several months; health authorities in China began two similar trials. While that was happening, Denison, Baric and a group of their colleagues at Emory University identified still another compound, called EIDD-2801, that hits the same viral vulnerability. In early April they published results showing that in mice, the new substance helped breathing and reduced the amount of many coronaviruses. In test-tube experiments with human lung cells, it drastically hindered SARS-CoV-2.

Several labs around the world, like Denison's and Baric's, have logged years of experience poking about the inner workings of coronaviruses because of SARS and MERS. By the time the new coronavirus was genetically sequenced and its structure revealed, scientists already had identified the enzymes and proteins that most coronaviruses use to spread from one infected human cell to another and also understood that the body could create an overly aggressive inflammatory response when the virus infected lung airway cells.

Because of this work, three main strategies for impeding the virus have emerged as the labs have turned to the current threat. One strategy is to find compounds like remdesivir and EIDD-2801 that gum up the virus's reproductive machinery when it enters a target cell. A second is to block the virus, like a bouncer outside a bar, from entering and infecting those cells in the first place. The third approach is to muffle the immune system's dangerously overactive response, a "cytokine storm" that can drown a victim in a mass of congestion and dying airway cells.

To find these drugs, researchers have turned to the Food and Drug Administration's list of some 20,000 compounds approved for human use and crawled through drug patent applications looking for compounds with promising mechanisms of action. The goal has been to find drugs that have been at least partly developed, avoiding years of making therapeutic molecules from scratch. The Milken Institute, a health advocacy think tank, counted 133 experimental COVID-19 treatments in mid-April. About 49 of these therapies are being rushed into clinical trials. Their effectiveness in people is not yet known, and scientists caution that such drugs, like other antivirals, are unlikely to be cures. But they could reduce symptoms enough to give patients' immune systems a chance to beat the virus on their own.

COPY STOPPERS

ALL CORONAVIRUSES use the same mechanism to reproduce, which involves an enzyme called viral RNA polymerase, so Baric says that was an obvious target. The polymerase makes lots of mistakes as it copies the virus, and it relies on another enzyme, known as an exonuclease, to "proofread" and fix them. Remdesivir appears to disable the proofreading enzyme. Then the virus's copying factory becomes sloppy and produces fewer new viruses.

EIDD-2801, the compound with promising animal and test-tube results reported in early April, aims at the same viral enzyme. But unlike remdesivir, which much be given intravenously, EIDD-2801 can be taken as a pill. For this reason, Baric and other researchers investigating EIDD-2801, including George Painter, a professor of pharmacology and president of the Emory Institute for Drug Development, which first produced the drug, suspect it may end up being more widely used than remdesivir.

In 2018 Painter and his colleagues identified EIDD-2801's activity during a search for a universal influ-

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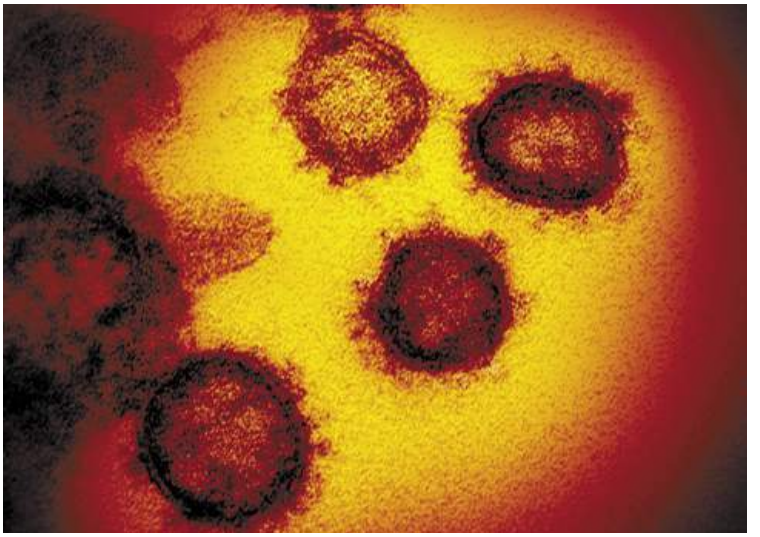
enza medicine. When SARS-CoV-2 emerged, Painter's group immediately shifted focus. EIDD-2801, like remdesivir, inhibits the coronavirus's self-copying operations, but it also works against virus variants with a mutation that made them resistant to the Gilead drug. In addition, EIDD-2801 is effective against a host of other RNA viruses, so it could serve as a multipurpose antiviral, much as some antibiotics can work against a wide variety of bacteria. For COVID-19, says Wayne Holman, co-founder of Miami-based Ridgeback Biotherapeutics, which has licensed the drug and is planning clinical trials, the goal is to have a pill that can be taken by patients at home early in the course of the disease to prevent it from progressing.

BLOCKING INFECTION

TO STOP SARS-COV-2 from penetrating cells in the first place, scientists are trying to develop antibodies that lock onto the viral protein that facilitates cell entry, a part of the virus known as the spike. Some of these neutralizing antibodies, made of a protein called immunoglobulin, may come from the blood of patients who have already cleared the virus. Several medical centers, including Johns Hopkins Hospital and the Mayo Clinic, are harvesting blood plasma from survivors and screening it for antibodies. In a technique known as convalescent therapy, doctors then transfuse it into hospitalized patients with life-threatening acute respiratory distress. Early studies of a few such patients suggest the approach may work—some patients' symptoms improved, and levels of the virus in their bodies dropped—but the work is very preliminary.

Takeda Pharmaceuticals, a Japanese firm, is also collecting plasma from recovered COVID-19 patients to identify antibodies. In that plasma, the company is identifying antibodies that show the most activity against SARS-CoV-2. Using these antibodies as a template, the Takeda researchers plan to synthesize a batch of even more active versions to create a potent cocktail of infection inhibitors, says Chris Morabito, head of research and development of plasma-derived therapies. The therapy—TAK-888—might enter clinical trials by year's end, Morabito says; the number "888" represents "triple fortune" in Chinese. Several other drugmakers, including Regeneron and Vir Biotechnology, are generating their own therapeutic antibodies and say they will also be tested in patients this year.

Another blockade strategy focuses on the cellular docking site that the virus uses. Josef Penninger, a molecular biologist at the University of British Columbia in Vancouver and founder of drug company Apeiron Biologics, is trying to lure the virus away from a chemical receptor called ACE2 in the outer wall of lung cells. The coronavirus spike protein binds to this receptor. Several years ago Penninger's lab synthesized a decoy version of ACE2. In test-tube experiments, the scientists found the synthetic molecule—APN01—attracted coronaviruses away from real human airway cells. The virus locked onto the decoy and was marooned there. "We are blocking the door for the virus and, at the same time, protecting tissues," Penninger says. Apeiron is planning clinical trials later this year for APN01, which must be administered in the hospital as an infusion to sick patients.



EMERGING from a cell, SARS-CoV-2 virus particles (*red circles*) will create a wider infection unless drugmakers find ways to block them.

OVERREACTIONS

IN THE SICKEST COVID-19 PATIENTS, a mass of mucuslike fluid accumulates in the lungs, preventing cells from absorbing oxygen. These are the patients that need ventilators. The fluid buildup is the result of an overactive immune response that involves a signaling chemical called interleukin-6 (IL-6). Biotech companies, including Regeneron and Genentech, have manufactured synthetic antibodies that can bind to IL-6 and mute the call to action that it sends out.

Northwell Health, a large system of 23 hospitals based in Long Island, N.Y., is one of more than a dozen centers participating in clinical trials of the IL-6 blockers, says Kevin Tracey, chief executive of the Feinstein Institutes for Medical Research, which is running the trials at Northwell sites. "The hospitals are being inundated with very sick patients suffering from serious pneumonia and acute respiratory distress," Tracey says. "The IL-6 drugs have a plausible mechanism of action. I'm optimistic they'll work."

None of these approaches are cures. Denison says the drugs under development may "reduce the severity" of an advanced COVID-19 episode, especially if they can be administered when initial symptoms—a mild cough, muscle aches or slight fever—first arise. In a hopeful future, a combination of various therapies may be able to thwart the virus on several different fronts, the way a cocktail of antivirals can beat back an HIV/AIDS infection. By limiting symptoms, drugs may be able to keep some patients out of the hospital and keep hospitalized patients off of ventilators. They can serve as a bridge to survival as other scientists rush to develop the real virus slayer: a vaccine. SA

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.

NIAID-RML

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SPECIAL REPORT

FRONTLINE TRAUMA

MEDICAL WORKERS ARE SOCIETY'S NEW HEROES. WHAT HAPPENS WHEN THE ACUTE CRISIS IS OVER?

By Jillian Mock

IN BRIEF

Health care workers are not just treating a flood of critically ill patients during the pandemic. **They are risking** their own health, witnessing higher rates of death and experiencing breakdowns of protocol and support. **These acute stresses** could lead to mental health issues, yet therapeutic support is lacking.

After his roughest days in a New York City emergency room, physician Matthew Bai feels his whole body relax when he sees his wife and 17-month-old daughter. "My light at the end of the tunnel is going home to family," Bai says. When Manhattan's Mount Sinai Hospital started to overflow with COVID-19 patients in late March, however, Bai and his wife decided she should take their toddler and stay with her parents in New Jersey. The risk of spreading the virus to his family was too great. Now Bai confronts a daily cascade of patients who are struggling to breathe, in an ER busier than he has ever witnessed it. On his mind, always, is whether he will be able to keep his staff safe. All doctors have bad shifts, but now those days repeat, piling up. At night, virtual story time with his daughter is nowhere as soothing as the real thing. "I honestly have no idea how I feel," Bai says. "I go to work, and at the end of the day, I go to sleep. I have no time to digest any of this."

Medicine is a stressful profession under normal circumstances. The physical demands, psychological strain and ineffective work processes can lead to burnout, a condition that affects up to 50 percent of physicians in the U.S., says Colin West, an internist who has studied physician well-being at the Mayo Clinic for more than 15 years. A 2018 review in the journal *Cureus* described it as "a combination of exhaustion, cynicism, and perceived inefficacy." Burned-out clinicians are more likely to quit their jobs. Their patients may have worse outcomes. Yet burnout cannot capture what doctors, nurses, paramedics and others are experiencing as coronavirus overwhelms the health care system. "Burnout is a chronic response to health care conditions," West says. "This is an unprecedented acute crisis."

As the pandemic upends much of society, frontline health care workers are shouldering the burden of a systemic lack of preparation. In the U.S., a sluggish government response, along with the bungled rollout of testing, allowed the virus to spread widely. Years of running lean operations left many hospitals without the resources to quickly expand care. Global demand for personal protective equipment (PPE) and ventilators made these crucial supplies scarce. Backup stockpiles proved too small, and efforts to bolster supplies were uncoordinated or, worse, forced hospitals and jurisdictions to compete with one another. Now ERs in hard-hit areas struggle to keep up with a flood of critically ill patients. Staff in eerily quiet hospitals elsewhere look on, wondering if the virus will overwhelm them next. Nurses facilitate final phone calls between the dying and their loved ones who are barred from entry. As morgues overflow, refrigerated trucks arrive to house the bodies.

"Our health care professionals are seeing incredibly sick people in what is really a tidal wave washing over them, and they are leaning into that work because it's what we do," West says. But leaning into extreme uncertainty for weeks and months on end could have significant impacts on their mental well-being. More than any other group, they are in danger of getting sick from the constant exposure to SARS-CoV-2. As of April, the virus has infected more than 9,000 health care workers in the U.S. and killed 27, according to the Centers for Disease Control and Prevention. Hundreds of clinicians have died worldwide. Like Bai, many worry about spreading the disease to their patients and loved ones; young medical residents are advising one another to write living wills. Some hospitals have muzzled their staffers, citing concerns over the spread of misinformation and patient privacy; around the world, clinicians who have spoken out about the resource shortages or shared their experiences have been reprimanded or fired by their institutions. Many experts predict that, taken together, these traumatic effects of the pandemic will reverberate long after the virus itself is contained.

Trauma is often associated with something overtly violent, such as a car accident or a shooting. But Dutch philosopher Ciano Aydin describes a situation as traumatic when it "violates" familiar expectations about someone's life and world, sending them into a "state of extreme confusion and uncertainty." In the case of this pandemic, prolonged uncertainty is compounded by the moral anguish health care professionals face when they do not have adequate resources to treat critically ill patients, says Wendy Dean, a psychiatrist and co-founder of the nonprofit Moral Injury of Healthcare.

Moral injury, a term borrowed from the military, occurs when a person does something that goes against his or her deeply held moral beliefs, Dean says. In medicine, it can occur when the business side of health care hinders a physician's ability to care for patients; for

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instance, if there are not enough ventilators for the number of COVID-19 patients who need them. Physicians are not used to doing triage, to choosing who gets lifesaving support and who does not, explains G. Richard Holt, an otolaryngologist and bioethicist at the University of Texas Health Science Center at San Antonio. "We're trained in treating one patient at a time, but in the worst of an epidemic, you have to think about the greatest good for the greatest number," Holt says. Studies in soldiers suggest moral injury impedes normal emotional, psychological and social functioning and often occurs in people with post-traumatic stress disorder. "I think the real reckoning is going to come when this is over," Dean says.

The emotional toll of COVID-19 is tricky to predict. During a natural disaster, medical professionals often deliver care after the immediate threat has passed, and those providers are able to go home and decompress at the end of an upsetting day, says Joshua Morganstein, chair of the American Psychiatric Association's Committee on the Psychiatric Dimensions of Disaster. When you are worried about bringing the disaster home with you, no place is safe. Health care workers are grappling with the upheaval of social and economic life along with the rest of us; they are exposed to the constant noise of grim news. Some are tuning out coronavirus coverage as a coping mechanism. "We have to figure out what our reaction would have looked like pre-iPhone," says Suneel Dhand, an internist who works at hospitals in Massachusetts. "I'm concerned about all the people absorbing so much doom and gloom through social media."

Jessica Gold, a psychiatrist at the Washington University School of Medicine in St. Louis, and other experts believe health care workers as a group could develop high rates of anxiety, depression, substance use issues, acute stress and, eventually, post-traumatic stress as a result of what they are experiencing on the pandemic front lines. Because this event is unprecedented, Gold worries the psychological damages will be unprecedented, too. Data from other outbreaks, while limited, support these concerns. A small study of health care workers during the 2003 SARS outbreak, for example, found that 89 percent of workers at high risk of contracting the virus reported negative psychological effects. Another study found SARS-related fear was correlated with symptoms of PTSD.

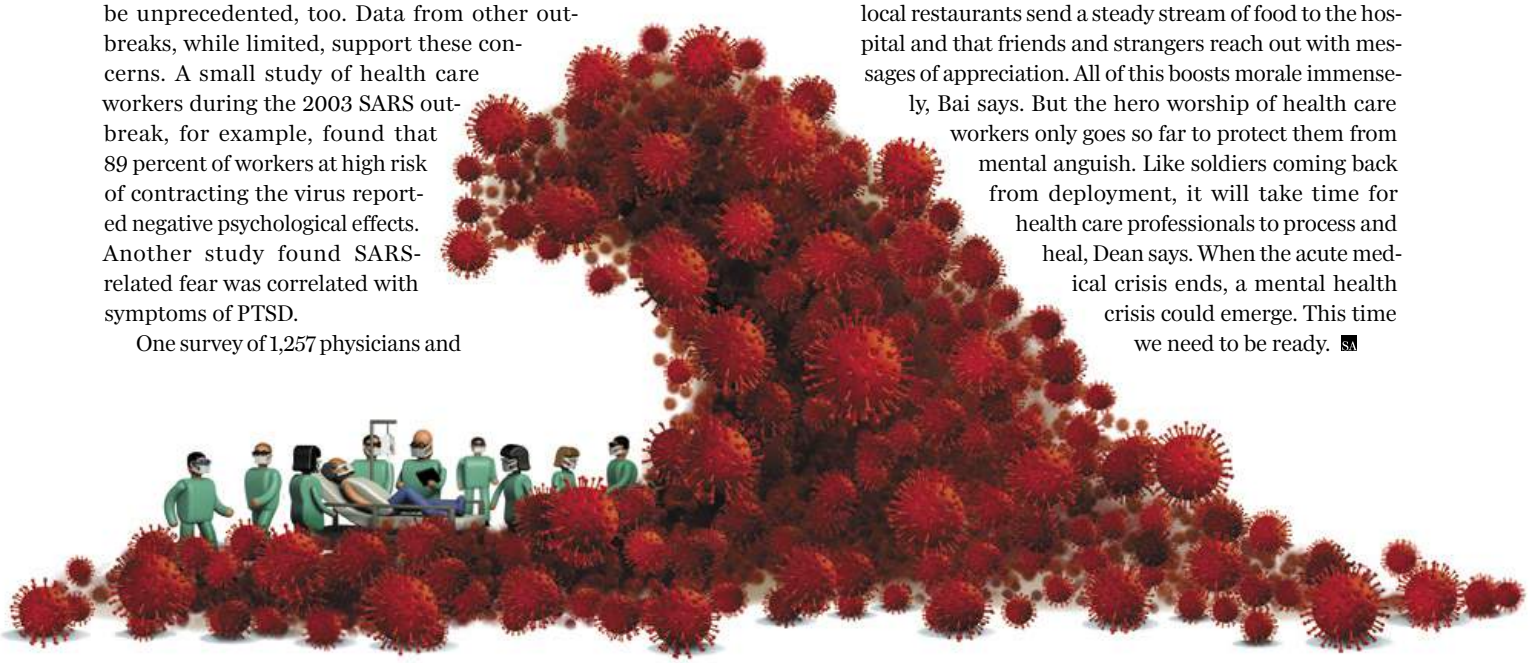
One survey of 1,257 physicians and nurses during the height of the COVID-19 pandemic in China found that about 50 percent of respondents reported symptoms of depression, 44 percent reported symptoms of anxiety and 34 percent reported insomnia. Medical professionals are already at risk for many of these conditions at baseline—medical occupations have among the highest rates of suicide—yet they are typically unlikely to seek help, Gold says. Most do not have the time or flexibility to go see a therapist during a standard nine-to-five workday, she notes, and the stigma still attached to psychological problems leads many to suffer silently. "We have never had a mental health system that could support the needs of the population in general, let alone the population that will now be in need," Gold says.

Institutions such as UNC Health in North Carolina have expanded therapy options for providers with telehealth and more flexible scheduling, as well as set up a support hotline. In the U.K., the COVID Trauma Response Working Group provides guidance, based on trauma psychology research, for proactive interventions. The right support can even foster resilience. "Some people will find they experience a sense of an increase in their own confidence or ability to manage future stressors," says Morganstein, describing a process called post-traumatic growth.

While these efforts are a start, Gold emphasizes that expanded mental health support needs to be ongoing and wide in scope, addressing systemic problems such as a nationwide mental health care professional shortage and regulatory hurdles that limit telemedicine services. Teletherapy, meditation apps and other virtual health services have already made inroads with the population at large in the past few months, and Gold and other therapists see it as a crucial tool for reaching health care workers as well.

In cities across the world, people in lockdown have gathered at their windows to clap and cheer for essential workers every evening. In New York, Bai reports that local restaurants send a steady stream of food to the hospital and that friends and strangers reach out with messages of appreciation. All of this boosts morale immensely, Bai says. But the hero worship of health care workers only goes so far to protect them from mental anguish. Like soldiers coming back from deployment, it will take time for health care professionals to process and heal, Dean says. When the acute medical crisis ends, a mental health crisis could emerge. This time we need to be ready. SA

Jillian Mock is a freelance science journalist based in New York City. She writes about the environment, climate change and health care, and her work has appeared in the *New York Times*, *Huffington Post* and *Discover*, among others.



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HOW THE HEALERS FEEL

Interviews by Jillian Mock and Jen Schwartz

Frontline clinicians have become the face of our pandemic. They represent the best of humanity, rising to treat critically ill patients, as well as the collateral damage from America's fragile health care system and disordered government response. Scientific American asked doctors, nurses and respiratory therapists working in hospitals across the country how they were coping with fear, processing grief and tending to their own well-being. Interviews were conducted in late March and early April, as COVID-19 was rapidly upending life in the U.S. These essays reflect that period of extreme uncertainty; they have been edited and condensed. SA

ANA DELGADO

Nurse Midwife and Clinical Professor

San Francisco, Calif.

There was a lot of talk early on about how this crisis was going to bring us all together. But what it has clarified for me is that we're not actually all in this together. It has laid bare what most reproductive justice advocates already knew: inequity and racism have always been around. I work at the county hospital. The impact of shelter in place has been stark for my pregnant patients, many of whom are undocumented and were already living paycheck to paycheck, and now are unemployed. A patient came in yesterday and burst into tears from her desperation. I feel extremely overwhelmed by the need.

There are a lot of injustices that we as clinicians are aware of and feel powerless to do much about. People call this "burnout," but one of my colleagues talks about how that seems associated with self-blame, like you got something wrong. Most people go into health care because of a deep commitment to supporting the health and wellness of their community. When you actually become a provider, you're thrust into this system that is not really set up to promote health and wellness, and you're constantly confronted with this discrepancy. The pandemic makes these issues worse, and it's painful to witness. That's not burnout, it's a deep moral injury that people are experiencing.

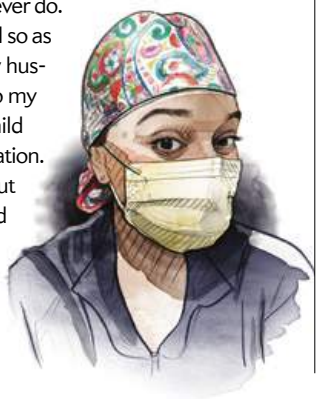
Yes, I have to go work in the clinic and be exposed to people who might be COVID-positive, and that's scary. But as a midwife, I still get to lay my hands on people, to touch and be with people on a daily basis. That's part of my antidote. I struggle a bit with the hero worship of health care workers that's going on. I want to be recognized for my hard work, but I feel like it will swing back to the other side, to mistrust and lack of support. That extreme exists because we don't have a true public health network in this country, a model for developing healers from our communities where there's a sense of trust. If that existed, everything would be different right now.

ROXY JOHNSON

Emergency Room Nurse

Dallas, Tex.

In late March I was running a low-grade fever and had to self-isolate at my house for several days before my COVID test came back negative. It was so hard to stay away from my family and even harder to stay away from my work, which I love. It felt like punishment, like I was losing my mind. I'll admit that I was drinking more than I ever do. In early April I decided to start staying in a hotel so as not to accidentally bring the virus home to my husband and two kids, who could also spread it to my immunocompromised dad, who helps with child care. For me, the hardest part has been the isolation. I've had an eerie sense of calm and peace about all of this up until now, but recently I've started to feel something inside that is not me. I think it's the separation, the loneliness of keeping everyone at arm's length. Sometimes I get in the car, blast music and just go. I ran out of gas on a joy ride last week.



MATTHEW BAI

Emergency Room Physician

New York City

I honestly have no idea how I feel. I don't have time to digest any of this. I go to work, and then I go to sleep. Training in emergency medicine in New York, with the speed and number of patients, probably prepared me somewhat for what's happening now. But nothing can prepare you for an event of this magnitude. Everything is in flux. The upside is realizing the level of flexibility that's possible in a hospital. I'm seeing new faces in the ER all the time—nurses and doctors from other departments, even surgeons, OBs and people flying in from all over the country. In the back of my head I'm constantly thinking, Can we manage our resources and keep our staff healthy for however long this lasts?

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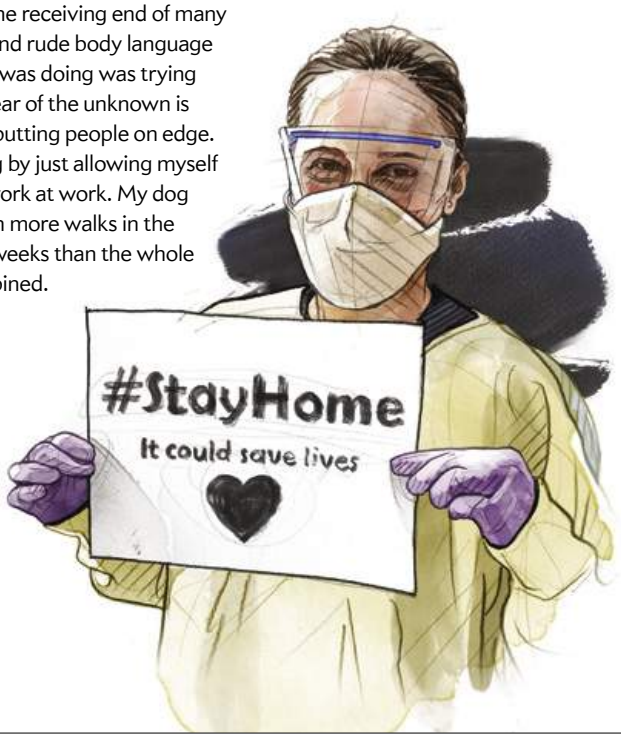
SARAH BRADT

Float Pool Nurse

Minneapolis, Minn.

You can never really be fully prepared for a pandemic. Thankfully, nursing is never routine, so we adapt quickly. I'm a float pool nurse, which means I work on almost every unit in my hospital. I rarely feel intimidated by something new. But many of my co-workers have been displaced and are now working in unfamiliar areas or jobs, creating chaos and stress. I've noticed the most tension on the new COVID rule-out floors. Many staff members are scared to even enter the unit and act like anyone working there is dirty. Patients have commented on how they feel like a burden. Nurses working on these floors are teaching everyone who enters a patient's room how to properly put on and take off our protective wear, and I have been on the receiving end of many eye rolls and rude body language when all I was doing was trying to help. Fear of the unknown is certainly putting people on edge. I'm coping by just allowing myself to leave work at work. My dog has gotten more walks in the past few weeks than the whole year combined.



JOHN BERK

Pulmonary Critical Care Physician and Associate Professor

Boston, Mass.

For providers, there's a really complex psychology to all this. Everyone realizes the importance of what they're doing but doesn't want to be the next person felled by COVID-19. You're grappling with fear of the unknown and your call to duty. My wife, who is also a doctor, and I have been at this game for longer than we care to admit, and we've never been in a situation where there was a real fear of interacting with patients like there is now.

In mid-March I was three days into a rotation in the medical intensive care unit, ramping up for the inevitable surge, when it was decided that those of us 60 and older would be pulled from clinical duty because of our higher risk of dying from COVID-19 infection. Now I have younger colleagues taking on a huge amount of work, and all of them have young families. There's a significant element of guilt in not contributing. We ancients are currently figuring out how we can provide services to lighten their burden. It's a nice gesture, but it's a complicated process.

PATTI MARSHALL GILPIN

Respiratory Therapy Navigator

Louisville, Ky.

I educate patients with chronic lung disease. My role right now seems a little silly; I can't educate people about something we don't understand. Worst-case scenario, I'll go back to doing the critical care with the therapists who are in the trenches. When you read about what's happening in New York and other areas on social media, it's very difficult not to be scared. There's a constant undercurrent of bracing for that potential surge. This huge push to ventilate more than one person on a single machine? Yeah, you should never do that. So we're getting support from each other about how we'd handle having to do the wrong thing.

It's humbling to see how everyone in health care is at the top of their game, improvising equipment, seeking out knowledge. I've watched transporters take patients from one place to another, interacting with them, being so optimistic when there's this palpable dread all over the hospital. I've seen amazing courage when staff have to do CPR on one of these patients, no hesitation when you have to intubate. But when it's over? My co-workers come into my office to vent and cry; some talk about problems with anxiety. When my shift ends, what do I do with this crap I've been carrying around all day, the things that happened, the things that could happen tomorrow? You can't even name it. Then you go home, and you can't have your typical social release because you fear contaminating your loved ones. Worrying that I'm going to spread this is the worst feeling of all.

Illustrations by Ina Stanimirova

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SPECIAL REPORT

THE VACCINE QUEST

ONLY GENETIC ENGINEERING CAN CREATE A PROTECTIVE SERUM IN MONTHS RATHER THAN YEARS

By Charles Schmidt

ON JANUARY 10, WHEN CHINESE researchers published the genome of a mysterious, fast-spreading, virus, it confirmed Dan Barouch's greatest worry. The genome was similar to that of the coronavirus that caused the 2003 SARS outbreak, yet it also had striking differences. "I realized immediately that no one would be immune to it," says Barouch, director of virology and vaccine research at Beth Israel Deaconess Medical Center in Boston.

Within days his laboratory and dozens of others around the world started designing vaccines that they hoped could protect billions of people against the SARS-CoV-2 virus, the biggest challenge to global health and prosperity since World War II. By early April almost 80 companies and institutes in 19 countries were working on vaccines, most gene-based instead of using traditional approaches, such as those that have been employed in influenza vaccines for more than 70 years. The labs predicted that a commercial vaccine could be available for emergency or compassionate use by early 2021—incredibly fast, given that vaccines to brand-new pathogens have taken a decade to be perfected and deployed. Even the Ebola vaccine, which was fast-tracked, took five years to reach widespread trials. If Barouch and his counterparts can offer a safe, effective concoction in a year, "it will be the fastest vaccine development in history," he says.

That is a big "if," however. Although labs have created several gene-based vaccines for other viruses, not one has been commercialized for a human illness.

A conventional vaccine injected into the body inserts select pieces of a virus in cells near the injection site. The immune system recognizes molecules on these pieces, called antigens, as threats and reacts by making antibodies, molecules that can find the virus anywhere in the body and neutralize it. Once this dress rehearsal happens, the immune system remembers how to quash the invaders, so it can stop a future infection.

The established approach is to grow weakened viruses in chicken eggs—or more recently in mammalian or insect cells—and extract the desired pieces. The process can take four to six months to get the right antigens for familiar viruses that change every year, such as influenza. It can take multiple attempts over years for a new germ. That is far too slow to combat a virus that has already spread to pandemic proportions.

Instead labs are turning to gene-based vaccines. Scientists use information from the genome of the virus to create a blueprint of select antigens. The blueprint is made of DNA or RNA—molecules that hold genetic instructions. The researchers then inject the DNA or RNA into human cells. The cell's machinery uses the instructions to make virus antigens that the immune system reacts to. Cells respond to the instructions as a normal part of their daily existence. This is the same trait infectious viruses exploit; they cannot reproduce on their own, so they use a cell's machinery to make copies of themselves. They burst out of the cell and infect more cells, widening the infection.

Virtually all the labs want to find a way to train human cells to make an antigen called the spike protein. It juts out from SARS-CoV-2 like a stud on a tire, allowing the virus to bind to a human cell and sneak inside. Almost all the labs are using one of three approaches to deliver the spike blueprint. The first is a DNA plasmid, typically a small, hoop-shaped molecule. A plasmid is a handy tool because if a virus mutates, researchers can readily swap in a new blue-

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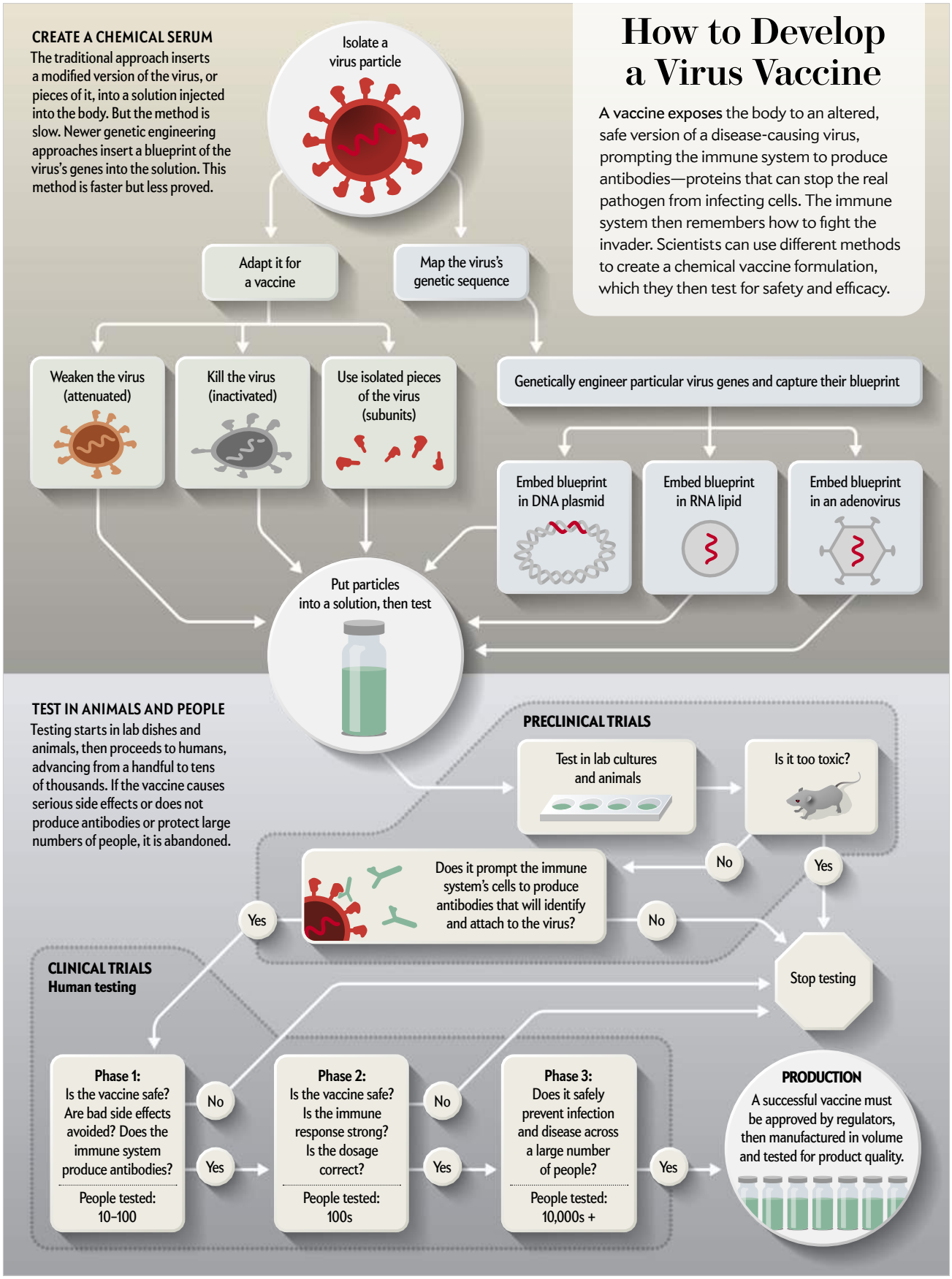
How to Develop a Virus Vaccine

A vaccine exposes the body to an altered, safe version of a disease-causing virus, prompting the immune system to produce antibodies—proteins that can stop the real pathogen from infecting cells. The immune system then remembers how to fight the invader. Scientists can use different methods to create a chemical vaccine formulation, which they then test for safety and efficacy.



Graphic by Jen Christiansen

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print. DNA-plasmid vaccines have been made for veterinary uses in fishes, dogs, swine and horses, but human applications have lagged, mostly because the vaccines have had difficulty passing through a cell's protective outer membrane to reach the machinery inside. One recent improvement is to inject the vaccine with an instrument that administers brief electrical charges to cells near the injection site, which open pores in the cell membranes so the vaccine can enter.

Inovio Pharmaceuticals, headquartered in Plymouth Meeting, Pa., is employing the DNA-plasmid approach. Several years ago it launched clinical trials targeting spike proteins of a different coronavirus disease called Middle East respiratory syndrome (MERS). According to chief executive officer Joseph Kim, the antibody levels in vaccinated people "are as good or better than those we see in blood samples from people who [naturally] recovered from MERS." The company adapted its platform—the plasmid and means for testing it—to make a vaccine for SARS-CoV-2.

DNA-plasmid vaccines work by transferring the genetic blueprint to RNA in the cell machinery, which makes the spike antigens. But scientists can skip the plasmid step by embedding a blueprint in a strand of RNA—a second approach known as RNA vaccines. The RNA is carried in lipids that are injected into the body; lipids are fatty molecules that can pass easily into cells. Research shows that RNA vaccines may be better than DNA plasmids at mobilizing the immune system to create antibodies. They also seem to induce more potent immunity—a stronger memory in the immune system—and therefore require lower doses. Some RNA vaccines are in early-stage clinical trials for other viral illnesses, including rabies, HIV and Zika. Moderna in Cambridge, Mass., is using this approach for SARS-CoV-2.

RNA vaccines are less stable than DNA-plasmid vaccines; common enzymes in the body can quickly degrade them. Heat can ruin them, too. RNA vaccines must generally be kept frozen or refrigerated, which creates logistical hurdles, particularly in poorer countries. DNA-plasmid vaccines are stable at higher temperatures.

Barouch and his collaborators at Johnson & Johnson are using a third approach: inserting the DNA blueprint into a common cold virus. When injected, this adenoviral vector, as it is called, infects human cells and delivers the blueprint it is carrying. Adenoviruses are good at getting into cells, yet past work shows that the human immune system readily recognizes some adenoviruses and attacks them before they can sneak in. Barouch is using an adenovirus that testing shows is unlikely to be recognized. Some experts also worry an adenovirus itself could replicate inside the body and cause disease. To address that possibility, Barouch's team is using an engineered virus that is nonreplicating—it cannot make copies of itself inside a human cell, because it needs a substance for replication the human body does not provide. In late April the University of Oxford began a limited human trial with another nonreplicating adenovirus.

Once a vaccine's basic functionality is confirmed in lab cultures, it is assessed in animals to see if it is safe and whether it elicits an immune response. Next it is tested in people—first small groups to check on safety and side effects, then increasingly larger numbers to see how effective it is. Inovio's DNA plasmid went into small-scale human trials on April 6—only three months after the SARS-CoV-2 genome was published. Moderna began small human trials of its RNA vaccine even sooner, on March 16, and in April the U.S. government pledged up to $483 million to speed mass production if the trials go well. Barouch's lab devised a prototype adenovirus vaccine in just four weeks. Johnson & Johnson, in collaboration with Barouch's lab, is now testing it in mice, ferrets and rhesus macaques. On March 30 the U.S. and Johnson & Johnson committed more than $1 billion to fund large human clinical trials, which are slated to begin in September if the limited testing proves out.

Although the time from outbreak to small tests has been far quicker than it would have been using the egg approach, there is no guarantee that the extended trials of genetically engineered vaccines will not take years. Fortunately, SARS-CoV-2 does not appear to mutate as quickly as influenza, suggesting that an effective vaccine, once developed, might offer protection for a long time.

In addition to efficacy, the experts are watching the trials for "disease enhancement"—the possibility that a vaccine might inadvertently worsen symptoms of COVID-19, the disease that SARS-CoV-2 causes. Ferrets given an experimental SARS vaccine in 2004 developed damaging inflammation. Kim says humans who were treated with the experimental SARS vaccines did not experience disease enhancement. But those formulations never made it to large-scale human trials because the outbreak—which sickened about 8,000 people in nearly 30 countries—burned out in just over a year.

Companies are accelerating the development time for a SARS-CoV-2 vaccine in part by testing vaccines in multiple animal species at once and in parallel with small numbers of people. Usually the process is one animal at a time, and people later, to make sure that side effects are small, that immune response is large and that disease is actually defeated. Lack of time warrants greater risk.

Protecting the globe against COVID-19 will require enormous manufacturing capacity. The DNA-plasmid and RNA vaccines have never been scaled up to millions of doses, and small firms such as Inovio and Moderna would not have such capacity in-house. According to Barouch, the adenovirus vaccine is more time-consuming at the outset, but once proved it "can be scaled up quickly." Johnson & Johnson used an adenovirus approach to generate millions of doses of a vaccine against Ebola, which are now in widespread human trials. A few groups are investigating other DNA techniques that could take longer.

No prototype vaccine is a clear favorite yet, according to Brenda G. Hogue, a virologist and coronavirus expert at Arizona State University. But she says the speed of the genetics work and the full weight companies are throwing behind it are encouraging: "I feel very positive." SA

IN BRIEF

To quickly create potential vaccines against COVID-19, researchers are using genetic engineering rather than traditional methods, which can take years.

Three different techniques based on DNA and RNA molecules are speeding to human trials, but whether they will work, or can be scaled up to millions of doses, is unclear.

Charles Schmidt is a freelance journalist based in Portland, Me., covering health and the environment. He has written for *Scientific American* about therapeutic viruses that can infect harmful bacteria and about dangerous contaminants in drinking water.

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SPECIAL REPORT

WHAT COMES NEXT

LARGE OUTBREAKS OF DISEASE IN THE PAST SUGGEST HOW COVID-19 COULD PLAY OUT

By Lydia Denworth

IN BRIEF

The end game will likely involve a mix of efforts that stopped historic outbreaks: social-control measures, medications and a vaccine.

We know how the COVID-19 pandemic began: Bats near Wuhan, China, hold a mix of coronavirus strains, and sometime last fall one of the strains, opportunistic enough to cross species lines, left its host or hosts and ended up in a person. Then it was on the loose.

What no one knows yet is how the pandemic will end. This coronavirus is unprecedented in the combination of its easy transmissibility, a range of symptoms going from none at all to deadly, and the extent that it has disrupted the world. A highly susceptible population led to near exponential growth in cases. "This is a distinct and very new situation," says epidemiologist and evolutionary biologist Sarah Cobey of the University of Chicago.

But past pandemics do offer hints of the future. While there is no one historical example to follow, humanity has gone through several large epidemics in the past 100 or so years that eventually stopped ravaging society. The ways they came to a halt offer guidance to a world looking for ways to restore health and some sense of normalcy. Three of those experiences, Cobey and other experts say, suggest that what happens next depends on both the evolution of the pathogen and of the human response to it, both biological and social.

A SPREADING PROBLEM

Viruses are constantly mutating. Those that trigger pandemics have enough novelty that the human immune system does not quickly recognize them as dangerous invaders. They force the body to create a brand-new defense, involving new antibodies and other immune system components that can react to and attack the foe. Large numbers of people get sick in the short term, and social factors such as crowding and the unavailability of medicine can drive those numbers even higher. Ultimately, in most cases, antibodies developed by the immune system to fight off the invader linger in enough of the affected population to confer longer-term immunity and limit person-to-person viral transmission. But that can take several years, and before it happens, havoc reigns.

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LEARNING TO LIVE WITH A DISEASE. The most famous example of this dynamic in modern history was the H1N1 influenza outbreak of 1918–1919. Doctors and public health officials had far fewer weapons than they do today, and the effectiveness of control measures such as school closures depended on how early and decisively they were implemented. Over two years and three waves, the pandemic infected 500 million and killed between 50 million and 100 million. It ended only as natural infections conferred immunity on those who recovered.

The H1N1 strain became endemic, an infectious disease that was constantly with us at less severe levels, circulating for another 40 years as a seasonal virus. It took another pandemic—H2N2 in 1957—to extinguish most of the 1918 strain. One flu virus kicked out another one, essentially, and scientists don't really know how. Human efforts to do the same have failed. "Nature can do it, we cannot," says virologist Florian Krammer of the Icahn School of Medicine at Mount Sinai in New York City.

CONTAINMENT. The severe acute respiratory syndrome (SARS) epidemic of 2003 was caused not by an influenza virus but by a coronavirus, SARS-CoV, that is closely related to the cause of the current affliction, SARS-CoV-2. Of the seven known human coronaviruses, four circulate widely, causing up to a third of common colds. The one that caused the SARS outbreak was far more virulent. Thanks to aggressive epidemiological tactics such as isolating the sick, quarantining their contacts and implementing social controls, bad outbreaks were limited to a few locations such as Hong Kong and Toronto. This containment was possible because sickness followed infection very quickly and obviously: almost all people with the virus had serious symptoms such as fever and trouble breathing. And they transmitted the virus after getting quite sick, not before. "Most patients with SARS were not that contagious until maybe a week after symptoms appeared," says epidemiologist Benjamin Cowling of the University of Hong Kong. "If they could be identified within that week and put into isolation with good infection control, there wouldn't be onward spread." Containment worked so well there were only 8,098 SARS cases globally and 774 deaths. The world has not seen a case since 2004.

VACCINE POWER. When a new H1N1 influenza virus, known as swine flu, caused a pandemic in 2009, "there was an alarm bell because this was a brand-new H1N1," Cowling says, and it was very similar to the 1918 killer. Swine flu proved less severe than feared. In part, Krammer says, "we were lucky because the pathogenicity of the virus wasn't very high." But another important reason was that six months after the virus appeared, scientists developed a vaccine for it.

Unlike measles or smallpox vaccines, which can confer long-term immunity, flu vaccines offer only a few years of protection. Influenza viruses are slippery, mutating rapidly to escape immunity. As a result, the vaccines must be updated every year and given regularly. But during a pandemic, even a short-term vaccine is a boon. The 2009 vaccine helped to temper a second wave of cases in the winter. As a result, the virus much more rapidly went the way of the 1918 virus, becoming a widely circulating seasonal flu, from which many people are now protected either by flu shots or by antibodies from a previous infection.

THE CURRENT END GAME

PROJECTIONS ABOUT HOW COVID-19 will play out are speculative, but the end game will most likely involve a mix of everything that checked past pandemics: Continued social-control measures to buy time, new antiviral medications to ease symptoms, and a vaccine. The exact formula—how long control measures such as social distancing must stay in place, for instance—depends in large part on how strictly people obey restrictions and how effectively governments respond. For example, containment measures that worked for COVID-19 in places such as Hong Kong and South Korea came far too late in Europe and the U.S. "The question of how the pandemic plays out is at least 50 percent social and political," Cobey says.

The other 50 percent will probably come from science. Researchers have banded together like never before and are working on multiple fronts to develop remedies. If any of the several antiviral medications currently in development prove effective, they will improve treatment options and lower the numbers who get seriously ill or die. A technique to screen for SARS-CoV-2 neutralizing antibodies, an indicator of immunity in recovered patients, could also prove very useful. Krammer and his colleagues have developed one such test, and there are others. Previously used only in local epidemics, these new serological assays won't end the pandemic, but they could make it possible to spot and use antibody-rich blood as a treatment for critically ill patients; more certainly, the tests will also get people back to work faster if those who fought off the virus and are immune can be identified.

It will take a vaccine to stop transmission. That will take time—probably a year from now. Still, there is reason to think a vaccine could work effectively. Compared with flu viruses, coronaviruses don't have as many ways to interact with host cells. "If that interaction goes away, [the virus] can't replicate anymore," Krammer says. "That's the advantage we have here." It is not clear whether a vaccine will confer long-term immunity as with measles or short-term immunity as with flu shots. But "any vaccine at all would be helpful at this point," says epidemiologist Aubree Gordon of the University of Michigan.

Unless a vaccine is administered to all of the world's eight billion inhabitants who are not currently sick or recovered, COVID-19 is likely to become endemic. It will circulate and make people sick seasonally—sometimes very sick. But if the virus stays in the human population long enough, it will start to infect children when they are young. Those cases are typically, though not always, quite mild, and so far the children appear less likely to develop severe disease if they get reinfected as adults. The combination of vaccination and natural immunity will protect many of us. The coronavirus, like most viruses, will live on—but not as a planetary plague. SA

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

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EVOLUTION

THE UNEXPECTED ORIGIN OF FINGERS

A remarkable fossil reveals that the digits in our hands evolved before vertebrates left the water to colonize land

By John A. Long and Richard Cloutier

Illustration by Chase Stone

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ELPISTOSTEGE WATSONI, a 375-million-year-old fish closely related to four-limbed animals, had digit bones in its pectoral fins that could have helped support the animal's weight on land.

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John A. Long is strategic professor in paleontology at Flinders University in South Australia. His research focuses on the early evolution of vertebrates, including the three-dimensionally preserved Devonian-age fossil fishes found in the Gogo formation in Western Australia. In 2020 he received the prestigious Bettison and James Award for lifelong achievement for his work as both a scientist and an author.

Richard Cloutier is a professor-researcher in evolutionary biology at the University of Québec at Rimouski. His research interests revolve around the evolutionary patterns and mechanisms of early vertebrates, as well as the evolutionary developmental biology of recent fishes and amphibians. He has been working on the fauna, paleoecology and paleoenvironment of the Devonian Miguasha fossil site for more than 30 years.

FIVE DIGITS RADIATING FROM A PALM, AN ARRANGEMENT BOTH FLEXIBLE AND STRONG—capable of playing a piano, wielding a hammer, offering a comforting touch. The hand is our most familiar body part, central to most everyday tasks, from dressing and driving to cooking and texting. Yet from an evolutionary standpoint, it remains largely mysterious, particularly when it comes to the earliest stage of its origin. Other four-limbed creatures—tetrapods, as they are known—have hands that look and function quite differently than ours do. In birds and bats, they help to form delicate wings; in elephants, they support limbs as big around as tree trunks. But the basic structure is the same. In 1859 Charles Darwin remarked on the similarities in *On the Origin of Species:* "What can be more curious than that the hand of a man, formed for grasping, that of a mole for digging, the leg of the horse, the paddle of the porpoise, and the wing of the bat, should all be constructed on the same pattern, and should include the same bones, in the same relative positions?"

IN BRIEF

How the hands of four-limbed creatures evolved from the fins of their fish ancestors has long been hard to pin down because of a dearth of fossils documenting the transition. **The recent discovery** of a complete skeleton of a 375-million-year-old fish is upending what researchers had surmised about the origin of hands and thus the rise of tetrapods.

Darwin proposed an elegant explanation: these diverse animals share this pattern because they evolved from a common ancestor that possessed limbs with digits. In the more than 160 years since Darwin advanced his revolutionary idea, evolutionary biologists have marshaled evidence from paleontology, genetics and embryology that has proved him right. Their efforts have illuminated the shared ancestry of tetrapods, which evolved from fish; shown that the bones that make up the human hand are also found in frogs and birds and whales; and identified some of the genes that control the development of hands and wings and flippers, among other variations. But the first chapter of that story—the bit where the hand and wrist evolved from bones in the fin of an ancestral fish—has remained murky at best because scientists have lacked sufficiently complete fossils of transitional creatures between fully aquatic fish and land-roving tetrapods.

This past March we unveiled an extraordinary fossil—a complete skeleton of a 375-million-year-old fish, *Elpistostege watsoni*—that goes a long way toward filling that gap in understanding. The fossil preserves in its fins bones comparable to the ones that make up our fingers, showing that digits evolved before vertebrates left the water. This discovery overturns the conventional wisdom about when and how the hand evolved and shines new light on the rise of tetrapods, a pivotal event in the history of life on earth.

MURKY ORIGINS

UNTIL RECENTLY, scientists' grasp of the evolutionary transition between fishes and early tetrapods hinged mainly on several spectacular fossils that seem to bridge these two groups. One is from a fish called *Panderichthys rhombolepis* from the Baltic region and dates to the Middle to Late Devonian period (around 384 million to 379 million years ago). With its elongated humerus and large radius and ulna (the upper arm bone and forearm bones, respectively, in tetrapods) and its tetrapodlike skull bone pattern, *Panderichthys* offered the first clues that the group of fishes to which it belongs were the closest fishes to the tetrapods. The group is called the elpistostegalians, after the then poorly known *Elpistostege* from eastern Canada.

In 2006 Neil Shubin of the University of Chicago and his colleagues announced the discovery of anoth-

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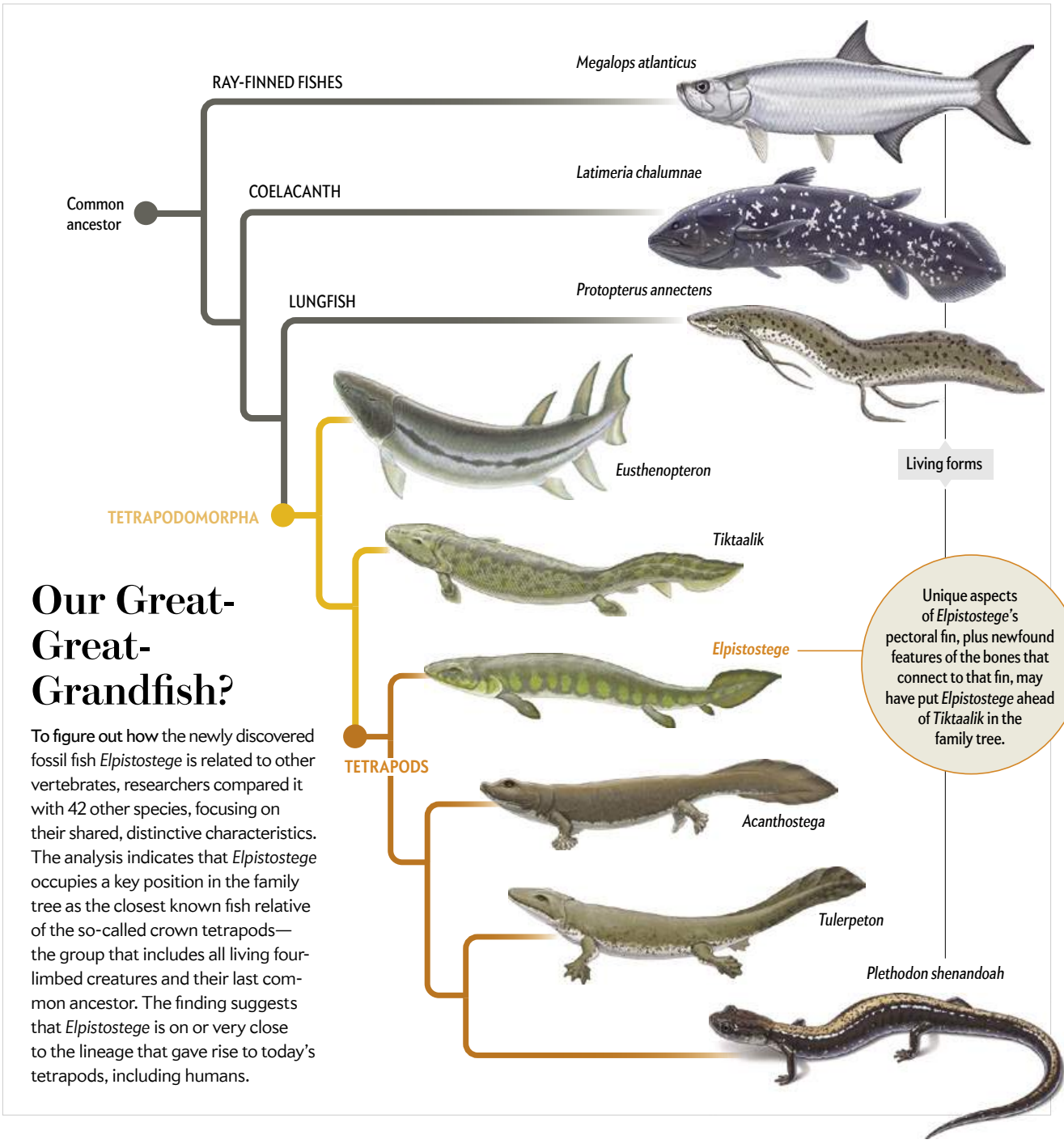

Our Great-Great-Grandfish?

To figure out how the newly discovered fossil fish *Elpistostege* is related to other vertebrates, researchers compared it with 42 other species, focusing on their shared, distinctive characteristics. The analysis indicates that *Elpistostege* occupies a key position in the family tree as the closest known fish relative of the so-called crown tetrapods—the group that includes all living four-limbed creatures and their last common ancestor. The finding suggests that *Elpistostege* is on or very close to the lineage that gave rise to today's tetrapods, including humans.

SOURCE: BRIAN CHOO

er elpistostegalian fish fossil, 380-million-year-old *Tiktaalik roseae* from the Canadian Arctic. *Tiktaalik* was a real game changer in revealing a slew of new data showing that the pectoral fin was highly advanced in these fishes—more so than any other known fossil—with both well-developed arm bones and mobile wrist joints. Its skull also had distinctive features, including a long, flat snout and a specialized braincase—traits shared by tetrapods.

Together, this and the other known elpistostegalian fish fossils suggested that a number of hallmark traits of tetrapods originated in their piscine predecessors, including land-worthy arm bones and joints. But what these fishes did not appear to have were fingers. In the case of *Panderichthys,* bony elements that many researchers initially thought were rudimentary digit bones were later rejected as such. And the *Tiktaalik* fossil, for its part, did not preserve the complete tip of the pectoral fin, where one would expect to find digit bones if the animal had them. The available evidence left experts to conclude that fingers were not part of the initial fin-to-limb transition. Instead they appeared to have evolved later, after tetrapods had already staked a claim on terra firma.

In science, however, knowledge is not written in stone. It is

Illustration by Emily S. Damstra

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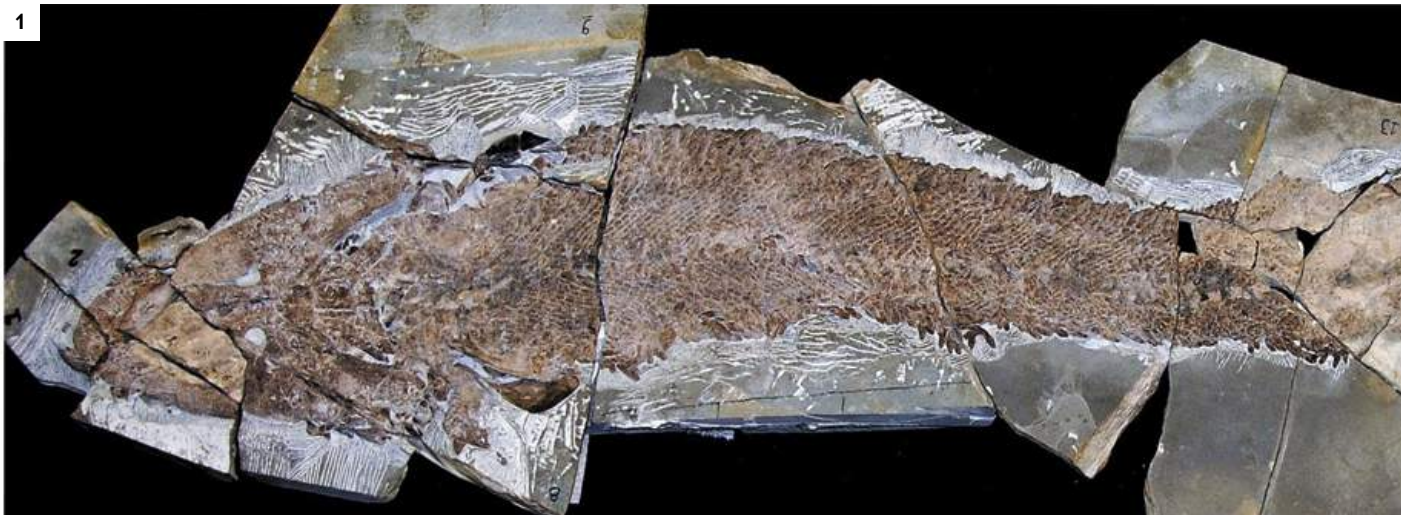

2

COMPLETE SKELETON of 375-million-year-old fish *Elpistostege watsoni* (*1*), discovered in Miguasha National Park in Quebec, is the first fossil fish from the fish-tetrapod transition to preserve the entire pectoral fin (*2*). This fish had in its fin digit bones equivalent to the ones that make up human fingers.

subject to change in light of fresh evidence. New discoveries can necessitate revision of the textbooks. Our recently described *Elpistostege* fossil, which was unearthed in 2010 at the UNESCO World Heritage Site of Miguasha in Quebec, is one such find. It is not a new species of elpistostegalian. Rather it is the original founding member of the band. But this time we have a complete, perfect specimen. And it has led us to propose a different theory of how fingers evolved and gave rise to the vertebrate hand structure that persists in the more than 33,800 species of tetrapods alive today, including humans.

To appreciate the role of *Elpistostege* in shifting our perspective on how hands evolved, it helps to know a bit about the history of its discovery. In the summer of 1937 two young British paleontologists were scouring the cliffs of Chaleur Bay along the southern shore of the windswept Gaspé Peninsula in eastern Canada. Thomas Stanley Westoll and William Graham-Smith were looking for Devonian-age fossils, and the cliffs were known to be an El Dorado for such treasures. Local collectors assisted the paleontologists in making their discoveries and sometimes sold them fossils. One of the fossils that Westoll purchased from them was a small, fragmentary skull roof that was to become a cornerstone in our understanding of the evolutionary transition between fishes and tetrapods.

Back in Westoll and Graham-Smith's day, scholars already suspected that tetrapods had evolved from the so-called lobe-finned fishes—creatures with fleshy, powerful fins, a group whose living representatives include the coelacanth and the lungfish. But they lacked fossils with intermediate anatomy to bolster the connection. Westoll's skull roof seemed like something that might help fill the gap. Given the pattern of its skull bones, Westoll thought it could be the long-sought-after skull of a primitive Devonian amphibian. He named this unique specimen *Elpistostege watsoni,* from the Greek for "hoped for" and "roof." In a brief paper published in 1938 in *Nature,* Westoll argued that the fossil provided "a perfect transition" between lobe-finned fishes and early four-legged animals.

Based on only a piece of skull, Westoll's argument was met with skepticism. More of the animal was needed. But although paleontologists came from all over Europe and America to collect fossils from the cliffs of Chaleur Bay, an area now designated Miguasha National Park, no one collected a new specimen of *Elpistostege.*

Some 30 years after Westoll's publication, however, serendipity intervened. Canadian fossil collector Allan Parent discovered the snout of an incomplete skull in the Miguasha Cliffs. It remained hidden in his private collection until his tragic early death. But in 1983 Parent's brother brought the snout to the attention of the

RICHARD CLOUTIER (1 and 2)

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Miguasha park director, Marius Arsenault, who in turn enlisted Hans-Peter Schultze, an eminent specialist on fossil fishes from the University of Kansas, to identify this unusual specimen. Schultze immediately realized its importance: similarities in the arrangement and shape of the cranial bones preserved in this fossil and Westoll's skull roof showed they belonged to the same species.

With more of the creature's anatomy revealed, ideas about its identity began to shift. The features visible on the new snout suggested that *Elpistostege* was not an amphibian but a highly advanced lobe-finned fish. In their 1985 paper describing the snout, Schultze and Arsenault specifically suggested that it was closely related to the Baltic fossil fish *Panderichthys*. They also discussed another enigmatic specimen, a fossil containing a patch of scales and some vertebrae that Miguasha chief biologist Marc Brassard and one of us (Cloutier) had found a couple of years earlier in the same cliffs. Considering the similarities in the surface textures of the scales preserved in this fossil and the snout, Schultze and Arsenault proposed that it, too, belonged to *Elpistostege*.

The attribution of the fossil containing the scales and vertebrae to *Elpistostege* was important. In addition to being the only material then known from below the creature's head, it had something the other two *Elpistostege* fossils did not: detailed provenance. The skull roof and snout were known to have been collected from the cliffs, but no one knew which rock layer they came from. In contrast, Brassard and Cloutier had recorded the exact stratigraphic location of the fossil they found: 90 meters above the lowermost layers of a distinctive geologic unit known as the Escuminac Formation.

In the years that followed, Cloutier and his collaborators returned to this part of the Escuminac Formation again and again to search for more remains of *Elpistostege*—to no avail. Still, the geologic and fossil evidence they did find allowed them to begin to reconstruct the animal's environment, a channel that fed into an estuary. A picture began to emerge of *Elpistostege* as the largest fish—and probably therefore the top predator—in the waters it shared with some 20 other species of fishes.

Eventually that paleoecological data would gain new relevance. Late in the afternoon of August 4, 2010, while on patrol in Miguasha, park warden and naturalist Benoît Cantin found an unusual piece of fossilized fish tail embedded in the lower Escuminac rock layers on the beach at the foot of the cliffs, less than 250 meters from the park's museum. The next morning Cantin, accompanied by two naturalist guides, unearthed the rest of the animal. It is the largest fossil ever found in the Escuminac Formation and arguably the most important one—a 1.57-meter-long complete skeleton of *Elpistostege*.

SEEING THROUGH STONE

WITHIN DAYS of Cantin's finding the fossil, Cloutier was invited to study it. Because most of the skeleton was still entombed in rock, the first order of business was to get a better look at it by using computed tomography (CT). Cloutier recruited Isabelle Béchard, one of his former master's students in paleontology, to help him image the specimen using a nonmedical CT scanner at the Institut National de la Recherche Scientifique (INRS) in Québec City. The scan showed that the specimen was absolutely complete—every single bone was preserved—but the resolution was not good enough to reveal the internal structure of the bones, which they wanted to be able to study. They had to find another CT scanner that provided better resolution. They decided that *Elpistostege* was going to travel some 3,900 kilometers south to the High-Resolution X-ray Computed Tomography Facility at the University of Texas at Austin, where each piece of the fossil would be scanned with the greatest precision available at the time.

Once the scanning was done, Cloutier and his colleagues began the meticulous work of preparing the fossil—removing the surrounding rock bit by bit to expose the bones within. They performed this work on a computer model of the fossil based on the CT scans as well as on the actual fossil. After a few months the body and the skull emerged from the rock, both virtually and in reality. The whole specimen was incredible, but the pectoral fins generated particular excitement because no one had ever seen a complete pectoral fin of an elpistostegalian before. Numerous skeletal elements were visible within the fins, surrounded by scales and fin rays. At first glance *Elpistostege*'s fin looked quite similar to that of *Tiktaalik,* but *Elpistostege*'s appeared to have additional bones in it. What were they?

In the years that followed, Cloutier and Béchard presented preliminary results of their analyses of the *Elpistostege* skeleton to colleagues at professional meetings. It was after one such presentation, in 2014 at the Society of Vertebrate Paleontology in Berlin, that Cloutier and one of us (Long) agreed over a beer to collaborate on the study of this remarkable fossil.

Long had been working on Devonian fish fossils from the Gogo Formation in Western Australia for many years. The skeletons of these ancient fishes are perfectly preserved in three dimensions, and some specimens show exceptional preservation of soft tissues as well. To study these fossils, which are found inside nodules of limestone, Long and his colleagues traditionally placed them in acid baths to dissolve the rock. More recently, they have shifted to imaging the fossils using CT and synchrotron scanners and sophisticated software to elucidate their fine anatomical structures before the acid baths, so that they can capture any soft-tissue preservation before the acid destroys it. The new *Elpistostege* specimen, with its exquisite preservation, seemed like a prime candidate for Long's approach to imaging and digital preparation.

In 2014 Long visited Cloutier's lab in Quebec and began working with his team on how to use different methods to process the imaging data from this fish. It took some trial and error with different types of data and software, but eventually we hit on a winning combination that would allow us to digitally isolate and study

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each bone. Alice Clement of Flinders University in Adelaide and Roxanne Noël and Vincent Roy, then master's students working under Cloutier, went on to carry out this work.

When Clement eventually began segmenting out the pectoral fin, we were at the edges of our seats. As the first complete elpistostegalian pectoral fin ever discovered, it was certain to contain vital clues to the transition from fins to limbs. The preliminary results did not disappoint. They not only confirmed Béchard's initial CT results suggesting the presence of extra bones in *Elpistostege*'s fin but also showed those bones in far greater detail. Now we could see that the fossil included an unexpected series of many small, tightly packed bones. Typically the end of the pectoral fin skeleton contains small bones called radials that support the rodlike fin rays. The bones evident in this part of *Elpistostege*'s fin were in the right place to be radials, but the large number of bones and the way some of them were arranged in discrete rows suggested that they were something else. We strongly suspected that these never-before-seen bones hidden in the pectoral fin of this ancient fish were actually digit bones similar to the ones found in the fingers of tetrapods. We identified two digits that were each composed of multiple, articulated bones, as well as three possible digits each composed of a single bone.

Why is the case for digit bones in the pectoral fins of *Elpistostege* more compelling than the earlier argument for digit bones in the pectoral fins of *Panderichthys?* The putative digit bones in *Panderichthys* are irregular in shape, and none of them show articulation with other bones in the standard way digit bones, or phalanges, do in the human hand. We surmise from comparison with the bones of the *Elpistostege* fin that the mystery bones in the *Panderichthys* pectoral fin are probably equivalent to some of the carpal bones in the wrists of tetrapods.

FISH OUT OF WATER

AS THE TEAM FINISHED isolating the entire pectoral fin and girdle such that every bone could be studied in every aspect, we also began segmenting out internal features of the skull and braincase. This work would help inform our understanding not only of *Elpistostege*'s anatomy but also of how it is related to other early fishes and to tetrapods.

To figure out where *Elpistostege* belongs in the family tree, we needed to compare it with other species, paying special attention to their shared distinctive features. Working with Mike Lee of Flinders, a leading expert on methods for ascertaining relations among species, we ran a phylogenetic analysis of 202 characteristics across 43 species. In the end, we were astounded to find that *Elpistostege* appears to be more closely related to the crown tetrapods—the group that includes all living tetrapods and their last common ancestor—than the well-known *Tiktaalik* is, though not by much. Our best guess is that the unique features of the pectoral fin, which is not fully preserved in *Tiktaalik,* plus some newly discovered features of the pectoral girdle (the bones that connect to the fins), pulled *Elpistostege* up a notch above *Tiktaalik* on the evolutionary ladder.

Combining what we see in the skeleton of *Elpistostege* with what the phylogenetic analysis tells us about its place in the family tree, we can reconstruct how the basic plan for the hands of tetrapods, including humans, originated. The presence of small rows of bones we identified as digits in the pectoral fin of *Elpistostege* shows that the arrangement first evolved in the fins of advanced lobe-finned fishes back at the start of the Late Devonian period, more than 380 million years ago. It is likely that they served to bear weight because having many tiny bones in alignment in this region would have given the outer part of the robust fin the flexibility needed to push the fish upward.

Why might a fish benefit from being able to maneuver in this way? The skull of *Elpistostege* contains a clue: at the back of the head is a pair of large holes called spiracles. Some modern-day fishes that breathe air have similarly large spiracles. For a long time, the function of these holes was uncertain. In a study published in 2014, Long worked with a team of ichthyologists at Scripps Institute of Oceanography in La Jolla, Calif., led by the late Jeff Graham, to nail it down. Analyzing the spiracles of the living bichir *Polypterus,* we showed that they are instrumental in breathing air. Assuming the spiracles served the same purpose in *Elpistostege,* the ability to employ the fins to do a push-up in the shallow rivers and estuary this fish inhabited—and thereby get the head out of water for a breath of fresh air—could have been advantageous.

Elpistostege was not necessarily restricted to the aquatic realm, however. Today's lungfish and some catfishes can propel themselves along land for short periods with their fins. With its far more powerfully built fins, *Elpistostege* was probably that much more capable of venturing ashore.

BABY STEPS

IN ADDITION to upending the received wisdom about when fins became limbs, our discovery of digit bones in *Elpistostege* bears on efforts to understand the genetic and developmental changes that powered this transformation. Just a few decades ago scientists interested in this question did not have much to go on. Back then, there were only a few examples of fossil fishes with pectoral anatomy transitional between fins and limbs, and they hinted only that the arm and forearm bones evolved gradually. In contrast, it looked as though tetrapods evolved the hand and wrist from the ancestral fish fin all at once. But was it actually possible for such drastic change to occur so abruptly? Or was the seemingly sudden origin of the hand and wrist simply an artifact of an incomplete fossil record?

In a milestone paper published in 1991, the late developmental biologist Peter Thorogood proposed that the hand and wrist really could have originated quite suddenly. He based his proposal on comparisons of embryological development in fishes and tetrapods. In early-stage embryos of both groups, a structure called the apical ectodermal ridge (AER) acts as a signaling center that guides development of the fin and limb, respectively. Located in the tip of the budding fin and limb, the AER secretes chemicals that promote the outgrowth of the underlying tissue. In fish, the AER is active for only a short while before it transforms into another signaling center, the apical ectodermal fold (AEF), which directs the formation of the fin rays. In tetrapods, however, the AER is much more active in directing development because it persists far longer in the embryo—it does not ever morph into the AEF; thus, the fin rays do not form. So it has more time to develop the other bones of the appendage, which are the basis for making a hand. Thorogood suggested that the loss of the AER-AEF transition—a relatively simple tweak in the grand scheme of things—could produce both the loss of the fin rays and other characteristics of the pectoral fins and the simultaneous gain of the bones needed to form a wrist and digits.

The discovery of *Tiktaalik,* the first fossil fish to show not just the fish equivalent of our arm bones and some of the proximal wrist

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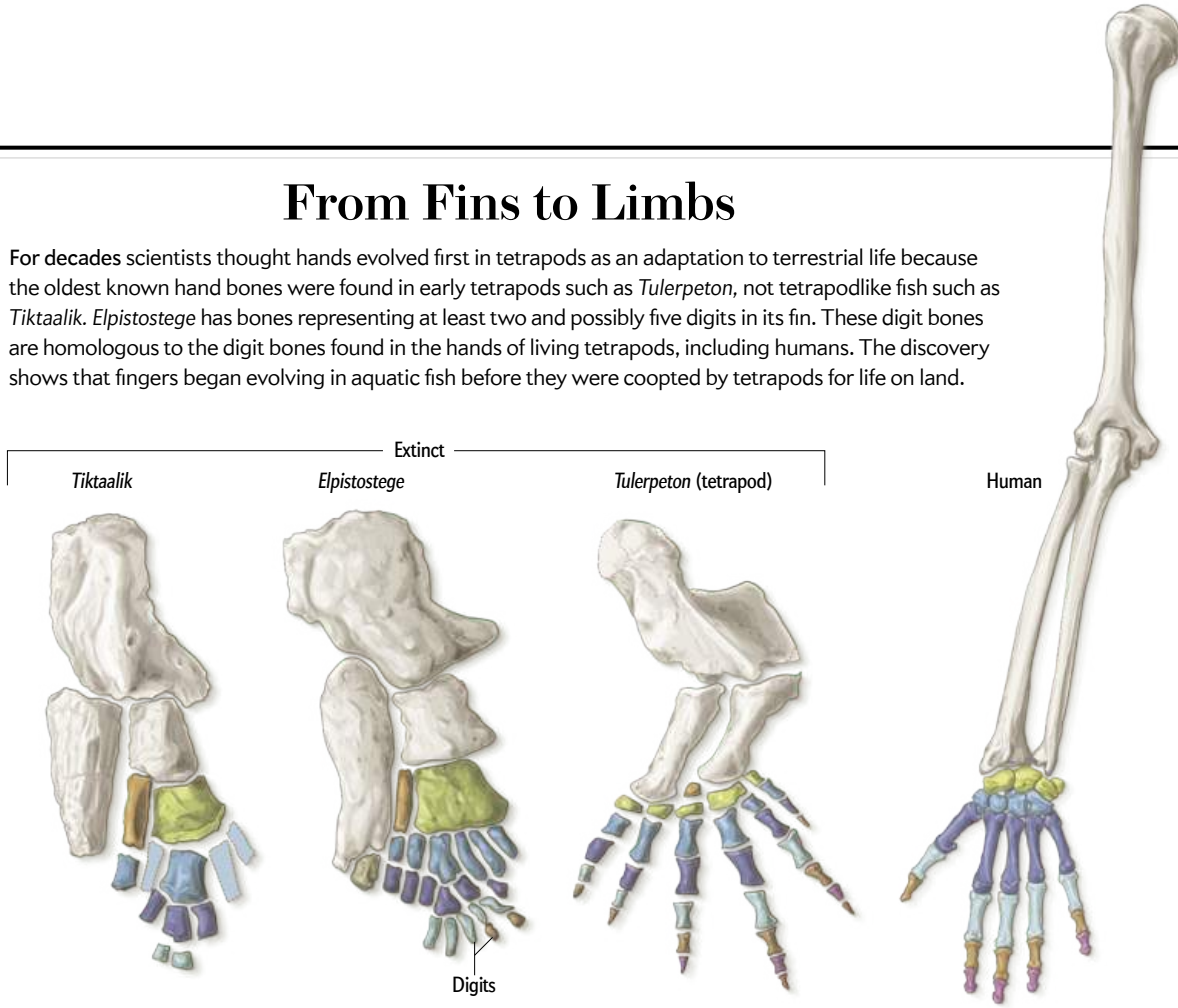
From Fins to Limbs

For decades scientists thought hands evolved first in tetrapods as an adaptation to terrestrial life because the oldest known hand bones were found in early tetrapods such as *Tulerpeton,* not tetrapodlike fish such as *Tiktaalik*. *Elpistostege* has bones representing at least two and possibly five digits in its fin. These digit bones are homologous to the digit bones found in the hands of living tetrapods, including humans. The discovery shows that fingers began evolving in aquatic fish before they were coopted by tetrapods for life on land.



bones (those closest to the center of the body) but also bones from the distal part of the fin corresponding to our distal wrist bones, spurred research into the genetic and developmental underpinnings of the fin-to-limb transition. Investigators were keen to figure out which bones in the ancestral fish fin evolved into wrist and hand bones and which genes were responsible for generating that new morphology. Members of the *Hox* family of genes, which are well known to direct the different regions of the embryo to develop into the head, tail, and so forth, seemed likely to be involved.

In 2007 Zerina Johanson of the Natural History Museum in London and her colleagues studied the activity of one of these genes, *HoxD13,* in one of the closest living relatives of tetrapods, the Australian lungfish. Previous research had shown that *HoxD13* is active in the developing tetrapod limb when the wrists and digits form. Johanson's team showed that the gene is also active during the development of the radial bones in the lungfish fin. But whereas in tetrapod limb development *HoxD13* has two phases of activity—an early phase associated with the arm and forearm development and a late phase associated with wrist and digit development—it appears to have only one interval of activity in lungfish-fin development, corresponding to the second phase of the gene's activity in the developing tetrapod limb. The work suggested that tetrapod digit bones evolved from the radial bones in the fish fin. But wrist and hand could not have originated as a package deal, as Thorogood proposed, because lungfish and other living and fossil lobe-finned fishes have radials or wrist bones without having digits. There had to have been at least two evolutionary events, one that produced digits and another that produced wrists.

Elpistostege further complicates the story. It suggests that, contrary to Johanson's argument, the radials of lungfish and other lobe-finned fish are not all equivalent to digits. Instead only the most distal ones are homologous to digit bones; the proximal radials are homologous to the wrist bones and the long bones of the palm. What is more, *Elpistostege* reveals yet another step in the fin-limb transition. Because it preserves both wrist bones and digits, as well as fin rays, *Elpistostege* shows that loss of the fin rays must have been another, separate phase in the evolution of the hand.

The anatomical condition of the pectoral fins and digits we have described in *Elpistostege* suggests that we still need to fine-tune our understanding of the genetic and developmental mechanisms that drove their evolution. Nevertheless, with the entire skeleton preserved and many further studies of it underway, this specimen of *Elpistostege* seems destined to serve as a Rosetta Stone to solve the mystery of how limbs evolved from fins—and thus how vertebrates conquered land. SA

SOURCES: JOHN A. LONG; AND "ELPISTOSTEGE AND THE ORIGIN OF THE VERTEBRATE HAND," BY RICHARD CLOUTIER ET AL., IN *NATURE* VOL. 579, MARCH 18, 2020

MORE TO EXPLORE

Fish Fingers: Digit Homologues in Sarcopterygian Fish Fins. Zerina Johanson et al. in *JEZ-B Molecular and Developmental Evolution,* Vol. 308B, No. 6, pages 757–768; December 15, 2007.

***Elpistostege* and the Origin of the Vertebrate Hand.** Richard Cloutier et al. in *Nature,* Vol. 579, pages 549–554; March 26, 2020.

FROM OUR ARCHIVES

Getting a Leg Up on Land. Jennifer A. Clack; December 2005.

scientificamerican.com/magazine/sa

Illustration by Daisy Chung

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ASTRONOMY

A Planet Is Born

High-resolution imaging of circumstellar disks—the swirls of dust left behind after stars form—is revealing hidden planets and insights about how solar systems evolve

By Meredith A. MacGregor

PROTOPLANETARY DISKS, imaged by the ALMA telescope, reveal baby solar systems forming. These spinning wheels of gas and dust are left over after stars are born and provide the ingredients for planets.

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THE WEEK I STARTED GRADUATE SCHOOL, THE FIRST SCIENCE PROJECTS WERE ANNOUNCED FOR THE new Atacama Large Millimeter/submillimeter Array (ALMA) telescope in Chile. This groundbreaking facility uses dozens of radio antennas working in concert to create images as detailed as those made by a single telescope 16 kilometers wide. With this extreme resolution, ALMA can see deeper and farther in millimeter- and submillimeter-wavelength light than any previous telescope. I leaped at the opportunity to join one of its first projects—a study of a disk of dust and rubble around a nearby star called AU Mic. The subject of our observations was something scientists had never seen in such detail before ALMA was built. Dust and rubble might not sound that exciting, but they are the raw materials planets are made of, and this observatory was giving us a chance to see the process in action.

IN BRIEF

The ALMA telescope, inaugurated in 2011, gave astronomers their first chance to see details in the disks of gas and dust that surround stars. **These so-called circumstellar disks** can teach scientists how distant solar systems formed and evolved, and features such as warps and clumps can signify the presence of otherwise impossible to see planets. **New telescopes planned** for the coming years could take the study of circumstellar disks to another level, possibly allowing us to image planets directly within disks.

It took another year for the data to be delivered. Modern astronomy is often done at a distance: rather than spending long nights at the remote mountain observatory, all we had to do was submit a computer script that told the telescope what to observe and when. Then we waited patiently (or, more often, impatiently) for our observations to be scheduled and completed. I can still remember the anticipation, the butterfly feeling in my stomach as I waited for the data download and, when it was finally ready, the awe when the image appeared on my computer screen—a long, thin blob of light with three bright spots: one in the center and two on either side at the edges.

What we were glimpsing was a solar system growing up. The central spot was actually the star, which we now know is flaring, sending bursts of high-energy particles out into space. The other two bright spots marked the edges of a disk of debris circling the central star, akin to the Kuiper Belt that orbits our sun. We think this band is the rubble left over after planets formed around AU Mic, a young M dwarf star about 32 light-years away. Other scientists have recently discovered two planets in the system: one about the mass of Jupiter and the other about the mass of Saturn, both orbiting fairly close to their star. Now we have an unprecedented opportunity to see how the material in the disk evolved and interacted with the newly formed planets.

Since that early image, the capabilities of ALMA have continued to expand, and the array now has new dishes, higher resolution and more wavelength coverage. Meanwhile the study of circumstellar disks and planet formation has exploded. ALMA has taken several hundred planetary baby pictures, helping us to build a new view of how such systems form and revealing troves of planets we never could have detected otherwise.

BABY PLANETS

STARS FORM out of vast regions of gas and dust called molecular clouds. The typical density of empty space is only one atom per cubic centimeter, but the thickest areas of molecular clouds can reach densities 10,000 to one million times this norm. When these spots, or "cores," become dense enough, they start to collapse under their own gravity to make stars. At the same time, the initial rotation of the collapsing core and the conservation of angular momentum naturally form a disk surrounding the newly born star. Astronomers call these collections of dust and gas "circumstellar" (meaning "around stars") disks.

When stars are still very young (only a few million years old), their circumstellar disks are relatively huge, often with about 1 to 10 percent of the mass of the central star in a typical system. For a star like the sun, that amounts to a disk with roughly 100 times the mass of Jupiter. These young, massive Frisbees are "protoplanetary" because we think this is where planets are actively

PAGE 54: ALMA (ESO,NAOJ AND NRAO), S. ANDREWS ET AL. AND N. LIRA

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forming. Rock, metal and ice condense out of the disk to form planetary seeds. As seeds start to collide and stick together, they grow larger and larger until they have enough gravity to start attracting more material through a process known as accretion. The baby protoplanets orbit within the disk and continue accumulating material, carving out gaps in the disk in a game of planetary Pac-Man. Nearly all stars that are younger than a few million years are surrounded by disks that most likely harbor a zoo of new planetary systems.

The protoplanetary disk phase lasts for several million years. After that point, most of the gas and dust from the initial circumstellar disk has cleared. How this clearing happens and over what timescales are areas of active research, but we think that a lot of the dust and gas in the original disk either migrates inward and falls onto the central star or is blown out by strong stellar winds. After approximately 10 million years, all that is left is a mature star surrounded by a new planetary system and a disk of remnant asteroids and comets. The total mass of this leftover material is low—likely less than 10 percent of the mass of Earth. Although there may still be enough mass in these "debris disks" to form small terrestrial planets or Pluto-like bodies, you can think of them as the fossil record of earlier planet formation. Their structure is sculpted through gravitational interactions with the newly formed planets, and their composition gives us clues as to what material was originally built into those planets.

Astronomers first discovered debris disks when the Infrared Astronomical Satellite (IRAS) was launched in 1983. It was the first satellite to survey the entire sky at infrared wavelengths (12 to 100 microns; a human hair is roughly 75 microns across). You can think of infrared radiation as heat. When IRAS scanned the infrared sky, astronomers discovered that many stars looked brighter than expected. Why? The answer proposed was dust. If these stars were surrounded by disks of dust, the grains would get heated by the star and then radiate thermal emission in the infrared range. From this inference, a new area of research was born. In fact, the first four debris disks discovered by IRAS—Vega, Beta Pictoris, Epsilon Eridani and Fomalhaut—are still studied and puzzled over today.

By using infrared telescopes to search for such bright spots, astronomers have confirmed that at least 20 to 25 percent of stars are surrounded by debris disks. Given our picture of how planetary systems form, one might logically conclude that all stars should be surrounded by remnant material—after all, statistics from the Kepler mission tell us that every star in the galaxy has at least one orbiting exoplanet. In fact, debris disks are probably more common than we know. Even our solar system has its own system of multiple debris disks—the asteroid belt and the Kuiper Belt. Yet the solar system is actually dust-poor compared with the systems around other stars we have been imaging. In fact, the deepest infrared surveys to date have been able to identify only disks with dust masses roughly an order of magnitude higher than what we see in our solar system. Does that make our cosmic home an oddball? We are not sure yet. We have been studying the most massive, most extreme disks, but there are probably many more low-mass disks to be found that will help us put our own planetary system into context.

HIGH IN CHILE'S Atacama Desert, the ALMA observatory uses dozens of antennas in tandem to capture images of distant planetary systems.

CLEM AND ADRI BACRI-NORMIER (WINGSFORSCIENCE.COM) AND ESO

Although astronomers began to infer the presence of dusty disks from early infrared observations in the 1980s, they did not know what they looked like. Before improvements in telescope technology were made in the 1990s and 2000s, only a single star system—Beta Pictoris—had been resolved. Notably, the Hubble Space Telescope employed coronagraphic imaging, a technique astronomers use to block the light from the central star in order to see dimmer surrounding objects, to image light scattering off small dust grains in circumstellar disks. Although many of these early images were indistinct, they gave the first indication that circumstellar disks actually have extended, complicated structures. In the case of the debris disk around Beta Pictoris, the first Hubble images showed a warp in the inner regions of the disk that astronomers thought might indicate an unseen planet. Direct imaging later confirmed this baby world.

A NEW TELESCOPE

THE WAVELENGTH OF LIGHT that we see reflected from dust roughly corresponds to the size of the dust grains—optical and near-infrared light comes from small dust grains tens of microns in size, whereas far-infrared and millimeter-wavelength imaging is sensitive to larger grains similar in size to sand. We think that these larger grains are better tracers of the underlying structure of circumstellar disks. Within a disk, there is a continuous cascade of collisions. Large comets and asteroids crash into one another and get ground down into smaller and smaller dust grains. The most massive objects in the disk are called planetesimals, and their locations are shaped by interactions with other planets in the system. If we can locate the planetesimals, that information can be used to infer the presence of

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Hunting for Planets

Astronomers think nearly every star in the galaxy has planets around it, although we cannot yet find all, or even most, of them. Each strategy scientists use to detect planets comes with its own strengths and weaknesses and biases toward certain types of worlds. Smaller Earth-like planets that make long orbits around their suns are particularly hard to find, for instance, so very few known exoplanets fit this category.

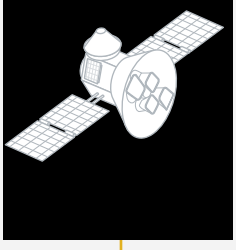
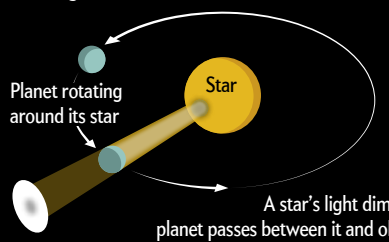
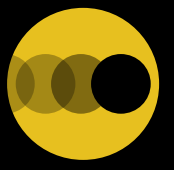
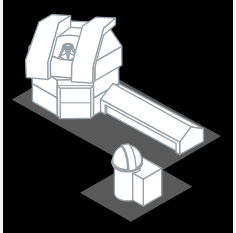
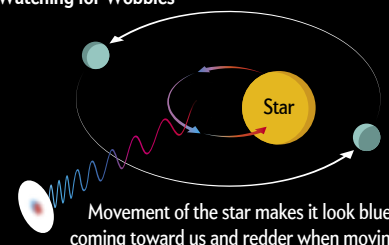
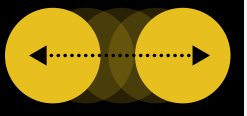
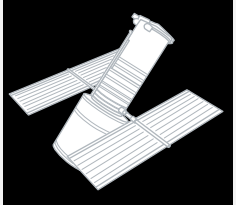
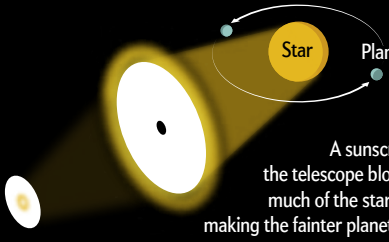
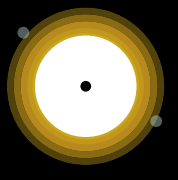
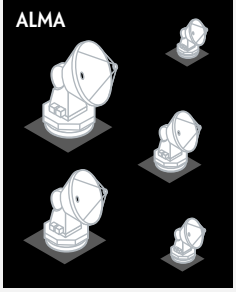
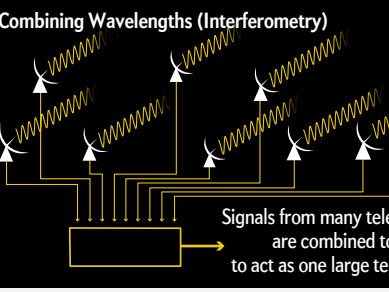
	Telescope Example	How It Works	Strengths
TRANSITS This technique looks for planets by monitoring the light coming from their host stars. Every time a planet orbits in front of the star we see the light dim—if the system is aligned with Earth just right. These periodic shadows can reveal not just the existence of a planet but also its diameter and orbit length.	TESS 	Searching for Shadows 	Best at detecting planets with quick orbits (3,155 and counting) 
RADIAL VELOCITIES This method searches for the telltale movements of a star caused by a planet's gravitational pull on it. Astronomers measure these movements by looking for a change in the frequency of a star's light caused by light waves bunching together as they travel toward us ("blueshift") and spreading apart as they travel away ("redshift").	WIYN 	Watching for Wobbles 	Best at detecting large planets with quick orbits (796 so far) 
DIRECT IMAGING Sometimes, if a planet is bright enough and orbits far from its star, telescopes can spot it directly. Usually this is only possible if astronomers block out its host star's light—a process called coronagraphy—to reveal the much dimmer light of the nearby planet. The vast majority of planets are impossible to image with current observatories, however.	HUBBLE 	Screening Light and Taking Pictures 	Best at detecting young, bright planets with wide orbits (50 so far) 
CIRCUMSTELLAR DISKS Gaps, warps and clumps in the disks of dust and gas around stars can reveal the presence of unseen planets. The disks are visible in long-wavelength light, which requires very large telescopes to see. In the absence of a single large scope, astronomers can combine many smaller telescopes spread over a larger distance to create a virtual observatory as wide as their separation.	ALMA 	Combining Wavelengths (Interferometry) 	Best at detecting large planets with wide orbits 

Illustration by Nigel Hawtin

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unseen planets, even if we can never observe those large bodies directly.

The tiniest dust grains are easily moved around by interactions with interstellar gas or are simply blown out by winds and radiation from the star itself. But because the larger sandlike grains are less affected by such forces, they offer us the best opportunity to uncover the underlying disk structure and unseen planets through their gravitational influence.

Therefore, we want to look at long wavelengths to study disk structure and to search for signatures of unseen planets. It seems straightforward—but of course, there is a catch. The resolution of a telescope is equal to the observing wavelength divided by the diameter of the telescope. Thus, as you increase the wavelength from the optical to the millimeter range, you have to dramatically increase the size of the telescope to achieve the same resolving power. Hubble has a diameter of 2.4 meters, which gives a resolution of 0.13 arc second for observations at a one-micron wavelength. If you wanted to achieve the same resolution at a wavelength of one millimeter, you would need to increase the telescope's diameter by a factor of 1,000 to more than two kilometers! We cannot build a telescope that large, so we have to use a technique called interferometry. Essentially, instead of a single two-kilometer-diameter telescope, an interferometer spreads multiple smaller telescopes out over two kilometers and combines their signals to achieve equally high resolution.

ALMA, which took its first images in 2011, is still the world's most powerful interferometer. Located at an elevation of roughly five kilometers in Chile's Atacama Desert, ALMA has 66 antennas that can be relocated to span baselines (the distance between any two antennas) of 150 meters to 16 kilometers. If you are familiar with the Washington, D.C., area, picture the White House Ellipse: in its most compact configuration, ALMA would fit entirely within it. In its most extended configuration, it would span the entire Capital Beltway. With such advancements in both sensitivity and resolution, we can now image fainter objects in greater detail than ever before. It is not an overexaggeration to say that ALMA has revolutionized our understanding of circumstellar disks.

In one of its first blockbuster disk images, taken in 2014, ALMA imaged HL Tau, a young system probably less than 100,000 years old. The photograph revealed that what had been assumed to be a continuous disk was carved into multiple rings and gaps. Given the young age of the system, if these gaps are actually sculpted by baby planets, planet formation must start earlier than originally thought. In another notable discovery, in 2018, the DSHARP (Disk Substructures at High Angular Resolution Project) survey looked at 20 protoplanetary disks with high resolution and found that every one of them had rings and gaps, and some even showed spiral structure. Apparently such features are not unique to HL Tau but are instead ubiquitous to young circumstellar disks.

PLANET DETECTION

IN ADDITION TO TEACHING US about the process of planetary formation, studying disks is also a good way to detect exoplanets we would otherwise be unable to find.

Telescope missions such as Kepler and TESS (the Transiting Exoplanet Survey Satellite) and many ground-based surveys have so far detected thousands of exoplanets. Yet most of these planets are more massive or are closer to their host star than the planets in our solar system are. These types of planets are not necessarily more common, though; they are simply easier for us to find. The two top methods of detecting exoplanets are the transit technique, which looks for periodic dimming of stars when planets orbit in front of them, and the radial velocity method, which traces planets through observation of the slight change in velocity they cause in their host stars because of their gravitational pull. Both methods favor large planets with short orbits because multiple orbits must be observed to confirm a detection, which means that astronomers using these methods might be missing a lot of planets. Neptune, for instance, has an orbital period of roughly 165 years: if you were studying our solar system from a different star, you would be waiting a very long time before you saw it transit the sun even once. The few planets we do know about that are at Neptune-like distances from their host star have been detected via direct imaging, which uses coronagraphy—blocking the light from the host star—to image the planet itself. This approach has its own observational biases, however, favoring young systems where the planets still retain significant heat from their formation.

To put the architecture of the solar system in context, we must be able to detect giant planets at large distances from their host stars in old systems. Now, with ALMA, this can be done by using the resolved structure of circumstellar disks, providing a powerful complement to other methods of exoplanet detection.

We can find Neptune-like planets, for instance, by studying features of disks sculpted by planets orbiting within them, such as warps, clumps and other asymmetries. In our own solar system, the classical Kuiper Belt is quite narrow because of the gravitational influence of Neptune. We think that during the early evolution of the solar system, Neptune initially formed closer to the sun and then migrated outward, sweeping up much of the remnant material in its wake to create the Kuiper Belt seen today. If we observe similar structures in extrasolar debris disks, we can use them to infer the presence of unseen Neptune analogues.

We can also learn more about planets we already know of by studying the disks they inhabit. The HR 8799 system has four directly imaged giant planets orbiting between analogues of our own asteroid belt and Kuiper Belt. With millimeter interferometry, we can resolve the structure of the system's outer Kuiper Belt analogue and determine the location of its inner edge. If we assume that the outermost planet in the system is responsible for carving out the disk, we can use the location of the

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DEBRIS DISKS, imaged by ALMA, represent a later stage of evolution than protoplanetary disks, after a star and its planets have formed. Their bright bands of rubble are akin to our solar system's Kuiper Belt.

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inner edge to constrain the possible mass of the planet as roughly six Jupiter masses. That may not seem like a significant feat, but it is far more precise than our previous best estimate of the planet's mass, which relied on theoretical models of how planets cool and dim over time. Using the disk's structure, we can provide an important independent check on those models.

ALMA observations of younger protoplanetary disks show a wealth of detailed structure; rings and gaps seem to be present in nearly every system. If all those gaps are carved by planets, we can assume there is a large population of unseen ice-giant planets present. Tying structure in young systems directly to planets is challenging, however, because other effects complicate modeling efforts. Older, more evolved systems are easier to interpret, but so far very few of these debris disks exhibit multiring structure. Recently we discovered a new gap in the HD 15115 debris disk located beyond where Pluto orbits in our system. Dynamical modeling suggests that this gap represents an ice-giant planet with a mass slightly less than that of Saturn. I suspect that as we obtain deep, high-resolution images of more of these evolved systems, more planet-induced features will come to light.

Furthermore, beyond the structure of circumstellar disks, we can also study their composition. Because these disks are the reservoirs and fossil records of planet formation, their composition is intimately tied to the composition of planets in these systems and to their formation history. Numerous common molecules emit light at millimeter wavelengths because of the bending and stretching of their molecular bonds. Scientists have detected dozens of organic molecules (including carbon monoxide, formaldehyde, methanol and ammonia, among many others) in the large gas reservoirs present in protoplanetary disks.

Our research has also uncovered a new mystery: Traditionally debris disks were assumed to be gas-poor because their initial gas reservoirs should be cleared within a few million years. ALMA has revealed that a number of debris disks contain carbon dioxide gas, but we interpret this as the result of comets colliding in the disk and releasing trapped ice in the form of gas as they are ground into small dust grains. A few systems challenge this picture, though, because they contain such a large amount of gas that it would take an unrealistically high rate of cometary collisions to produce it. This discovery prompts a question: Is it possible for primordial gas to remain in these disks for tens of millions of years? As of yet, we do not have an answer.

A MULTIWAVELENGTH FUTURE

IT HAS BEEN EXCITING for me to grow up as a scientist while the field of planet-formation research has grown up around me. I began working on my Ph.D. as ALMA first opened its eyes on the sky, and I am beginning my first faculty position as we move into an exciting new future of multiwavelength astronomy. ALMA has revolutionized our understanding of circumstellar disks, revealing complexities in structure and chemical composition that could have only been guessed at a few decades ago. But ALMA cannot answer all the questions we want to explore. All the debris disks I have discussed in this article are analogues of the Kuiper Belt, cold rings of dust in the outer regions of their solar systems. So far astronomers have struggled to image an analogue of the asteroid belt—we can still detect such features only through their excess infrared light, as we did in the early days with IRAS.

To image the inner regions of extrasolar systems, we need shorter wavelengths that are sensitive to hotter dust. The James Webb Space Telescope (JWST) is due to launch in 2021, and we expect it to take the first picture of one of these asteroid belt analogues. Beyond that, JWST will operate at wavelengths that directly trace emission from silicates (minerals such as olivine and pyroxene, which are also found on Earth) and that constrain the mineral composition of disk grains.

Looking even further into the future, the next generation of "Extremely Large Telescopes" is being constructed now, and these instruments will see their first light in the mid- to late 2020s. These telescopes will have diameters greater than 24 meters, more than five times larger than any current ground-based telescopes, and they may be able to directly image some of the planets we can only infer now from ALMA disk observations.

The Decadal Survey on Astronomy and Astrophysics—a field-wide effort to decide on priorities for future funding—is underway now. Under consideration are four NASA flagship missions that could make huge advances in planetary science in the 2030s and beyond. The Origins Space Telescope, a cryogenically cooled infrared observatory, could trace how water from star-forming regions ends up in circumstellar disks, provide statistics on low-mass disk populations, and much more. Other candidates such as the Large Ultraviolet/Optical/Infrared Surveyor and the Habitable Exoplanet Observatory are direct-imaging missions that could detect and characterize many exoplanets, some of which could be Earth-like.

Regardless of which of these missions is ultimately selected, the one thing I know for sure is that our understanding of the solar system and of its formation and its place in the universe of exoplanet systems is changing every day. The butterfly feeling in your stomach while you wait to see what each new observation looks like—it never goes away. SA

ALMA (ESO/NAOJ AND NRAO)

MORE TO EXPLORE

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CLIMATE CHANGE

WHAT SHOULD CARBON COST?

Smart math, combined with fundamental policy choices, can determine a practical tax that will drive down CO_2 emissions

By Gilbert E. Metcalf

Illustrations by Katie Edwards

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Gilbert E. Metcalf is a professor of economics at Tufts University who specializes in climate economics. He is a research associate at the National Bureau of Economic Research and author of *Paying for Pollution: Why a Carbon Tax Is Good for America* (Oxford University Press, 2019).

ASK ANY ECONOMIST HOW WE SHOULD RESPOND TO CLIMATE CHANGE, AND THEY will tell you that the most effective strategy is to put a price on greenhouse gas emissions, ideally through a carbon tax. This reflects a basic economic principle: the waste produced from any activity is a cost that has to be paid. We pay for throwing away our garbage, for cleaning our wastewater, and we should pay for the carbon dioxide waste we create from activities such as burning fossil fuels.

IN BRIEF

Economists agree that a carbon tax is the most effective way to reduce carbon dioxide emissions. But taxes passed by certain countries range wildly from less than $1 to $121 per ton. In the U.S., models seem to converge at $40 to $47. ("Ton" refers to "metric ton.")

The key is calculating the social cost of carbon. That requires a discount rate on investments, knowing the damage CO_2 emissions will impose on the economy, and the risk of potential disasters.

When setting a tax rate, policy makers may factor in revenue generation, specific emissions-reduction targets or insurance against catastrophe.

We can put a price on our pollution with a carbon tax or with a cap-and-trade program, as European countries have done for power plants and industry. Cap and trade sets an overall limit on emissions (the cap). Firms with low costs of reducing emissions cut their releases and sell allowances to firms with high costs, which continue emitting, while the set of participants stays within the limit. But prices in cap-and-trade arrangements have proved to be volatile, and the systems need strong oversight to avoid problems.

Why bother? A carbon tax provides greater clarity about the price of emissions, which the business community values. And the U.S. already has a well-developed tax collection system, which works smoothly for collecting excise taxes on many fossil fuels.

For reasons like these, economists such as Gregory Mankiw, former head of the U.S. Council of Economic Advisers under President George W. Bush, have prominently supported a carbon tax. The bipartisan Climate Leadership Council, an international policy institute, published a statement in 2019 that argues that "a carbon tax offers the most cost-effective lever to reduce carbon emissions at the scale and speed that is necessary." As of this writing, the statement is signed by 3,589 economists—including the three living former chairs of the Federal Reserve, 27 Nobel laureates and 15 former chairs of the Council of Economic Advisers. How the U.S. addresses climate change has become a major topic in the presidential campaign, and there are eight bills in Congress, one with 80 co-sponsors, to put a price on our carbon pollution.

Still, enacting a carbon tax will be a big political lift. If a window does open for it, climate scientists, economists and politicians need to be ready to pounce. They will need to get it right the first time. And they will need to explain why a specific tax rate is justified.

Determining that rate seems to be straightforward: set the tax per ton of CO_2 equal to the damage inflicted by its release. But how do we properly assess the damage?

HARM FROM EMISSIONS

ECONOMISTS TYPICALLY CALCULATE climate damages with integrated assessment models (IAMs)—large computer models that capture feedbacks between the economy and the climate. They use a series of equations that characterize the global economy, the worldwide circulation of CO_2 emissions arising from economic activity, and damages resulting from atmospheric and upper-ocean temperature increases. IAMs are so important that in 2018 the Nobel Prize in economics was awarded to Yale University economist William D. Nordhaus, for his pioneering work on them.

IAMs such as Nordhaus's dynamic integrated model of the climate and economy (DICE) have become influential in policy analysis. The Obama administration used three IAMs, including DICE, to determine a dollar value that government should use in cost-benefit analyses for proposed new regulations,

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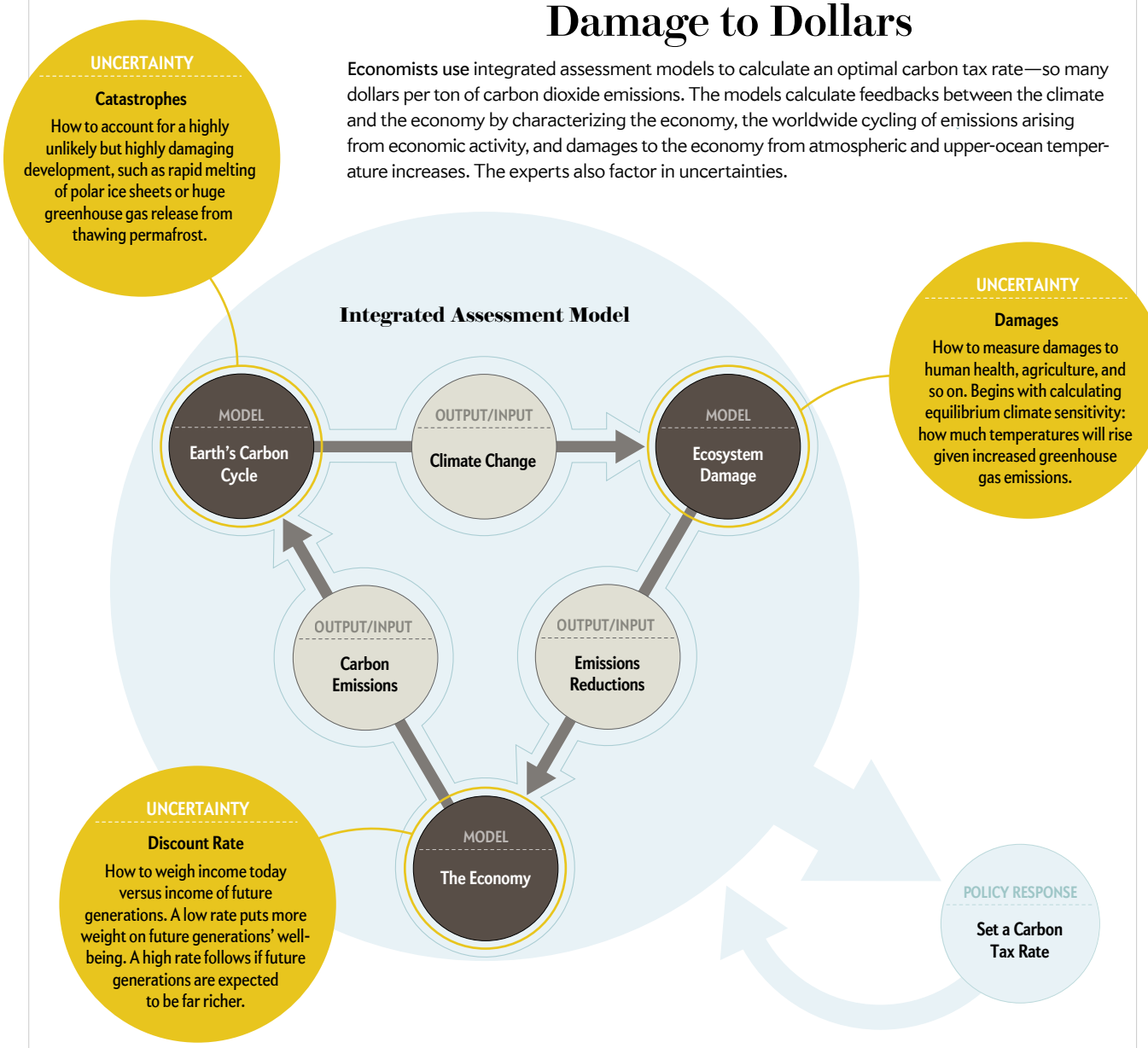
Damage to Dollars

Economists use integrated assessment models to calculate an optimal carbon tax rate—so many dollars per ton of carbon dioxide emissions. The models calculate feedbacks between the climate and the economy by characterizing the economy, the worldwide cycling of emissions arising from economic activity, and damages to the economy from atmospheric and upper-ocean temperature increases. The experts also factor in uncertainties.



Graphic by Jen Christiansen

including the 2011 tightening of automotive fuel-economy standards.

The models seem to answer the question of how to set the right carbon tax rate. But the damage estimates depend on pinning down several assumptions that have great uncertainty. Three challenges stand out. The first is weighing income today against the income of future generations; for that we need a discount rate, a number that is also important to many policy decisions, such as setting the Social Security tax or funding large infrastructure projects. The second challenge is measuring the damages from our CO_2 emissions. Third is how to factor in the possibility of low-probability, high-damage outcomes—so-called catastrophes.

Estimates for the optimal tax rate can vary widely depending on how these factors are treated. In the end, IAMs can give us a solid starting point for a U.S. carbon tax, but the models disagree on the "right" number. Moreover, we have to consider societal and political pressures. Those influences can be huge: 15 European countries have already set carbon taxes, and they range from $2 to $96, with a couple outliers at less than $1 and one at $121.

SOCIAL COST OF CARBON

THE IDEA of using a tax to pay for social damages dates back more than 100 years. The influential University of Cambridge economist Arthur C. Pigou maintained

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that if pollution creates a cost (damage) for someone that is not paid by the polluter, then government should impose a tax on the polluting activity equal to the damages. Pigou, in effect, gave Adam Smith's so-called invisible hand a green thumb.

Burning one ton of coal, for example, produces roughly two tons of carbon dioxide, by combining carbon atoms with oxygen in the air. If the damages from each ton of carbon dioxide equaled, say, $50, then Pigou's prescription would be to levy a $100 tax per ton of coal. In that way, the cost of coal would include the cost to society of burning it: the social cost of carbon (SCC). To estimate this cost, we need an IAM. Enter Nordhaus.

Nordhaus published his first paper about the DICE model in 1992. It estimated that in 2015 the SCC would be $4.54 per metric ton of carbon dioxide. When 2015 came around, and after updates to the model, he raised his estimate to $31. Assuming optimal policy, the SCC would grow to just over $100 per ton by 2050 and to $265 by 2100. (All those numbers are in 2010 dollars.)

A U.S. carbon tax of $40 per ton that increases 5 percent each year would put the country well on track to becoming carbon-free by midcentury.

These estimates are in the middle range among major IAMs. For example, when the Obama administration estimated the SCC for assessing new regulations, it used the DICE model, along with two other well-known models: FUND and PAGE. The 2050 estimates from the FUND model were about half those of the DICE model, and estimates from PAGE were nearly double.

These numbers sound solid, but Massachusetts Institute of Technology economist Robert Pindyck argues that IAMs are useless because they are surrounded by too much uncertainty. His view is extreme, but we do need to take seriously the issues he and others have raised. Let us examine the three key IAM assumptions that can greatly impact the SCC: the discount rate, the damage function and potential catastrophes.

DISCOUNTING FUTURE GENERATIONS

ANY DECISION involving costs and benefits that are separated in time requires a discount rate. Consider an asset that will pay me $1,000 in 10 years. How much is that asset worth today? Assume I could put some money in an account that pays interest of 3 percent a year. With compounding, $744 invested today would grow to $1,000 in 10 years. In other words, the value of $1,000 in 10 years is $744 today. More precisely, the present discounted value of $1,000 in 10 years is $744, when discounted at 3 percent.

When governments need to choose a discount rate, they sometimes use the return people expect for investing in the marketplace. The U.S. Office of Management and Budget, for example, generally recommends a 7 percent discount rate for assessing government regulations because it is the approximate return on investment in the private sector in recent years.

For long-lived projects, the difference between a 7 percent discount and a 3 percent discount is huge. The present discounted value of $1 million in 250 years is 4.5 cents today at 7 percent. The value is $618 today at 3 percent. The higher the discount rate, the less we should be spending today to reduce future emissions.

Discounting at 7 percent seems reasonable for government projects that last for five to 15 years, but it is not reasonable for climate-related actions, where the benefits from today's investment could last for 200 years or more. But because people do not typically make 200-year investments, there is no relevant market rate to go by. That is true even for government-led infrastructure investments. Most of these projects, for example, the Erie Canal, have useful lives of 50 to 100 years before they need to be rebuilt or are abandoned because of innovation—in the canal's case, by railroads, then highways.

If market rates are not a good guide, perhaps we can use economic theory. Economist Frank Ramsey, a peer of Pigou, argued that the discount rate for long-term outlooks should take into account two considerations. The first reflects an ethical decision about how to treat different generations. This leans toward a low discount rate, on the grounds that we should not treat future generations differently than we do our own. Second, the discount rate should take into account changes in income over time; the richer future generations are compared to us, the less we should feel compelled to incur costs now to make them better off. That leans toward a high discount rate.

In 2006 British economist Nicholas Stern wrote a review of climate change for the U.K. government, taking both these factors into account. His so-called Stern Review concluded that the correct discount rate for climate policy was 1.4 percent. At that rate, $1 million in 250 years is worth nearly $31,000 today, far more than the $618 calculated using a 3 percent discount rate. Given his calculations, Stern argued that the costs of climate change were five times the costs of cutting emissions. The Stern Review was highly influential around the world in shaping the narrative about the need to make dramatic and rapid reductions in emissions now.

As a practical matter, we have to square approaches that lead to high and low discount rates. One resolution is that a discount rate should not remain constant over time; it should decline. If uncertainty about future income grows greater the further we go into

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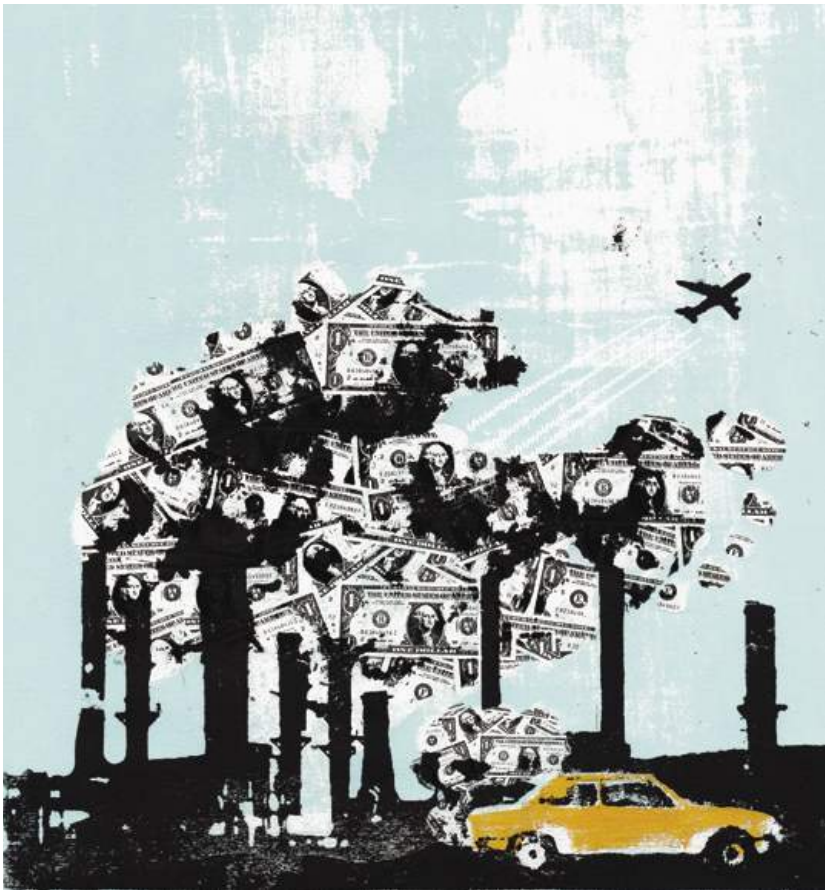
the future, for example, then we need a precautionary factor. The late Harvard University economist Martin Weitzman argued that a discount rate of 4 percent should be used in the near term, whereas 1 percent should be used for the distant future (76 to 300 years), with a gradual decline for time periods in between.

In the end, economists do not have clear guidance on the "best" discount rate, in part because of the ethical choices involved across generations. Small changes in the discount rate, however, can lead to large changes in the SCC—an important factor in setting a carbon tax.



UNCERTAIN DAMAGE

THE SECOND UNCERTAINTY in setting a price on carbon is the damage CO_2 emissions will impose on the economy. In the DICE model, damages are, roughly speaking, a function of the square of the temperature increase. This approach is a shorthand for the complex impacts of warming, such as lower agricultural productivity, higher death rates from heat and diseases, loss of species, geopolitical risks such as drought-driven human migrations, and so on.

Nordhaus, like other IAM modelers, based his damage function on a review of the existing literature. This is good news because scientists have made great progress in measuring the damages from climate change. But no one can capture all possible injury. To compensate, Nordhaus increased his damage estimates by one quarter. His function leads to worldwide damages equal to 8.5 percent of global income for a planetary temperature increase of six degrees Celsius. In contrast, U.S. gross domestic product fell by more than 25 percent during the Great Depression from 1929 to 1933.

Scientists have a way to quantify the likelihood of a big temperature rise. In 1896 Swedish chemist Svante Arrhenius used a series of detailed measurements to estimate that doubling the atmospheric CO_2 concentration would warm Earth by four degrees C. This relation, now known as the equilibrium climate sensitivity, has proved remarkably durable. Unfortunately, little progress has been made in narrowing the uncertainty around it. The Intergovernmental Panel on Climate Change's Fifth Assessment Report (the most recent) states that equilibrium climate sensitivity is "likely in the range 1.5° C to 4.5° C, extremely unlikely less than 1° C, and very unlikely greater than 6° C." But the swing in damages between 1.5° C and 4.5° C is huge. IAM modelers can deal with this kind of uncertainty by making thousands of model runs, varying key parameters. They then report central estimates, and upper and lower bounds, to give policy makers a sense of the uncertainty around SCC values.

This is not entirely satisfactory. Weitzman said there is a "worrisome amount of probability" that equilibrium climate sensitivity could be above 4.5 degrees C. This enters the realm of extreme consequences.

THE PRICE OF CATASTROPHES

CATASTROPHES are low-probability, high-damage events. Weitzman cited a long litany of the "known unknowns" that could lead to catastrophes, such as rapid sea-level rise from quick melting of the Greenland and West Antarctic ice sheets or from significant changes in ocean-circulation patterns. He also considered "unknown unknowns," such as runaway climate feedbacks we have not yet identified. One example might be that warming thaws all permafrost on Earth, which releases huge amounts of CO_2 and methane, creating runaway heating. This is not just academic talk. Investment firm JPMorgan Chase recently released a report to bank clients that warns, "We cannot rule out catastrophic outcomes where human life as we know it is threatened."

On a graph, a normal distribution of the likely rise in temperature would look like a hump: a low tail at the left (unlikely), leading to a high hump in the middle (most likely), and a low tail on the right (unlikely). As our knowledge improves about how the climate is responding to our emissions, we can refine

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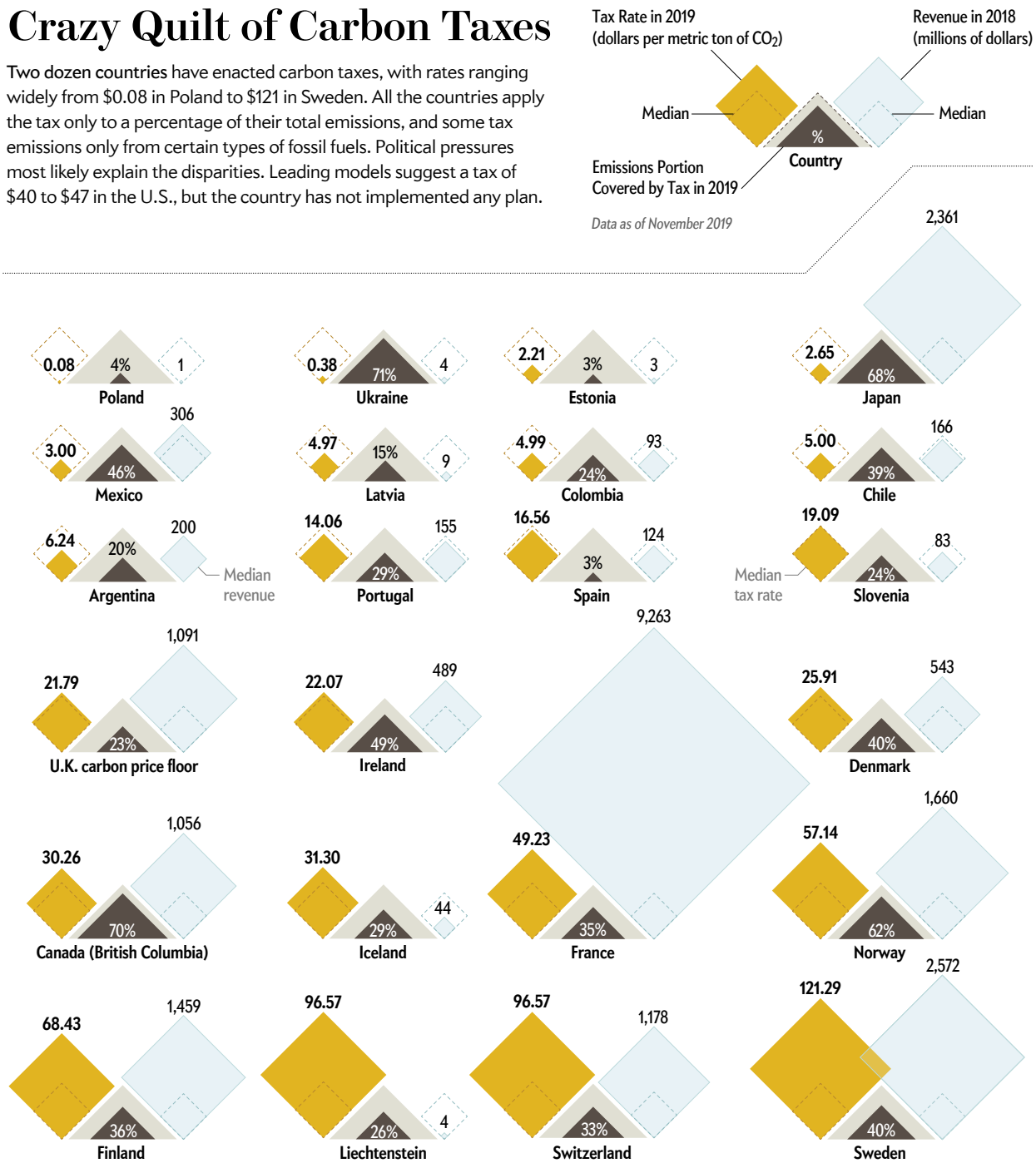
Crazy Quilt of Carbon Taxes

Two dozen countries have enacted carbon taxes, with rates ranging widely from $0.08 in Poland to $121 in Sweden. All the countries apply the tax only to a percentage of their total emissions, and some tax emissions only from certain types of fossil fuels. Political pressures most likely explain the disparities. Leading models suggest a tax of $40 to $47 in the U.S., but the country has not implemented any plan.



this distribution. It appears that the distribution will be "fat-tailed," meaning the probability of very large temperature increases (the tail to the right) goes to zero more slowly than in a normal distribution. This creates a fundamental problem for IAMs, which Weitzman called the Dismal Theorem: society should be willing to pay an infinite amount to avoid low-probability, high-damage events because expected damages are infinite. Clearly, society cannot do that.

Weitzman was not quite sure what to make of his theorem. He argued that researchers should focus more on understanding catastrophic events, to reduce our uncertainty about their likelihood and consequences. That knowledge can better inform policy choices required to respond appropriately to possible catastrophes.

SOURCE: WORLD BANK GROUP

Graphic by Sonja Kuijpers, Studio Terp

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HOW TO PROCEED

IN THE MEANTIME, we need to determine the SCC and carbon tax rate. Uncertainties about the discount rate, damages, climate sensitivity and possible catastrophes mean that any estimate of the SCC is uncertain. The only thing we can say for sure is that the SCC must be greater than zero; any pollutant incurs a cost. It is heartening to see greater collaboration between economists and scientists—signaled by the science journal *Nature* appointing an economics editor—because it will lessen such uncertainties.

For policy makers, IAMs can provide a starting point for setting a schedule of carbon tax rates for the next few decades. For example, the three models the U.S. government used in 2016 for analyzing potential regulations gave a range of estimates for the SCC in 2020. Assuming a 3 percent discount rate, Nordhaus's DICE model suggested a mean 2020 tax rate of $47 per metric ton of carbon dioxide. Mean estimates from the other two models were $23 and $84.

Nordhaus's rate is very close to the $40 per ton rate suggested by the Climate Leadership Council. It is also close to the average initial tax rate in the seven carbon tax bills filed in Congress. In its base case, the council's tax rate would increase 5 percent each year, leading to a tax of $65 in 2030 and $173 in 2050. An economic model from Stanford University and Resources for the Future suggests that the Climate Leadership Council's proposal would create an immediate 18 percent reduction in emissions and a 50 percent reduction by 2035, relative to a U.S. economy without a carbon price. This would put the country well on track to becoming carbon-free by midcentury.

The tax would also generate a lot of revenue for the federal government. A U.S. Treasury study estimated that a carbon tax of this magnitude would raise more than $1.5 trillion over the next decade, after accounting for losses in business and related tax revenues from the tax. Focusing on revenue is a fiscal argument for a tax that might appeal to congressional policy makers who, at some point, will need funds to close a spiraling budget deficit. Or the revenue could pay for some of the zero-carbon infrastructure called for in the Green New Deal. Such an approach focuses on a carbon tax's role as a fiscal instrument more than as an environmental instrument. The government could also give carbon tax revenues back to households through a "carbon dividend," as the Climate Leadership Council has proposed.

A different strategy would focus on emissions reductions, not revenue potential. After all, taxing CO_2 will not actually guarantee a given emissions reduction, even though raising the cost of emissions will definitely drive them down. Economists, for example, have run a model of the U.S. economy that indicates a $43 tax per ton starting in 2019 would have been sufficient for the U.S. to meet the Paris Agreement goal of a 28 percent emissions reduction by 2025.

Alternatively, a carbon tax could be viewed purely as an insurance policy against catastrophes. The tax would not eliminate the risk but would help reduce it. We could call this the Grand Canyon effect. If I stand at the edge of the Grand Canyon taking in the view, there is a risk that a sudden wind gust could cause me to lose my balance and fall over the edge. By taking a step back, I reduce that risk. By slowing the rate of emissions, we reduce the risk of a catastrophic climate event.

A hybrid approach would set a tax on CO_2 and periodically update the tax rate depending on how much progress the U.S. is making toward reducing emissions. But updating is problematic. Enacting a carbon tax is going to be a political fight for Congress. Once done, Congress is unlikely to have the appetite to periodically reopen the debate by reviewing and adjusting tax schedules. We can get around that by including a "policy thermostat" in the initial legislation. For example, the legislation could include explicit emissions-reduction targets over 10 and 20 years and a process for adjusting the tax rates automatically if the country is not on track to hit those targets. A number of the U.S. carbon tax proposals use this approach.

If the U.S. moves forward with a carbon tax, it has to consider important design issues: What to do with the tax revenue. What to do for workers in carbon-intensive sectors of the economy. How to incentivize carbon capture and sequestration. Whether to tax the carbon dioxide embedded in imported goods. And whether there is a political trade-off to be had in relaxing some environmental regulations in return for a carbon tax.

Additional policies will be needed, too. Certain greenhouse gas sources may not be amenable to taxation and might be more cost-effectively addressed through regulation. One example is methane emissions from oil and gas fields. Trying to measure and tax them is unrealistic; requiring technologies that reduce the leakage is more effective. More fundamentally, we will need more funding for R&D to invent and bring to market affordable zero-carbon energy technologies and perhaps cost-effective carbon capture and storage technologies.

Putting a price on our emissions now is essential. Here is a simple reason why: 2019 was the second hottest year on record worldwide, and the past five years were the hottest of the past 140. SA

MORE TO EXPLORE

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TALES OF THE DYING BRAIN

CONSCIOUSNESS

Surviving a close brush with death can leave a lasting legacy in the mind—and may tell us about how the brain functions under extreme conditions

By Christof Koch

IN BRIEF

Near-death experiences are triggered during singular life-threatening episodes when the body is injured by a heart attack, shock, or blunt trauma such as an explosion or a fall.

These events share broad commonalities: becoming pain-free, seeing a bright light at the end of a tunnel, or detaching from one's body and floating above it and even flying off into space.

Why the mind should experience the struggle to sustain its operations in the face of a loss of blood flow and oxygen as positive and blissful rather than as panic-inducing remains a mystery.

Illustrations by Brian Stauffer

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A YOUNG ERNEST HEMINGWAY, BADLY INJURED BY an exploding shell on a World War I battlefield, wrote in a letter home that "dying is a very simple thing. I've looked at death, and really I know. If I should have died it would have been very easy for me. Quite the easiest thing I ever did."

Years later Hemingway adapted his own experience—that of the soul leaving the body, taking flight and then returning—for his famous short story "The Snows of Kilimanjaro," about an African safari gone disastrously wrong. The protagonist, stricken by gangrene, knows he is dying. Suddenly, his pain vanishes, and Compie, a bush pilot, arrives to rescue him. The two take off and fly together through a storm with rain so thick "it seemed like flying through a waterfall" until the plane emerges into the light: before them, "unbelievably white in the sun, was the square top of Kilimanjaro. And then he knew that there was where he was going." The description embraces elements of a classic near-death experience: the darkness, the cessation of pain, the emerging into the light and then a feeling of peacefulness.

Christof Koch is chief scientist of the MindScope program at the Allen Institute for Brain Science and author of *The Feeling of Life Itself—Why Consciousness Is Widespread but Can't Be Computed.* He serves on *Scientific American*'s board of advisers.

PEACE BEYOND UNDERSTANDING

NEAR-DEATH EXPERIENCES, or NDEs, are triggered during singular life-threatening episodes when the body is injured by blunt trauma, a heart attack, asphyxia, shock, and so on. About one in 10 patients with cardiac arrest in a hospital setting undergoes such an episode. Thousands of survivors of these harrowing touch-and-go situations tell of leaving their damaged bodies behind and encountering a realm beyond everyday existence, unconstrained by the usual boundaries of space and time. These powerful, mystical experiences can lead to permanent transformation of their lives.

NDEs are not fancy flights of the imagination. They share broad commonalities—becoming pain-free, seeing a bright light at the end of a tunnel and other visual phenomena, detaching from one's body and floating above it, or even flying off into space (out-of-body experiences). They might include meeting loved ones, living or dead, or spiritual beings such as angels; a Proustian recollection or even review of lifetime memories, both good and bad ("my life flashed in front of my eyes"); or a distorted sense of time and space. There are some underlying physiological explanations for these perceptions, such as progressively narrowing tunnel vision. Reduced blood flow to the visual periphery of the retina means vision loss occurs there first.

NDEs can be either positive or negative experiences. The former receive all the press and relate to the feeling of an overwhelming presence, something numinous, divine. A jarring disconnect separates the massive trauma to the body and the peacefulness and feeling of oneness with the universe. Yet not all NDEs are blissful—some can be frightening, marked by intense terror, anguish, loneliness and despair.

It is likely that the publicity around NDEs has built up expectations about what people should feel after such episodes. It seems possible, in fact, that distressing NDEs are significantly underreported because of shame, social stigma and pressure to conform to the prototype of the "blissful" NDE.

Any close brush with death reminds us of the precariousness and fragility of life and can strip away the layers of psychological suppression that

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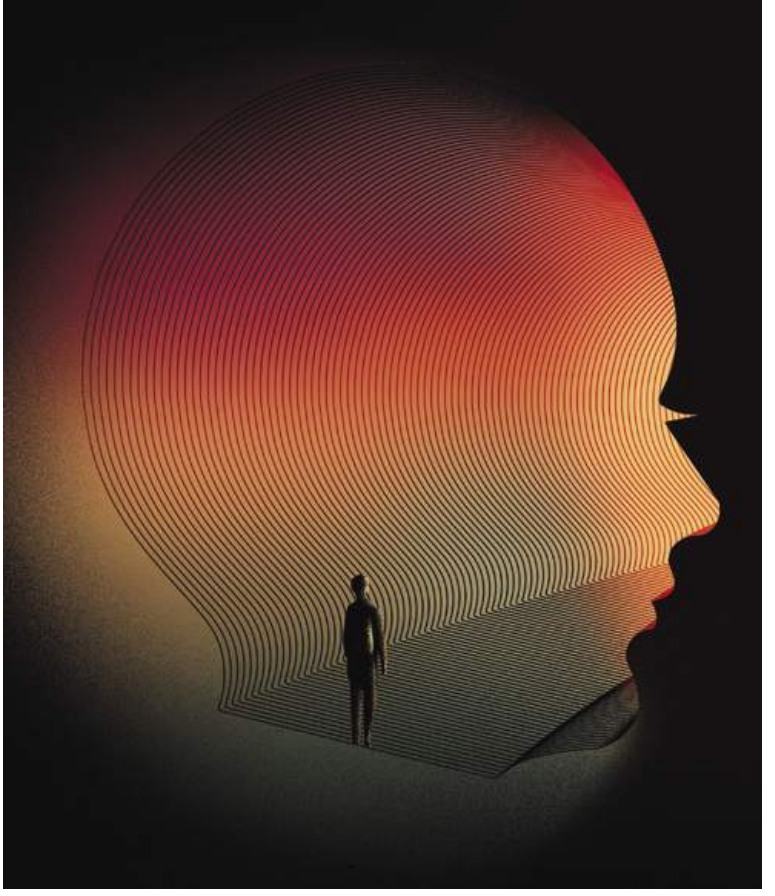

shield us from uncomfortable thoughts of existential oblivion. For most, these events fade in intensity with time, and normality eventually reasserts itself (although they may leave post-traumatic stress disorder in their wake). But NDEs are recalled with unusual intensity and lucidity over decades.

A 2017 study by two researchers at the University of Virginia raised the question of whether the paradox of enhanced cognition occurring alongside compromised brain function during an NDE could be written off as a flight of imagination. The researchers administered a questionnaire to 122 people who reported NDEs. They asked them to compare memories of their experiences with those of both real and imagined events from about the same time. The results suggest that the NDEs were recalled with greater vividness and detail than either real or imagined situations were. In short, the NDEs were remembered as being "realer than real."

NDEs came to the attention of the general public in the last quarter of the 20th century from the work of physicians and psychologists—in particular Raymond Moody, who coined the term "near-death experience" in his 1975 best seller, *Life after Life,* and Bruce M. Greyson, one of the two researchers on the study mentioned earlier, who also published *The Handbook of Near-Death Experiences* in 2009. Noticing patterns in what people would share about their near-death stories, these researchers turned a phenomenon once derided as confabulation or dismissed as feverish hallucination (deathbed visions of yore) into a field of empirical study.

I accept the reality of these intensely felt experiences. They are as authentic as any other subjective feeling or perception. As a scientist, however, I operate under the hypothesis that all our thoughts, memories, percepts and experiences are an ineluctable consequence of the natural causal powers of our brain rather than of any supernatural ones. That premise has served science and its handmaiden, technology, extremely well over the past few centuries. Unless there is extraordinary, compelling, objective evidence to the contrary, I see no reason to abandon this assumption.

The challenge, then, is to explain NDEs within a natural framework. As a longtime student of the mind-body problem, I care about NDEs because they constitute a rare variety of human consciousness and because of the remarkable fact that an event lasting well under an hour in objective time leaves a permanent transformation in its wake, a Pauline conversion on the road to Damascus—no more fear of death, a detachment from material possessions and an orientation toward the greater good. Or, as in the case of Hemingway, an obsession with risk and death.

Similar mystical experiences are commonly reported when ingesting psychoactive substances from a class of hallucinogens linked to the neurotransmitter serotonin, including psilocybin (the active ingredient in magic mushrooms), LSD, DMT (aka the Spirit Molecule), and 5-MeO-DMT (aka the God Molecule), consumed as part of religious, spiritual or recreational practices.

THE UNDISCOVERED COUNTRY

IT MUST BE REMEMBERED that NDEs have been with us at all times in all cultures and in all people, young and old, devout and skeptical (think, for instance, of the so-called *Tibetan Book of the Dead,* which describes the mind before and after death). To those raised in religious traditions, Christian or otherwise, the most obvious explanation is that they were granted a vision of heaven or hell, of what awaits them in the hereafter. Interestingly, NDEs are no more likely to occur in devout believers than in secular or nonpracticing subjects.

Personal narratives drawn from the historical record furnish intensely vivid accounts of NDEs that can be as instructive as any dry, clinical case report, if not more so. In 1791, for instance, British admiral Sir Francis Beaufort (after whom the Beaufort wind scale is named) almost drowned, an event he recalled in this fashion:

> *A calm feeling of the most perfect tranquility succeeded the most tumultuous sensation.... Nor was I in any bodily pain. On the contrary, my sensations were now of rather a pleasurable cast.... Though the senses were thus deadened, not so the mind; its*

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Local brain regions go offline one after another. The mind, whose substrate is whichever neurons remain intact, then does what it always does: it tells a story shaped by a person's experience, memory and cultural expectations.

> *activity seemed to be invigorated in a ratio which defies all description; for thought rose after thought with a rapidity of succession that is not only indescribable, but probably inconceivable, by anyone who has been himself in a similar situation. The course of these thoughts I can even now in a great measure retrace: the event that had just taken place.... Thus, traveling backwards, every incident of my past life seemed to me to glance across my recollection in retrograde procession ... the whole period of my existence seemed to be placed before me in a kind of panoramic view.*

Another instance was recorded in 1900, when Scottish surgeon Sir Alexander Ogston (discoverer of *Staphylococcus*) succumbed to a bout of typhoid fever. He described what happened this way:

> *I lay, as it seemed, in a constant stupor which excluded the existence of any hopes or fears. Mind and body seemed to be dual, and to some extent separate. I was conscious of the body as an inert tumbled mass near a door; it belonged to me, but it was not I. I was conscious that my mental self used regularly to leave the body.... I was then drawn rapidly back to it, joined it with disgust, and it became I, and was fed, spoken to, and cared for.... And though I knew that death was hovering about, having no thought of religion nor dread of the end, and roamed on beneath the murky skies apathetic and contented until something again disturbed the body where it lay, when I was drawn back to it afresh.*

More recently, British writer Susan Blackmore received a report from a woman from Cyprus who had an emergency gastrectomy in 1991:

> *On the fourth day following that operation I went into shock and became unconscious for several hours.... Although thought to be unconscious, I remembered, for years afterwards, the entire, detailed conversation that passed between the surgeon and anaesthetist present.... I was lying above my own body, totally free of pain, and looking down at my own self with compassion for the agony I could see on the face; I was floating peacefully. Then ... I was going elsewhere, floating towards a dark, but not frightening, curtain-like area ... Then I felt total peace. Suddenly it all changed—I was slammed back into my body again, very much aware of the agony again.*

The underlying neurological sequence of events in a near-death experience is difficult to determine with any precision because of the dizzying variety of ways in which the brain can be damaged. Furthermore, NDEs do not strike when the individual is lying inside a magnetic scanner or has his or her scalp covered by a net of electrodes.

It is possible, though, to gain some idea of what happens by examining a cardiac arrest, in which the heart stops beating (the patient is "coding," in hospital jargon). The patient has not died, because the heart can be jump-started via cardiopulmonary resuscitation.

Modern death requires irreversible loss of brain function. When the brain is starved of blood flow (ischemia) and oxygen (anoxia), the patient faints in a fraction of a minute and his or her electroencephalogram, or EEG, becomes isoelectric—in other words, flat. This implies that large-scale, spatially distributed electrical activity within the cortex, the outermost layer of the brain, has broken down. Like a town that loses power one neighborhood at a time, local regions of the brain go offline one after another. The mind, whose substrate is whichever neurons remain capable of generating electrical activity, does what it always does: it tells a story shaped by the person's experience, memory and cultural expectations.

Given these power outages, this experience may produce the rather strange and idiosyncratic stories that make up the corpus of NDE reports. To the person undergoing it, the NDE is as real as anything the mind produces during normal waking. When the entire brain has shut down because of complete power loss, the mind is extinguished, along with consciousness. If and when oxygen and blood flow are restored, the brain boots up, and the narrative flow of experience resumes.

Scientists have videotaped, analyzed and dissected the loss and subsequent recovery of consciousness in highly trained individuals—U.S. test pilots

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and NASA astronauts in centrifuges during the cold war (recall the scene in the 2018 movie *First Man* of a stoic Neil Armstrong, played by Ryan Gosling, being spun in a multiaxis trainer until he passes out). At around five times the force of gravity, the cardiovascular system stops delivering blood to the brain, and the pilot faints. About 10 to 20 seconds after these large *g*-forces cease, consciousness returns, accompanied by a comparable interval of confusion and disorientation (subjects in these tests are obviously very fit and pride themselves on their self-control).

The range of phenomena these men recount may amount to "NDE lite"—tunnel vision and bright lights; a feeling of awakening from sleep, including partial or complete paralysis; a sense of peaceful floating; out-of-body experiences; sensations of pleasure and even euphoria; and short but intense dreams, often involving conversations with family members, that remain vivid to them many years afterward. These intensely felt experiences, triggered by a specific physical insult, typically do not have any religious character (perhaps because participants knew ahead of time that they would be stressed until they fainted).

By their very nature, NDEs are not readily amenable to well-controlled laboratory experimentation, although this might change. For instance, it may be possible to study aspects of them in the humble lab mouse—maybe it, too, can experience a review of lifetime memories or euphoria before death.

THE FADING OF THE LIGHT

MANY NEUROLOGISTS HAVE NOTED similarities between NDEs and the effects of a class of epileptic events known as complex partial seizures. These fits partially impair consciousness and often are localized to specific brain regions in one hemisphere. They can be preceded by an aura, which is a specific experience unique to an individual patient that is predictive of an incipient attack. The seizure may be accompanied by changes in the perceived sizes of objects; unusual tastes, smells or bodily feelings; déjà vu; depersonalization; or ecstatic feelings. Episodes featuring the last items on this list are also clinically known as Dostoyevsky's seizures, after the late 19th-century Russian writer Fyodor Dostoyevsky, who suffered from severe temporal lobe epilepsy. Prince Myshkin, the protagonist of his novel *The Idiot,* remembers:

> *During his epileptic fits, or rather immediately preceding them, he had always experienced a moment or two when his whole heart, and mind, and body seemed to wake up to vigor and light; when he became filled with joy and hope, and all his anxieties seemed to be swept away forever; these moments were but presentiments, as it were, of the one final second (it was never more than a second) in which the fit came upon him. That second, of course, was inexpressible. When his attack was over, and the prince reflected on his symptoms, he used to say to himself:… "What matter though it be only disease, an abnormal tension of the brain, if when I recall and analyze the moment, it seems to have been one of harmony and beauty in the highest degree—an instant of deepest sensation, overflowing with unbounded joy and rapture, ecstatic devotion, and completest life?… I would give my whole life for this one instant.*

More than 150 years later neurosurgeons are able to induce such ecstatic feelings by electrically stimulating part of the cortex called the insula in epileptic patients who have electrodes implanted in their brain. This procedure can help locate the origin of the seizures for possible surgical removal. Patients report bliss, enhanced well-being, and heightened self-awareness or perception of the external world. Exciting the gray matter elsewhere can trigger out-of-body experiences or visual hallucinations. This brute link between abnormal activity patterns—whether induced by the spontaneous disease process or controlled by a surgeon's electrode—and subjective experience provides support for a biological, not spiritual, origin. The same is likely to be true for NDEs.

Why the mind should experience the struggle to sustain its operations in the face of loss of blood flow and oxygen as positive and blissful rather than as panic-inducing remains mysterious. It is intriguing, though, that the outer limit of the spectrum of human experience encompasses other occasions in which reduced oxygen causes pleasurable feelings of jauntiness, light-headedness and heightened arousal—deepwater diving, high-altitude climbing, flying, the choking or fainting game, and sexual asphyxiation.

Perhaps such ecstatic experiences are common to many forms of death as long as the mind remains lucid and is not dulled by opiates or other drugs given to alleviate pain. The mind, chained to a dying body, visits its own private version of heaven or hell before entering Hamlet's "undiscovered country from whose bourn no traveler returns." SA

MORE TO EXPLORE

The Handbook of Near-Death Experiences: Thirty Years of Investigation. Edited by Janice Miner Holden, Bruce Greyson and Debbie James. Praeger, 2009.

Leaving Body and Life Behind: Out-of-Body and Near-Death Experience. Olaf Blanke, Nathan Faivre and Sebastian Dieguez in *The Neurology of Consciousness*. Second edition. Edited by Steven Laureys, Olivia Gosseries and Giulio Tononi. Academic Press, 2015.

FROM OUR ARCHIVES

Is Death Reversible? Christof Koch; October 2019.

scientificamerican.com/magazine/sa

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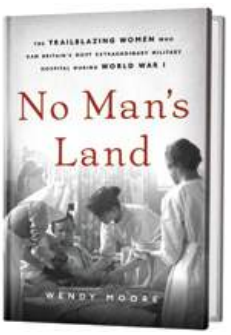
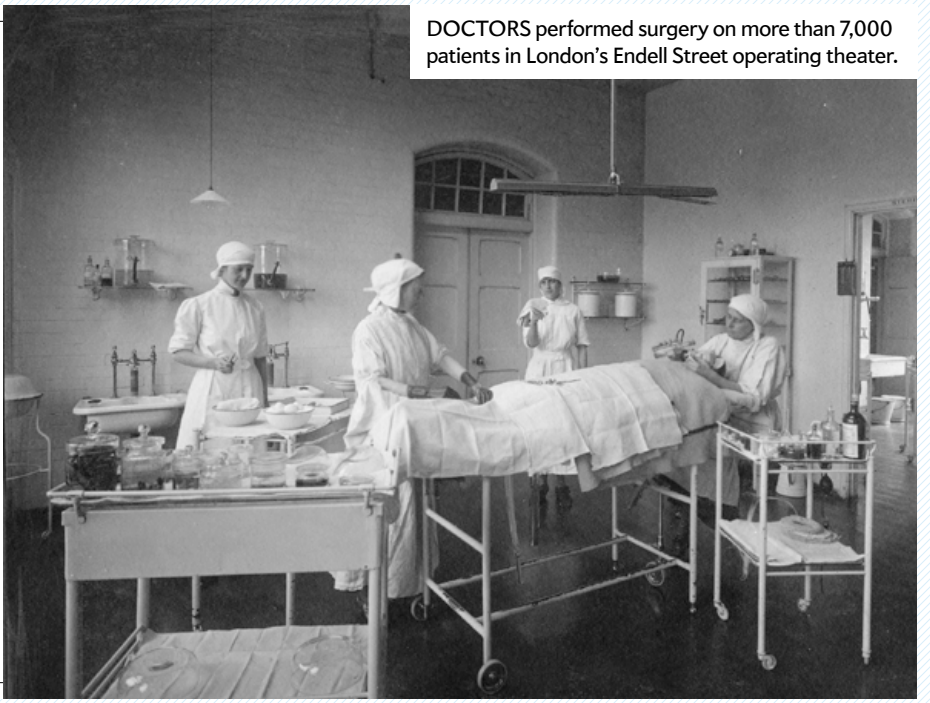
RECOMMENDED

By Andrea Gawrylewski

No Man's Land: The Trailblazing Women Who Ran Britain's Most Extraordinary Military Hospital during World War I

by Wendy Moore. Basic Books, 2020 ($30)





DOCTORS performed surgery on more than 7,000 patients in London's Endell Street operating theater.

When World War I began, the relatively few English women who had medical degrees were effectively blocked from practicing in prominent hospitals and were relegated to low-paying and low-profile positions. Doctors Louisa Garrett Anderson and Flora Murray were therefore astonished when, in 1915, the British Army requested that they assemble a 1,000-bed military hospital in London. Journalist Moore eloquently brings to life the story of the two women who fought for women's rights and set up Endell Street Hospital—nicknamed the Suffragettes' Hospital and staffed entirely by women. Despite receiving accolades for their achievements, when peacetime came, most women doctors met with the same prejudices and sexism they had faced before the war. As Moore writes, the sad and brutal truth was that many of these women looked back on wartime as the happiest days of their lives.

How Innovation Works: And Why It Flourishes in Freedom

by Matt Ridley. Harper/HarperCollins, 2020 ($29.99)

The 18th-century Englishwoman Lady Mary Wortley Montagu did not invent inoculation, the practice of exposing people to disease to generate immunity. But after she learned about it on a trip to Constantinople, the smallpox-scarred writer championed its adoption in the Western world. With stories like Montagu's, journalist Ridley focuses less on the invention of a new concept and more on "the long struggle to get an idea to catch on, usually by combining it with other ideas." By tracing this struggle for a variety of concepts, from public health techniques to creations such as the steam engine and the computer, Ridley constructs a fascinating theory of innovation, including its prehistoric roots, how it will shape the future and what makes it successful. Sheer dumb luck may help. *—Sophie Bushwick*

A Furious Sky: The Five-Hundred-Year History of America's Hurricanes

by Eric Jay Dolin. Liveright, 2020 ($29.95)

A single hurricane can alter the paths of (or end) countless lives and overwrite entire cities, but only by looking at storms in aggregate can humans begin to grasp their magnitude. Writer Dolin employs both perspectives, detailing individuals' journeys through noteworthy U.S. (and non-U.S.) hurricanes, as well as how the tempests shaped history—plus how changing technology affected what scientists learned about each of them. From word of mouth to telegram, radar to hurricane-chasing plane, and computer modeling to orbiting satellite, every new development brought humans closer to understanding the source and structure of these storms—and predicting where they will go next. As powerful hurricanes become more common, Dolin writes, honing our reactions to them will be more important than ever. *—Sarah Lewin Frasier*

The Woman Who Cracked the Anxiety Code: The Extraordinary Life of Dr. Claire Weekes

by Judith Hoare. Scribe, 2020 ($20)

After a misdiagnosis led to a stay at a tuberculosis sanatorium in the late 1920s, heart palpitations caused Claire Weekes constant worry. Confiding in a friend who had been a WWI soldier, she learned what she had was "nerves"—what we now call anxiety—and was essentially the fear of fear. Journalist Hoare chronicles Weekes's life, from an early career in zoology to an attempt at singing professionally to becoming a doctor at age 42. Eventually she developed a simple but effective treatment for her ailment. In best-selling books, she explained the biology of fear and how to retrain the response to it, advocating for accepting and "floating" through the experience instead of fighting it. This biography restores Weekes's often overlooked contributions to anxiety treatment. *—Andrea Thompson*

ELEANOR ROOSEVELT NATIONAL HISTORIC SITE, NATIONAL PARK SERVICE, COOK-DICKERMAN COLLECTION

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

How Small Is Small?

It all depends on the context

By Naomi Oreskes

Quantifying things is an overarching goal in science, but recent events have left me pondering just why that is. After all, we've long known that numbers can be precise but inaccurate. The textbook exemplar is Lord Kelvin, the 19th-century British physicist who insisted that unless you could quantify a thing, your knowledge of it was of a "meager and unsatisfactory kind."

Yet he was responsible for one of history's most infamous examples of a fallacious quantitative argument. It concerned the geologic principle of uniformitarianism, which states that processes we can observe can be used to interpret Earth's history. Kelvin insisted it was wrong because it had led geologists to conclude that Earth was billions of years old. Kelvin's own calculations ended up placing the age at no more than 20 million to 40 million years; ergo the methods geologists had used must be faulty.

Kelvin's paper on the topic is perhaps the most arrogant in the history of science: the body of *The "Doctrine of Uniformity" in Geology Briefly Refuted* is one paragraph long, with one additional paragraph laying out his calculations. But it was Kelvin who ended up being refuted. He had made (at least) two faulty assumptions: one, that Earth began in a molten state and has been cooling ever since, and two, that there is no source of heat other than that left over from the planet's formation. (Today scientists think our planet began as gas and dust; we know that radioactive decay is a major source of heat and that Earth is 4.5 billion years old.)

Calculations can never be better than the assumptions that guide them, but if numbers are fallible, then what exactly is their point? One answer is that they give us the ability to compare one thing against another using a common scale. It's a whole lot easier to compare 1,000 to 100 than it is to compare "canoe" to "pineapple." Another is specificity: we know how much larger 1,000 is than 100, but it's not necessarily clear what we mean when we call something simply "large" or "small." Indeed, two recent scientific debates both hinged on the question "How small is small"?

The first is about the risks of eating red meat. Last year a group of researchers argued that Americans should not bother to reduce their consumption of red and processed meats, because any health benefits would be "small." The second is about the impact of fossil-fuel subsidies. A paper in *Nature* examined whether eliminating them would have much of an effect on carbon dioxide emissions. The authors concluded that the effect would be "limited." (Full disclosure: I am an author on a paper challenging that finding.)

How are we to judge these claims? Critics have a point when they suggest that we should not expect people to change their lives—or governments to change their policies—if the benefits of those changes have not been demonstrated or if they have been

demonstrated but are insubstantial. But how do we judge what is substantial and what is not? In the case of red meat, the authors wrote: "Dose-response meta-analysis results from 17 cohorts with 2.2 million participants provided low-certainty evidence that decreasing unprocessed red meat intake may result in a very small reduction of overall lifetime cancer mortality (7 fewer events per 1,000 persons with a decrease of 3 servings/wk)."

Is seven fewer cancer deaths per 1,000 people "very small"? In a population of 331 million Americans, that's 2.3 million people! In comparison, as of late March this year, the Centers for Disease Control and Prevention estimated flu deaths in the 2019–2020 season (which are calculated separately from those caused by COVID-19) at 23,000 to 59,000. It would be accurate—and perhaps more informative—to say that eating three fewer servings of red meat a week could save 100 times more lives than eliminating a year's worth of deaths from seasonal flu.

In the case of fossil fuels, the authors wrote: "Subsidy removal would lead to a small decrease in global CO_2 emissions: 0.5–2 gigatons.... This is much less than the Nationally Determined Contributions (NDCs) from the Paris Agreement, which add up to a decrease of between 4–8 Gt from fossil fuels and industry." Yes, a range of 0.5 to two is less than four to eight, but is it "much less"? Maybe, but the authors would have been equally correct if they had said that subsidy removal would amount to at least 6 percent of the Paris commitments and possibly as much as 50 percent.

Admittedly, scientists are often admonished to speak in plain English, and "small" and "very small" are plain English. But when the numbers they refer to are *not* small, they become misleading. SA

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Illustration by Chanelle Nibbelink

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Gone Viral

Hello from the pandemic's earlier days

By Steve Mirsky

This morning I had a surprisingly lengthy discussion with my wife about whether it was Wednesday or Thursday. I'm writing this in early April from New York City, currently the global epicenter of the COVID-19 outbreak. We've already been mostly indoors for weeks, and the days have a sameness that brings to mind the movie *Groundhog Day,* but with body counts.

As this is allegedly a humor column, I'll look for some humor in this horror. Thankfully, there's the earnest Australian astrophysicist who meant well when he started shoving mini but relatively mighty magnets up his nose.

According to the British newspaper the *Guardian,* 27-year-old Daniel Reardon was trying to "invent a device that stops people touching their faces during the coronavirus outbreak." Reardon's usual focus is on using data from pulsar timing arrays to search for nanohertz-frequency gravitational waves, so magnets are a bit out of his bailiwick.

The idea, we'll call it, was for a user to wear magnets on his or her wrists and also somewhere near the face. Some circuitry would initiate a buzzing sound when the magnets got close together. The buzz would remind wearers not to mug their mugs. But the best-laid plans of aardvarks and astrophysicists oft go agley.

Failing and then flailing, a bored Reardon put a magnet in his nostril. Thus it began. He ended up with four magnets jammed in his breathing holes, each strongly attracting the others. An attempt to pull the magnets out with pliers also went agley when the tool itself became magnetized, leading to some spooky nose action at a rather small distance—think of a diminutive metal wand with a sole magic power: the ability to move your nose around from an inch away. Reardon wound up at a hospital, thus burdening the very health care system he meant to relieve.

We now go from shoving things up one's nose to pulling things out of one's derriere. In early April, Georgia governor Brian Kemp and New York mayor Bill de Blasio said we had just learned asymptomatic people could spread the virus. Yeah, no.

In an article posted on February 28 on the *New England Journal of Medicine*'s Web site, Bill Gates wrote that there was "strong evidence that [the virus] can be transmitted by people who are just mildly ill or even presymptomatic." The scientific citation for that claim was a letter published at NEJM.org on February 18.

Of course, Gates is not a medical researcher. But he is very, very rich. Which you'd think would be sufficient to gain the trust of politicians. Take Donald Trump. (Yeah, yeah.) The president was presumably born with some potential for competence, eventually achieved incompetence, and now we have had that incompetence thrust upon us. On March 27 he said of the coronavirus causing COVID-19, "You can call it a germ. You can call it a flu. You can call it a virus. You know, you can call it many different names. I'm not sure anybody even knows what it is."

In response to that sterling example of nihilistic blather (our sister journal *Nature* published genome-sequence info on February 3 about what was clearly a virus), I'll go to Laurie Garrett, author of the 1994 pandemic bible *The Coming Plague* and still on the beat. On April 1 she was on a Sustain What? Webcast, part of a series launched in March by Andrew Revkin, the longtime journalist now running a communication and sustainability initiative at Columbia University's Earth Institute. Garrett recounted leaving her Manhattan apartment recently to buy milk:

> The streets were full of people. And they were all young people who'd somehow gotten the message that this is only dangerous for old people … and a lot of politicians are the major vehicles of this misinformation … and if [young people] get infected it's no biggie. Well, it is a biggie! Because you can infect others. You can pass your virus on. You perpetuate the epidemic. And, yes, you can get sick … and so the consequences of any statement by any leader that isn't rooted in solid science … is socially irresponsible, is costing lives, is actually killing people.

After a tour of the Centers for Disease Control and Prevention (in the capital of Kemp's state) on March 6, Trump bragged about how well he understands medical science. "Maybe I have a natural ability," he said. "Maybe I should have done that instead of running for president." A risk-analysis comparison leads me to think Hippocrates would have approved. SA

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

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Illustration by Matt Collins

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JUNE

1970 Gene Switches

"How are genes controlled? All cells must be able to turn their genes on and off. For example, a bacterial cell may need different enzymes in order to digest a new food offered by a new environment. As a simple virus goes through its life cycle, its genes function sequentially, directing a series of timed events. As more complex organisms develop from the egg, their cells switch thousands of different genes on and off, and the switching continues throughout the organism's life cycle. This switching requires the action of many specific controls. During the past 10 years one mechanism of such control has been elucidated in molecular terms: the control of specific genes by molecules called repressors.—Mark Ptashne and Walter Gilbert"

Gilbert was the co-winner of the 1980 Nobel Prize in Chemistry for his work on nucleic acids.

1970

1920

1870

1920 Voice Amplification

"The loud-speaking telephone system which has been placed in the Coliseum at Chicago has been in process of development for about ten years. The work was mostly done in the laboratory on one of the busiest and noisiest waterfront streets in New York. Amidst all the rattle and bang of a thousand teams and motor trucks pounding the stone pavement, teamsters were startled to hear a strange voice, apparently close to their ears, deliberately and clearly reciting some rhyme like 'Hickery, dickery, dock, the mouse ran up the clock.' Those teamsters could hardly see the horn on the roof of the lofty laboratory building, nor guess that tests were being made which would facilitate the nomination of a presidential candidate."

1

1870: Elegant bridge by John A. Roebling makes the most of iron construction materials.

1870 Machine Age

"A single establishment in this city—the Singer Sewing Machine Company—turns out five hundred sewing machines per diem. The works are run night and day."

Wired for Beauty

"The Allegheny Bridge at Pittsburgh: We believe we express a general opinion among engineers and architects when we say that the bridge which forms the subject of our engraving this week is one of the most elegant structures of its class on this continent. Nothing can exceed the grace of its outline when seen from a favorable point of view. This beautiful bridge was designed and erected in 1860, by the late John A. Roebling."

The Sixth Street Bridge was demolished in 1892 to make way for a more robust structure capable of withstanding modern traffic.

SCIENTIFIC AMERICAN, VOL. XXII, NO. 25; JUNE 18, 1870 (1); *SCIENTIFIC AMERICAN*, VOL. CXXIV, NO. 23; JUNE 4, 1921 (2)

2

EPIC TALES

CELEBRATING 175 YEARS

Bridges: An "Index of Civilization"

The engineering skill to build bridges across natural barriers speaks volumes about humanity's capacity to facilitate future travel needs. Neolithic wood walkways above marshes in England date back some 6,000 years. Wood gave way to stone, then iron. The availability of cheap steel from the Bessemer process in the late 19th century opened up a new era of bridge building: graceful steel forms spanned greater and greater distances. In November 1921 an article noted that bridges mark "the progress of mankind in the art of construction, considered as an index of its civilization and culture." Today the longest bridge—over canals, rice paddies and lakes—is 102 miles long and carries the Beijing-Shanghai high-speed rail link. —*D.S.*

1921: Overly expensive design for the future George Washington Bridge spanning the Hudson in New York City.

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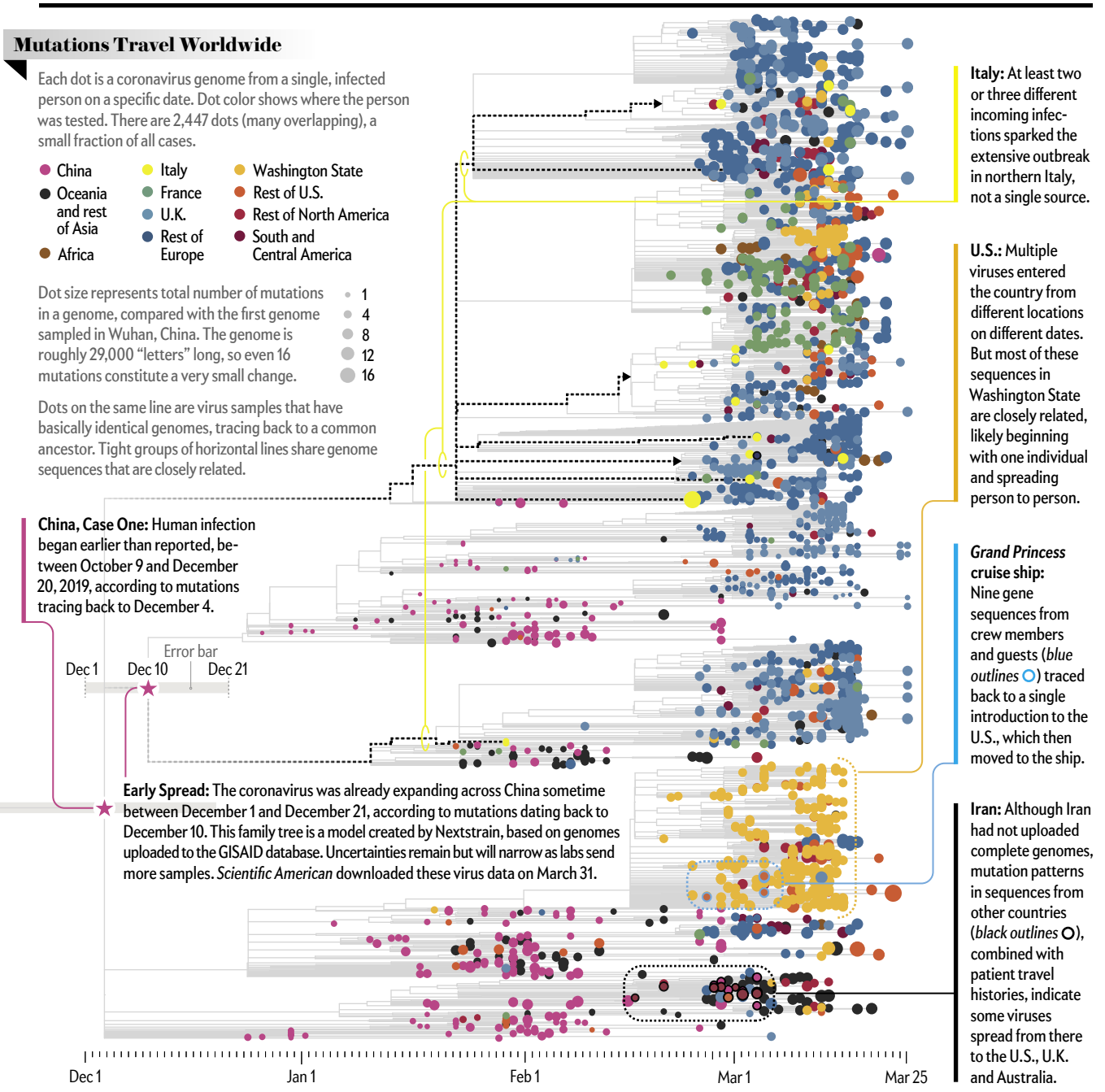
Text by Mark Fischetti | Graphic by Martin Krzywinski



How COVID-19 Spread Like Wildfire

Virus mutations reveal the story

The world struggled to understand how COVID-19 spread during the pandemic's first four months, but genetic sequences of the coronavirus reported by laboratories tell the real story—when the virus arrived in each place and where it came from. The sequences, which advance from left to right in the graphic, show that the virus jumped from an animal to humans in China, humans transmitted it to one another within China, then people traveling from there spread it globally person to person. The virus had not mutated significantly as of March 31, 2020; human contact created the pandemic, not a wildly evolving pathogen. Mapping the spread also substantiates actions that could have best mitigated it: faster, wider testing in China; earlier, stricter global travel bans and isolation of infected people; and more immediate social distancing worldwide.

SOURCE: NEXTSTRAIN (ENABLED BY DATA FROM GISAID) HTTPS://NEXTSTRAIN.ORG/NCOV

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