DECEMBER 2022

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Moral Injury

Opioids and Inequality

Rethinking Autism Therapy

A New Era for Astronomy

How the James Webb Space Telescope is transforming our view of the universe

DECEMBER 2022

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ON THE COVER

The James Webb Space Telescope's first cache of cosmic images proves it is everything astronomers hoped it would be. The observatory's stunning pictures of nebulae, distant galaxies and planets are wowing scientists, and its early data promise to help solve several astronomical mysteries.
Image by NASA, ESA, CSA, STScI and Webb ERO Production Team.

Photograph by Gioncarlo Valentine

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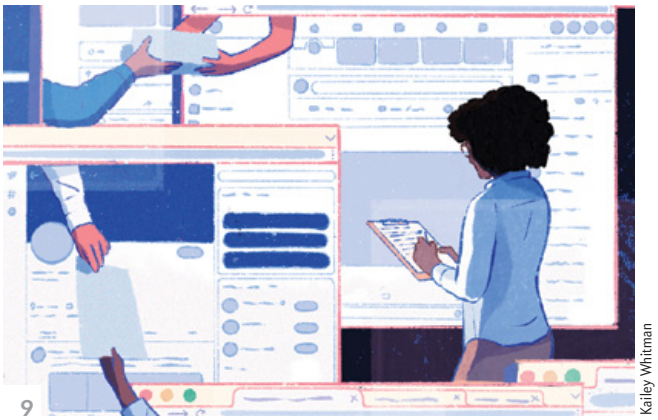

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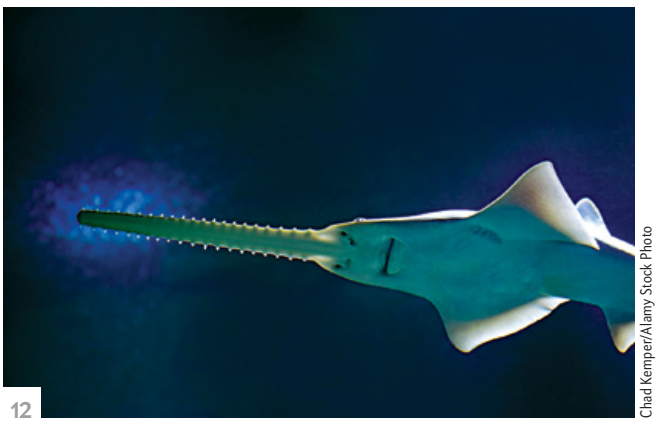

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Cosmic View

Aren't the first images from the James Webb Space Telescope absolutely stunning? We were thrilled and hopeful when JWST finally launched last Christmas Day after decades of delays, and the first images and data from the telescope are even more fascinating than astronomers anticipated. In our special report, introduced on page 26, journalist Jonathan O'Callaghan shows how these images of the most distant galaxies ever seen are already changing cosmologists' understanding of the universe's early history (*page 28*). Astrophysicist Fabio Pacucci shares the excitement of discovering galaxies in "empty" space on page 39. For the best explanation you'll see of how JWST works, turn to the graphics on page 42 from our space and physics editor Clara Moskowitz and graphics editor Jen Christiansen. The package ends with a gorgeous gallery of JWST images (*page 46*), with text from Clara, who produced the collection. We hope this is just the beginning of JWST's ability to help us explore the universe.

Moral injury is newly being recognized as a serious and widespread type of psychological trauma. It starts when people are forced to do something that violates their moral code, such as when a hospital has more patients than it can treat and doctors and nurses have to triage health care. Psychiatrists are finding evidence of moral injury in teachers, lawyers, people who served in the military, and more. They suspect many cases are unrecognized because people aren't familiar with the concept. As science writer Elizabeth Svoboda explains on page 52, understanding this type of trauma can be the first step to healing.

Opioid addiction in the U.S. is a growing problem, and the death rate from drug overdoses continues its horrifying rise. Addiction is also a fixable problem, but people with addiction disorders—in particular Black people—aren't getting the evidence-based treatments that can save their health and lives. On page 60, Melba Newsome, a health, science and environmental writer, and photographer Gioncarlo Valentine depict doctors, scientists and advocates working to improve health care and social support for people with opioid use disorder.

With this issue, we're celebrating copy director Christi Keller's 40th anniversary with *Scientific American*. Christi runs the department that copyedits and fact-checks everything we publish, keeps our schedules and deadlines, handles corrections, manages our relationships with our printers, and makes sure every page is of the highest quality. She helped us transition from a purely print magazine to a print-plus-digital publication, and she and her diligent team helped us pivot smoothly from in-office to remote work during the pandemic. When I started my job as editor in chief, I asked my predecessor, Mariette DiChristina, whether there's someone on staff who is the social core, who knows how everyone else is doing, and she immediately said, "It's Christi."

As part of our virtual celebration of Christi's tenure, creative director Mike Mrak showed a mocked-up cover of *Scientific American* with Christi's picture and witty headlines, many of which were misspelled or grammatically incorrect. Christi would like everyone to know that she is grateful for their faith in her to carry on at her "home away from home."

When you subscribe to the magazine in print or online, give a gift subscription, or read or share our work, you help support a wise, kind, enthusiastic and incredibly dedicated staff. Thank you for being part of our *Scientific American* family.

Illustration by Nick Higgins

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August 2022

OCEAN GLOW

I read Michelle Nijhuis's article "The Mystery of Milky Seas" with great interest. I was in the U.S. Navy in 1975, and my ship was doing a cruise in the Indian Ocean early that year. We encountered the kind of bioluminescence Nijhuis describes, which was truly amazing. The experience was not just limited to watching the ocean: We had a lot of fun with this phenomenon by filling buckets of seawater with our fire mains and then spilling them across the deck. The action of spilling the seawater caused additional bioluminescence. Also, watching the ship's wake was especially thrilling. I didn't realize the milky seas phenomenon had not been studied in "depth" (bad pun?) very much until recently.

PHIL DAWSON *Everett, Wash.*

CRITICAL CLIMATE SCIENCE

"Wishful Thinking in Climate Science," by Naomi Oreskes [Observatory], provides a crucial message that hardly gets mentioned. Between "conservative" (best-case) estimates of warming and sea-level rise, which *systematically* underestimate impacts, promises of future magic technology and promotion of the "every little bit helps" attitude promising that many tiny personal actions will save us, the message generally being promoted about climate change is that everything will be fine. Everything will not be fine.

ERIC J. WARD *West Palm Beach, Fla.*

"The message generally being promoted about climate change is that everything will be fine. Everything will not be fine."

ERIC J. WARD *WEST PALM BEACH, FLA.*

Oreskes declares that the technology to capture and sequester carbon dioxide doesn't exist. She dismisses the Orca project in Iceland because of its high unit cost and criticizes other projects that use CO_2 for enhanced oil recovery, speculating that the CO_2 "may migrate … to the atmosphere."

There are several active carbon capture and storage (CCS) projects outside the U.S., notably in Norway and Canada, that demonstrate the science does exist. Some have been operating for years and at scale: The North Sea–based Sleipner project has been sequestering about a million metric tons a year for about 25 years, and the more recent Quest project in Alberta has sequestered about the same amount annually. Of course, as with most technologies, the science is not settled. It is evolving and will continue to do so.

That Oreskes, a science historian, chose to ignore the data is ironic, given that "Florence Nightingale's Data Revolution," by RJ Andrews, in the same issue, describes how Nightingale made the compelling case for looking at such information more than 165 years ago.

ROBERT SKINNER *Energy research adviser, Office of the Vice-President (Research), University of Calgary, Alberta*

In "Climate Damage from Science" [Observatory; July], Oreskes argues that several scientific areas have a large carbon footprint, including large observatories, space-based telescopes and conferences. These just don't pass the commonsense test. To the casual observer, an observatory is just a big office building with a dome on the roof. Both have lots of computers and servers, and both have people working during either the day or night. The telescope's workings are probably low users of power. And how a space-based telescope could contribute to a carbon footprint on Earth is puzzling. I also have trouble understanding how moving a particular conference from San Francisco to the middle of the country would save travel, as Oreskes describes. Instead of 50 percent of the attendees traveling across the U.S. to a West Coast conference, for example, 100 percent would travel halfway across it, resulting in the same total travel.

My point isn't to question these rather dramatic claims as much as to wonder why Oreskes didn't report the explanations for them. It would be nice to know how this carbon pollution happens and how it fits into overall emissions. How else can a scientist evaluate the relative costs and benefits of their work?

RICHARD COCHRANE *Clarks Summit, Pa.*

ORESKES REPLIES: Skinner is correct that the science of CCS exists. CO_2 can be pumped into and stored underground. My topic, however, was not the science but the technology. *Nearly all the world's CCS projects are actually adjuncts to fossil-fuel production. Most so-called carbon storage projects are enhanced oil recovery projects. They pump carbon dioxide into working oil and gas fields to flush out fossil fuels that would otherwise be stuck underground, lengthening the life of the fields. The efforts he notes are a little different but not much: The Sleipner project is part of a natural gas field. It captures CO_2 that would otherwise contaminate the gas. The cleaned-up gas is then sold and burned. The Quest project is part of the Athabasca Oil Sands Project in Alberta, one of the most environmentally and socially destructive fossil-fuel projects on Earth. Quest captures CO_2 produced during the conversion of bitumen into usable crude oil. That oil is also sold to be burned, thus exacerbating the climate crisis.*

Storing these bits of CO_2 is better than releasing them to the atmosphere, but the amounts involved are tiny, compared with the releases associated with fossil-fuel combustion: globally, more than 36 billion metric tons in 2021 alone. And it's not clear

that these projects are even a net gain. One report found that Quest produced more carbon than it stored. Its operator Shell has acknowledged that Quest was designed as a "demonstration project." If we had time to wait, these projects might one day pay off. But time has run out. At best, CCS is a costly distraction. At worst, it locks in more fossil-fuel investment and infrastructure at the very moment when we need to be phasing them out.

To answer Cochrane's questions: Astronomical observatories and space-based telescopes use astronomical amounts of energy. They are energy-intensive to design, build and launch and require enormous amounts of computational power. And unlike ordinary office buildings, astronomical facilities often run around the clock.

As for conference travel, the one under discussion was the annual meeting of the American Geophysical Union. Many of its participants come from Europe, so moving it from San Francisco to Chicago (where the conference is being held this year) means more people will travel less, considerably reducing the overall carbon footprint. Of course, making the meeting mostly or entirely virtual would reduce it far more.

ERRATA

"Quick Hits," by Joanna Thompson [Advances], incorrectly said that the supernova that may have forged a space rock found in Egypt in 1996 most likely occurred some 4.6 billion years ago at the outskirts of our solar system. Rather the theory is that the supernova occurred within a giant dust cloud and eventually led to the dust solidifying on the outskirts of our solar system in the early stages of its formation, which began about 4.6 billion years ago.

"The Mystery of Milky Seas," by Michelle Nijhuis, should have described Pierre Aronnax as a marine biologist in Jules Verne's 1870 novel *Twenty Thousand Leagues Under the Sea*.

In "Every Inch of the Seafloor," by Mark Fischetti, the illustrations should have been credited to Maciej Frolow.

"3,117,275,501 Bases, 0 Gaps," by Clara Moskowitz and Martin Krzywinski [Graphic Science], should have said that in 2022 scientists added 251,330,203 bases for a totally gapless genomic sequence.

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INSPIRING APPROACHES TO CANCER CARE

Redefining cancer care takes a community. Winners of the 2022 Cancer Community Awards are finding ways for communities to get access to the best care available.

This past year has been groundbreaking in cancer care. Continued advancements in areas like precision medicine are providing renewed hope for people with cancer. At the same time, those working in oncology continue to recognize the enormous role that community partnerships play in providing education and equitable access for all who need it most. "Building trust at the community level is crucial to strengthening care in an equitable way and improving outcomes for all people with cancer," says Chatrick Paul, Senior Vice President and Head of US Oncology Business at AstraZeneca.

Though much progress in this direction has been made in the past three decades, many underserved patient groups and rural communities still face a persistent lack of access to cancer education, screening and quality treatment.

The Cancer Community Awards (or C2 Awards)—presented by AstraZeneca's YOUR Cancer Program and Scientific American Custom Media—honor people and organizations working to improve and expand cancer care on many levels, from impacting how someone feels after diagnosis to enhancing the ability to provide the right treatment for the right person at the right time. "The C2 Awards are an integral part of our YOUR Cancer program, which is consistent with our mission of eliminating cancer mortality for all people and working alongside the community to champion unsung heroes and stories that produce meaningful change," Paul says. "By elevating diverse heroes and the work they do, we hope to inspire new ways of delivering care to those in need."

CHATRICK PAUL
SENIOR VICE PRESIDENT AND HEAD OF US ONCOLOGY BUSINESS AT ASTRAZENECA

To encourage others to take that first step, we asked the winners of the 2022 Cancer Community Awards what inspired them, what makes them hopeful about the future of cancer care, and what could advance care for all people. Here's what they said.

2022 CATALYST FOR PRECISION MEDICINE WINNER
MARC R. MATRANA, MD
DIRECTOR OF PRECISION MEDICINE AND ENDOWED PROFESSOR OCHSNER HEALTH

What about cancer care today makes you most hopeful for the future?

As someone involved in cancer research, I'm always amazed at the number of new drugs, new breakthroughs and new ideas that are coming out each and every day. When I think about the things that could have the biggest impact for those who suffer from cancer, I think about the inequalities that we have for accessing new technologies and treatments. The biggest impact across the board would be if all patients had equal access to the new therapies, experimental treatments, and clinical trials. We tell our patients when they go on clinical trials that they're receiving the medicines of tomorrow, today. All patients should have that access.

2022 CATALYST FOR CHANGE WINNER
CHARLES R. ROGERS, PHD
ASSOCIATE PROFESSOR MEDICAL COLLEGE OF WISCONSIN

In your work, if you could point to one thing that would advance cancer care for all who need it, what would it be?

If we have funding that can allow more colonoscopies for people who are uninsured, under age 45, or who simply do not have the funds to get a colonoscopy, that's a life-saving game changer. If we provide more funding for research on topics that are debatable and understudied, that's another game changer. If we provide more funding for resources to prevent barriers to early detection screening, that, too, is a game changer, for example, providing a weekend colorectal cancer screening option for people who have to work during the week or providing a van service for people who may not have reliable transportation to get to the doctor to get screened.

2022 CATALYST FOR CARE WINNER
SPARROW'S NEST OF THE HUDSON VALLEY
Represented by **KRISTA JONES**, *FOUNDER AND EXECUTIVE DIRECTOR*

What inspired you to create an organization that provides food to cancer patients in New York's Hudson Valley?

I have witnessed firsthand what a cancer diagnosis looks like, and it is an emotional battle. To think of people doing that alone is heartbreaking to me. I wanted to figure out how I could ease some of that burden. Back in 2012, my grandiose plan was that one day we would have farmland, grow our own vegetables, and have our own facility that housed the kitchen where we cook and deliver 300 homemade meals a week to families facing cancer. We have the ball rolling for our grand plan—a permanent home for the Nest in our community.

2022 CATALYST FOR EQUITY WINNER
CENTER FOR HEALTH OUTCOMES AND POPULATION EQUITY
Represented by
DAVID W. WETTER, PHD
DIRECTOR

What would make cancer care more available to everyone?

One of the things that has really changed in the past few years has been the powerful movement around health equity and the requirements that comprehensive cancer centers need to meet. It would benefit so many people if we could make progress on health inequity. We need to be able to provide preventive services to everybody, regardless of their ability to pay, and provide pathways to treatment if we find cancers. We do not have that right now, and we struggle with that constantly in our work. Healthcare should be a right, not a privilege.

2022 PRESIDENT'S AWARD WINNER
DOUGLAS FAIR, MD
ASSOCIATE PROFESSOR UNIVERSITY OF UTAH

Why does today's cancer care make you hopeful?

It is the people working in cancer care. So often, physicians get the spotlight, but everybody at a cancer hospital—nurses, administrators, our administrative staff, our technicians, the team that cleans the floors—are all pulling the weight. They are doing the best that they can, in their own way, to create an environment that is healing and supportive. Everyone is trying to tackle these issues. It's so inspiring to see people get passionate about an issue that's affecting patients and row the boat in the same direction, really dedicating time, effort, and resources to help fix problems.

The fourth annual C2 Awards included an esteemed panel of judges spanning health systems, research institutes, advocacy groups, and other organizations working to transform cancer care from one person's disease into a true community effort.

To learn more about this year's winners and the C2 Awards, please visit YourCancer.org.

AstraZeneca YOUR cancer THE Cancer Community AWARDS

Bringing Harmony to Earth

As 2022 winds down, we reflect on how successes in space affect our lives on Earth

By the Editors

The close of a calendar year is a chance to reflect on the relentless procession of time into the present and any new beginnings the future holds. Humans are enamored with the end of the year—not only for nostalgia's sake but also for the cognitive clarity it offers amid so much uncertainty.

As we look back, then, what was most significant about 2022? The COVID pandemic continues to plague the world. Its dizzying spectrum of destabilizing symptoms has helped fuel the resurgence of fascism everywhere, including the U.S. Meanwhile the specter of atomic annihilation stalks the globe again, via Russia's ruinous aggression against Ukraine, which is increasingly a not-so-proxy war with NATO. Staggered by these and other blows, the world's economy appears to be spiraling into yet another recession.

Against the dark background of such events, we may find some hope by gazing up into the heavens. In the long arc of time, when the dust settles on 2022, the most significant happenings on Earth may arise from events that were celestial in nature.

This year marked a bittersweet milestone in humanity's still nascent efforts to transcend the limits of our lonely, beleaguered world: the 50th anniversary of the last footsteps on the moon, made in 1972 by the late Apollo astronaut Eugene Cernan. That such feats were achieved so long ago is inspirational, but there is bleakness in the fact that 50 years on they remain unparalleled. In that span, however, the technologies required for such voyages have gradually spread across the globe, so that now crewed lunar exploration—perhaps even settlement—lies in reach of numerous nations and even private companies. These efforts dovetail with seemingly outdated dreams of establishing an enduring human presence on worlds beyond Earth. But, reimagined for the 21st century, being "multiplanetary" could become less about pursuing some dubious extraterrestrial Manifest Destiny and more about finding bold ways to reduce our crushing collective weight on the biosphere.

And 2022 brought us a new eye on the cosmos: the U.S.-led multinational James Webb Space Telescope (JWST). The project is in some respects the most ambitious and exacting technological construct ever built and, having persevered through more than two decades of development, now offers not only unexpected discoveries about our deepest cosmic origins and current galactic context but also further proof that we mere humans can come together to perform extraordinary, seemingly impossible tasks.

Perhaps most significant of all, however, was the successful Double Asteroid Redirection Test, or DART, a spacecraft sent by NASA to smash into and decisively shift the orbit of a small space rock, Dimorphos. Never before has humanity reached out to so deliberately strike such a lasting chord in the music of the spheres. Dimorphos's altered trajectory will now resonate through the solar system's motions until the sun itself goes dim. Given sufficient forewarning (which thankfully could come from JWST and other telescopic sentinels), the technique could be used in the future to deflect planet-threatening impactors, fending off the gruesome fate that befell the dinosaurs some 66 million years ago. Although DART was an American mission, its potential benefits extend to all now living and even those yet to be born—and are thus eminently worth celebrating.

What's certain—and certainly significant—is that the very same rapid, rampant technological developments that have allowed such achievements also require resource consumption on a scale that is rendering our global civilization more fragile. But this does not mean, as shortsighted critics insist, that striving to send humans to live and work in space must be an escapist technofantasy abdicating our stewardship over Earth.

DART demonstrated that we possess the power to prevent one kind of natural apocalypse—a subtle hint that eventual further advances in our off-world capabilities might also help us prevent many possible others of our own making. Against long odds, the success of JWST showed us the power of institutional persistence and international collaboration in daring to attempt audacious things. And each new astronautical foray is a constant reminder of our common humanity, irrespective of other labels applied by virtue of race, gender, nationality or creed. At year's end, let us remember that our actions and aspirations in outer space define us just as much as anything we do right here on Earth. SA

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Illustration by Meredith Lynne Miotke

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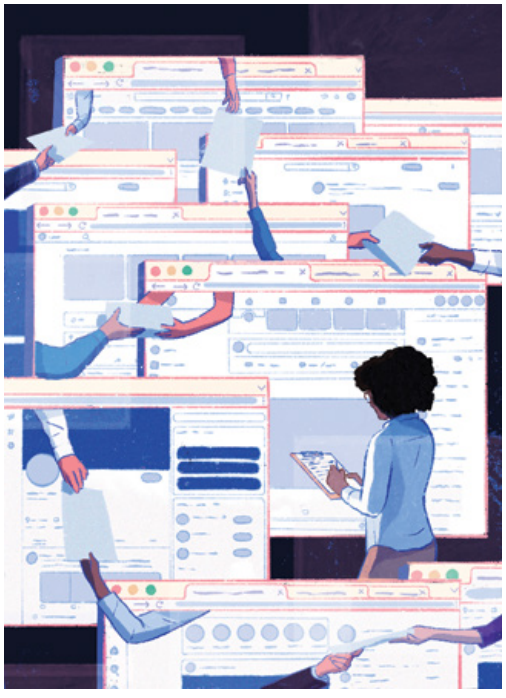
Social Media Companies Must Share Data

They could inform studies on misinformation

By Renée DiResta, Laura Edelson, Brendan Nyhan and Ethan Zuckerman

Billions of people around the globe use social media platforms to make sense of their world. Companies such as Meta, Twitter and TikTok control these forums but face little public oversight or accountability. Despite collecting vast amounts of data about every interaction that takes place on their pages, they share little information with researchers, preventing us from understanding the effects of social media on individuals and society. After two decades of minimal regulation and many significant crises, it is time to require more transparency from social media companies.

We are particularly concerned about the way social media has become a conduit for the spread of false and misleading information about every issue of concern to society, including the U.S. 2020 election, the January 6 Capitol insurrection, the COVID pandemic and the war in Ukraine. We don't know what the next crisis will be, but we do know that when it happens, false claims about it will circulate on these platforms.



Social media companies have conducted extensive internal research about misinformation and polarization on their platforms. Unfortunately, they are stingy about releasing data and publishing research, especially when the findings might be unwelcome (although notable exceptions exist). To enable public understanding of what is happening on the platforms, lawmakers and regulators must require social media companies to release data to independent researchers, especially data on the *structures* of social media—such as content-recommendation algorithms—so we can better analyze their effects.

For example, platforms have assured legislators that they are taking steps to counter misinformation and disinformation such as flagging content and conducting fact-checks. Are these efforts effective? Do they support societal values and users' privacy? Without independent evaluations, we run the risk of creating laws and regulations that do not adequately address harms or that inadvertently make problems worse.

The conversation around transparency and accountability has grown deeper and more substantive, but it still lacks important context. Lawmakers and regulators frequently ask us to better explain why we need access to data, what research it would enable, and how that research would help the public and inform regulation of social media platforms. We've created a list of questions we could answer if social media companies began to share more data, either within privacy-protecting environments or in an aggregated form that ensures users can't be identified.

Misinformation is often more engaging than other types of content. Why is this the case? What features of misinformation are most associated with heightened user attention and virality? A better understanding of why misinformation is so engaging could help platforms recommend misinformation less often.

The delivery-optimization techniques that companies use to maximize ad revenue can be biased in harmful and illegal ways. Are some user groups more likely than others to see potentially harmful ads, such as consumer scams? Are others less likely to see useful ads, such as job postings? How can ad networks be less discriminatory?

Social media companies attempt to combat misinformation by labeling content of questionable provenance. How do platforms decide what to label? Do these labels reduce the spread of misinformation or attract attention to posts that users might otherwise ignore? Do people start to ignore labels as they become more familiar?

Internal research at Twitter showed that its algorithms tend to amplify right-leaning politicians and political news sources more than left-leaning accounts. Are algorithms used by other social media platforms prone to systemic political bias as well?

Minority groups sometimes feel their views are silenced online as a consequence of platform-moderation decisions. Do choices about what content to allow affect some groups disproportionately? Are platforms allowing some users to block others through the misuse of moderation tools or through systemic harassment designed to silence certain viewpoints?

Some companies, such as Twitter and Reddit, have been open to cooperating with researchers, but we can't depend on the ongoing goodwill of a few. In our fast-changing information environment, we should not regulate and legislate by anecdote. Lawmakers must ensure our access to data we need to keep users safe. SA

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Illustration by Kailey Whitman


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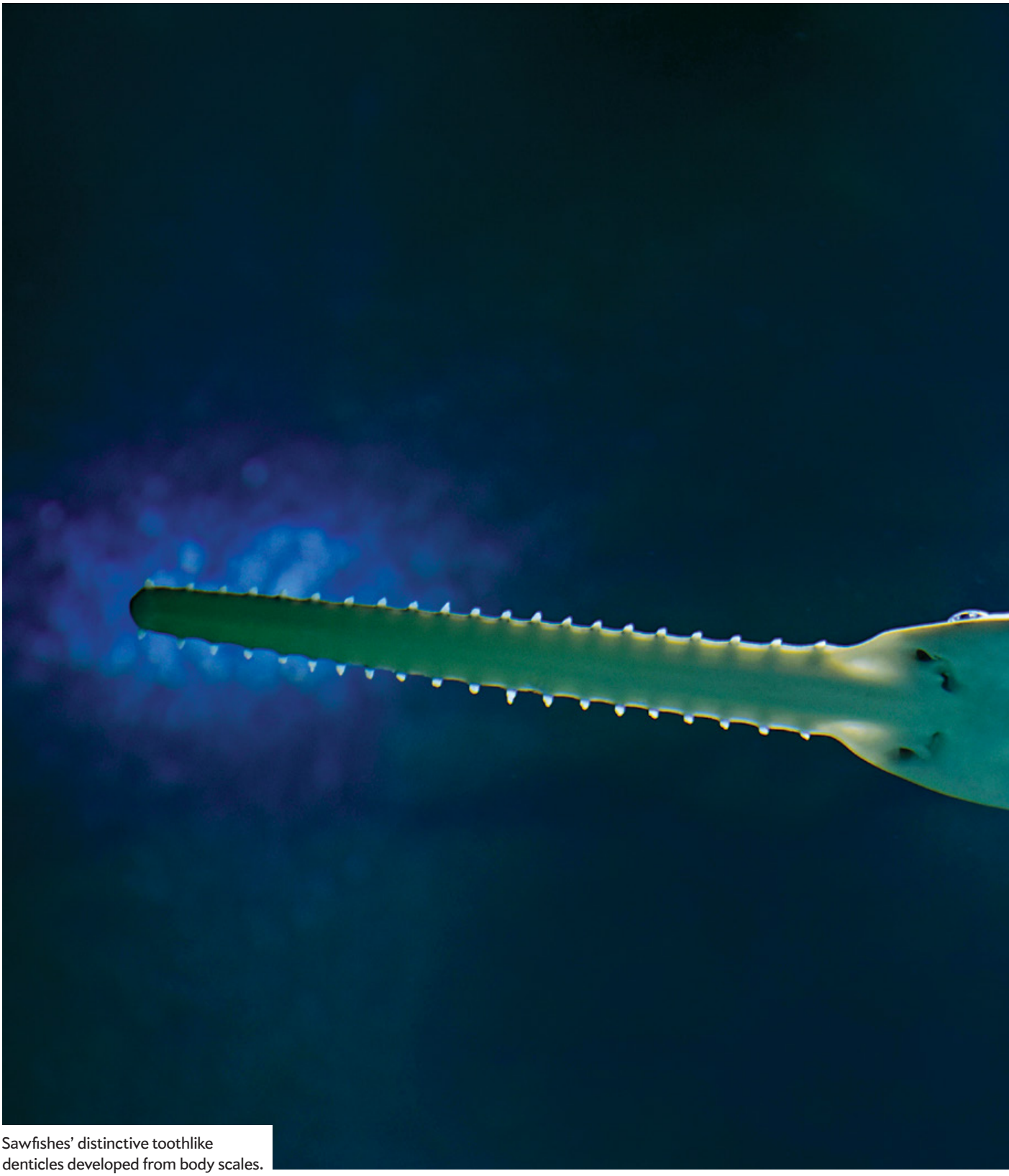


Sawfishes' distinctive toothlike denticles developed from body scales.

Chad Kemper/Alamy Stock Photo

INSIDE

EVOLUTION

Scaling Up

Sawfish fossils help to explain the ancient origins of teeth

You probably don't think of yourself as a scaly creature, but the hardened structures behind your lips may say otherwise. New analysis of one of the world's weirdest animals—the sawfish—supports the idea that teeth first appeared when ancient fishes' body scales migrated into their mouths about 400 million years ago.

Early teeth offered jawed fish a major evolutionary boost. "If you're feeding, unless you're sucking in really small plankton-type stuff, there are definitely advantages to being able to grab hold of objects in the mouth," says Per Ahlberg, a paleontologist at Uppsala University in Sweden, who was not involved in the new study. Biting was a big leap forward; chewing, Ahlberg notes, came later. And all toothed animals living now—from trout to humans to crocodiles—appear to have descended from a single group of jawed fish, says University of Chicago paleontologist Yara Haridy, who was also not involved in the research.

But scientists have conflicting ideas about the source of the earliest teeth. Hard, protective body scales, made of mineralized tissue such as dentine or enamel, could have migrated into the mouth—a hypothesis known as outside-in. Or teeth could have developed internally, from the same tissue as gills, a hypothesis known as inside-out. The new sawfish study, published in the *Journal of Anatomy*, offers fresh evidence in favor of an outside-in origin.

The study authors gathered fossils from the extinct sawfish species *Ischyrhiza mira*, which lived some 70 million years ago. They analyzed the fossils' rostral denticles, the spikes that jut from the sides of a sawfish's snout to aid in foraging and self-defense. Rostral denticles look like teeth, but they're actually specialized body scales.

Unlike previous studies of extinct and current sawfish, this one probed the internal structure of the scales' hard outer layer, called enameloid. "It's basically the primitive form of [tooth] enamel," Haridy says.

When the researchers scratched away the outer layers of these scales with sandpaper and acid and then

observed them under a scanning electron microscope, they were stunned by the level of complexity they found. The scientists had expected a homogeneous structure like that of many other body scales, says Pennsylvania State University paleontologist Todd Cook, lead author of the new study. But instead they saw distinct regions of microcrystals that resist mechanical stress. "In fact, the overall organization of the enameloid resembled that of modern shark teeth," Cook says.

Although rostral denticles didn't become teeth themselves—sawfish ancestors already had teeth—this discovery indicates that scales like the ones on a fish's bodily surface have the capacity to evolve a toothlike internal structure, and they could have done so at least once before. Cook says it is less likely that such a similar structure would have developed independently from the very different internal throat tissue.

"This finding is in support of outside-in," says Ann Huysseune, an evolutionary developmental biologist at Ghent University in Belgium, who was not involved in this study. "But I'm not surprised—it's one of many arguments in favor."

Ahlberg notes that an animal's scale-forming outer body tissue meets its internal tissue somewhere around the mouth. But the exact boundary between the two is difficult to determine in ancient fish—and this boundary's location is key to understanding which type of tissue first generated teeth. Fossils don't preserve most soft tissue, so researchers can only make inferences about such tissue's properties or examine present-day equivalents. For example, Huysseune studies the mouths of modern zebra fish to better understand tooth formation and origins.

To Ahlberg, it is clear that external tissue can produce complex, toothlike scales. The sawfish study is a vivid example of that mechanism in action. But can internal throat tissue, or mixed internal-external tissue close to the mouth, do the same? That's still uncertain, Ahlberg says.

Supporters of the inside-out hypothesis say the answer is yes. For a time, Haridy says, the group's main point of evidence was a set of eel-like creatures that had apparently developed mineralized toothlike structures in the throat and on the mouth—but nowhere else on the body. Several papers published in the 1990s and 2000s used these eels as a cornerstone of the inside-out idea, but later research suggested the structures were unique to the lineage and were unrelated to vertebrate teeth. For now scientists continue to hunt for modern analogues and fossilized examples of early prototeeth.

Pinning down the origins of teeth probably won't immediately improve our lives in any tangible ways, Ahlberg says—although he mentions a hypothetical far-future scenario in which humans learn how to continuously regrow teeth the way most nonmammals can. "But I think it's inherently interesting to understand how our body has come into being," he says. "It's this peculiar thing we inhabit, and it has evidence of a very long and strange history." —*Daniel Leonard*

NEUROSCIENCE

Food for Thought

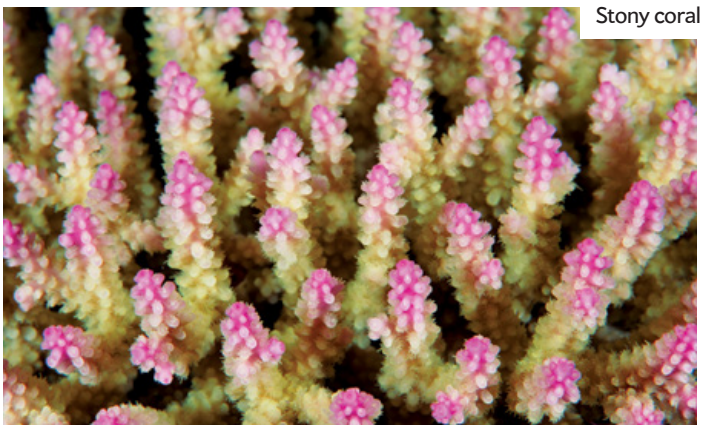
Weirdly efficient neurons power birds' powerful brains

Scientists once thought bigger brains made smarter animals. But birds fly in the face of that logic: with a brain smaller than a walnut, they can develop sophisticated tools and remember where they hid food. Now research published in *Current Biology* suggests birds can pull this off because their brain neurons use less energy than those of mammals, letting their bodies support a higher proportion of these cells.

A 2016 study showed that avian brains are denser than those of many other animals. For example, a macaw's 20-gram brain holds as many neurons as a squirrel monkey's 30-gram brain. But neurons drain energy; researchers have found that a human brain uses a fifth of the body's energy despite being only 2 percent of its mass, notes avian neuroscientist Kaya von Eugen of Ruhr University Bochum in Germany. She and others wondered how birds' small bodies and energy budgets—based on how much food they consume—can support so many neurons.

To find out, the researchers turned to the common pigeon. They injected glucoselike molecules marked with a radioactive chemical into the veins of 10 pigeons, then used a scanner to track the radioactivity as it moved through the birds' brains. By examining this movement and taking blood samples, the researchers determined how much glucose each gram of brain tissue consumed. Then, using neurons-per-gram data from the 2016 paper, they calculated how much glucose each neuron used every minute.

When compared against the neuronal energy budget of rodents, humans and other primates, a pigeon neuron used three times less energy than the average



Stony coral

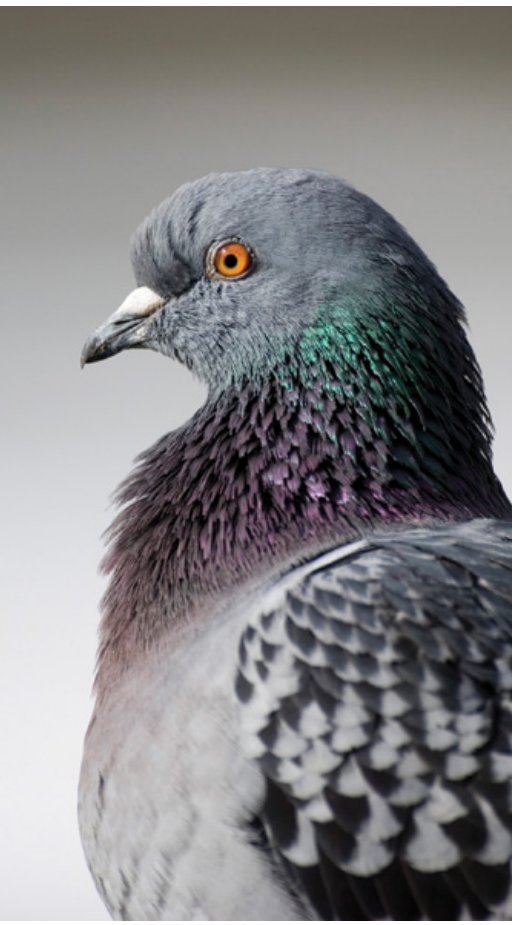
Gary Bell/Oceanwide/Minden Pictures

TECH

Coral Hygiene

Dental technology reveals baby corals in 3-D

A routine dentist's tool may soon help with more than just oral health. A new study has found that dental imaging scanners can double as portable devices to track the growth of baby corals—a crucial predictor of how reefs will fare amid climate change.



Education Images/Getty Images

mammal's neuron—a "really surprising" result, von Eugen says. Although avian neurons are likely smaller than a typical mammal's, she adds, the difference in energy use "is so big that this cannot be the only explanation." Perhaps, she suggests, avian brains are organized so that neurons can more easily exchange signals, or maybe birds' warmer body temperatures let neurons function faster. The authors speculate that complex cognitive needs such as song and flight could have pushed the evolution of more efficient brain cells.

The finding is "pretty remarkable," says Vanderbilt University neuroscientist Suzana Herculano-Houzel, who worked on the 2016 study but was not involved in the new research. Based on the density disparities between mammal and bird brains, she says, the energy difference is "exactly the math you'd expect." Birds may have evolved this trait simply to work with their limited energy supply, Herculano-Houzel adds, rather than to accommodate advanced processing needs.

Both Herculano-Houzel and von Eugen are curious about neuron energy use in other birds; von Eugen is particularly interested in chickens, crows, parrots and even birds' closest living relatives on the tree of life—crocodiles. *—Tess Joosse*

Heat stress can kill mature coral reefs and curtail their regrowth. "Growth, reproduction and survival are the main things that we're always looking at in terms of how healthy reefs are," says marine biologist Kate Quigley of the Australian Institute of Marine Science. By modeling baby corals in 3-D, researchers can track how well they branch, develop complex shapes and reach reproducing size. If harsh water conditions make corals grow too slowly, a reef won't recover.

Corals this small are difficult to model in 3-D; researchers can CT scan them, dip them in wax or laboriously stitch the measurements together from a commercial 3-D scanner—but these methods can be slow and provide lower-resolution views. So one day, as Quigley's dentist used a wandlike device that focused light to create a detailed 3-D tooth model, Quigley got an idea. If this device could measure her chompers' crevices in detail, she thought, it should be able to scan tiny living corals, too—both teeth and coral are calcium-based and wet.

For a study published in *Methods in Ecology and Evolution*, Quigley tested the scanning wand and found that it offered a cheap, easy and portable way to model baby corals significantly faster and at higher resolution than currently available techniques. This tool could let scientists more easily examine how coral species endure stress.

"Baby corals are critical for reef restoration and recovery from disturbances like hurricanes and thermal heat waves. Unfortunately, they are the stages we know least about because they are so difficult to measure accurately without great expense," says Hawai'i Institute of Marine Biology researcher Joshua Madin, who was not involved in the study. "This paper is a great example of taking a mature technology developed in another field and applying it to coral reef science."

—Susan Cosier

WEATHER

Ocean Air

Why lightning strikes less often at sea

Although most rain on Earth falls over the oceans, lightning at sea is surprisingly rare—and for decades scientists weren't sure why. A recent study suggests salt spray could be getting in the way of clouds charging up for a lightning strike.

Thick clouds that form overhead during storms can become electrified when upward-moving air helps them grow tall enough that the upper parts of the cloud freeze into a mixture of granular, rounded snow pellets called graupel and microscopic ice crystals. As these ice and snow particles bump into one another, they transfer electrical charges: the larger graupel grains tend to become negatively charged, and the smaller ice crystals end up with a positive charge.

These charged ice crystals are so light that updrafts of air bring them to the top of the cloud, whereas heavier graupel tend to sink. Over time this separation generates an electrical field between the cloud's positively charged top and negatively charged bottom. When the charge difference either between the top and bottom of the cloud or between the cloud and the ground grows big enough, lightning strikes.

But if large, water-absorbent particles of sea salt—abundant in ocean spray—are present, the tiny droplets that typically condense on microscopic dust and soot to form clouds grow much more rapidly, becoming heavy enough to fall as rain well before the cloud can grow tall enough to charge up. Although this mechanism for dampening lightning at sea has been suggested before, evidence for it had not yet been found in global weather observations.

To do that, researchers from China, Israel and the U.S. gathered global measurements of clouds and lightning strikes, plus the expected distributions of particles such as pollutants, dust and salt in the atmosphere. They used these records to examine how cloud systems with different combinations of the particles evolved over time—documenting when and if rainfall and lightning occurred. The team found that areas with salt spray see up to 90 percent less lightning.

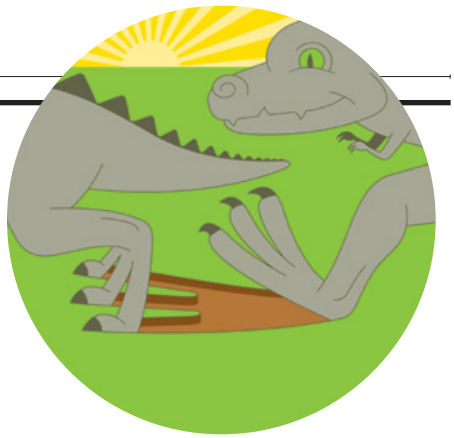
"We were able to separate the effects of the small particles and the large [sea-spray] particles," says atmospheric scientist Daniel Rosenfeld of the Hebrew University of Jerusalem, who co-authored the study in *Nature Communications*. These effects are often ignored when climate scientists try to predict when and where rain will fall, he adds. "If you don't take [them] into account in weather prediction models—and even more so in climate prediction models—you don't get the picture right, you don't get the precipitation right," Rosenfeld says.

But the fine particles, called aerosols, are not the only factor acting on clouds' complex interior. Other atmospheric differences over land and the oceans caused by local weather conditions, such as wind and temperature, might also play a role in how often lightning occurs. "It is very challenging to single out the aerosol effect from [these other weather conditions] based on observational analysis only," says Jiwen Fan, an Earth scientist studying interactions among aerosols, clouds, precipitation and climate at Pacific Northwest National Laboratory.

Fan, who was not part of the new study, suggests detailed computer modeling of the processes within thick storm clouds would help further clarify the importance of sea-salt spray in determining when and where lightning strikes might occur. —*Sasha Warren*

Lightning is rare over the ocean.

NurPhoto/Getty Images



PALEONTOLOGY

Dino Buddies

Tiny tyrannosaurs traveled together

Paleontologists know little about what giant, bone-crushing tyrannosaurs were like as babies. Hatchling fossils are rare and provide few hints about these foot-high carnivores' behavior. But now miniature trackways, found in rock roughly 72 million years old, offer evidence that baby tyrannosaurs traveled in pairs.

Paleontologists first found the trackways during a riverbank survey of southwestern Alberta's St. Mary River Formation. The site is rife with tracks made by many dinosaur species—"a busy time at the beach," as Royal Tyrrell Museum of Palaeontology researcher Donald Henderson and his colleagues describe it in the *Canadian Journal of Earth Sciences*. Among the fossil footprints are seven miniature dinosaur trackways suggestive of individuals moving in pairs. "The form of the small tracks, as well as the pace lengths, is a good match to what could be produced by hatchling [tyrannosaurs] *Albertosaurus* or *Gorgosaurus*," Henderson says, noting that the tracks' pointed claw tips suggest a predator.

Existing knowledge about tyrannosaur behavior comes mostly from fossilized bitten bones and a few scarce tracks. Injured skulls show that tyrannosaurs fought by biting one another on the face, and trackways found in British Columbia indicate that adults sometimes socialized together. "Tyrannosaurs weren't just chompy, killing macho machines," says fossil track expert Lisa Buckley, who was not involved in the new study. The newfound tracks hint that hatchlings formed groups after leaving the nest, similar to some herbivorous dinosaurs—as well as living crocodiles and large ground birds.

Buckley says it's possible the tracks came from a different carnivore type, but either way the discovery adds to what is known of dinosaur lives. "No matter which theropod group was responsible," she says, "the footprints in this paper are fascinating because they show evidence of group behavior." —*Riley Black*

Illustration by Thomas Fuchs

COMPUTER GRAPHICS

Contour Math Revealed

A new solution to an old problem in the geometry of illustration

Nearly 60 years ago computer scientist Ruth Weiss of Bell Labs published a pioneering algorithm to turn three-dimensional objects into two-dimensional drawings from any angle. But she ran into a problem with depicting outlines—an issue that has remained a computational geometry riddle for decades. With the ubiquity of computer animation today, this "hidden line problem" is now even more pressing.

The trickiest part of rendering a 3-D model in 2-D, a crucial step in computer animation, is the deceptively simple matter of the contour: the 2-D visual outline of the 3-D object. In a perfect world, a contour could be delineated with infinite precision—but the real world demands finite values. So modern algorithms start by covering the entire 3-D model with a mesh of tiny triangular "tiles," then determining whether each tile would be facing a viewer or facing away. Next, algorithms use these tiles to build line segments that serve as the contour. But the results can create faulty, flickering lines when used in a stylized animation—and researchers were unsure why.

It has proved impossible to generate a triangle mesh fine enough to avoid every error of this kind. As Meta Reality Labs researcher Stéphane Grabli, an Oscar nominee for visual effects, explains, "The feeling was that with enough subdivision, it should be possible to create a mesh that allows exact visibility computation for these contours. This turned out to be wrong." The resulting errors limit the complexity of nonphotorealistic illustration styles, Grabli adds.

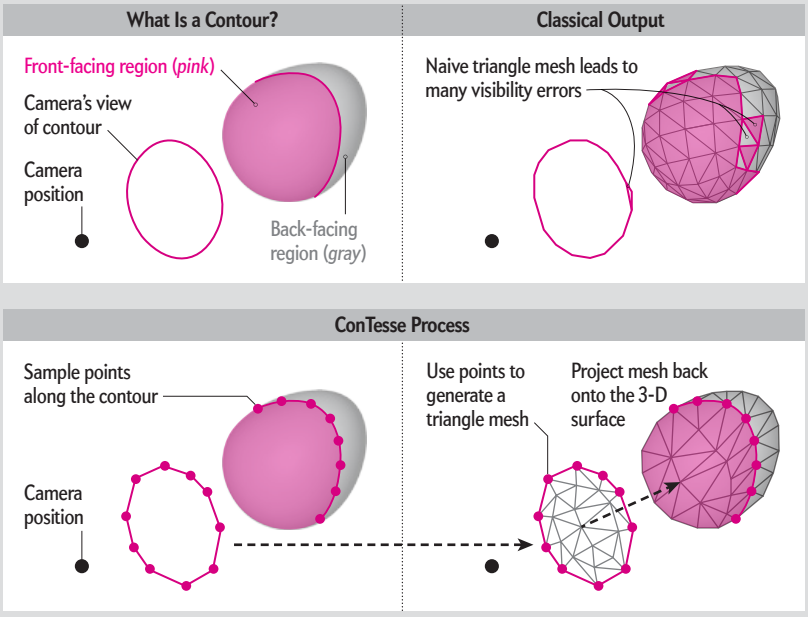
Now, in *ACM Transactions on Graphics*, University of British Columbia computer scientist Chenxi Liu and her colleagues propose an algorithmic solution, called ConTesse, that focuses on fixing the contour rather than the mesh. Zooming in by a factor of 1,600 on algorithm-generated contours, Liu identified small twists where the contour lines incorrectly crossed one another—and thus the tiles could not be consistently identified as facing toward or away from the viewer. "I experimented with many surfaces and saw that the algorithm failed on most of them," she says.

The researchers' new algorithm first traces a 3-D shape's edges with line segments, then squashes this approximate contour down to 2-D and tries to tile its interior with triangles. Wherever that interior mesh mistakenly crosses over itself, the algorithm modifies that part of the contour, such as by untwisting it or adding finer line segments. The algorithm then regenerates the mesh using the repaired contour and projects it all back onto the 3-D object for a final visibility check.

The team's innovation was to realize that the problem was with the contour itself. Previously it was unclear that such invalid contours were even possible, so fixes treated the flickering symptoms rather than the cause, Liu says. Grabli, who was not involved in the new research, concurs: "The paper proves why early solutions couldn't work." —*Lyndie Chiou*

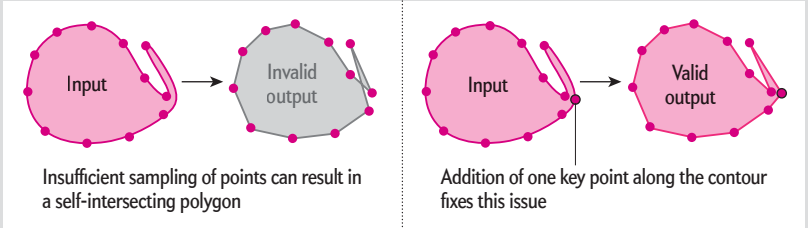
How ConTesse's Contour Generation Works

In the classical version of this process, a program first generates a triangle mesh and tiles it onto the surface of a 3-D object. But this makes the contour, or "edge" as perceived by the camera, difficult to define. ConTesse instead first approximates a contour and uses that to generate a mesh, avoiding the typical errors of other algorithms.



Avoiding Invalid Curves

Contour generation can become tricky when the 3-D object includes skinny or tightly curved elements. In those cases, ConTesse might add extra points or uncross the contour to avoid incorrect twists in the topology.



Source: "ConTesse: Accurate Occluding Contours for Subdivision Surfaces," by Chenxi Liu et al., in *ACM Transactions on Graphics*; June 2022

Graphic by Aaron Hertzmann and Pierre Bénard (restyled by Amanda Montañez)

MACHINE LEARNING

Transformer Squad

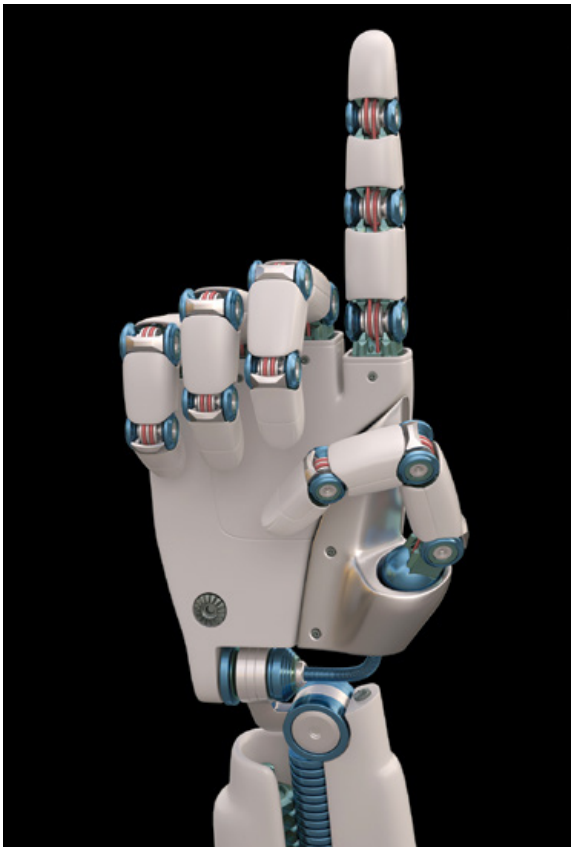
Teaching a new robot old tricks

Robots of all shapes and sizes increasingly populate workplaces, from factories to operating rooms. Many of the bots rely on attaining new skills by trial and error through machine learning. A new method helps such skills transfer between differently shaped robots, avoiding the need to learn tasks from scratch each time. "Practically, it's important," says Xingyu Liu, a computer scientist at Carnegie Mellon University and lead author of the research, presented this past summer at the International Conference on Machine Learning. "And research-wise, I think it's a cool fundamental problem to study."

Let's say you have a robot arm with a humanlike hand. You've trained its five fingers to pick up a hammer and whack a peg into a board. Now you want a two-fingered gripper to do the same job. The scientists created a kind of bridge of simulated robots between the two that slowly shifts in shape from the original form to the new one. Each intermediate robot practices the designated task, tweaking an artificial neural network until it reaches a threshold success rate, before the controller code is passed on to the next robot in the chain.

To transition between virtual source and target robots, the team created a shared "kinematic tree"—a set of nodes representing limb parts connected by links representing joints. To transfer hammer-whacking skills to the two-fingered gripper, the team adjusted the sizes and weights of the nodes for three of the fingers to zero. In each intermediate robot, the finger sizes and weights got a little smaller, and the network controlling them had to learn to adjust. The researchers also tweaked their training method so the leaps between robots weren't too big or too small.

The Carnegie Mellon system, called REvolveR (for Robot-Evolve-Robot), outperformed baseline training methods such as teaching the target robot from scratch. To reach a 90 percent success rate with the gripper, on the hammer task and in other experiments involving moving a ball and opening a door, the best alternative training method required from 29 to 108 percent more trials than REvolveR did, even though the alternative method used more informative training feedback. In further experiments, the researchers tested their process on other types of virtual robots, such as adding new leg sections to a spiderlike bot and having it relearn how to crawl.



KTSDESIGN/Science Source

"I think the idea is nice," says University of Oxford computer scientist Vitaly Kurin, who studies robotics and machine learning and was not involved in the work. Although arranging challenges so an AI can transfer skills between tasks is not new, he says, "this interpolation from one robot to another one for transfer is something I haven't thought of before."

—Matthew Hutson

OCEAN EXPLORATION

Science in Images

By Andrea Gawrylewski

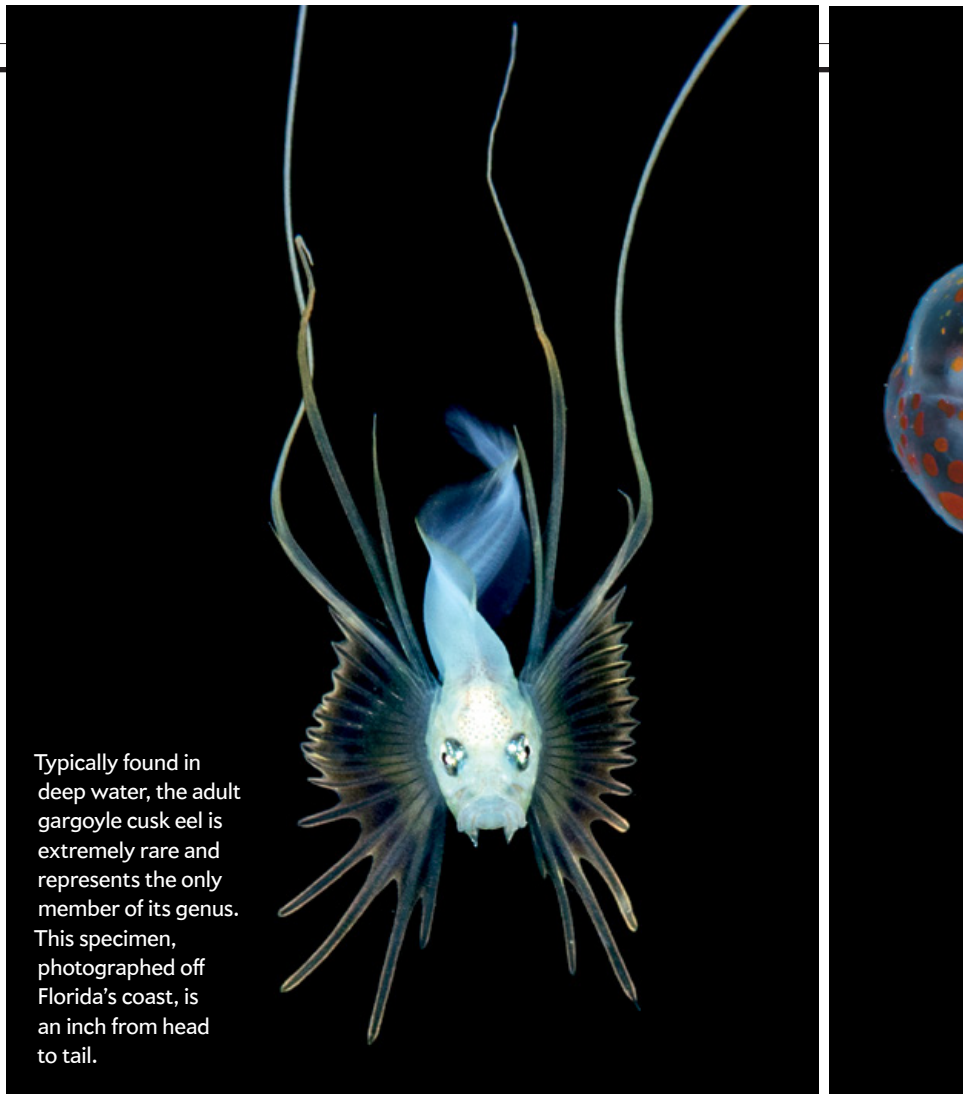
Every night at sundown, a great mass of mostly small sea creatures rises from the depths into the topmost layers of the planet's oceans. An estimated 11 billion tons of animal biomass migrate thousands of feet upward each night—and then, before the sun rises, return to the dimly lit "twilight zone" below. The animals make this journey to feed on organic material closer to the water's surface, traveling at night to avoid the larger predators swimming there.

The nighttime migration was first discovered in the 1940s, when U.S. Navy sonar technology began pinging off masses of objects in the water column. Since then, adventurous researchers, hobbyists and photographers have been diving at night to observe these creatures.

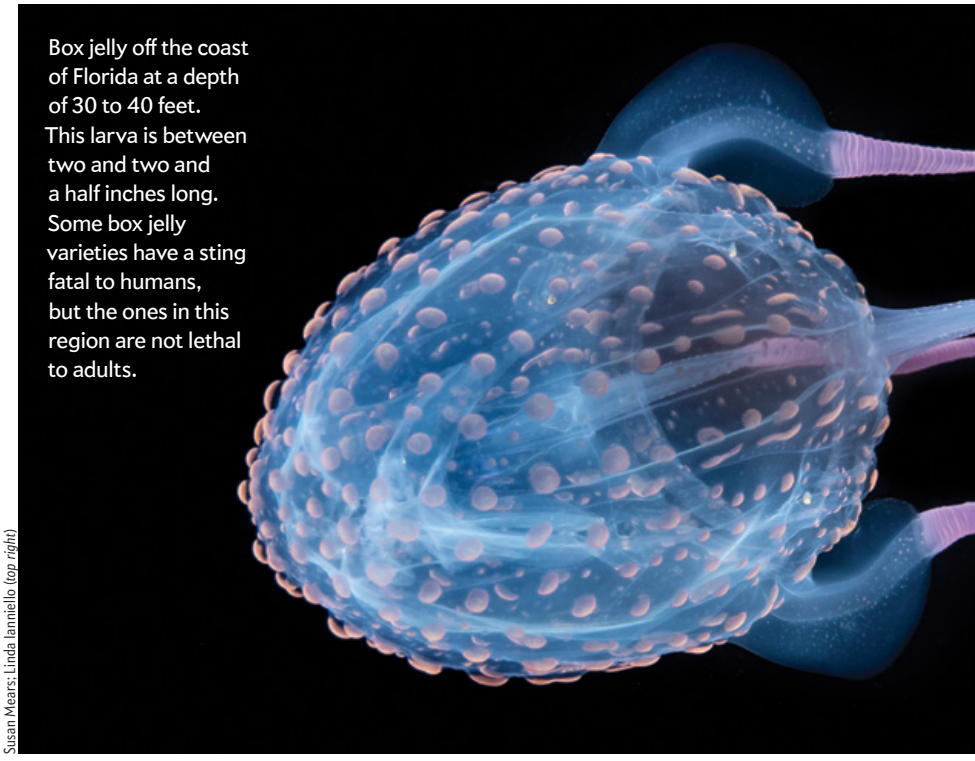
Blackwater scuba divers descend as deep as 60 feet, tethered to their boats by a rope. A light (handheld or attached to a camera, for example) illuminates the dark water around the divers in small patches, helping them spot and photograph tiny animals. Some are no bigger than a pea; most are transparent and fast-moving.

Hoping to identify some of the creatures they've encountered, divers Linda Ianniello and Susan Mears, along with Susan's husband, Jim Mears, began posting pictures of their finds to a blackwater diving Facebook group. Soon scientists at the Smithsonian Institution and the Florida Museum of Natural History started helping identify specimens, many of which had never been seen in their natural environment and unmangled by fishing nets. The researchers and amateur photographers quickly developed a useful information exchange. Several photographed specimens have yet to be fully identified at the species level, but the images still help to document a crucial yet little understood part of the ocean ecosystem.

To see more, visit ScientificAmerican.com/science-in-images

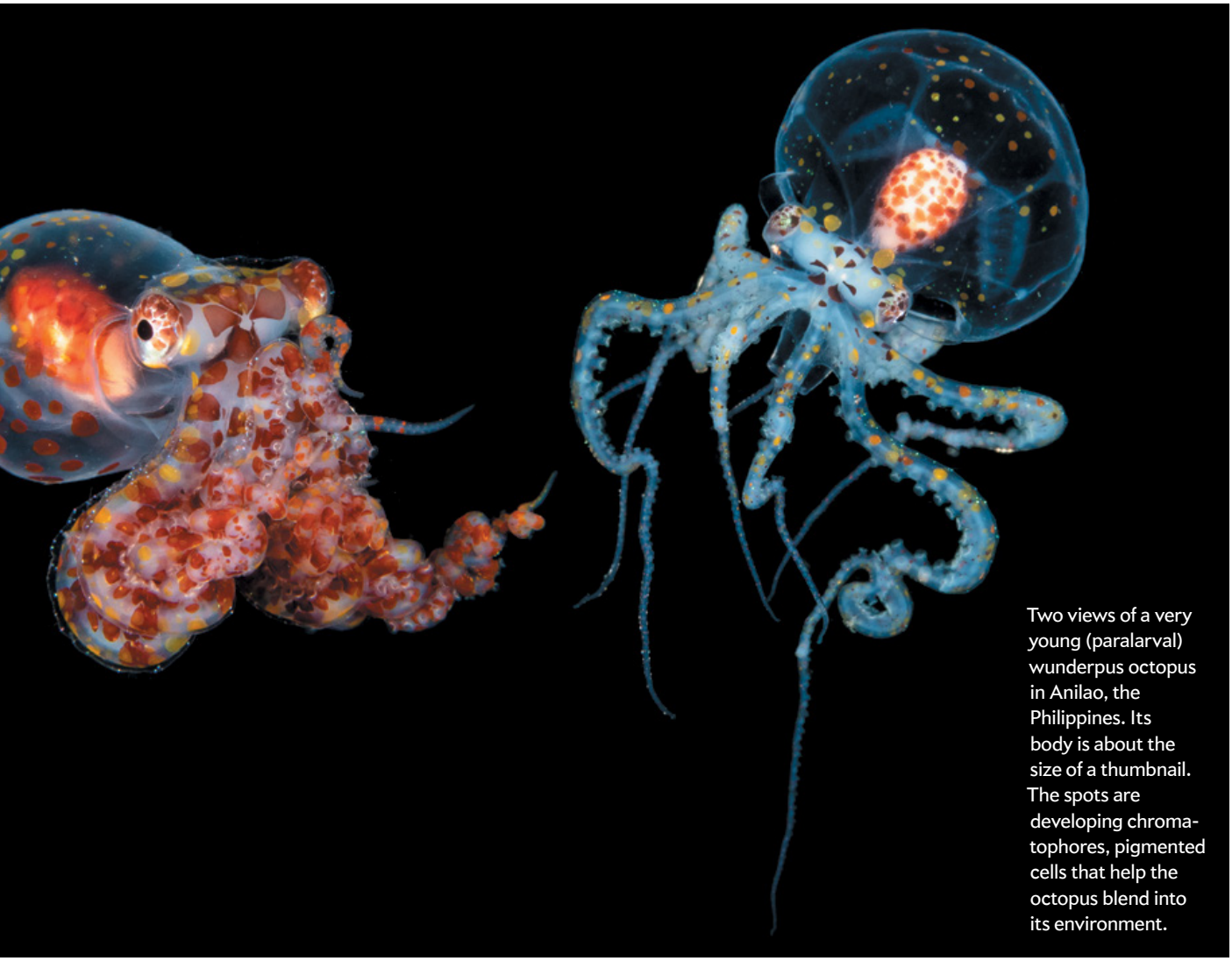


Typically found in deep water, the adult gargoyle cusk eel is extremely rare and represents the only member of its genus. This specimen, photographed off Florida's coast, is an inch from head to tail.

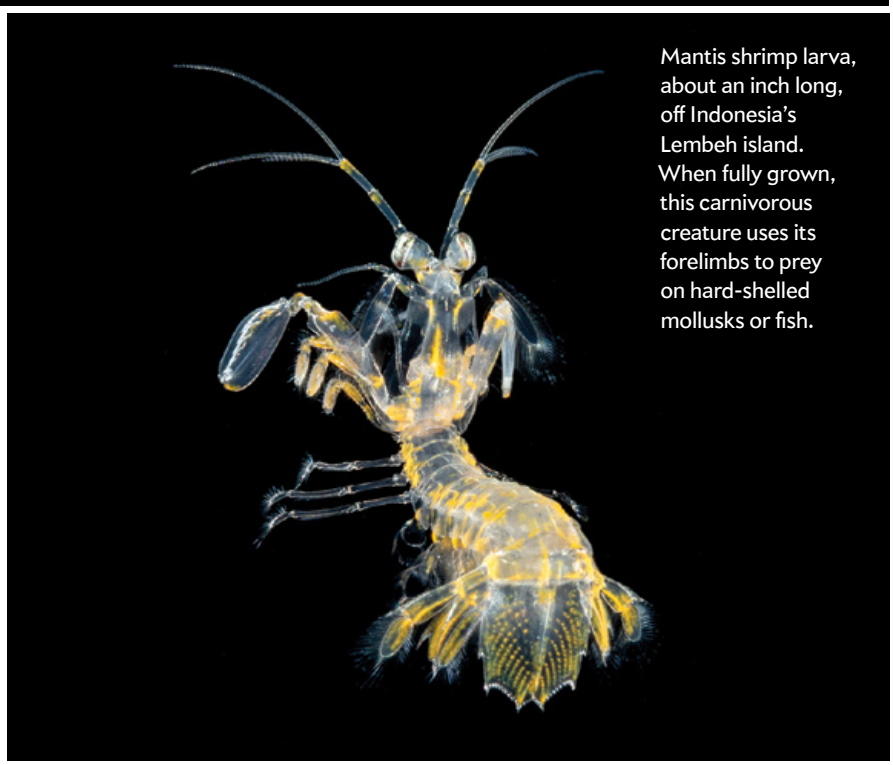


Box jelly off the coast of Florida at a depth of 30 to 40 feet. This larva is between two and two and a half inches long. Some box jelly varieties have a sting fatal to humans, but the ones in this region are not lethal to adults.

Susan Mears; Linda Ianniello *(top right)*



Two views of a very young (paralarval) wunderpus octopus in Anilao, the Philippines. Its body is about the size of a thumbnail. The spots are developing chromatophores, pigmented cells that help the octopus blend into its environment.



Mantis shrimp larva, about an inch long, off Indonesia's Lembeh island. When fully grown, this carnivorous creature uses its forelimbs to prey on hard-shelled mollusks or fish.

NEWS AROUND THE WORLD

Quick Hits

By Daniel Leonard

AUSTRALIA

An "innovation arms race" may be brewing between humans and trash-can-raiding cockatoos in Sydney's suburbs. Humans keep trying new defenses, such as placing bricks or rubber snakes on their bin lids, but the birds continue developing strategies to open them.

BRAZIL

Fossilized teeth revealed Brasilodon, a rodentlike animal that lived 225 million years ago, as the oldest known mammal. Scant fossil evidence had made the animal hard to classify, but new analysis suggests that its teeth are mammalian rather than reptilian.

DENMARK

Denmark has become the first United Nations member state to pay for "loss and damage" caused by its greenhouse gas emissions. Its $13-million donation will go toward recovery efforts in the countries hit hardest by climate change.

GERMANY

The world's first commuter train route powered entirely by hydrogen is in the works in the state of Lower Saxony. The trains emit only water and steam, offering a green alternative to diesel fuel.

INDONESIA

Skeletal analysis uncovered the earliest known limb amputation: 31,000 years ago a child on the island of Borneo had the lower part of his leg surgically removed. The bone shows signs of healing, indicating the child survived the procedure.

PANAMA

A multiyear study along the Panama Canal shows that lightning shapes the composition of forests by killing some tree species more often than others. Species with dense wood and large water-carrying tissues can thrive despite lightning strikes, whereas palm trees (which lack these features) almost always die when struck.

For more details, visit www.ScientificAmerican.com/dec2022/advances

Gray mangroves are sensitive to water level.

Gary Bell/Oceanwide/Minden Pictures

ECOLOGY

Mangrove Moon

Scientists solve a swampy whodunit

The mystery emerged in 2015, when nearly 10 percent of the seemingly healthy mangrove forest along northern Australia's Gulf of Carpentaria suddenly died. Scientists initially blamed this crucial ecosystem's die-off solely on an unusually strong El Niño, a weather pattern that periodically siphons water away from the western Pacific and lowers local tides. But a new study published in *Science Advances* reveals that El Niño had a stealthy accomplice: the moon.

Researchers analyzed more than 30 years of national satellite data to narrow down the suspect list. "It was just the most phenomenal data set," says the study's lead author Neil Saintilan, a biogeographer at Macquarie University in Australia. A pattern quickly emerged—about every 18 to 19 years, mangrove tree cover along the Gulf of Carpentaria thinned out significantly before bouncing back to normal within a couple of years. And roughly nine years after each such die-off, the mangrove canopies became unusually dense.

That regularity gave the researchers an important clue. "Nature's usually pretty chaotic," Saintilan says. "If something is superregular, it's probably some kind of orbital cycle."

"The 18.6-year cycle is essentially driven by what we call a 'wobble'" in the moon's orbit, says climate dynamics researcher Sophie Wilmes, who studies tides at Bangor University in Wales and was not involved in the mangrove investigation. Lunar gravity affects daily ocean tides worldwide. As the moon's orbit oscillates, or wobbles, over 18.6 years, it creates regular, sustained periods of unusually high or low tides in certain places. This effect is especially strong in the Gulf of Carpentaria; its low tides can drop by an average of 40 centimeters because of its location relative to the equator and the shape of Australia's coastline.

Indeed, the researchers found that Australia's 2015 mangrove die-off fell 18 and a half years after the previous one. And because of the 2015 El Niño, the trees were hit with a low-tide double whammy: El Niño decreased tides an additional 40 centimeters, a fatal blow to water-loving mangroves.

Although the orbital mechanics of the moon's wobble have been studied extensively, "there hasn't been much work that looks at its impact on ecology," Wilmes says, "so it's a really cool paper." In the future, Saintilan and his colleagues hope to look at whether this phenomenon affects mangrove forests in other parts of the world. They also want to study how sea-level rise driven by climate change will alter this natural ecological pattern. A moderate rise might mitigate some of the tidal drop, helping to preserve mangrove forests, but an extreme rise could drown the trees at the cycle's highest tidal point. "We might be able to anticipate when—or if—we'll start to see some big problems in terms of mangroves coping," Saintilan says.

—Joanna Thompson

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Richard Blanco is a professional civil engineer and a poet. He read his poem "One Today" at the second inauguration of President Barack Obama, who selected him to serve as the fifth Presidential Inaugural Poet in U.S. history.

Uncertain-Sea Principle

after Werner Heisenberg

the more I try to measure *x*
the less I can measure *y*

the more I know where I am
I scribble my name across the sand
the less I know where I'm going
the burnt-orange moon rises, cools, disappears

the more I know where I'm going
the ebb of each wave seduces me
the less I know how to get there
silhouettes of sailboats sleep till morning

the more I know how to get there
freighter lights burn on the horizon
like candelabras floating toward port
the less I know when I'll arrive
sea oats sway to the wind's pitch
like inverted pendulums of timelessness.

the more I know when I'll arrive
the tide rises on cue to kiss the shore hello
the less I know where I am
seagulls abandon the sea every night

the less I try to solve for *y*
the more I can solve for *x*

the less I know where I am
rustling palms protest losing
their green to the darkness
the more I know where I've been
the sea gives and gives itself to the shore
yet returns again and again to itself

the less I know where I've been
the ocean vanishes into the midnight sky
the more I know who I can be
the midnight sky vanishes into the ocean

the less I know who I can be
there's no horizon in the stark night
the more I know who I am
even in the dark my eyes shape clouds

the less I know who I am
I erase my name with a wave of my palm
the more I know that I am, here
I clutch a fistful of sand, breathe, listen

the more I try to determine my *I*
the less I can determine my *self*

Author's Note: This stereoscope or contrapuntal poem can be read in more than one way, such as left to right across the two columns or down first one column and then the other.

Abstract Aerial Art/Getty Images

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

Rethinking Autism Therapy

A person can function well in the world without acting "normal"

By Claudia Wallis

When I began reporting on autism about 15 years ago, therapists would talk about achieving the "optimal outcome" for children on the autism spectrum. What they meant was changing the classic behaviors associated with the condition—suppressing repetitive actions such as hand flapping, drilling young kids to make eye contact, rehearsing speech and social interactions—so that ultimately the children would no longer meet the diagnostic criteria for autism. It was an elusive goal that only a tiny percentage could reach. Today it is widely seen as wrong-minded.

"We've moved away from thinking of autism as a condition that needs to be eliminated or fixed to thinking about autism as part of the neurodiversity that exists across humankind," says Geraldine Dawson, director of the Duke Center for Autism and Brain Development in Durham, N.C. "The question then becomes, How do we best support people who are autistic, and how would you measure improvement if you are conducting clinical trials?" Dawson, along with two colleagues, wrote about this shift in a recent article in *JAMA Pediatrics*. It reflects a widespread reevaluation of the goals of therapy and metrics for success, driven in part by the self-advocating voices of people on the spectrum. They have fostered a greater appreciation for what society gains from having different kinds of brains contribute to our world, as well as a greater awareness of the negative impacts of insisting that people with autism behave in ways that are unnatural for them.

This reassessment doesn't mean that early intervention is any less important for young children diagnosed with autism. As in the past, therapies should aim to remediate the defining impairments of the condition, which include challenges communicating and establishing social relationships, and to reduce harmful and disruptive behaviors, such as head banging and tantrums. But today an optimal outcome will depend on the abilities and desires of the individual and the person's family and will not necessarily emphasize conforming to typical behavior.

For example, therapists need not focus on changing behaviors that are essentially harmless. Dawson cites the case of a teenager who told his therapist he no longer wanted to work on sustaining eye contact. "That should be okay," she says. "If you think about the people you know, there are those who make a lot of eye contact and others who make less." Similarly, she adds, "if someone rocks back and forth because it makes them feel calmer, I feel that our society should be accepting of different ways of being in the world."

The neurodiversity movement, which fights stigma, has encouraged scientists to study the high cost of forced conformity for people with autism. A 2018 paper, for example, found a link between trying hard to "pass" as nonautistic and a higher risk of suicide. The struggle to keep up a "neurotypical" appearance pulls attention from other things, says Ari Ne'eman, who co-founded the Autistic Self Advocacy Network. "If you're constantly policing where your eyes are pointing and second-guessing yourself about if you're talking too much about the things that interest you, all of that is energy and cognitive load that doesn't get spent elsewhere." Ne'eman, who is autistic and a Ph.D. candidate in health policy at Harvard University, remains concerned that bias against certain behaviors is built into the tools clinicians use. Too often therapists are "'teaching to the test' of typical appearance," he wrote in a 2021 piece in the *AMA Journal of Ethics*.

The watchwords of the neurodiversity movement are "nothing about us without us." That means autistic people and their families help to define therapy goals. "If you were a nonverbal six-year-old and at 12 you are able to speak, whether through an iPad or with your voice, that can be an optimal outcome," says autism researcher Connie Kasari of the University of California, Los Angeles, who often works with minimally verbal people on the spectrum. "They can be very happy," she observes. "They can be working. It comes down to how you define success within your world."

The old goal of losing the autism diagnosis is not a priority for many people on the spectrum, Dawson says, and "when we follow people to see if losing the diagnosis is associated with a better quality of life, it just is not." What is a priority, she says, is having a meaningful job and relationships: "being as independent, joyful and productive as possible." Just like for any human being. SA

Illustration by Katie Thomas

A NEW ERA FOR ASTRONOMY

How the James Webb Space Telescope is transforming our view of the universe

Close your eyes and imagine "space," and there's a good chance your mind will pull up a picture taken by Hubble. The space telescope became a household name in the 1990s as the images it captured appeared on TV and in magazines, newspapers and movies. Over the decades it created a shared visual lexicon of outer space and seeded multiple generations' imaginations with visions of glowing nebulae, haunting planets and faraway galaxies. More than 30 years after launch, Hubble is still going strong. But now its successor promises to outdo it.

The first photos from the James Webb Space Telescope (JWST) went out to the world on July 12, 2022, and they are stunners. The clarity and level of detail are unprecedented. Seeing the telescope's new views of some familiar objects—from the oft-photographed Carina Nebula to the planet Neptune—feels like putting on new glasses with a stronger prescription. Only the first batches of JWST photos have been released so far, but each image has created a stir, suggesting that in the coming years the telescope's pictures will infiltrate the public subconscious just as thoroughly as Hubble's.

The triumph is especially sweet given what it took for JWST to get here. Scientists started planning it more than three decades ago, and the effort to build the observatory fell so far behind schedule and so far over budget that many feared it would never be launched at all. When the telescope finally lifted off on December 25, 2021, with an ultimate price tag of nearly $10 billion, astronomers felt a rush of relief. In the subsequent six months JWST proved to be working even better than planned, and astronomers really began to enjoy themselves.

Now scientists are ecstatic. In the three months after the initial results from the telescope were released, scientists submitted some 200 papers interpreting them to the preprint server arXiv. A deluge is sure to follow—the telescope's initial observing time is already spoken for by the lucky researchers whose proposals won out in a highly competitive peer-reviewed selection process.

In the following pages, we've collected some of the cosmic portraits JWST has given us so far. On page 42, we show how scientists create finished images from the telescope's raw data. On page 28, journalist Jonathan O'Callaghan explains how some of those photos have already thrown the field of cosmology into crisis. And on page 39, astrophysicist Fabio Pacucci describes how Hubble and JWST have changed science by taking pictures of "empty" space.

Soon the first image we call to mind when we think about space may well be one of JWST's. How long it will run and what its ultimate legacy will be are still open questions. But it's certainly off to a shining start.

—Clara Moskowitz, Senior Editor

THE TARANTULA NEBULA is a nursery of dust and gas where new stars are being born. Hot young stars sparkle in blue at the center of this image from JWST's NIRCam, and rusty ripples at the outskirts represent cooler gas where future stars will form.

NASA, ESA, CSA, STScI and Webb ERO Production Team

BREAKING COSMOLOGY

JWST's first images include unimaginably distant galaxies that challenge theories of how quickly these structures can form

By Jonathan O'Callaghan

GALAXIES from the depths of cosmic time appear in a small crop from "deep field" observations taken by the James Webb Space Telescope (JWST). The most distant objects in such images may reveal surprising new details about the early universe.

Jonathan O'Callaghan is a freelance journalist covering commercial spaceflight, space exploration and astrophysics.

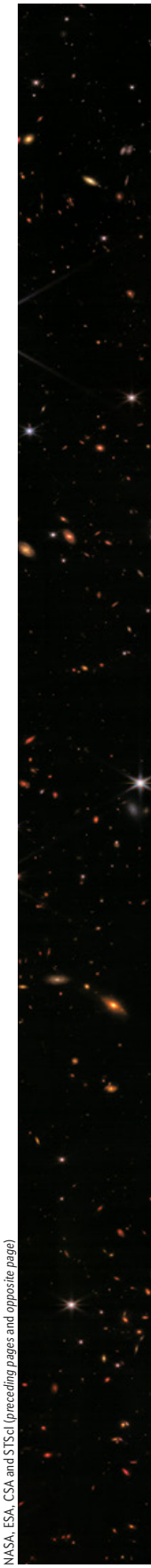
ROHAN NAIDU WAS AT HOME WITH HIS GIRLFRIEND WHEN HE FOUND THE GALAXY that nearly broke cosmology. As his algorithm dug through early images from the James Webb Space Telescope (JWST) late one night this past July, Naidu shot to attention. It had sifted out an object that Naidu recognized was inexplicably massive and dated back to just 300 million years after the big bang, making it older than any galaxy ever seen before. "I called my girlfriend over right away," Naidu says. "I told her, 'This might be the most distant starlight we've ever seen.'" After exchanging excited messages with one of his collaborators "with lots of exclamation marks," Naidu got to work. Days later they published a paper on the candidate galaxy, which they dubbed "GLASS-z13." The Internet exploded. "It reverberated around the world," Naidu says.

The discovery of this galaxy, just weeks into JWST's full operations, was beyond astronomers' wildest dreams. JWST—the largest, most powerful observatory ever launched from Earth—was built to revolutionize our understanding of the universe. Stationed 1.5 million kilometers away from earthly interference and chilled close to absolute zero by its tennis court–sized sunshade, the telescope's giant segmented mirror and exquisitely sensitive instruments were designed to uncover details of cosmic dawn never before observed.

This is the scarcely probed era—no more than a few hundred million years after the big bang itself—in which the very first stars and galaxies coalesced. How exactly this process unfolded depends on exotic physics, ranging from the uncertain influences of dark matter and dark energy to the poorly understood feedbacks between starlight, gas and dust. By glimpsing galaxies from cosmic dawn with JWST, cosmologists can test their knowledge of all these underlying phenomena—either confirming the validity of their best consensus models or revealing gaps in understanding that could herald profound new discoveries.

Such observations were supposed to take time; initial projections estimated the first galaxies would be so small and faint that JWST would find at best a few intriguingly remote candidates in its pilot investigations. Things didn't quite go as planned. Instead, as soon as the telescope's scientists released its very first images of the distant universe, astronomers such as Naidu (at the Massachusetts Institute of Technology) started finding numerous galaxies within them that, in apparent age, size and luminosity, surpassed all predictions. The competition for discovery was fierce: with each new day, it seemed, claims of yet another record-breaking "earliest-known galaxy" emerged from one research group or another. "Everyone was freaking out," says Charlotte Mason, an astrophysicist at the University of Copenhagen. "We really weren't expecting this."

In the weeks and months following JWST's findings of surprisingly mature "early" galaxies, theorists and observers have been scrambling to explain them. Could the bevy of anomalously big and bright early galaxies be illusory, perhaps because of flaws in analysis of the telescope's initial observations? If genuine, could they somehow be



NASA, ESA, CSA and STScI (*preceding pages and opposite page*)

THE INTERACTING galaxies of Stephan's Quintet, as seen by JWST, approximately 290 million light-years away from Earth. Covering one fifth of the moon's diameter, this mosaic is constructed from almost 1,000 separate images and reveals never-before-seen details of this galaxy group.

NASA, ESA, CSA and STScI

explained by standard cosmological models? Or, just maybe, were they the first hints that the universe is more strange and complex than even our boldest theories had supposed?

At stake is nothing less than our very understanding of how the orderly universe we know emerged from primordial chaos. JWST's early revelations could rewrite the opening chapters of cosmic history, which concern not only distant epochs and faraway galaxies but also our own existence here in the familiar Milky Way. "You build these machines not to confirm the paradigm but to break it," says JWST scientist Mark McCaughrean, a senior adviser for science and exploration at the European Space Agency. "You just don't know how it will break."

DEEP LOOKS FOR COSMIC DAWN

ONE MIGHT SAY JWST'S observations of early galaxies have been billions of years in the making, but more modestly they trace back to the Space Telescope Science Institute (STScI) in 1985. At the time the Hubble Space Telescope was still five years away from launching on a space shuttle. But Garth Illingworth, then deputy director of the STScI, was surprised one day when his boss, then

AN IMAGE FROM JWST reveals hundreds of previously invisible newborn stars in the stellar nursery known as the Carina Nebula, a vast agglomeration of gas and dust some 7,600 light-years from Earth.

director Riccardo Giacconi, who died in 2018, asked him to start thinking about what would come after Hubble much farther down the road. "I protested, saying we've got more than enough to do on Hubble," Illingworth recalls. But Giacconi was insistent: "Trust me, it'll take a long time," he said. So, Illingworth and a handful of others got to work, drawing up concept ideas for what became known as the Next Generation Space Telescope (NGST), later renamed to JWST after a former NASA administrator.

Hubble would be transformational, but astronomers knew its capabilities would be limited by its observations in visible light. As light from a very distant galaxy travels across the cosmic abyss, it is stretched by the expansion of the universe—a broadening of wavelengths known as redshift. The higher the redshift value, the more stretching the light has experienced, and thus the more distant its source galaxy. Redshifts for early

NASA, ESA, CSA and STScI

galaxies are so high that their emitted visible light has stretched into infrared by the time it arrives at our telescopes, which is why Hubble could not see them. The NGST, for comparison, would observe in infrared and would boast a very large (and very cold) starlight-gathering mirror, allowing it to peer much deeper into the universe. "Everybody realized that Webb would be the telescope for looking at early galaxies," Illingworth says. "That became the primary science goal."

The need for the telescope was highlighted in December 1995, when astronomers pointed Hubble at a seemingly empty patch of the sky for 10 consecutive days. Many experts predicted the extended observation would be a waste of resources, revealing at best a handful of dim galaxies, but instead the effort was richly rewarded. The resulting image, the Hubble Deep Field, showed the "empty" spot was filled with galaxies by the thousands, stretching back 12 billion years into the 13.8-billion-year history of our universe. "There were galaxies everywhere," says Illingworth, now an astrophysicist at the University of California, Santa Cruz. The Hubble Deep Field showed that the early universe was even more crowded and exciting than most anyone had expected, offering observational treasures to those who took the time and care to properly look. Yet, impressive as Hubble's Deep Field was, astronomers wanted more.

After more than two decades of labor at a cost of some $10 billion, JWST finally launched on Christmas Day 2021. The telescope reached its deep-space destination a month later, where it

A SIDE-BY-SIDE COMPARISON shows JWST's remarkably detailed observations of the Southern Ring Nebula in near-infrared light (*left*) and mid-infrared light (*right*). Located more than 2,000 light-years from Earth, the nebula is composed of shells of gas and dust expelled from a dying star, which in each image can be seen near the nebula's core.

would endure exhaustive testing to ensure its optimal performance. By July 2022 it was ready to begin its long-awaited first year of science observations, known as Cycle 1. Part of the telescope's early time was devoted to high-impact programs across a range of disciplines from which data would immediately be made public. Two of those, CEERS (the Cosmic Evolution Early Release Science Survey) and GLASS (the Grism Lens–Amplified Survey from Space), independently spent dozens of hours looking for galaxies in the early universe by staring at separate small portions of the sky. Not much was expected—perhaps a slightly more ornate version of the Hubble Deep Field but nothing more. Steven Finkelstein of the University of Texas at Austin, the lead on CEERS, says extremely distant galaxies were predicted to pop up only "after a few cycles of data" from multiple programs.

Instead, much to the surprise of astronomers, extremely distant galaxies came into view immediately. Hubble's record for the most distant known galaxy had been GN-z11, spotted in 2015 at a redshift of 11 thanks to a 2009 upgrade that enhanced the telescope's modest infrared capabilities. A redshift of 11 cor-

responds to a cosmic age of about 400 million years, a point at the brink of when galaxy formation was thought to begin. But from the very first GLASS data, two teams—one led by Naidu in that breathless late-night discovery—independently found GLASS-z13 at a redshift of 13, some 70 million years farther back in time.

In their quest for quick results, the researchers relied on redshift estimates derived from simple brightness-based measurements. These are easier to obtain but less precise than direct measurements of redshift, which require more dedicated observation time. Nevertheless, the simplified technique can be accurate, and here it suggested a galaxy that was unexpectedly bright and big, already bearing a mass of stars equivalent to a billion suns, just a few hundred times less than that of the Milky Way's stellar population, despite our own galaxy being billions of years more mature. "This was beyond our most optimistic expectations," says Tommaso Treu, an astronomer at the University of California, Los Angeles, and the lead on GLASS.

The record didn't last long. In the following days, dozens of galaxy candidates from CEERS and GLASS sprang into view with estimated redshifts as high as 20—just 180 million years after the big bang—some with disklike structures that were not expected to manifest so early in cosmic history. Another team, meanwhile, found evidence for galaxies the size of our Milky Way at a redshift of 10, less than 500 million years after the big bang.

Such behemoths emerging so rapidly defies expectations set by cosmologists' standard model of the universe's evolution. Called Lambda CDM (LCDM), this model incorporates scientists' best estimates for the properties of dark energy and dark matter, which collectively act to dominate the emergence of large-scale cosmic structures. ("Lambda" refers to dark energy, and "CDM" refers to dark matter that is relatively sluggish, or "cold.") "Even if you took everything that was available to form stars and snapped your fingers instantaneously, you still wouldn't be able to get that big that early," says Michael Boylan-Kolchin, a cosmologist at the University of Texas at Austin. "It would be a real revolution."

HOW TO BUILD A GALAXY

TO UNDERSTAND THE DILEMMA, a brief refresher is needed. In the first second after the big bang, our universe was an almost inconceivably hot and dense soup of primordial particles. Over the next three minutes, as the cosmos expanded and cooled, the nuclei of helium and other very light elements began to form. Fast-forward 400,000 years, and the universe was cold enough for the first atoms to appear. When the universe was about 100 million years old, theorists say, conditions were finally right for the emergence of the first stars. These giant fireballs of mostly hydrogen and helium were uncontaminated by heavier elements found in modern-day stars, so they possessed significantly different properties. Larger and brighter than today's stars, these first suns coalesced in protogalaxies—clusters of gas that clung to vast, invisible scaffolds of dark matter. Gravity guided the subsequent interactions between these protogalaxies, which eventually merged to form larger galaxies. This process of becoming, of the early universe's chaos giving way to the more orderly cosmos we know today, is thought to have taken about a billion years.

NASA, ESA, CSA, STScI and Webb ERO Production Team

THE CARTWHEEL GALAXY displays its characteristic dust-rich "spokes" and starry inner and outer rings in this near-infrared view from JWST. These features ripple like shock waves from the galaxy's center, the site of a high-speed collision with another galaxy some 400 million years ago.

JWST's discovery of bright galaxies in the early cosmos challenges this model. "We should see lots of these little protogalactic fragments that have not yet merged to make a big galaxy," says Stacy McGaugh, a cosmologist at Case Western Reserve University. "Instead, we're seeing a few things that are already big galaxies." Some of these galaxies may be impostors, much closer galaxies shrouded in dust that makes them look dimmer and farther away when brightness-based measurements are used. Follow-up observations of GLASS-z13 in August by the Atacama Large Millimeter Array (ALMA) in Chile, however, suggest that is not the case for this candidate, because ALMA did not see evidence for large amounts of dust. "I think we can exclude low-redshift interlopers," says Tom Bakx, an astronomer at Nagoya University in Japan, who led the observations. Yet the lack of dust means ALMA struggled to see the galaxy at all, showing how difficult it could be for telescopes to confirm observations made using JWST's advanced capabilities. "The good news is there's nothing detected," Naidu says. "The bad news is there's nothing detected." Only JWST, in this case, can follow up itself.

The most startling explanation is that the canonical LCDM cosmological model is wrong and requires revision. "These results are very surprising and hard to get in our standard model of cosmology," Boylan-Kolchin says. "And it's probably not a small change. We'd have to go back to the drawing board." One controversial idea is modified Newtonian dynamics (MOND), which posits that dark matter does not exist and that its effects can instead be explained by large-scale fluctuations in gravity. To date, JWST's observations could support such a theory. "MOND has had a lot of its predictions come true—this is another one of them," says McGaugh, who is one of the idea's leading proponents. Others remain unconvinced. "So far everything that we've tried to test MOND hasn't been able to really provide a satisfactory answer," says Jeyhan Kartaltepe, an astrophysicist at the Rochester Institute of Technology.

One simpler solution is that galaxies in the early universe could have little or no dust, making them appear brighter. This scenario could confound efforts to calculate the galaxies' true masses and could perhaps also explain ALMA's difficulty spotting GLASS-z13. "It could be that supernovae didn't have enough time to produce the dust, or maybe in the initial phases [of galaxy formation] the dust is expelled from galaxies," says Andrea Ferrara, an astronomer at the Scuola Normale Superiore in Italy, who has proposed such a possibility. Alternatively, Mason and her colleagues suggest that in its observations of the early universe JWST may so far be seeing only the very brightest young galaxies, as they should be the easiest to spot. "Maybe there's something happening in the early universe that means it's easier for some galaxies to form stars," she says.

David Spergel, a theoretical astrophysicist and current president of the Simons Foundation in New York City, agrees. "I think what we're seeing is that high-mass star formation is very efficient in the early universe," he says. "The gas pressures are higher. The temperatures are higher. That has an enormous impact on the environment for star formation." Magnetic fields might have arisen earlier in the universe than we thought, driving material to kick-start the birth of stars. "We might be seeing a signature of magnetic fields emerging very early in the universe's history," Spergel says.

A RUSH TO BREAK THE UNIVERSE

THE RAPID FLOW of scientific papers from JWST's initial observations is no fluke; when the first data started streaming down, astronomers were eagerly waiting. "People had been working on their pipelines for years," Boylan-Kolchin says. Instead of the traditional peer-review processes, which can take months, astronomers published on arXiv, a website where scientific papers can be uploaded after minimal review by moderators but well before formal peer review. This new form of peer review is unfolding in near real time on Twitter and other social media platforms. "It's science by arXiv," Naidu says. The resulting frenzy was intense—and surprising. "I expected a lot of activity," says Nancy Levenson, STScI's interim director. "But I underestimated the amount."

The result was that scientific results could be rapidly publicized and discussed, but some fear at a cost. "People were rushing things a little bit," says Klaus Pontoppidan, JWST's project scientist at STScI. "The gold standard is a refereed, peer-reviewed paper." Early calibration issues with JWST, for example, may have affected some results. Nathan Adams at the University of Manchester in England and his colleagues found there could be dramatic changes, with one galaxy at a redshift of 20.4 recalibrated to a redshift of just 0.7. "We need to calm down a little bit," Adams says. "It's a bit too early to say we've completely broken the universe."

Such issues are unlikely to eradicate all of JWST's high-redshift galaxies, however, given their sheer number. "It's more likely that the early universe is different from what we predicted," Finkelstein says. "The odds are small that we're all wrong." Astronomers are now racing to conduct follow-up observations with JWST. Levenson says she's currently reviewing about a dozen proposals from various groups asking for additional JWST observing time, most of which are seeking to scrutinize high-redshift galaxy candidates. "Considering the excitement and importance of these early discoveries, we thought it was appropriate to ask for a little bit of time to confirm them," says Treu, who put forward one of the proposals.

More upcoming programs are set to hunt for distant galaxies, such as COSMOS-Webb, led by Kartaltepe, which is expected to hugely increase the known population of early galaxies by observing a wider swath of sky for hundreds of hours. "We estimate there are thousands we'll be able to detect," she says. Future proposals might look for evidence of those first protogalaxies, perhaps using the explosive deaths of supersized first stars in especially luminous and energetic supernovae as markers for their existence. Some estimates suggest JWST could see as far as a redshift of 26, just 120 million years after the big bang, a cosmic blink of an eye. Much other work will be done to follow up the growing list of high-redshift candidates. "Even confirming a handful of these would be quite amazing," Naidu says. "It would demonstrate we're not getting fooled."

JWST has ushered in a new era of science, and despite the uncertainties, the rapid communication of new discoveries has invigorated astronomers. "It's been fantastic," Treu says. "It's really wonderful to see the community so engaged and excited." Now the question is, if we can truly believe what we are seeing, is it time to reappraise our understanding of the dawn of time? "We're peering into the unknown," Mason says. SA

Fabio Pacucci is an Italian astrophysicist at the Center for Astrophysics | Harvard & Smithsonian, where he holds the Clay and Black Hole Initiative fellowships. Follow him on Twitter @fabio_pacucci

THE BOUNTY OF "EMPTY" SPACE

Deep-field images uncover more of the universe than we ever thought possible

By Fabio Pacucci

THIS PAST JULY ASTRONOMERS WORKING WITH THE JAMES WEBB SPACE TELESCOPE (JWST) released the deepest astronomical image ever obtained, leaving the world in awe. Against the background of a galaxy cluster named SMACS 0723, seen as it appeared 4.6 billion years ago, myriad galaxies of different shapes and sizes appear like bright gems in the darkness of the cosmos. Some of these lighthouses were already shining when the universe was just a few hundred million years old. To understand how we reached this remarkable achievement—how astronomers have sailed to galactic islands so remote from us in space and time, collecting photons whose journey started breathtakingly close to the big bang—it helps to know how deep-field observations came to be.

The origin of Webb's first deep field is best traced to the early 1990s, with the launch of JWST's predecessor, the Hubble Space Telescope. The concept of deep-field observations was still in its infancy back then. Hubble was primarily designed for targeted observations. Astronomers would point the telescope to a source at a specific spot in the sky and expose (or "integrate") as needed, depending on the source's brightness. But Hubble could also be used for deep-field imaging, which is the opposite: astronomers would point the telescope to a sky region devoid of any visible source and use a very long exposure time to observe as many faint sources of light as possible, thereby reaching "deep" into the cosmos. From its perch in low-Earth orbit, above our planet's starlight-scattering atmosphere, Hubble was the best platform for deep-field imaging astronomers had ever known.

Not everyone thought the approach would prove revolutionary. In a famous article published in *Science* in 1990, John Bahcall of the Institute for Advanced Study in Princeton, N.J., and his colleagues argued that a deep-field image from Hubble would not reveal significantly more galaxies than ground telescopes. Bahcall, a giant in astrophysics, was widely known for his work on the problem of solar neutrinos and his calculations of the distribution of stars around a massive black hole. He contributed fundamentally to the development of the Hubble Space Telescope from its original concept in the 1970s to its launch. Bahcall thought Hubble deep-field images could be used to study the sizes and shapes of faint galaxies and to take a census of quasars (a rather old-fashioned word for accreting supermassive black holes), but he didn't believe they would reveal new populations

of galaxies. Such tepid expectations tamped down any urgency to try deep-field imaging with Hubble.

The first attempt occurred around the winter holidays of 1995, after a much needed optics repair. The telescope spent 10 days of exposure time pointed at the Ursa Major constellation, staring at a tiny patch of the sky just one-thirteenth the moon's angular diameter. Weeks later, when astronomers saw the resulting image—known as the Deep Field North—they immediately realized it was a Christmas gift for the ages. Because the Milky Way's stars are sparse in the target region, Hubble was able to probe the cosmic abyss as if through a peephole. The telescope saw almost 3,000 faint galaxies of different shapes and sizes—many more than expected, some of them as far as 12 billion light-years away. Hubble was not only exploring space.

Hubble's deep fields captured more than 10,000 galaxies in one of astronomy's first "big data" challenges.

It was also probing time, gathering starlight that had been emitted eons ago, during earlier epochs of the universe. The image quickly became iconic.

A crucial question arose: Was the galaxy-rich region revealed by the Deep Field North the norm throughout the universe, or did astronomers just happen to point the telescope toward a Pantagruelian crowding of galaxies? In 1998 Hubble obtained the Deep Field South. The exposure was similar, but the telescope pointed toward the southern celestial hemisphere, as far as possible from the first spot. This new image confirmed that the universe contained many more galaxies than previously thought, especially at vast distances. In addition to their scientific and inspirational value, these and other Hubble deep-field surveys were a technical triumph, capturing more than 10,000 galaxies in one of astronomy's first "big data" challenges.

Deep-field imaging is not restricted to the visible realm of the spectrum. At the turn of the millennium, the Chandra X-ray observatory, a revolutionary NASA mission launched in July 1999 and still active today, captured the first high-energy deep field. The Chandra Deep Field South was obtained by integrating for about one million seconds over a piece of the sky that was devoid of hydrogen clouds and dust from the Milky Way. The Chandra Deep Field South uncovered the extreme universe, revealing hundreds of black holes, some very remote. The image wasn't as visually spectacular as the Hubble photographs, but it was dense with science. Chandra later imaged the same field for a total exposure of about seven million seconds, capturing one of the deepest fields ever obtained in x-ray. In 2003 a new image called Chandra Deep Field North was released, containing data from more than 500 x-ray sources.

In 2006 scientists released the Hubble Ultra Deep Field, which was taken using an instrument called the Advanced Camera for Surveys that was added to the telescope during a servicing mission in 2002. This historic shot contained thousands of galaxies, some that we now know were shining when the universe was less than one billion years old. The Ultra Deep Field showed the history of galaxy formation in unprecedented detail. Distant galaxies conclusively appeared to be smaller and more irregular in shape than closer ones, providing substantial evidence to support galaxy evolution theories.

The technology used for Ultra Deep Field provides essentially the deepest image that can be obtained in optical wavelengths. If a galaxy is too far away, its optical light is shifted outside the visible range and into the infrared regime; this is a consequence of the cosmological redshift, in which the expansion of the universe stretches out the wavelengths of light traveling through enormous expanses of intergalactic space. It would take an infrared camera to look farther in space and time. With the addition of a new near-infrared camera to Hubble, an infrared Ultra Deep Field was obtained in 2009, revealing galaxies shining only 600 million years after the big bang. A decade later, in 2019, a deep field produced with NASA's Spitzer infrared space telescope was released. Both these images are rich with galaxies at the cosmic dawn.

Hubble's Frontier Fields campaign, completed in 2017, was the real prologue to JWST's first deep image. During this observational campaign, Hubble was pointed toward six large concentrations of galaxies. According to Einstein's theory of general relativity, a substantial density of mass along the line of sight can bend and thus amplify the light incoming from a background source, an effect called gravitational lensing. The Frontier Fields campaign used these galaxy clusters as a magnifying glass to see even farther away. Besides being filled with swarming galaxies, the Frontier Fields images are adorned with strange arcs of light, representing the stretched and amplified images of background galaxies much more distant than the cluster and possibly too faint to be directly observed with Hubble. These shots revealed some of the most distant galaxies and the first gravitationally lensed supernova.

It's been almost 200 years since the advent of photography, when humanity first managed to directly capture and record photons to make images. Today highly complex cameras onboard a space telescope one million miles away are shaking our knowledge of the universe, opening new windows onto space and time. A relatively short time separates these two events, but they are linked by the same goal: achieving a deeper understanding of nature by looking at what our eyes cannot see. SA

R. Williams/STScI, Hubble Deep Field Team and NASA/ESA

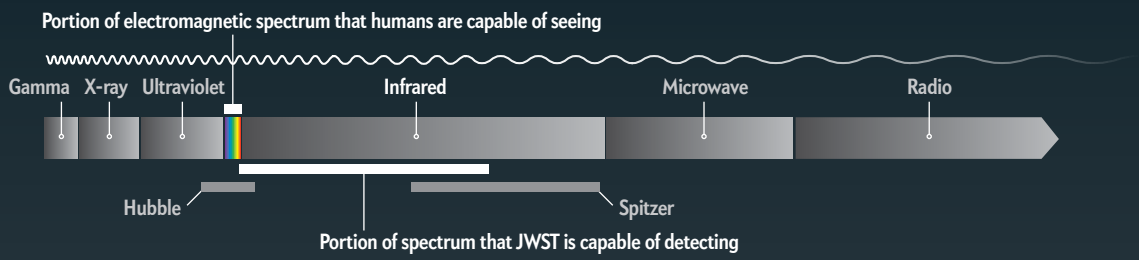
HUBBLE Space Telescope's first deep-field image, taken in 1995, surprised scientists with its horde of galaxies.

How JWST's images are made

Text by Clara Moskowitz | Graphics by Jen Christiansen

Behind the Pictures

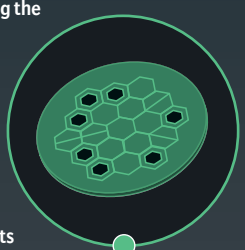
As light travels through space, it gets stretched by the expansion of the universe. This is why many of the most distant objects shine in infrared light, which is longer in wavelength than visible light. We can't see this ancient light with our eyes, but the James Webb Space Telescope (JWST) was designed to capture it, revealing some of the first galaxies ever to form.



Six Data Collection Components ...

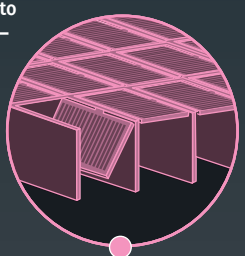
Aperture Masking

A perforated metal plate blocks some of the light entering the telescope, allowing it to simulate an interferometer, which combines data from multiple telescopes to achieve higher resolution than a single lens. The technique reveals more details of very bright objects close together, such as two stars nearby on the sky.



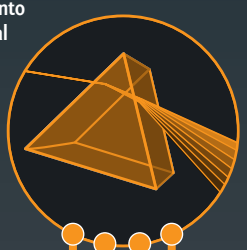
Micro Shutter Array

A grid of 248,000 small doors can open or close to measure spectra—light spread into its constituent wavelengths—from up to 100 points in a single frame.



Spectrographs

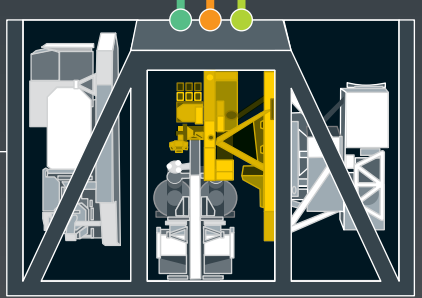
Gratings or prisms separate incoming light into spectra to reveal the intensity of individual wavelengths.



... Distributed across Four Instruments

Fine Guidance Sensor (FGS)/ Near-InfraRed Imager and Slitless Spectrograph (NIRISS)

The FGS is a guide camera that helps to point the telescope in the right direction. It's packaged together with the NIRISS, which has a camera and a spectrograph to take images and spectra in the near-infrared range.



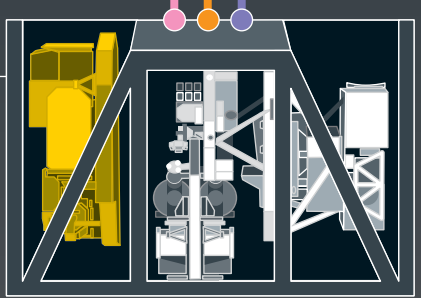
Rear view inside the instrument module

Data collection range:

Near-infrared (up to 5 microns)

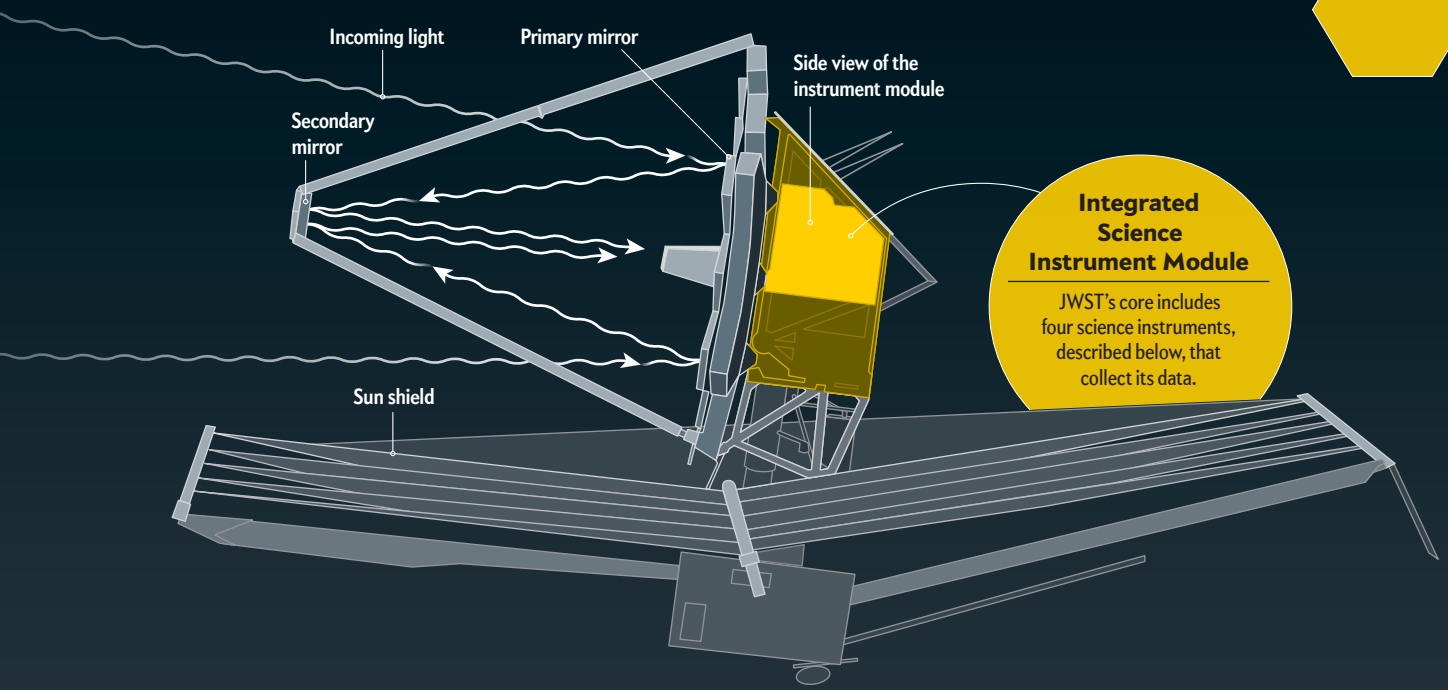
Near-Infrared Spectrograph (NIRSpec)

This dedicated spectrograph can capture 100 spectra simultaneously with its micro shutter array. It's the first space instrument capable of taking spectroscopy for so many objects at once.



Data collection range:

Near-infrared (up to 5 microns)



Integrated Science Instrument Module

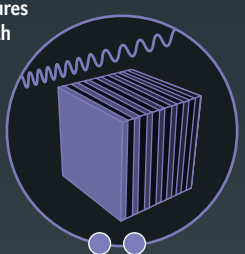
JWST's core includes four science instruments, described below, that collect its data.

Cameras

JWST has three cameras—two that capture light in the near-infrared wavelength range and one that works in the mid-infrared.

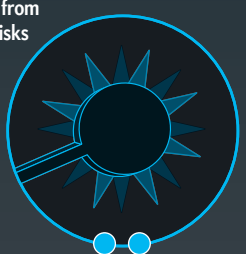
Integral Field Unit

A combined camera and spectrograph captures an image, along with spectra for each pixel, revealing how the light varies across the field of view.



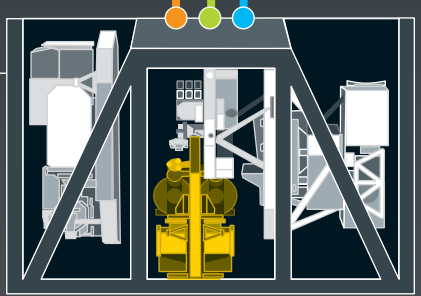
Coronagraphs

Glare from bright stars can blot out fainter light from planets and debris disks orbiting those stars. Coronagraphs are opaque circles that block that bright starlight to let the weaker signals through.



Near-Infrared Camera (NIRCam)

The only near-infrared instrument with a coronagraph, NIRCam will be a key instrument for studying exoplanets whose light would otherwise be drowned out by their nearby star's glare. It will capture high-resolution images and spectra in the near-infrared.

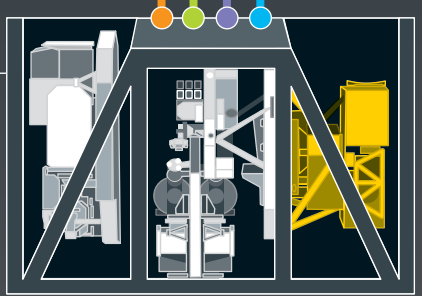


Data collection range:

Near-infrared (up to 5 microns)

Mid-Infrared Instrument (MIRI)

This combination camera and spectrograph is JWST's only instrument capable of seeing in the mid-infrared, where cooler objects such as debris disks around stars and extremely distant galaxies emit their light.



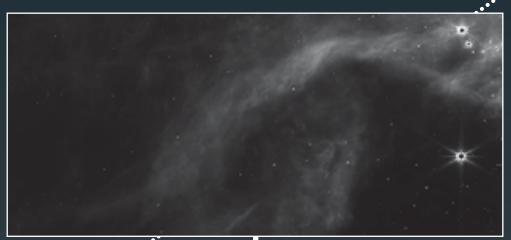
Data collection range:

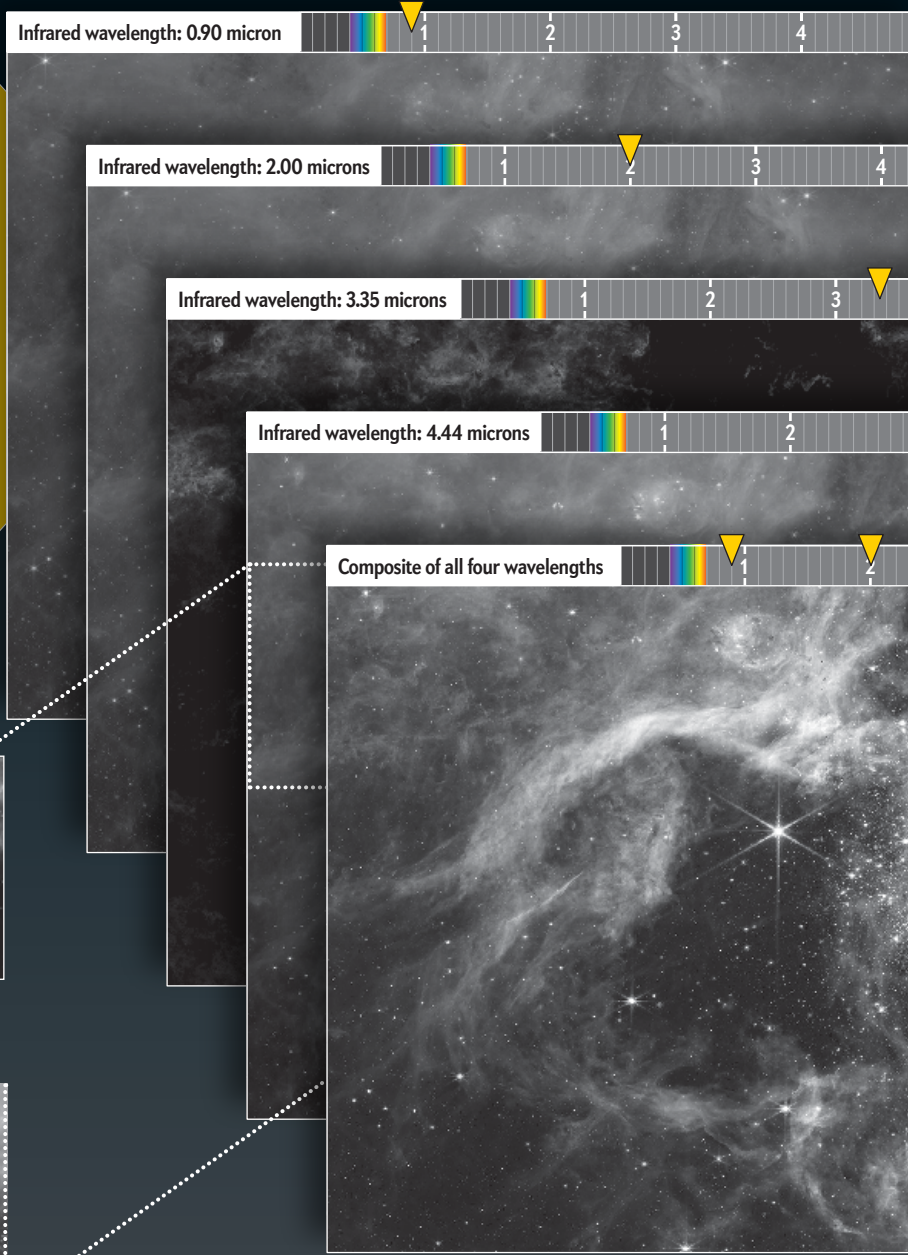
Mid-infrared (5 to 28 microns)

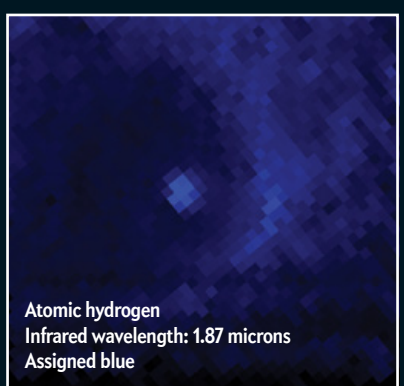
Sources: NASA; ESA; STScI; Andi James and J. Olmsted, STScI (*references*)

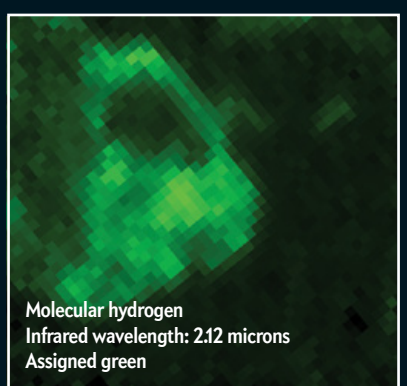
Are the Pictures "Real"?

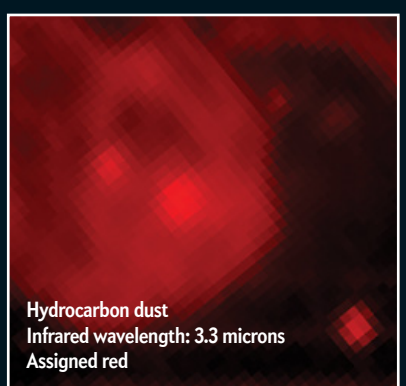
Scientists have to make adjustments to turn JWST's raw data into something human eyes can appreciate, but its photos are "real," says Alyssa Pagan, science visuals developer for the Space Telescope Science Institute. "Is this exactly what we'd see if we were there? The answer to that is no because our eyes are not built to see in infrared, and also the telescope is far more sensitive to light than our eyes." In that sense, the telescope's enhanced vision gives us a truer representation of what these cosmic objects look like than our relatively limited eyes could do. JWST can take images in up to 27 filters that capture different ranges of the infrared spectrum. Scientists first isolate the most useful dynamic range for a given image and scale the brightness values to unlock the most details. They then assign each infrared filter a color from the visible range of the spectrum—the shortest wavelengths get blue, and longer wavelengths move to green and red. After these are added together, all that's left are the normal white balancing, contrast and color adjustments that any photographer might make.

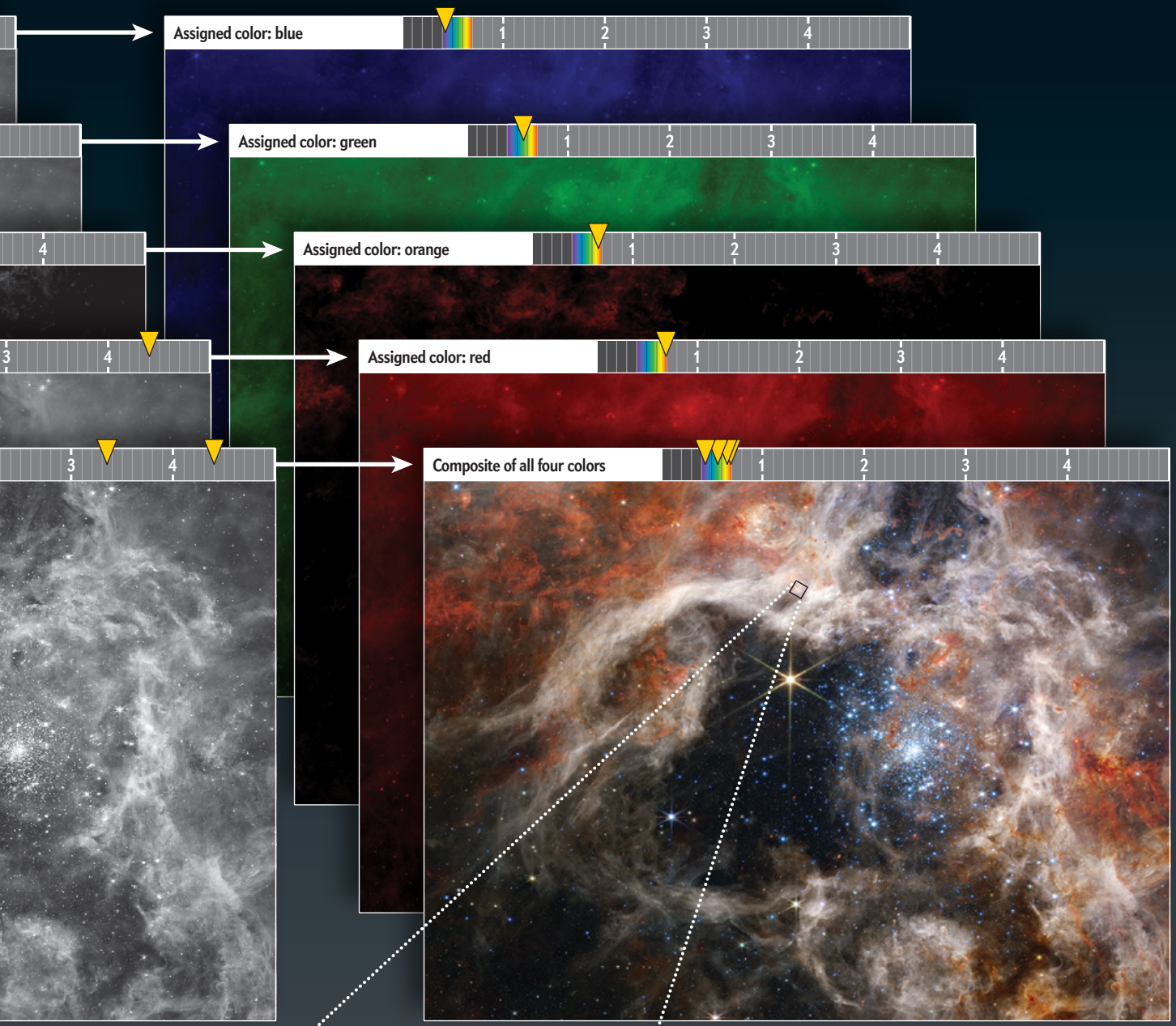


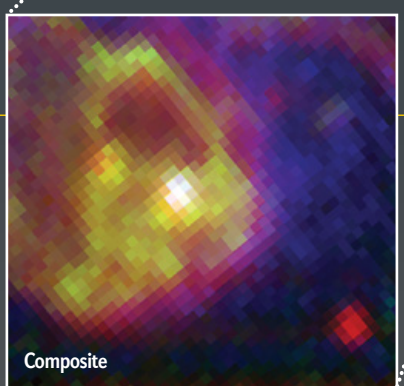












Data Details

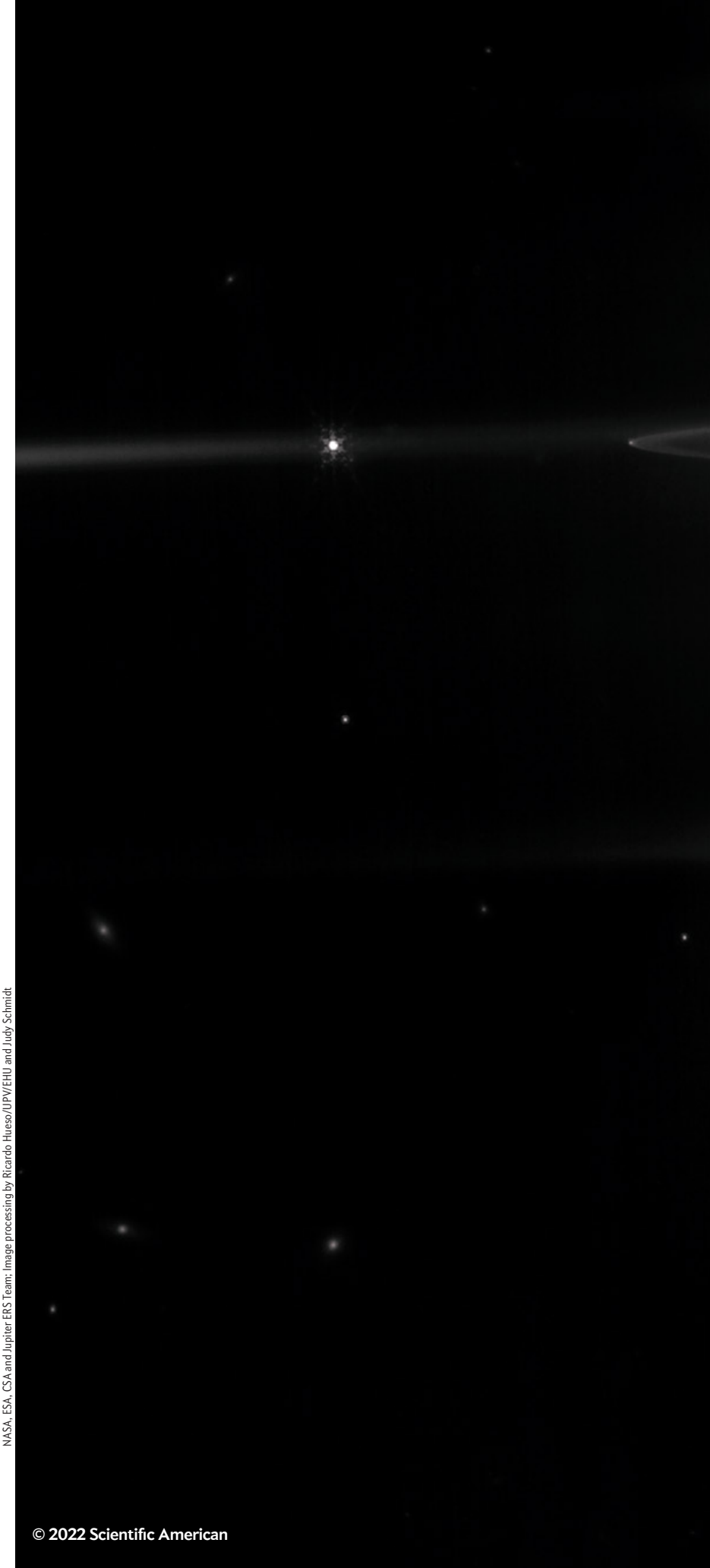
Although the full-color images are captivating, many of the exciting discoveries show up one wavelength at a time. Here the NIRSpec instrument reveals different features of the Tarantula Nebula via different filters. The wavelength emitted by atomic hydrogen (*blue*), for instance, comes from a central star as well as from a bubble surrounding it. In between are the signatures of molecular hydrogen (*green*) and complex hydrocarbons (*red*). The data suggest that a cluster of stars in the frame's lower right is blowing a front of dust and gas toward the central star.

Image source: NASA, ESA, CSA, STScI and Webb ERO Production Team

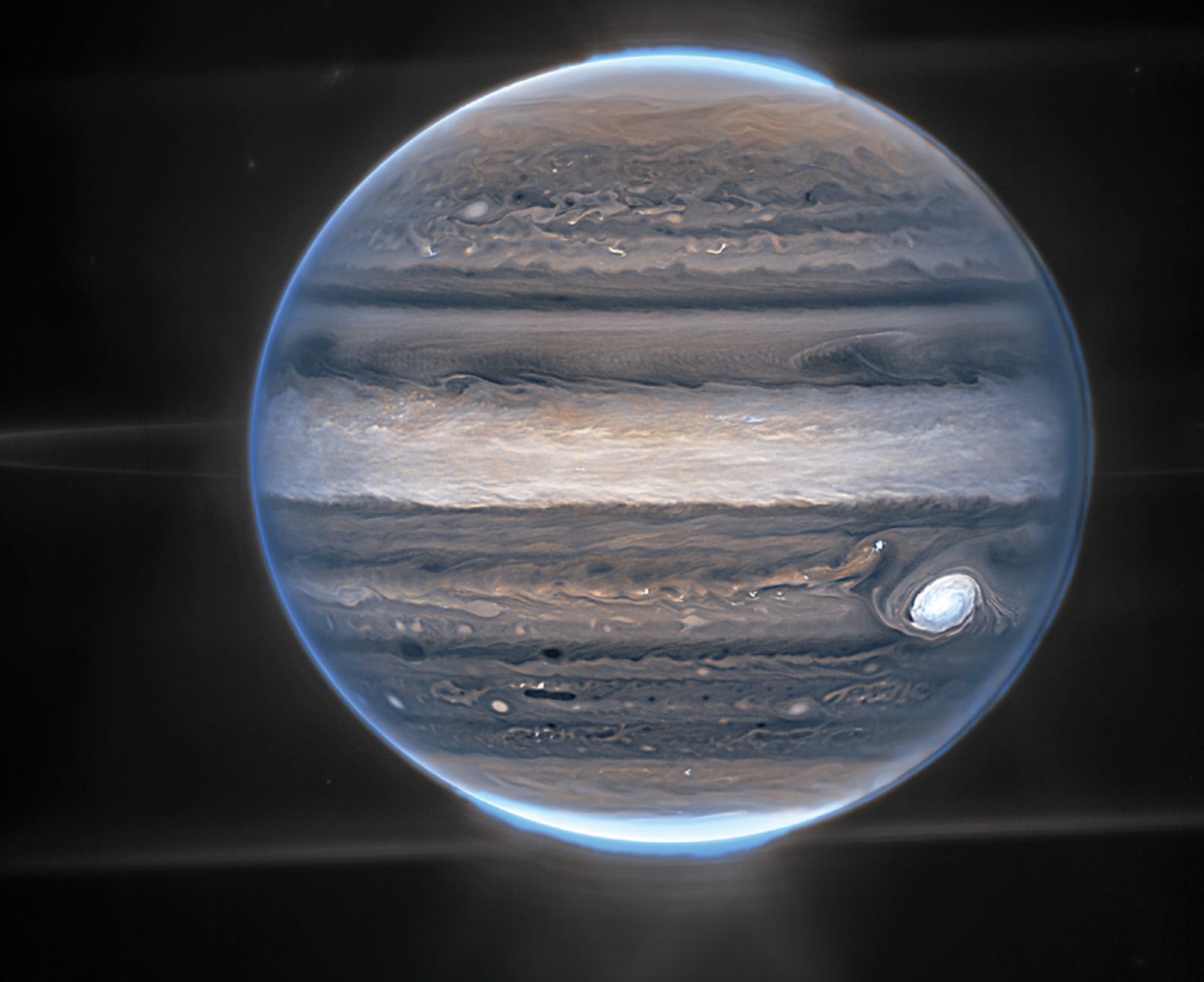
COSMIC PORTRAITS

JWST's new views of familiar space sights reveal details never before seen

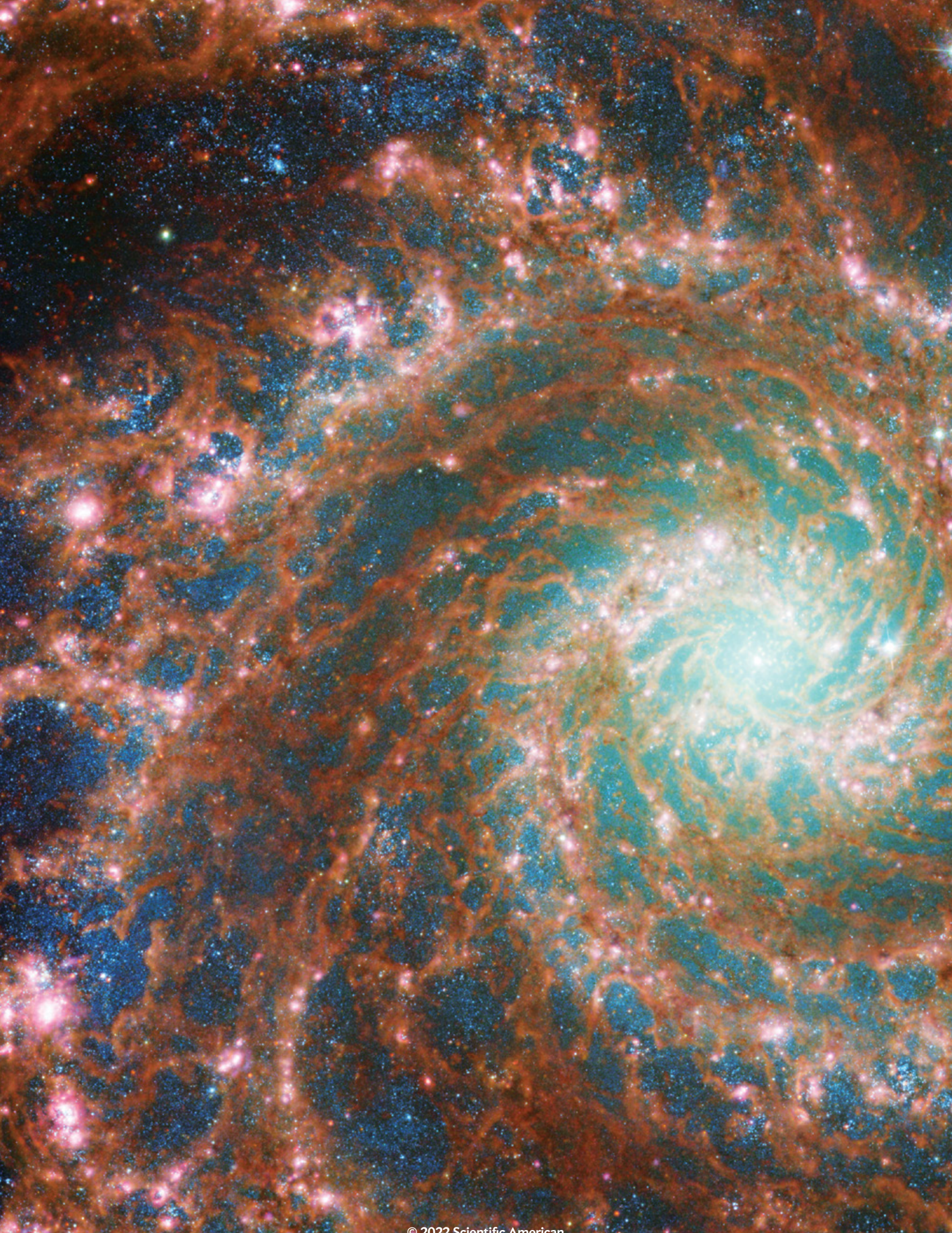
By Clara Moskowitz



NASA, ESA, CSA and Jupiter ERS Team: Image processing by Ricardo Hueso/UPV/EHU and Judy Schmidt



JUPITER'S RINGS, its moons Amalthea (*bright point at left*) and Adrastea (*faint dot at left tip of rings*), and even background galaxies are visible in this image from JWST's NIRCam instrument. Whiter areas on the planet represent regions with more cloud cover, which reflects sunlight, especially Jupiter's famous Great Red Spot; darker spots have fewer clouds. Perhaps the most stunning feature is the blue glow of the planet's auroras at the north and south poles. These light shows result when high-energy particles streaming off the sun hit atoms in Jupiter's atmosphere. Auroras are found on any planet with an atmosphere and a magnetic field, which steers the sun's particles to the poles; besides Earth and Jupiter, telescopes have seen auroras on Saturn, Uranus and Neptune.



THE PHANTOM GALAXY, M74, forms mesmerizing swirls in this photo combining observations from JWST and Hubble. Visible-light data from Hubble showcase the starlight in this spiral, including older, redder stars at the galaxy's glowing core and younger, bluer stars on its outskirts. The infrared light captured by JWST, however, highlights the gas and dust threaded through the spiral arms, as well as a bright cluster of stars at the heart of the galaxy. Each telescope sees a different aspect of this cosmic wonder, and the combined image offers a fuller picture than ever before.

ESA/Webb, NASA and CSA, J. Lee and PHANGS-JWST Team; ESA/Hubble and NASA, R. Chandar; Judy Schmidt

JWST ENABLED this first-ever view of Neptune's rings in infrared, revealing their delicate gossamer glow. The photo also shows seven of the planet's moons, including its largest satellite, Triton, the bright blue dot to Neptune's upper left. The moon's frozen nitrogen surface reflects 70 percent of the sunlight it receives, causing it to shine powerfully in the infrared. Distant galaxies sprinkle the background of this wide-field shot. In the inset, Neptune's layers of rings are clearly visible: two thin, bright ovals and two fainter, spread-out layers. Gleaming spots caused by methane ice clouds in the planet's atmosphere dapple its lower half.

Joseph DePasquale/STScI, Anton M. Koekemoer/STScI, NASA, ESA, CSA and STScI

FROM OUR ARCHIVES

Origami Observatory. Robert Irion; October 2010.
A Telescope's Long Journey. Clara Moskowitz and Matthew Twombly; January 2022.

scientificamerican.com/magazine/sa

PSYCHOLOGY

An Invisible Epidemic

Moral injury results when a person's core principles are violated, such as during wartime or a pandemic, and it afflicts millions

By Elizabeth Svoboda

Illustration by Ashley Mackenzie

Elizabeth Svoboda is a science writer in San Jose, Calif., and author of *What Makes a Hero?: The Surprising Science of Selflessness* (Current, 2013).

IN EARLY 2021 EMERGENCY ROOM PHYSICIAN TORREE MCGOWAN HOPED THE WORST OF THE PANDEMIC was behind her. She and her colleagues had adapted to the COVID-causing virus, donning layers of protection before seeing each patient, but they'd managed to keep things running smoothly. The central Oregon region where McGowan lived—a high desert plateau ringed by snow-capped mountains—had largely escaped the first COVID waves that slammed areas such as New York City.

Then the virus's Delta variant hit central Oregon with exponential fury, and the delicate balance McGowan had maintained came crashing down. Suddenly, COVID patients were streaming into the ERs at the hospitals where she worked, and she had to tell many patients she was powerless to help them because the few drugs she had didn't work in late stages of the disease. "That feels really terrible," McGowan says. "That's not what any of us signed up for."

It wasn't just COVID patients McGowan couldn't help. It was also everyone else. People still approached a health-care emergency with the expectation that they were going to be taken care of right away. But in the midst of the surge, there were no beds. "And I don't have a helicopter that can fly you between my hospital and the next hospital," she says, "because they're all full." A patient with suspected colon cancer showed up bleeding in the ER, and McGowan's inner impulses screamed that she needed to admit the woman immediately for testing. But because there were no beds left, she had to send the patient home instead.

The need to abandon her own standards and watch people suffer and die was hard enough for McGowan. Just as disorienting, though, was the sense that more and more patients no longer cared what happened to her or anyone else. She had assumed she and her patients played by the same basic rules—that she would try her utmost to help them get better and that they would support her or at least treat her humanely.

But as the virus extended its reach, those relationships broke down. Unvaccinated COVID patients walked into the exam room maskless, against hospital policy. They cursed her out for telling them they had the virus. "I have heard so many people say, 'I don't care if I make someone sick and kill them,'" McGowan says. Their ruthlessness simultaneously terrified and enraged her—not least because she had an immunocompromised husband at home. "Every month I do hours and hours of continuing education," McGowan says. "Every patient that I've ever made a mistake on, I can tell you every bit about that. And the thought that people are so callous with a life, when I place so much value on somebody's life—it's a lot to carry."

Moral injury is a specific trauma that arises when people face situations that deeply violate their conscience or threaten their core values. Those who grapple with it, such as McGowan, can struggle with guilt, anger and a consuming sense that they can't forgive themselves or others.

The condition affects millions across many roles. In an atmosphere of rationed care, doctors must admit a few patients and turn many away. Soldiers kill civilians to complete assigned missions. Veterinarians must put animals down when no one steps up to adopt them.

The trauma is far more widespread and devastating than most people realize. "It's really clear to us

that it is all over the place," says psychiatrist Wendy Dean, president and co-founder of the nonprofit Moral Injury of Healthcare in Carlisle, Pa. "It's social workers, educators, lawyers." Survey studies in the U.S. report that more than half of K–12 professionals, including teachers, moderately or strongly agree that they have faced morally injurious situations involving others. Similar studies in Europe show that about half of physicians have been exposed to potentially morally injurious events at high levels.

Even these figures may be artificially low, given scant public awareness of moral injury: many people do not yet have the vocabulary to describe what is happening to them. Whatever the exact numbers, the mental health effects are vast. In a King's College London meta-analysis that surveyed 13 studies, moral injury predicted higher rates of depression and suicidal impulses.

When COVID swept the planet, the moral injury crisis became more pressing as ethically wrenching dilemmas became the new normal—not just for health-care workers but for others in frontline roles. Store employees had to risk their own safety and that of vulnerable family members to make a living. Lawyers often could not meet clients in person, making it nearly impossible to represent those clients adequately. In such situations, "no matter how hard you work, you're always going to be falling short," says California public defender Jenny Andrews.

Although moral injury doesn't yet have its own listing in diagnostic manuals, there is a growing consensus that it is a condition that is distinct from depression or post-traumatic stress disorder (PTSD). This consensus has given rise to treatments that aim to help people resolve long-standing ethical traumas. These treatments—vital additions to a broad range of trauma therapies—encourage people to face moral conflicts head-on rather than blotting them out or explaining them away, and they emphasize the importance of community support in long-term recovery. In some cases, therapy clients even create plans to make amends for harms committed.

Even if moral injury research is a young and growing field, scientists and clinicians already agree that a key step toward healing for morally injured people—whether in therapy or not—has to do with grasping the true nature of what they're facing. They're not hopeless, "bad seeds" or uniquely irredeemable. They may not fit the criteria for PTSD or another mental illness. Instead they're suffering from a severe disconnect between the moral principles they live by and the reality of what is happening or has happened. In moral injury, "that sense of who you are as a person has been brought into question," Dean says. "We have a lot of people saying, 'This is the language I've been looking for for the past 20 years.'"

ANCIENT ORIGINS

ALTHOUGH VA PSYCHIATRIST Jonathan Shay coined the term "moral injury" in the 1990s, the phenomenon predates its naming by millennia. In the ancient Greek epic *The Iliad,* the hero Achilles loses his best friend Patroclus in battle and then inwardly tortures himself because he failed to shield Patroclus from harm. When world wars broke out in the 20th century, people labeled as "battle fatigued" the returning soldiers who bore mental scars. In reality, many of them were tortured not by shell shock but by wartime deeds they felt too ashamed to recount. In the 1980s University of Nebraska Medical Center ethicist Andrew Jameton observed that this kind of moral distress was not confined to the military realm. It often "arises when one knows the right thing to do," he wrote, "but constraints make it nearly impossible to pursue the right course of action."

When COVID swept the planet, the moral injury crisis arose as ethically wrenching dilemmas became the new normal.

What spurred the first rigorous study of moral injury, however, was the multitude of U.S. soldiers struggling after serving in wars in Vietnam, Iraq and Afghanistan. Psychologist Brett Litz of the Veterans Affairs Boston Healthcare System saw quite a few vets of these conflicts who weren't responding well to counseling after their deployments ended. They seemed to be stuck in stagnant grief over acts they'd committed, such as killing civilians in war zones. They reminded Litz of one of his past therapists who'd seemed oddly detached, never mentally present in the room. Afterward Litz found out why. "Probably months before I went to him, he had opened his car door, and he killed a child who was just biking down the road," Litz says. "He was as broken as can be. I witnessed firsthand what that was."

In long conversations with veterans, Litz grew convinced he was witnessing a condition that was different from PTSD and depression. PTSD typically takes root when someone's life or safety is threatened. But much of the lingering trauma Litz saw in vets had nothing to do with direct personal threat. It was related to mounting guilt and hopelessness, "the totality of the inhumanity, the lack of meaning and the participation in grotesque war things," he says. "They were pariahs—or felt that way, at least."

Building on Shay's earlier work, Litz resolved to develop a working concept of moral injury so that researchers could study it in depth and figure out how best to treat it. "I thought, 'This is going to affect our

TORREE McGOWAN, a Central Oregon emergency physician, had to cope with challenges of care that went against her core moral principles.

Richard Darbonne

culture, and there are going to be broad impacts,'" he says. "We needed to bring science to bear. We needed to define the terms."

To that end, Litz and his colleagues published a comprehensive paper on moral injury in 2009, outlining common moral struggles veterans were facing and proposing a treatment approach that involved making personally meaningful reparations for harm done. He noted, too, that not all "potentially morally injurious events" cause moral injury. If you kill someone, and you feel totally justified in having done so, you may not experience moral injury at all. Moral injury tends to turn up when you have a vision of the world as fundamentally fair and good and something you've done or witnessed destroys that vision.

Litz's paper soon caught the attention of Rita Nakashima Brock, then a visiting scholar at Starr King School for the Ministry in California. A theologian and antiwar activist, Brock was preparing to convene the Truth Commission on Conscience in War, an event where returned soldiers would testify about the moral impact of engaging in battle.

Brock's antiwar activism had personal roots. After her father, a U.S. Army medic, returned from Vietnam, he withdrew from his family. When he did speak to his loved ones, he lashed out with an escalating rage. "My dad was so different that I didn't even want to be at home anymore," she says. After Brock's father died, she pieced together more of his story with a cousin's help. He had worked with a guide while deployed, a young Vietnamese woman who was later tortured and killed. He was horrified at what had happened—and

likely also racked with guilt because he knew his ties to the guide could have put her in danger.

As soon as Brock saw Litz's moral injury paper, something clicked. "When my colleague and I read it, we said, 'Oh, my God, this is what the whole thing is about,'" she recalls. "We sent it to everybody testifying and said, 'Read this.'"

CHRONICLING THE UNSPEAKABLE

AFTER BROCK'S 2010 Truth Commission, her committee set forth a key objective: creating programs to inform the public about moral injury. With a grant from the private Lilly Endowment, Brock established a moral injury research and education program at Texas's Brite Divinity School. Later Tommy Potter—then a development officer at Brite—mentioned Brock's work to his childhood friend Mike King, CEO of the national nonprofit Volunteers of America (VOA), and Brock and King arranged a time to meet.

VOA had long focused on helping marginalized populations, and when Brock described the moral injury concept to King, "it just instantly resonated with every area of our work," King says. "It is profoundly there with veterans. But I could see it in our work with folks coming out of incarceration and certainly with health care." So in 2017 VOA put up about $1.3 million in funding to create the Shay Moral Injury Center in Alexandria, Va., named for Jonathan Shay. Brock became the center's first director, heading up research and training programs aimed at understanding and treating moral injury.

Meanwhile moral injury research at Litz's lab and elsewhere was starting to take flight. In 2013, along with his health-care colleagues, Litz debuted and road tested what he called the Moral Injury Events Scale, a measure of exposure to events that can cause moral injury. The scale assessed things such as how much people felt they'd violated their morals, how much they felt others had betrayed important values and the level of distress they experienced as a result. Other investigators have confirmed moral injury can come with significant mental health burdens: in a 2019 study of five VA clinics across the U.S., people who'd experienced moral injury consistently had a higher risk of suicide than control participants.

Other research also backs up Litz's initial hunch that moral injury is distinct from PTSD, although the two conditions sometimes overlap. A 2019 study by researchers at the Salisbury VA Healthcare System in North Carolina reports that moral injury has different brain signatures than for PTSD alone: People with moral injury have more activity in the brain's precuneus area, which helps to govern moral judgments, than those who only have PTSD. And after people suffer moral traumas, they display different brain glucose metabolism patterns than those who suffer direct physical threats, according to a 2016 study by researchers at the University of Texas Health Science Center at San Antonio and their colleagues. The results support developing theories that moral injury is a unique biological entity.

As Brock's Shay Moral Injury Center was being established, she forged connections with powerful people who could get the word out about moral injury—including Margaret Kibben, the current chaplain at the U.S. House of Representatives. Kibben holds regular events for House members, and one of her recent talks was about moral injury. The event drew about three times more members than usual, Brock reports, "and they all wanted to talk about their experience." Brock and Kibben's partnership reflects a growing trend in the study of moral injury: collaboration between scholars and clergy members who aim to chronicle the unspeakable and to help people through it. Moral injury "does really bring together a lot of disciplines," says psychologist Anna Harwood-Gross of Metiv, the Israel Psychotrauma Center in Jerusalem. "It's rare to see articles written by chaplains and psychologists together."

As COVID ravaged the planet from 2020 onward, moral injury research and inquiry took a distinct new turn. Health-care workers spoke out about how rationing care was affecting them psychologically, and Dean and her colleagues Breanne Jacobs and Rita Manfredi, both at the George Washington University School of Medicine and Health Sciences, published a journal article that urged employers to monitor moral injury's effects. "We need time, energy and intellectual capacity to make peace with those specters," they wrote.

The moral injury Dean sees in health care often doesn't stem from one-time, cataclysmic events. Many providers are suffering what she calls "death by a thousand cuts"—the constant, stultifying knowledge that they have to give people subpar care or none at all. "They think they suck. They think they're inadequate," says trauma surgeon Gregory Peck of New Jersey's Rutgers Robert Wood Johnson Medical School. "No one's putting their finger on 'You don't suck. This is moral injury you're suffering.'" Psychiatrist Mona Masood, who founded the Physician Support Line in 2020, has heard countless doctors agonize over daily moral compromises. "We'll hear, 'Am I really a failure? Have I failed my calling? Am I something not human anymore?'"

OFF-AXIS

THOSE WORDS would surely resonate with McGowan. During an increase in COVID cases, as we approach a hospital where she works regular shifts, an ambulance pulls out of the parking lot, lights flashing, underneath looming clouds. "That's probably another transfer," McGowan says. Someone, in other words, has claimed one of the few available COVID beds in the region, meaning someone else—someone just as sick—may have to do without. Inside the ER, a barebones suite of rooms and hallways, glove boxes and black cords dangle from the walls. As we walk around, we spot warning signs of other moral compromises

ahead. A scrawled note on a hallway whiteboard reads, "Critical shortage of green top tubes. 0-day supply of blue tops." When these tubes run out, McGowan explains, she may not be able to order blood tests patients need—and, as a result, may have a hard time figuring out what's wrong with them.

On many days during the pandemic, McGowan has struggled with the dislocation of shuttling between the ER—a personal hell of COVID deniers, irate family members and dying patients—and the outside world, which feels disturbingly normal. How, she wonders, can people nonchalantly chat and sip coffee when, minutes before, she sent someone home who could barely breathe? How can her own moral world be knocked so profoundly off-axis while the larger world continues to spin with scarcely a wobble?

McGowan sees a therapist to help her process the situations she's faced, which she says has been helpful. Yet she continues to grapple with the fallout of moral dilemmas, reflecting a growing consensus that traditional therapy may not always be enough to help morally injured people get past lingering demons. Those who seek help sometimes make headway with basic cognitive-behavioral therapy (CBT), the current gold standard among insurers. Some researchers think CBT approaches are sufficient to treat moral injury.

But one sticking point with CBT is that it focuses on correcting clients' distorted thought patterns. For people with moral injury who've experienced wrenching events that upend their entire value system, ethical distress is genuine, not the product of distorted thinking, Harwood-Gross says. If people with moral injury simply try to retrain their thoughts, they may be left unsatisfied and unhealed.

Therapies for PTSD can likewise fall short for morally injured patients, in Harwood-Gross's experience. PTSD-focused approaches teach clients to adapt to traumatic triggers, such as fireworks that sound like gunshots, but this exposure approach doesn't really help them resolve deep ethical conflicts. Effective moral injury counseling is "more about the processing," Harwood-Gross says. "There has to be that movement: 'How do I see it for what it is and, from there, develop something more meaningful?' It's a more spiritual approach."

Recognizing moral injury's unique challenges, psychologists such as Litz have been creating therapies that more directly address clients' needs. Litz and other providers have pioneered a moral injury treatment called adaptive disclosure. Researchers at Australia's La Trobe University and University of Queensland have developed a similar approach called pastoral narrative disclosure. The latter involves discussing moral issues with a chaplain or other spiritual adviser rather than a doctor.

These therapies stress the importance of moral reckoning. They encourage clients to accept uncomfortable truths: "I led that attack on Iraqi civilians"; "I sent that suffering patient home without treatment." Then, with clients' input, counselors can help them develop strategies for making amends or pursuing closure—say, apologizing to a family whose child they injured.

Early evidence suggests these approaches make headway where others can't. In Litz's initial trial of adaptive disclosure on 44 marines, participants' negative beliefs about both themselves and the world diminished. Most also said the therapy helped to resolve their moral dilemmas.

Earlier this year Litz wrapped up a 173-person clinical trial of adaptive disclosure at VA sites in Boston, Minneapolis, San Diego, San Francisco and central Texas. The trial's results have not yet been published, but Litz found that, in general, adaptive disclosure boosted participants' level of functioning over time. Litz says his goal is not to wipe people's moral slates clean but to restore their ability to thrive. "You'll never not feel awful when you think about what happened," Litz adds. "That's going to be the new normal. The question is 'How do you rehabilitate and live a good-enough life?'"

For Brock's VOA team, moral injury rehabilitation also involves a suite of peer-support programs. The Shay Moral Injury Center's core group offering, Resilience Strength Training (RST), is a 60-hour, in-person program where people with moral injury share stories about events that caused it, engage in talks about forgiveness (for themselves or others), and do exercises to help them define their value system and purpose going forward. In a survey study at two VOA program sites, participants scored an average of 46 percent higher on a scale of post-traumatic growth and 19 percent higher on a scale of perceived meaning in life than they had before starting the program. Although the in-person program paused during the pandemic, plans to restart it are currently underway.

In 2020 VOA created an online version of RST for health workers and others called Resilience Strength Time (ReST). Free ReST sessions run a few times a week, and attendees sign up for as many as they want.

During a recent ReST video meeting, several people showed up to talk for an hour about their moral challenges on the health-care front lines. One spoke about feeling helpless as she watched a patient verbally abuse a nurse giving vaccines. Peer-session leaders Bruce Gonseth and Jim Wong, both war vets, listened closely to each attendee's dilemma and empathized, often sharing recollections of similar situations they had faced. "To me, what we experienced in the war was exactly what frontline workers are experiencing: the invisible enemy," Wong told the group. "You may feel like you're letting other people down. You may observe others engaging in harmful behaviors. You're not alone. We're here to support you."

In most therapeutic relationships, a power differential exists between therapist and client. VOA's groups, where members and facilitators take turns

being vulnerable, put participants on a more even footing. This openness builds bonds that support people's recovery, ensuring their moral struggles won't isolate them. "These are people who know them well and intimately, and it matters," Brock says. "Moral injury is a relationship break—you have an identity crisis. You have to establish new relationships that sustain you."

Therapies addressing moral injury that bolster clients' sense of purpose share a common goal with treatments developed by Austrian psychologist Viktor Frankl, who believed that a personal search for meaning could fuel trauma recovery. To survive his imprisonment in Nazi camps, including Auschwitz, Frankl focused on what motivated him to go on—his boundless love for his wife, his commitment to rewrite a research manuscript the Nazis had destroyed. "Everything can be taken from a man but one thing," Frankl wrote, "the last of the human freedoms—to choose one's attitude in any given set of circumstances, to choose one's own way." After his liberation in 1945, Frankl refined a treatment approach called logotherapy, which emphasized that a sense of purpose could help people endure the gravest suffering.

As Frankl would have done, therapists such as Litz and Harwood-Gross encourage clients to accept the depth of inhumanity in the world rather than attempt to blot out awareness of that inhumanity. The essential question—the same one Frankl confronted—then becomes: "In the midst of what has happened and what is still happening, how can I find meaning in life?"

Partnerships between clinicians and religious leaders have helped facilitate that search for meaning, Brock says. Mental health treatment can feel like a formalized setup in which "the role of the professional is not to be personal," she says. But clergy often excel at connecting on a more informal, human level—an asset in dealing with morally injured people who have come to doubt their own humanity. "Chaplains don't bill by the hour," Brock says. "They spend the time they need to spend with people."

NO EASY WAY OUT

MORAL INJURY TREATMENTS are a needed safety valve for people battling guilt and ethical vertigo. Even so, as old hands on the front lines note, nudging the morally injured toward self-repair goes only so far. Therapy can help you move on from past choices, but unless your employer hires more staff or supplies more resources, chances are you'll have to keep making decisions that violate your ethics, compounding your trauma. A lot of problems that cause moral injury "require systemic solutions on a much broader level," says Andrews, the California public defender.

Yet many organizations are taking the easy way out, Dean says. Instead of launching systemic reforms that could help head off moral injury, they're offering "wellness solutions" such as massages and meditation tips, which can amount to putting a Band-Aid on a broken bone. "If I have to listen to another 'eat well, sleep well, do yoga' conversation, I'm going to throw up," says New York City ER doctor Jane Kim. What would be better, she thinks, is in-depth, system-wide conversations about what frontline workers actually need to do their jobs ethically, not what outside wellness providers assume they need. She argues that reforms based on these frank internal assessments would benefit both workers and those they serve. "We care for other people," she says. "But if we are broken ourselves, how can we possibly help others?"

As the pandemic drags on, similar thoughts occupy McGowan's mind. Although COVID hospital admissions have decreased somewhat in her area, workers have been quitting in droves, which means there still aren't enough providers to give patients adequate treatment. "I compare it to the Bataan Death March. There's no end in sight," McGowan says. On a bookshelf in her light-filled farmhouse, a plaque reads, "You never know how strong you are until being strong is the only choice you have."

Therapies stress the importance of moral reckoning by encouraging people to accept uncomfortable truths.

The windows overlook a parched expanse of field—McGowan's farmer husband grew just a fraction of his usual hay crop last year because of a drought. In some ways, they face the same existential dilemma: What do you do when forces beyond your control shrivel your highest intentions?

To counter thoughts of hopelessness, of failing her medical calling, McGowan tries to focus on specific acts of good she's been able to perform. When she's not in the ER, she serves as a lieutenant colonel in the Oregon Air National Guard, and her unit has vaccinated more than 100,000 people against COVID.

Mentoring other doctors, too—offering advice as they process the same kinds of harrowing choices and regrets she's had—has buoyed her. "That's helped me learn to be a little bit kinder to myself," McGowan says. "The same words that I tell them, I try to repeat to myself: You did the best that you could." She inhales, hesitating. "And you are still a good doctor. I would still let you take care of my family." SA

FROM OUR ARCHIVES

Nurses Struggle through a New COVID Wave with Rage and Compassion. Kathryn Ivey; ScientificAmerican.com, January 11, 2022.

scientificamerican.com/magazine/sa

"I HAD NEVER SEEN DEATH the way I've seen death when it comes to opioid addiction," says Thomas Gooch, a recovery counselor in Nashville, Tenn. On his phone, Gooch displays a picture of his wife, who died of an overdose.

HEALTH

Overdose of Inequality

The face of the opioid epidemic has changed, from white and middle class to Black and brown people. They are dying because of biases in medical treatment

By Melba Newsome

Photographs by Gioncarlo Valentine

Melba Newsome is an award-winning science, health and environmental reporter. She lives in Charlotte, N.C.

Gioncarlo Valentine is an award-winning photographer and writer from Baltimore. Backed by his seven years of social work experience, Valentine examines issues faced by marginalized populations, most often focusing his lens on the experiences of Black and LGBTQIA+ communities.

IN ONE WAY OR ANOTHER, THOMAS GOOCH HAS SPENT MORE THAN 30 years struggling with illegal drugs. The 52-year-old Nashville, Tenn., native grew up in extreme poverty. He was first incarcerated in 1988 and spent the next 15 years in and out of jail for using and selling narcotics. "Until 2003," Gooch says. "That was the first time I went to treatment and the last time I used." Since then, for most of 19 years, Gooch has been trying to get others into recovery or just keep them alive. He handed out clean needles and injection-drug equipment—which reduce injuries, infections and overdose deaths—in Nashville's hardest-hit communities. In 2014 he founded My Father's House, a transitional recovery facility for fathers struggling with substance use disorder.

But despite Gooch's long experience, the opioid epidemic recently has brought a level of devastation to the Black community that has shocked him. "I had never seen death the way I've seen death when it comes to opioid addiction," he says. "There's been so many funerals, it doesn't even make sense. I personally know at least 50 to 60 individuals who died from overdoses in the last 10 years." That staggering body count includes Gooch's recently estranged wife in 2020 and a former partner in 2019.

A million people in the U.S. have died of opioid overdoses since the 1990s. But the face—and race—of the opioid epidemic has changed in the past decade. Originally white and middle class, victims are now Black and brown people struggling with long-term addictions and too few resources. During 10 brutal years, opioid and stimulant deaths have increased 575 percent among Black Americans. In 2019 the overall drug overdose death rate among Black people exceeded that of whites for the first time: 36.8 versus 31.6 per 100,000. And with the addition of fentanyl, the synthetic opioid that's 50 to 100 times more powerful than morphine, Black men older than 55 who survived for decades with a heroin addiction are dying at rates four times greater than people of other races in that age group.

The reasons for this dramatic change come down to racial inequities. Research shows that Black people have a harder time getting into treatment programs than white people do, and Black people are less likely to be prescribed the gold standard medications for substance use therapy. "If you are a Black person and have an opioid use disorder, you are likely to receive treatment five years later than if

LOFTIN WILSON, program manager for the NC Harm Reduction Coalition in Durham, N.C., uses his van (*top*) to reach people with substance use disorders. He gives out supplies, including opioid overdose rescue kits (*far right*), safe single-use cookers for drug injections (*center*), and condoms (*left*).

YVONNE ALLOWAY, who has opioid use disorder, sits in her doctor's Washington, D.C., office after being treated with Suboxone. The medication reduces dependence on opioids and decreases the severity of withdrawal symptoms.

you're a white person," says Nora D. Volkow, director of the National Institute on Drug Abuse at the National Institutes of Health. "Treatments are extraordinarily useful in terms of preventing overdose death so you can actually recover. Five years can make the difference between being alive or not." Black people with substance use problems are afraid of being caught up in a punitive criminal justice system and are less likely to have insurance good enough to allow them to seek help on their own. And the COVID pandemic disrupted many recovery and harm-reduction services, particularly for people of color.

Gooch blames straight-out racial discrimination in the health-care system, too. "When we call different places to try to get people into treatment, the question they ask is 'What drug do they use?'" he recounts with exasperation. "If you say 'crack,' all of a sudden they ain't got no bed available. If you say opioids and heroin, they will find a bed because that's the demographic they want. A couple of times I told patients that the only way they're going to get help is to get drunk and turn themselves into Vanderbilt Hospital because Vanderbilt will hold them for five days, and that'll get them into treatment."

Gooch is one of the people trying to improve access to therapies for addiction and change the overall dysfunctional dynamic. Other groups are bringing more effective addiction treatments within prison walls, reducing the chances of recidivism on release. A proposed federal law would make therapy with the commonly used addiction medication methadone less onerous for an impoverished population, as well as less stigmatizing. And Volkow is using her platform at the NIH to highlight the overwhelming research-based evidence for better ways to understand and treat addiction.

ACCESS TO TREATMENT

THE NATION'S HISTORIC RELUCTANCE to treat addiction as a health-care issue rather than a criminal justice one has resulted in a health-care system where too few people of any race—just 10 percent—receive treatment for substance use disorder. Several factors, such as stigma and an inability to afford or access care, make the numbers considerably more dismal among people of color. Even after a nonfatal overdose, Black patients are half as likely to be referred to or access treatment as non-Hispanic white patients, according to federal government data.

A growing recognition that criminalization and incarceration do little to curb illegal drug use or improve public health or safety has led to harm-reduction policies such as Good Samaritan laws—statutes that provide limited immunity for low-level drug violations and increase availability of naloxone, a drug that can reverse overdose. But racial disparities have emerged in the application and effectiveness of both measures. A study from RTI International found that Black and Latino intravenous drug users have inequitable access to the medication.

Loftin Wilson, program manager for the NC Harm Reduction Coalition in Durham, N.C., who has worked in the field for more than a decade, says the problems with inequality lead to distrust in the system, which creates a vicious cycle in which people who need help won't go to institutions that can pro-

vide help. People entering treatment worry, with good reason, that dealing with the social service system can cause them to lose their employment, housing or even custody of their children. "That's another example of the negative experiences people who use drugs have. They definitely don't land equally on everybody, and people don't experience them all the same way. It is a vastly different experience to be a Black drug user seeking health care than for a white person," Wilson says.

University of Cincinnati psychologist Kathleen Burlew notes, as Volkow does, that when Black patients enter treatment, they are more likely to do so later than white people and are less likely to complete it. In addition to mistrust, she says, the less favorable outcomes result from factors such as clinician bias and lack of racial and ethnic diversity among treatment providers.

Federal resources, such as grants to support local opioid use disorder clinics and programs, also tend to favor white populations. According to 2021 data from the Substance Abuse and Mental Health Services Administration, 77 percent of the clients treated with grant funding were white, 12.9 percent were Black and 2.8 percent were Native American. The disparity is even more pronounced in some states. For example, in 2019 North Carolina announced that white people made up 88 percent of those served by its $54-million federal grant, compared with 7.5 percent for Black people. Native Americans accounted for less than 1 percent of those served.

MEDICATION INEQUALITY

RESEARCH HAS SHOWN that there is a bias among health-care providers against using medication-assisted treatment (MAT), which combines FDA-approved drugs with counseling and behavioral therapies. Substance use specialists consider it the best approach to the opioid use problem. Yet a study published in *JAMA Network* found that about 40 percent of the 368 U.S. residential drug programs surveyed did not offer MAT, and 21 percent actively discouraged people from using it. Many addiction treatment programs are faith-based and see addiction as a moral problem, which leads to the conclusion that relying on medication for abstinence or sobriety simply trades one form of addiction for another. Many general practitioners who lack training in addiction medicine have this misconception.

The three medications approved by the FDA are buprenorphine, methadone and naltrexone. Buprenorphine and methadone are synthetic opioids that block brain opioid receptors and reduce both cravings and withdrawal. Naltrexone is a postdetox monthly injectable that blocks the effects of opioids. Very few insurance providers in the U.S. cover all three medications, and according to the Centers for Disease Control and Prevention, the full range of medications is far less available to Black people.

Research suggests that economics and race influence who receives which medications. Buprenorphine, for instance, is more widely available in counties with predominantly white communities, whereas methadone clinics are usually located in poor communities of color.

To use methadone, patients must make daily visits to a clinic to receive and take the medication under the supervision of a practitioner. This requirement makes it difficult to do things that build a normal life, such as attending school and obtaining and maintaining a job. There is also the stigma of standing in a public line known to everyone passing by as a queue for addic-

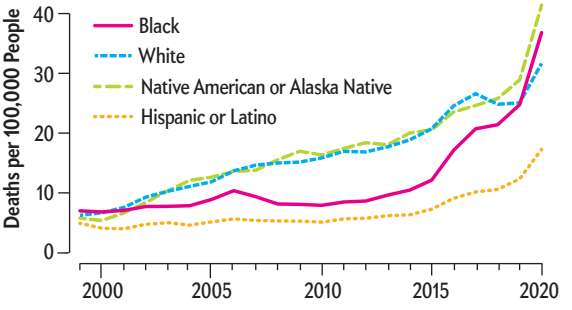
Drugs, Death and Race

Drug overdoses hit groups of all backgrounds, but data indicate that in recent years, those hardest hit have shifted from white people to people of color. Breaking out statistics by demographic group and location can infringe on privacy, but studies that have done this carefully point to an overall trend.

All Drugs across the U.S.

Deadly drug overdoses climbed sharply among Black people around 2018–2020. For the first time since 1999, the rate was higher than among white people. Native Americans had the biggest increase. The arrival of toxic drugs such as fentanyl, on top of inequalities in living conditions, seems to have spurred the rise.

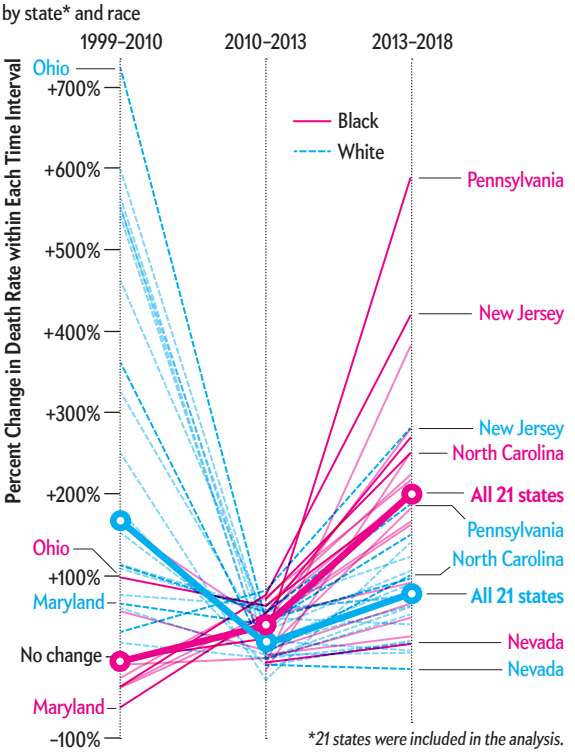
U.S. Drug Overdose Death Rates
per 100,000 people, by race and/or ethnicity



Opioids in 21 States

The rate of change in opioid-involved deaths dropped for white people in the first decade of this century and then climbed after 2013. For Black people, an early, smaller rate of increase turned into a steep rise. Some states had bigger changes than others.

Relative Change in Opioid-Involved Overdose Death Rates
by state* and race

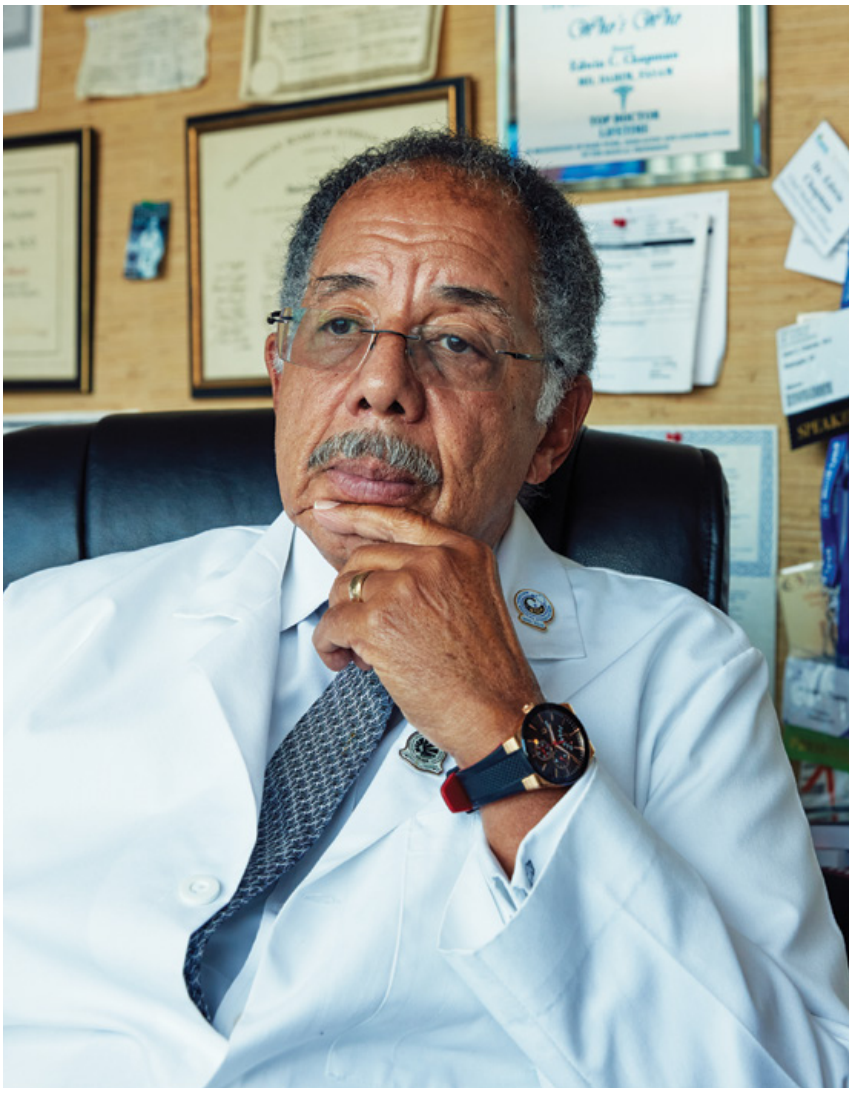


Sources: "Evaluation of Increases in Drug Overdose Mortality Rates in the US by Race and Ethnicity before and during the COVID-19 Pandemic," by Joseph R. Friedman and Helena Hansen, in *JAMA Psychiatry*, Vol. 79; March 2022 (*drug overdose data*); "African Americans Now Outpace Whites in Opioid-Involved Overdose Deaths: A Comparison of Temporal Trends from 1999 to 2018," by Debra Furr-Holden et al., in *Addiction*, Vol. 116; March 2021 (*opioid-involved death rate data*).

Graphic by Jen Christiansen

tion treatment. "The treatment model was developed [during the Nixon administration] based on racism and a stigmatized view of people with addiction without any thought of privacy or dignity or treating addiction like a health problem," says Andrew Kolodny, medical director of the Opioid Policy Research Collaborative at Brandeis University. The stigma is made worse by methadone's classification as a Schedule II controlled substance, which is defined as a substance with a high potential for abuse, potentially leading to severe psychological or physical dependence. This categorization pushed the medication into a quasicriminalized status and the clinics into minority communities.

Buprenorphine, however, is a completely different story. When opioid use problems increased in white communities, Congress acted to create less stigmatizing treatment options. The Drug Addiction Treatment



EDWARD CHAPMAN, a doctor in Washington, D.C., treats patients with opioid use disorder in his office (*above* and *left*). He offers them medication-assisted treatment such as buprenorphine, which blocks opioid receptors in the brain.

Act of 2000 ("DATA 2000") lifted an 86-year ban that prevented treating opioid addiction with narcotic medications such as buprenorphine, which today is sold under the brand names Subutex and Suboxone. The majority of doctors who got special federal licenses to prescribe it accept only commercial health insurance and cash, so the drug is usually offered to a more affluent population, which in the U.S. means white people. About 95 percent of buprenorphine patients are white, and 34 percent have private insurance, according to a national study of data through 2015.

John Woodyear is an addiction treatment specialist in Troy, a small rural town in south central North Carolina where the epidemic is exacting an increasingly heavy toll on the Black and Native American populations. Overall overdose death rates increased 40 percent from 2019 to 2020, but death rates among those two groups in particular went up 66 and 93 percent, respectively. Yet Woodyear, who is Black and practices in a town that is 31 percent Black, says his patients are 90 percent white. People come to the clinic through word of mouth or referrals from friends. As long as Woodyear's patients are mostly white, new patients will be mostly white as well, he says.

One exception to this racial pattern is Edwin Chapman's clinic in the Northeast neighborhood of Washington, D.C., one of the district's predominantly Black and most impoverished communities. Chapman, a physician, often prescribes buprenorphine to his patients with opioid use problems, and the overwhelming majority of them are Black. He says that to prescribe the drug, physicians like him must get past certain roadblocks. "The insurance companies in

many states put more restrictions on patients in an urban setting, such as requiring prior authorization for addiction treatment," he says. Further, "to increase the dose above 16 or 24 milligrams, you may have to get a prior authorization. The dosing standards were based on the white population and people who were addicted to pills. Our surviving Black population often needs a higher dose of buprenorphine."

Chapman says few physicians in private practice are willing to treat these patients. "They don't really feel comfortable having these patients in their office, or they aren't really prepared to deal with the economic and mental health issues that come with this population," he explains; those disorders include bipolar disorder and schizophrenia, among others.

People have their own biases that keep them away from medication such as buprenorphine, Wilson says. Many view it as simply trading one drug for another. "They think, 'If I'm going to take this step, why not just go to detox and not take any medications at all?'" he says. "There's a big cultural misunderstanding about the fact that [these] medications are the only evidence-based treatment for opioid use disorder. Short-term detox isn't the most appropriate intervention for most people."

Gooch agrees that the bias is real. He facilitates recovery groups at a program operated by a group from Meharry Medical College, a historically Black institution. Yet "I haven't seen one Black person yet," Gooch says. "Some think it's a setup. There's so much distrust, they have a hard time thinking it's legal. It's just the culture of Black people. Many are religious and think [taking the drug] is wrong."

"Those [misconceptions] are holdovers from our having been miseducated from the outset," Chapman says. "Whites have done a tremendous job educating their community that this is a medical problem, a disease. In the African American community, drug addiction has always been and continues to be seen as a moral problem, and incarceration was the treatment."

HOPE FOR CHANGE

IN THE NOVEMBER 2021 ISSUE of *Neuropsychopharmacology,* Volkow argued that it is long past time for a new approach to drug addiction that would address these misconceptions within the most affected populations and biases among providers. "We have known for decades that addiction is a medical condition—a treatable brain disorder—not a character flaw or a form of social deviance," she wrote.

Volkow argues that treatment reform should start with prison and the criminal justice system. Even though there is no difference along racial lines in who uses illegal drugs, Black people nonetheless were arrested for drug offenses at five times the rate of white people in 2016. The racial disproportionality in incarcerated drug offenders does not reflect higher rates of drug law violations, only higher rates of arrest among racial and ethnic minorities. Currently the number of arrests for heroin (which more Black people use) exceeds the arrests for diverted prescription opioids (which more white people use), even though the latter is more prevalent.

These unequal arrests and incarcerations add to the racial inequalities in drug treatment and survival rates. An estimated two thirds of people in U.S. correctional settings have a diagnosable substance use disorder, and approximately 95 percent will relapse after their release. In the two weeks postrelease, the risk of overdose increases more than 100-fold, and the chances of death increase 12-fold.

Paradoxically, that makes prisons and jails—institutions with the most obvious and overt racial disparities—the places with the greatest potential to bring about effective change. Volkow points to a recent NIH study as proof that starting substance disorder treatment during incarceration lowers the risk of probation violations and reincarcerations and improves the chances of recovery. But only one in 13 prisoners with substance use problems receives treatment, according to a Pew data analysis.

Some local programs have started to tackle some of these issues. In Pittsburgh, the Allegheny Health Network's RIvER (Rethinking Incarceration and Empowering Recovery) Clinic opened in May 2021. Its goal is to reduce recidivism among people with addictions by providing care for the formerly incarcerated immediately on their release from jail, regardless of their ability to pay. Since opening, the clinic's caregivers have engaged with hundreds of people.

New York City recently became the first municipality in the country to sanction overdose prevention centers where people with substance use disorder can use drugs under medical supervision. Two sites, one in East Harlem and the other in Washington Heights, opened in December 2021. They have had more than 10,000 visits and prevented nearly 200 overdoses by administering the medication naloxone.

There are other signs of change, too. California signed a law that requires every treatment provider in the state to provide a "client bill of rights" to notify patients of all aspects of recommended treatment, including no treatment at all, treatment risks and expected results. And federal authorities loosened methadone regulations during the pandemic. Instead of daily in-person visits, more patients were allowed to use telehealth consultations and take doses home. Senators Ed Markey of Massachusetts and Rand Paul of Kentucky have introduced a bill that would make that change permanent. Among other programs and initiatives across the country, these are an indication that drug treatment policy may be headed in a more equitable, evidence-based direction. SA

GOOCH (*right*) sits in the kitchen of My Father's House, a recovery facility he founded in Nashville, alongside Charles Gordon, a resident. Gooch says the health-care system discriminates against the Black population, and Black people with addiction problems have difficulty getting treatment from private doctors and hospitals.

FROM OUR ARCHIVES

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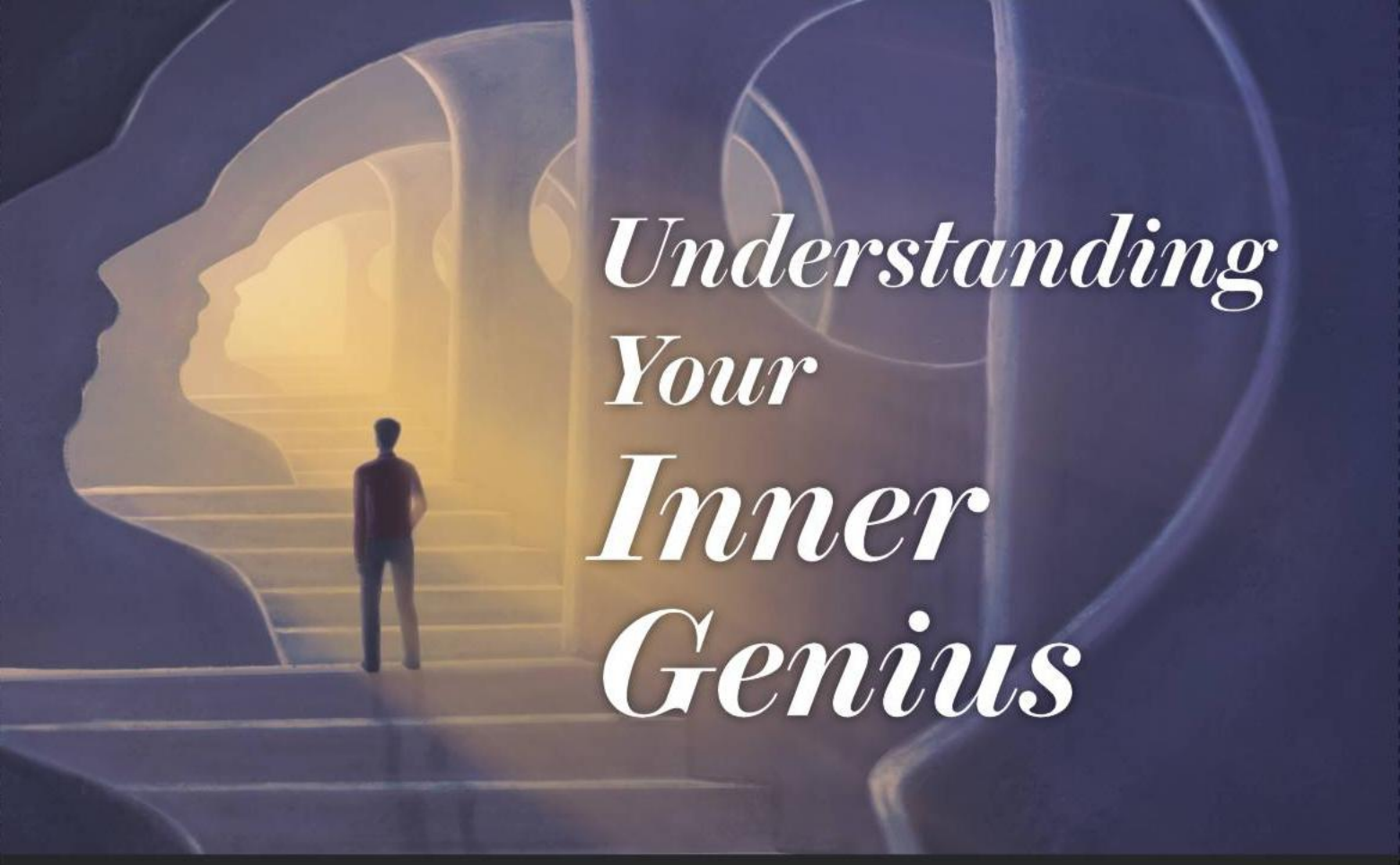

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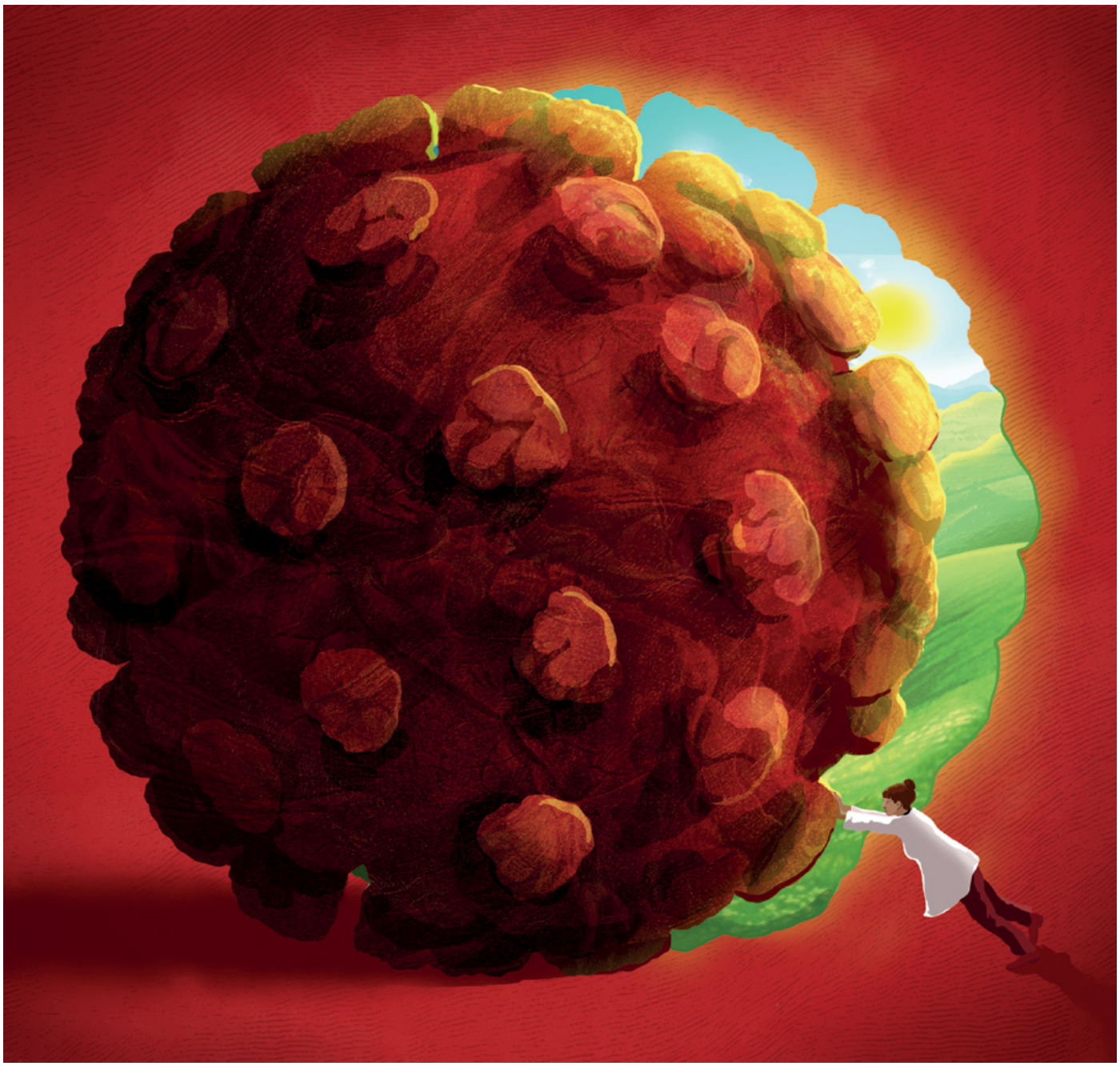

The global challenge of infectious disease

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The COVID-19 pandemic is not over, and already its cost is staggering. The disease could have contributed to around 17 million deaths. And, by 2024, the hit to the global economy could reach US$12.5 trillion. Everyone has experienced an extraordinary few years that few people would want to repeat. If the world is to avoid a similar or worse event in the future, countries must ensure that they are better prepared to deal with pandemics.

The response to the SARS-CoV-2 virus is far from perfect. High points, such as the speed at which effective vaccines were developed, contrast with low points, such as the unequal distribution of those vaccines around the world. The pandemic can teach us many valuable lessons that, if acted on, will put the world in a much better position to respond to future threats (see page S20).

Many eyes are on viruses that jump from animals to people — most pandemics in recent decades have emerged in this way (S11). Machine learning could help to predict what the next pandemic-causing pathogen will be, or where it might first infect people (S12). Climate modelling could also inform plans for infectious-disease outbreaks (S15).

Such work will at most reduce the frequency of pandemics. When an outbreak inevitably strikes, health-care professionals must have the tools and training to spot it and take action to limit its spread (S8). Delaying transmission is crucial to fighting infectious diseases, which, as history tells us, are very difficult to eradicate after they have gone global (S18). Some strategies that could help to achieve this can operate in the background — far-ultraviolet lamps, for instance, could disinfect the air in public spaces (S16). But many others require public buy-in, and the sometimes confused messaging around COVID-19 revealed weaknesses in how public-health authorities communicate health advice (S4).

Researchers have laid a path to better pandemic preparedness. Leaders of governments and industry must now follow it (S7).

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Richard Hodson
Senior supplements editor

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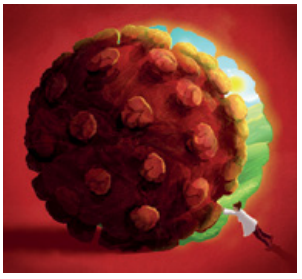

On the cover
A scientist rolls away a virus, revealing a brighter world. Credit: Sam Falconer

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ILLUSTRATION BY SAM FALCONER

The art of persuasion

Health policymakers need to cultivate social trust and plan effective communication strategies well before the next pandemic. **By Elizabeth Svoboda**

When Robb Willer looks back on the early days of the COVID-19 pandemic – when leaders still had a chance to stop the virus from bringing the world to a halt – there's a fateful moment that stands out. In February 2020, global health authorities spoke in one voice, advising the public not to wear masks to prevent infection.

"Seriously people – STOP BUYING MASKS!", tweeted the then US surgeon general Jerome Adams, stressing that masks would not protect the general public from the virus. The World Health Organization (WHO) similarly advised that masks should only be used by health-care workers or people with a cough or fever.

But the message was soon reversed. Scientists knew that masks helped to prevent airborne viral infections; the early mask guidance was mainly geared towards preserving supplies for health workers. Once people realized that the authorities had not acted in their best interest, resentment began to smoulder.

The mask-messaging fiasco "was a big credibility mistake", says Willer, a sociologist at Stanford University in California. "It hurt the response that they weren't honest." Leaders should always be transparent about why pandemic health measures are being implemented, he says, even if some facts are tough to swallow.

Although COVID-19 isn't yet in the rear-view mirror, policymakers are already discussing how its lessons should shape our response to future pandemic threats, including the current outbreak of monkeypox. A fresh flood of behavioural-science research supports their plans. This work lends insight into which policies and campaigns are most effective at convincing people to follow health guidance that helps to stop the spread of disease.

The messages that have the most influence are not always the ones that policymakers assume will work. Appeals to the empathy and responsibility of the public, delivered by people whom listeners trust, can work better than outright mandates. Offering rewards for vaccination might be less effective than simply issuing reminders. Timing is also crucial – what motivates people at one stage of a pandemic might be less effective later. And, as the mixed messaging around masks shows, honesty is a baseline requirement.

The process of refining public-health outreach should be under way well before the next pandemic hits, says Matthew Goldberg at Yale University in New Haven, Connecticut, whose research focuses on persuasion. "We need to be doing the work now," he says, "so that when the time arises, people can act quickly."

Make it easy

To help society mount a collective defence against pathogens, researchers say that leaders should enlist human-behaviour specialists to play a much bigger part in health policy. This has been the Achilles heel of governments during the COVID-19 pandemic, says Armand Balboni, an infectious-disease researcher and chief executive of pharmaceutical firm Appili Therapeutics in Halifax, Canada. "Social

scientists, anthropologists and psychologists were not used nearly enough," Balboni says.

Part of crafting effective public-health messages is finding ways to avoid restricting people's choices outright. Although health-related mandates are sometimes necessary during a pandemic, they can provoke a backlash and complicate further efforts to stem the spread of disease. Some businesses, for example, have rebelled against enforced closures during the pandemic. Instead, behavioural economist Varun Gauri at the think tank the Brookings Institution in Washington DC, advocates for a 'nudge' strategy that makes doing the responsible thing require very little effort. "The one thing that's close to universal in behavioural science is, we're all lazy," says Gauri.

Making it easier to do the right thing could be as simple as placing hand-sanitizer units in more-accessible locations. In one study[1], this strategy boosted people's compliance with hand-hygiene advice without the need for mandates. And a study[2] by behavioural scientist Katy Milkman at the University of Pennsylvania, Philadelphia, suggests that repetition is a powerful nudge strategy. People were more likely to have a vaccination when researchers sent them reminders compared with a control group, confirming previous ideas that reiterating messages gets results.

Some persuasion strategies that make intuitive sense, however, do not seem to have the desired result. After the first COVID-19 vaccines were rolled out in the United States, local and state officials invested millions in the idea that waving money at people would convince them to get the jabs. Leaders tried straight cash incentives, whereby people collected a set sum for getting vaccinated, as well as lotteries, in which vaccinated people were entered into a draw to win a cash prize.

But the concept often flopped. One study[3] that gauged the effectiveness of vaccine lotteries found that vaccination rates were not significantly higher in lottery states than in non-lottery ones. Guaranteed cash payouts were somewhat more likely to encourage vaccination, a meta-analysis showed[4]. Still, the evidence on incentive-based persuasion "is pretty disheartening in general", Milkman says.

She is now studying a twist on the lottery strategy that might deliver more value for money — a regret lottery. This involves telling people that their name has been entered into a draw to win a large amount of money, but if their name is pulled from the hat and they have not been vaccinated then they will have to decline the reward. When Milkman and her team tried this in Philadelphia[5], vaccine rates in the area increased slightly compared with those in other, similar areas that did not have a regret lottery. "The one data point we have looks promising," Milkman says, but further research is needed to confirm the finding.

Our better nature

Although personal gain might not be a strong motivator, empathy could be. Encouraging feelings of empathy in people could make them more likely to choose to protect others during a pandemic. One group of researchers reported[6] that people who watched a video of a 91-year-old man describing being unable to visit his sick wife because of the COVID-19 pandemic were more likely to want to practice physical distancing than people in a control group who were not shown the film. Emotional appeals, therefore, could nudge people towards adopting helpful behaviours.

"The one thing that's close to universal in behavioural science is, we're all lazy."

Invoking empathy can work even in populations that are suspicious of pandemic control measures. In a survey[7] of more than 6,000 people in the United States and Europe, researchers found that people opposed to vaccines were most likely to draw back from their stance when presented with appeals to protect the health of others. They were less moved by the messages noting that they personally stood to benefit from the jab. The researchers say that policymakers should therefore stress vaccines' collective benefits, such as protecting others and keeping the economy humming. Most people don't like to be told what to do, Balboni says. "What is really helpful is when you can get people to take ownership or responsibility — that by and through their behaviour, they can actually protect other people."

Winning over the most sceptical in society also involves making sure they get accurate information. During the COVID-19 pandemic, disinformation played a major part in sowing division and undermining the authority of health officials, Gauri says. That paved the way for fast viral spread and low vaccination rates.

To keep fake news from gaining a foothold, Milkman says, health departments need to be transparent and honest when they communicate with the public. That doesn't mean describing every aspect of a crisis in detail, but it does mean ensuring that the messaging at the heart of health campaigns is bulletproof. Leaders disregarded this principle when they told people that masks were not effective, and in turn people began to ignore official health communication. This allowed conspiracy theories an opportunity to slither in.

Behavioural researchers also want to give people the skills they need to better distinguish between bona fide health advice and conspiracy theory. Jon Roozenbeek, a psychologist at the University of Cambridge, UK, is testing a strategy of 'immunizing' people against disinformation by exposing them to controlled doses of it — just as a live-virus vaccine protects people from a full-blown infection. He has built this approach into a series of free video games. One of them, called *Go Viral!*, teaches people to be sceptical of pandemic fake news by playing at being outrageous disinformation czars, publishing false headlines such as "I was silenced for trying to speak out about unsafe coronavirus vaccine!"

After playing an inoculation game, people interpret fake-news tweets as less reliable than they did before, and they're better able to spot deceptive tactics in a series of fake headlines[8]. "The robustness is quite good from a 15-minute intervention," Roozenbeek says.

But preparing the public is only a start. To limit the toll of disinformation in future pandemics, Gauri thinks public-health authorities will need to take a bigger, legislative approach to the problem. "If you've got a good regulatory scheme in place to prevent it, that's really crucial," he says. That could mean, for example, creating transparency laws that require online platforms to inform users of the source of suspect health content, without promoting active censorship of that content.

A trusted voice

The source of health information is important not only for helping people to tell fact from fiction. One of the major insights that behavioural scientists gleaned from the 2014 Ebola epidemic in West Africa was that the messenger mattered even more than the message being conveyed. People were more comfortable following lifesaving recommendations and seeking Ebola treatment if local leaders, rather than Westerners, communicated health guidelines. "If you didn't have spokespeople who were credible, respected, trusted authorities within the community, it didn't really matter what the content of your message was," Willer says. "If you're an untrusted outsider, you can't get anywhere."

One team of researchers has memorably shown the lifesaving wallop a well-chosen pandemic messenger can pack[9]. The team culled footage of former US president Donald Trump urging people to have the COVID-19 vaccine, then wove the clips into a 27-second YouTube video. When the researchers aired the Trump message online in US counties with low vaccination rates, hundreds of thousands more

Former US surgeon general urges people to wear masks — contradicting previous advice.

HUM IMAGES/UNIVERSAL IMAGES GROUP VIA GETTY IMAGES

people got vaccinated. "For the most opposed people," Willer says, "he was arguably the most respected person in the world to tell them."

In future pandemics, well-chosen pastors, community leaders or local influencers could be used more liberally to promote essential public-health messaging. Although some celebrities and sports stars did this during the COVID-19 pandemic, health authorities could reach out to a wider pool of candidates who have their own distinct followings. "If we can find those people early, or even pre-record them, that might be useful to have that ready to go when the time comes," Gauri says.

The timing of public-health messaging is also important to its success — the earlier that health departments issue clear guidance on responding to a pandemic, the better. That's because people are most open to persuasion when they first learn the facts about a situation, Willer says. "You want to jump on the critical windows when they appear."

A study of the Italian population, which was among the hardest hit by the first waves of COVID-19, found that almost everyone believed public-health messaging during the early stages of the pandemic — even people who did not generally trust the government[10]. That high level of buy-in cleared the way for strict quarantine strategies that limited the pandemic's spread.

But once people start to feel saturated with information, the power of public-health messaging can start to wane. When people received informational messages about how COVID-19 spreads, these messages decreased trips outside the home only for those who had started socially distancing in the past couple of weeks[11]. For those who had already been practising distancing for a month or more, the messages had almost no effect, and even decreased adherence to distancing guidelines.

Once people have been bombarded with messaging on a certain topic, "your message is going to struggle to have influence in that cacophony of voices", Willer says. At that point, the best chance to impart the message has passed.

Preventive behaviour

Health officials have a long way to go to craft pandemic communications that prompt unified public action. The next-level goal — stimulating behaviour in advance of a pandemic that will reduce the chances of one erupting — might, therefore, seem unrealistic. But pre-emptive action is better than reactively attempting to tamp down global disease spread. And some researchers are asking whether behavioural science can be marshalled to help achieve that goal.

Because some pathogens can jump readily from wild animals to humans, coordinated public-health messaging about the importance of safe animal handling could be instrumental in heading off the next pandemic. Disease-detection platforms, such as the National Respiratory and Enteric Virus Surveillance System of the US Centers for Disease Control and Prevention (CDC), could also allow swift action to stave off pandemics.

But to get the public on board with following animal-handling guidance and responding to virus alerts early, leaders need to start promoting trust in health officials now, says Tom Kenyon, former director of the CDC's Center for Global Health and chief executive of the global health non-profit organization Project HOPE in Washington DC.

To foster that outcome, Kenyon thinks that governments should allocate more funding to local public-health departments so that they can raise their profile in communities before the next lethal virus emerges. That way, he argues, residents will understand better how health departments work to protect people and will be more likely to heed official guidelines about how to prevent a pandemic from taking hold. "People know the police station, the fire station, the mayor's office. They don't know the health department," Kenyon says. "The first thing is to demonstrate to the public what good public-health infrastructure does for them on a day-to-day basis." Countries with low levels of COVID-19 spread are consistently those where people have high levels of trust in their governments and communities, researchers have reported[12].

Reaching the levels of trust needed to stamp out pandemics will be a slog — and missteps over the past few months in response to the spread of monkeypox, such as mixed messaging about whether or not the virus is sexually transmitted, show that health departments have a long way to go. But researchers stress that better containment is possible — thanks to growing knowledge about how to promote coordinated public action. "It's not hopeless," Milkman says.

At the heart of improved preparedness efforts, Balboni says, should be the recognition that when leaders communicate clearly and honestly about the rationales behind pandemic policies, much of the public will respond. "When we can show people why it's important that they change their behaviour — not just 'Do it because I said so' — you actually start to push people in a direction that's helpful."

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

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Leaders must act to prevent pandemics

Heads of state and government have the power to guard against inevitable future pandemics, say Joanne Liu, Helen Clark and Michel Kazatchkine.

In the past two decades, the time between deadly international disease outbreaks has shortened, and the human and economic cost of these outbreaks has grown. In 2002, severe acute respiratory syndrome (SARS) led to 800 deaths and US$40 billion in economic losses. The 2014 Ebola outbreak in West Africa caused more than 11,000 deaths and $53 billion in economic and social losses. In early 2020, COVID-19 spread rapidly worldwide, and is estimated to have contributed to more than 17 million deaths, with economic losses estimated to reach $12.5 trillion by 2024. Delays in alerting the world to these threats led to wider spread and more loss of life.

The next infectious-disease threat could be even more deadly and costly. Political leaders can choose to prevent it. In May 2021, we and our colleagues on the Independent Panel for Pandemic Preparedness and Response published an evidence-based package of actions for transformational change that could make COVID-19 the last pandemic of such devastation (see go.nature.com/3iqfqhm). In short, we recommend a change in mindset towards faster detection and reporting of outbreaks and threats by an independent, well-financed World Health Organization (WHO). Presidents and prime ministers would lead a council to coordinate multisectoral action and promote accountability. Medical countermeasures would be available everywhere they are needed. This transformed system would be backed by an international fund that finances measures to prevent and respond to new health threats.

To stop the next health threat, heads of state and government must lead — nationally, and in solidarity. With some exceptions, the COVID-19 pandemic has been characterized by too many words and not enough action, despite its clear threat to global health, economies and security. The global COVID-19 summits have brought welcome funding announcements and leaders have spoken at WHO gatherings, but action has not been sustained.

We think that a leader-level global council is required to identify gaps in preparedness and response, mobilize finances, hold public and private stakeholders accountable, and provide leadership at the first hint of a threat. This council should be established by a political declaration negotiated by the United Nations General Assembly.

Global pandemic prevention is estimated to cost $10.5 billion each year — a sizeable sum, but a fraction of the cost of not being prepared. A new fund for pandemic prevention, preparedness and response, approved by the board of the World Bank in June, is too new to evaluate properly. However, early signs indicate that it is based on an outdated 'donor–beneficiary' model, with high-income countries having too much influence and insufficient money being pledged. Instead, we recommend an inclusive, global public investment funding model that gives lower-income countries a seat at the table and disburses funds based on a country's needs and finances.

The role of the WHO must also be considered. If it is to remain the coordinating authority for global health, member states must give it the authority, independence and funding to perform that role well. The WHO was too slow to declare a public-health emergency of international concern (PHEIC) when the SARS-CoV-2 virus emerged. Work is now under way to amend the international health regulations, which govern global responses to international public-health threats, to give the WHO clear authority to communicate freely on disease outbreaks, declare a PHEIC based on evidence and investigate without hindrance. However, these amendments are not scheduled to be accepted until May 2024, and changes won't come into force until even later. This creates a dangerous interim period, during which the WHO must be bold and sound the alarm should new threats arise. The relative speed with which it called a PHEIC for the current monkeypox outbreak was encouraging, although some think it should have come sooner.

The area of reform that faces the most resistance, from industry and some countries, is the guarantee that appropriate medical countermeasures be available where they are most needed. Vaccines and therapeutics are a global common good — they are meant to slow the spread of disease and protect lives during a health emergency, not be a profit-making opportunity. Countermeasures should be equitably distributed on the basis of public-health need, and research and development must be tailored to the settings in which these products will need to operate — 'ultra-cold chain' vaccines, for example, cannot be easily delivered in warm, lower-income countries.

Evaluating the successes and failures of the Access to COVID-19 Tools (ACT) Accelerator, an initiative launched in April 2020, should reveal the practical next steps to achieve an equitable system. The pandemic preparedness treaty currently being negotiated at the WHO could also ensure an end-to-end system for medical countermeasures, from research and development to delivery, that considers the public-health needs of countries of all income levels. These considerations must include support for manufacturing worldwide, to prevent wealthy countries prioritizing their populations during a health emergency at the expense of lower-income nations.

These recommendations are not exhaustive. Other actions, such as building trust in public-health interventions, and investing in strategies to minimize the risk of pathogens moving from animals to humans, are also essential. Political leaders now have a clear choice: to watch while a new disease with pandemic potential emerges and spreads, or to lay the foundations required to thwart it. Given the damage done by COVID-19, it's hard to fathom why this is a choice at all.

"The next infectious-disease threat could be even more deadly and costly."

Joanne Liu is director of the Pandemic Emergency Readiness Lab at McGill University, Montreal, Canada. **Helen Clark** was co-chair of the Independent Panel for Pandemic Preparedness and Response, and is the former prime minister of New Zealand. **Michel Kazatchkine** is the special adviser to the joint United Nations programme on HIV/AIDS (UNAIDS) for Eastern Europe and Central Asia.
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ILLUSTRATION BY SAM FALCONER

Ready to respond

How health-care professionals and public-health officials can work in concert to detect and stop disease outbreaks. **By Kristina Campbell**

In January 2020, news outlets around the world reported a disease outbreak in China caused by a new pathogen. For a while, the now all-too familiar disease called COVID-19 appeared to be mostly contained in China — at the start of the final week of January, there were 2,700 confirmed cases in the country and only around 40 cases elsewhere. The rest of the world scrolled past the headlines, failing to see what was coming.

Tom Inglesby, a physician and director of the Johns Hopkins Center for Health Security at the Bloomberg School of Public Health in Baltimore, Maryland, however, recognized some alarming signs in China. Health-care workers were becoming ill in large numbers; young, healthy people were dying; large temporary hospitals were being built, and officials ordered the shutdown of a city larger than any in the United States. Inglesby knew that disease spread of that magnitude anywhere in the global community was everybody's business. He started to push for an acceleration of pandemic preparedness, including COVID-19 testing, in the United States.

Around the same time, warning bells were similarly ringing for infectious-disease epidemiologist Jennifer Nuzzo. She became increasingly dismayed in the months that followed, watching rates of morbidity and mortality rise around the globe because of a general lack of preparedness for disease outbreaks. In April, she took on a position as director of the newly established Pandemic Center at Brown University School of Public Health in Providence, Rhode Island, so she could work to ensure the world never again finds itself so unprotected. She says governments and other organizations around the world must take action now to make sure that, when the next pandemic inevitably emerges, health-care professionals will be empowered to stop the spread earlier and limit its impacts.

Curbing infectious disease rests on several medical pillars. The ability to identify outbreaks as they emerge in frontline settings, and sharing that information with other institutions, is important. So, too, is the preparedness of health-care providers to respond when pandemics do hit; clear, well-drilled plans of action and secure access to vaccines and other essential medical supplies are crucial. And not just for some nations: the world's ability to find and stop the next pandemic is only as good as its weakest link.

Frontline vigilance

Disease outbreaks can be caused by various types of pathogen, including viruses, bacteria, fungi and parasites. Finding a pathogen with pandemic potential starts with testing people who are ill, and finding out exactly which pathogen is causing their symptoms.

Cecilia Sorensen, an emergency medicine physician and director of the Global Consortium on Climate and Health Education at Columbia University in New York City, describes hospital emergency departments as "sentinel systems" for infectious disease,

because they're often the first places people go to when experiencing unusual symptoms. "That decision point in emergency rooms sets the stage for what happens next," she says.

Often it's the emergency medicine physicians who make decisions about what information to gather from a person through laboratory testing, at least initially. Sorensen emphasizes that, in a pandemic-aware world, these professionals need to be meticulous about diagnosis, staying alert to symptoms that don't fit the typical pattern for the region. "Emergency providers need to have a really high index of suspicion," she says. Maintaining frontline health-care professionals' awareness of what might be spreading in another region, as well as what is endemic in their own, can help to prompt diagnoses that they otherwise might not have considered. But in reality, Sorensen says, the supply of this valuable information to those on the front lines is inconsistent.

The ability of medical personnel to correctly diagnose an infection also depends on hospitals' disease-testing capacity. Inglesby pushed for testing in the early days of the COVID-19 pandemic, so that medical teams could find out for certain whether they were dealing with the new pathogen that was spreading around the world. The US Centers for Disease Control and Prevention (CDC) created such a test, but Inglesby thinks that it did not find its way into clinical labs and public-health settings quickly enough.

At present, the diagnostics available in any given hospital usually reflect the illnesses they most commonly encounter. As a result, health-care workers often do not have easy access to tests that would allow them to confirm an unusual illness for their region, as might be the case in the early days of a pandemic. To rectify this, Sorensen thinks that hospitals should establish relationships with laboratories that can test for diseases that aren't in their own wheelhouse, so that these labs can be called on quickly when needed. In the United States, for example, a hospital in Colorado that might not regularly test for tick-borne Lyme disease could develop a relationship with a laboratory in the northeast of the country that does so regularly.

Senjuti Saha, a molecular microbiologist and director of the Child Health Research Foundation in Dhaka, says that the range of available diagnostics in hospitals in low- and middle-income countries is often particularly limited — physicians commonly encounter illnesses for which they cannot identify a cause. Not only does this reduce the likelihood that people will get appropriate treatment, but it also tends to mask outbreaks, since it remains unclear whether illnesses in an area are caused by many different pathogens or the same one.

Genomic testing can be a helpful tool in these cases. Saha's group has used a genomic sequencing facility to analyse cases of meningitis in the local community that were caused by unknown pathogens. Sequencing samples of cerebrospinal fluid from children who had meningitis showed, to the researchers' surprise, that in some cases their condition stemmed from an otherwise unnoticed outbreak of the chikungunya virus, a mosquito-borne pathogen. This allowed the group to design a test for the pathogen that the nearby hospital's diagnostic lab could use in future to detect outbreaks of the virus faster.

"It shouldn't be the case that one or two countries have most access to a vaccine."

Others are trying to replicate Saha's setup. A report from the World Health Organization (WHO) in March laid out how to use genomic data as part of broader surveillance of pathogens with epidemic and pandemic potential[1]. And the Africa Pathogen Genomics Initiative, backed by several governmental and philanthropic organizations, is supporting efforts to increase the use of genomic sequencing for disease surveillance across the continent.

Sharing and comparing

Obtaining accurate information about disease occurrence in a single hospital or region is the first step in preventing future pandemics. The next is to ensure that data collected by various health-care providers and testing labs are shared and collated, to allow health organizations and government officials to grasp the bigger picture.

Although the International Health Regulations, signed by 196 countries, include a commitment to share information about extraordinary disease outbreaks with the rest of the world, individual countries sometimes struggle to coordinate even their own internal data. Early in the COVID-19 pandemic in the United States, for example, health officials in many states collected information from hospitals but were not required to send the disease data to the federal government. This hampered efforts to create an overall picture of cases in the country. Congress later passed laws requiring hospitals and states to share data with federal officials, but this is COVID-19-specific and not expected to be permanent. Inglesby says better federal authority to get information on infectious-disease outbreaks from US states should be a high priority. "We need to be ready for the next pandemic and not have to wait for new legislation," he says.

Tieble Traore, technical officer for emergency preparedness at the WHO's regional office emergency hub in Dakar, says that after the Ebola outbreak in West Africa between 2014 and 2016, the WHO has led efforts to strengthen information-sharing practices in Africa. Under a strategy adopted in 2016, health officials now encourage robust community participation to improve data sharing about threats to public health. Health-care workers and volunteers — ranging from local political and religious leaders to birth attendants — identify potential health problems in the community and report the information by text message to their nearest health facility. If a serious public-health problem is suspected, the health facility is required to report data on disease cases to the district, regional or national level within 24 hours for further scrutiny.

Data sharing and integration is being improved globally, too. The Rockefeller Foundation, a medical research organization based in New York City, is collaborating with a health-research foundation, Wellcome, in the United Kingdom to develop an independent early-warning system to detect emerging pathogens (or new variants of known pathogens) so they can be quickly contained. The system is based on technology that pulls together disparate data sets for analysis. The UK government has also launched a surveillance network called the Global Pandemic Radar in partnership with the WHO and several other organizations, to track disease outbreaks wherever they occur. The initiative expands surveillance infrastructure and data sharing agreements already in place for other infectious diseases, such as HIV, tuberculosis and malaria.

A state of readiness

In the best-case scenario, a local disease outbreak is promptly detected and controlled. But should a cluster of disease somewhere in the world grow into a pandemic threat, health-care systems everywhere must be ready to mount a response.

Nuzzo thinks that practice drills for infectious disease crises are crucial for pandemic prevention. Exercises similar to fire or earthquake drills support a culture of preparedness, and create an understanding among medical providers that outbreaks will continue to happen and that a complete shutdown is not the only option. Hospitals and government health agencies must not only plan for pandemics, Nuzzo says, but also "regularly exercise those

Senjuti Saha (left) conducts tests to detect chikungunya virus in cerebrospinal fluid.

APURBA RAJIB MALAKER

plans so that they're not dusty and unknown when the outbreak happens".

Taiwan, for example, conducts a vaccination drill every year in the form of a seasonal influenza mass vaccination campaign[2]. Unlike more haphazard approaches to flu vaccination in some countries that might see shortages, or doses slowly distributed across a season, the exercise simulates a rapid medical countermeasure during a pandemic, in which vaccines or medicines would need to be distributed widely and rapidly. Not only does it familiarize the general public with where to access vaccines in an emergency, but it also creates relationships between the different stakeholders who assist with emergency medical preparedness. Traore says that staff in the WHO African region also emphasize the need for training or simulation exercises to maintain operational readiness.

In addition to being well-drilled, a good response to a pandemic also relies on having the capacity to handle a spreading disease — a particular issue in resource-limited settings. "Capacity comes from access," says Desiree LaBeaud, a paediatric infectious-disease specialist at Stanford University in California who collaborates with researchers in Kenya. "Access to knowledge, access to diagnostics, treatments, vaccines, medical care, and then trained individuals and social capital." Without this capacity, local health professionals might quickly become overwhelmed during a disease outbreak, leaving the population vulnerable.

Researchers have called for further investigation of best practices for building capacity in the most challenging global settings, such as places with protracted conflicts or political instability[3]. Global partnerships and relationships, however, can aid this capacity informally for many low- and middle-income countries, provided the relationships are built long before a pandemic puts them to the test.

One crucial aspect of capacity-building is vaccines. With emerging pathogens, developing and manufacturing a vaccine must happen quickly. Efforts are under way to streamline vaccine development and production: for example, an international foundation called the Coalition for Epidemic Preparedness Innovations is spearheading a campaign for research that will allow vaccines to be developed for new pathogens within 100 days of identification. And researchers have proposed a 10- to 20-year investment in leveraging knowledge of 'prototype' viral pathogens from each known family or genus to develop vaccine candidates in case they are needed.

Inglesby says that once a safe, effective vaccine is developed for a pathogen, systems need to be in place to manufacture at scale, all around the world. This would require working with industry, ensuring the right financing and partnerships for technology transfer. "It shouldn't be the case that one or two countries have most access to a vaccine because the vaccine is produced in those countries," he says. LaBeaud concurs, and points out that if COVID-19 vaccines had been distributed more equitably, we might not have had to deal with variants that subsequently arose.

Some efforts have been made to establish international, multi-disciplinary health teams that can snap into action anywhere in the world when an outbreak reaches a certain scale. The WHO-led Global Outbreak Alert and Response Network is made up of more than 150 organizations committed to tackling pandemics in their early stages[4], although it relies heavily on volunteers. Bill Gates has proposed a similar network, which would use a group of fully paid international pandemic responders. But Saha advocates building local, decentralized capacity, in Bangladesh and other countries, to decrease reliance on help from others that might vanish in times of crisis.

For her, capacity building is about reducing 'parachute science', in which researchers from resource-rich countries enter resource-limited places and "get their shoes dirty for an afternoon". "The samples flow out of the country, analysis is done somewhere else, and we lose our ownership," she says.

Instead, Saha would rather see local scientists learn how to use the necessary technologies and get excited about solving problems with them. "A lot of the work we do as scientists comes from passion," Saha says. "If you don't have that passion, if you haven't handled the sequencing yourself, there's no way you'll be able to explain it to a policymaker or advocate for change."

Nuzzo is optimistic that COVID-19 can create an awareness of, and commitment to, pandemic preparedness. She compares the situation to the devastating fires in US cities at the turn of the twentieth century that sparked a shift in fire safety and preparedness in the country. Fire departments help to prevent uncontrolled blazes ruining lives; sustained funding of pandemic preparedness could do the same thing for infectious-disease outbreaks. In June, the World Bank approved the creation of a global fund to strengthen pandemic prevention, preparedness and response activities, intended to help close gaps in capacity.

Inglesby stresses that, to stay on top of infectious diseases, health-care providers at every level must take responsibility, whether they are international organizations, government agencies, states or regions, or local hospitals. "Sustained leadership commitment and awareness is what will make everything possible," he says. And as the COVID-19 pandemic has made abundantly clear, the whole world must be prepared. "We're all together on this one little planet, working together," says LaBeaud. No pandemic response, however well thought out and funded, can be truly effective if it is applied in just one portion of the globe.

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Q&A

GLENN J. ASAKAWA/UNIV. COLORADO BOULDER

Sara Sawyer: Virus detective

Viruses are finely tuned to their hosts, but mutations can and have produced strains that can jump from animals into humans. Sara Sawyer, a virologist at the BioFrontiers Institute of the University of Colorado, Boulder, spoke to *Nature* about what a virus must do to make the leap between species, and describes a worrying discovery her laboratory has made regarding a future threat.

How do animal viruses infect humans?
Most animal viruses cannot infect humans — we ingest viruses all the time, and most of them pass straight through. To do us harm a virus has to trick its way inside our cells, so it can use them as a factory for making more of itself. Animal viruses need to pull off several tricks to do this.

First, they need to evade all aspects of our immune system — no small task. Second, they need to replicate in our cells. It's rare that a virus that's been evolving under the selective pressures of an animal host would just pop into a human and be able to do all those things.

Can animal viruses typically replicate in human cells?
Almost never. Viruses interact with tens to hundreds of host proteins to replicate themselves. Animal viruses are adapted to use the animal versions of these proteins, not the human versions. However, in the rare instance that an animal virus can replicate even weakly in a human cell, that's a worry — the minute you have a virus able to replicate, you have a virus that's able to evolve.

Errors that are made as viruses copy their genomes are fodder for evolution. A replicating animal virus might accumulate mutations that make it better at using that human cell as a replication factory, or better able to evade human defences. And once the animal virus is in a human, natural selection will work in favour of mutations that make the virus successful. Some animal viruses will be 50 mutations away from being able to replicate in humans; another might be just one mutation away.

How can you find out if an animal virus is close to jumping across to humans?
To understand which viruses are a hair's breadth away from being able to thrive in humans, we have to work out how many obstacles the virus needs to overcome — how many viral-replication steps aren't working in humans, and how many of our immune blocks are active.

For instance, we might first see whether the virus can engage a receptor on human cells to gain entry. One way we can do that is to take a cell line from the animal host, knock out the receptor the virus uses and replace it with the human version. If the virus can still replicate at normal levels, that means it can use the human receptor just fine. If we only get 50% of the expected replication, that tells us that the human version works for this virus, but it's not ideal. And if we see no replication, that means that the virus can't use the receptor yet.

> **"We weren't happy to see that the human version was completely functional."**

We can repeat that process with every protein we know might be important for every task the virus must perform, substituting them one at a time. That allows us to pinpoint what's stopping the virus from replicating in human cells, and differentiate viruses that need to overcome only one or two obstacles from those that are a long way off.

Which viruses are close to jumping into humans?
Viruses that infect primates are of particular interest. Primates provide a physiological environment so similar to ours that we see primate viruses jumping into humans time and time again — Zika virus, HIV and dengue virus all came from primates.

We recently studied a family of viruses called simian arteriviruses, about which little is known. These viruses have uncanny similarities to the simian immunodeficiency viruses that gave rise to HIV and the AIDS pandemic. Like HIV, these simian arteriviruses could be highly lethal if they were to jump into humans, and our research suggests that they might be capable of it (C. J. Warren *et al. Cell* https://doi.org/jgnv; 2022).

What did you uncover about simian arteriviruses' ability to jump into humans?
Simian arteriviruses are endemic to some species of African primates. In captive-primate facilities, these viruses have led to outbreaks that cause haemorrhagic fever and death. We used simian haemorrhagic fever virus (SHFV) as a representative of this virus family, and first identified CD163 as the receptor it uses to enter cells. We weren't happy to see that the human version was completely functional for the virus.

Then we asked whether SHFV can use all the other machinery of the human cell to replicate. Not only did we find human cell lines in which it could do that, but also in one case, SHFV produced an astronomical number of copies of itself. Next, we showed that, in at least one cell type, SHFV seems to resist the interferon response, a crucial component of innate immunity. The last item on our checklist is our adaptive immune system, such as antibodies, which is what would hopefully save the day if the worst happened. Unfortunately, like HIV, SHFV is part of a group of viruses against which humans have no existing immunity.

What should we be doing about this?
We need to be watching for arterivirus infections in humans, which have currently never been observed. For instance, we could run blood tests on people in the regions of Africa where primates are endemically infected with arteriviruses to see whether anybody has antibodies to these viruses — if they do, that would suggest a previous infection. Unfortunately, there are no antibody tests for these viruses yet.

Interview by Simon Makin
This interview has been edited for clarity and length.

JEROME FAVRE/BLOOMBERG VIA GETTY

Live chickens on sale at a market in Hong Kong in 2013, during an outbreak of avian influenza in people.

Predicting a pandemic

Machine learning could help to identify the viruses most likely to spill over from animals to people and cause future pandemics. **By Simon Makin**

In February 2021, seven Russian poultry-farm workers were reported to have been infected with H5N8 avian influenza. This subtype of bird flu had never been known to infect people before, and the virus's genetic sequence was quickly uploaded to the genetic data repository GISAID. For Colin Carlson, a biologist at Georgetown University in Washington DC, it presented an opportunity. "I immediately thought, 'I want to run this through FluLeap'," he says.

FluLeap is a machine-learning algorithm that uses sequence data to classify influenza viruses as either avian or human. The model had been trained on a huge number of influenza genomes – including examples of H5N8 – to learn the differences between those that infect people and those that infect birds. But the model had never seen an H5N8 virus categorized as human, and Carlson was curious to see what it made of this new subtype.

Somewhat surprisingly, the model identified it as human with 99.7% confidence. Rather than simply reiterating patterns in its training data, such as the fact that H5N8 viruses do not typically infect people, the model seemed to have inferred some biological signature of compatibility with humans. "It's stunning that the model worked," says Carlson. "But it's one data point; it would be more stunning if I could do it a thousand more times."

The zoonotic process of viruses jumping from wildlife to people causes most pandemics. As climate change and human encroachment on animal habitats increase the frequency of these events, understanding zoonoses is crucial to efforts to prevent pandemics, or at least to be better prepared.

Researchers estimate that around 1% of the mammalian viruses on the planet have been identified[1], so some scientists have attempted to expand our knowledge of this global virome by sampling wildlife. This is a huge task, but over the past decade or so, a new discipline has emerged — one in which researchers use statistical models and machine learning to predict aspects of disease emergence, such as global hotspots, likely animal hosts or the ability of a particular virus to infect humans. Advocates of such 'zoonotic risk prediction' technology argue that it will allow us to better target surveillance to the right areas and situations, and guide the development of vaccines and therapeutics that are most likely to be needed.

However, some researchers are sceptical of the ability of predictive technology to cope with the scale and ever-changing nature of the virome. Efforts to improve the models and the data they rely on are under way, but these tools will need to be a part of a broader effort if they are to mitigate future pandemics.

Virus hunting

Some researchers have long argued that expanding our knowledge of viral diversity will help to manage pandemic threats. PREDICT, a US$200-million project funded by the US Agency for International Development (USAID), spent around a decade looking for animal viruses. By the time it ended in 2020, it had identified 949 new viruses in samples from wildlife, livestock and people, in 34 countries.

Some of PREDICT's findings might seem prescient, in hindsight. A 2017 study[2] estimated that there are thousands of undiscovered coronaviruses in bats (widely thought to be the source of the virus SARS-CoV-2), and predicted that southeast Asia would be home to the greatest number of viruses in the family to which SARS-CoV-2 belongs. It also associated activities that involve high levels of human–wildlife contact, such as wildlife markets, with a higher prevalence of coronaviruses.

Another 2017 study[3] collected data on which viruses infect which mammals, creating a database of virus–host associations. "The goal was to understand which viruses are capable of infecting people, what animals we're most often getting new viruses from and the underlying factors that drive those patterns," says ecologist and study leader Kevin Olival at the EcoHealth Alliance in New York City, a non-profit body focused on bio-surveillance and conservation. The team's analysis showed that the proportion of viruses in a given host species that can infect humans is affected by how closely related humans are to that species, as well as factors that influence human–wildlife contact, such as the human population density and the degree of urbanization in that species' geographical range. The team used statistical modelling to predict animal groups and regions that were likely to harbour a large number of undiscovered viruses — bats featured prominently, along with rodents and primates, in regions including South America, Africa and southeast Asia. The researchers also found traits associated with a virus being zoonotic, such as the range of species it can infect.

The team says this information can help to guide surveillance efforts. "It allows us to forecast areas most at risk," says Jonna Mazet, an epidemiologist at the University of California, Davis, who directed PREDICT. Identifying specific threats also allows local researchers and health-care workers to tailor mitigation and response capabilities. "It allows communities to say 'we have this, this and this, and we can reduce our risk in these ways'," says Mazet.

"With a trillion points, you could predict spillover like the weather."

PREDICT was intended to be just a pilot project. "It generated a lot of data, but it was a drop in the bucket," says Olival. "We need something bigger." Researchers therefore proposed the Global Virome Project (GVP) in 2016, seen as a global partnership of government agencies, non-governmental organizations and researchers, with the aim of discovering most of the viruses in mammals and birds (from which most zoonotic viruses originate). However, in the face of criticism from some researchers, it has never been funded. It exists today as a non-profit organization, aiming to provide countries with the knowledge required to carry out their own viral surveys, Mazet says. A smaller, much less costly project called Discovery and Exploration of Emerging Pathogens — Viral Zoonoses (DEEP VZ) was launched by USAID in October 2021.

One criticism of the GVP is that the scale of the task is simply unmanageable. PREDICT researchers estimate[4] that there are 1.67 million unknown viruses in mammals and birds, and although this figure is contested, there is no doubt that the virome is vast. It is also constantly changing, so one-off discovery efforts would not be enough. "RNA viruses evolve at a hefty rate," says Edward Holmes, a virologist at the University of Sydney in Australia. "So you'd have to keep doing it."

There is also scepticism that the project would have identified potential pandemics. "I have no problem with it in terms of understanding virus evolution and ecology," Holmes says. "But as a predictive tool to understand what comes next, it's a non-starter." One issue is that some host species and viral families have been intensively studied, but others have hardly been touched. Existing data are also skewed towards viruses that have already spilled over[5]. As a result, most predictions so far have been based on "completely biased data", says Jemma Geoghegan, a virologist at the University of Otago in New Zealand. Moreover, even when a virus is discovered and its genome is sequenced, many factors that can influence its potential to spark a pandemic, such as its ability to infect humans and be transmitted from person to person, will still be unclear. "You've then got to do all these experiments, which will take years and cost a fortune," says Holmes.

This is where machine learning might provide a short cut. Rather than attempting to fully characterize every new virus, models could be used to flag high-priority targets for further investigation. "What we need is a triaging system downstream, so we know which viruses need to be characterized with in-depth virology studies," says Sara Sawyer, a virologist at the University of Colorado, Boulder.

Inside the models

When a virus is discovered, often little is known about it other than its genetic sequence. Models that can triage viruses using only their genomes would therefore be particularly useful. Nardus Mollentze, a computational virologist at the University of Glasgow, UK, and his colleagues have developed one such model, which assesses viruses in part by using a measure of their genetic similarity to parts of the human genome[6]. Evolutionary pressure on viruses can result in genetic segments that resemble those in the host's genome — either to evade the innate immune system or to aid replication. When tested on a library of 861 known viruses, the algorithm could classify them as zoonotic or not with 70% accuracy.

Mollentze has since joined the Viral Emergence Research Initiative (Verena), a consortium of researchers seeking to develop and improve zoonotic prediction models. Mollentze collaborated with Verena researchers to combine his algorithm with techniques that exploit knowledge of which viruses infect which hosts, including methods for inferring unknown host–virus associations. This combined approach raised performance by roughly ten percentage points[7]. In future, knowledge of how viruses interact with hosts on a molecular level could be incorporated. "It's going to be all about proteins and biochemistry," says Carlson, who directs Verena. "That's the future of this."

ATTILABARSAN/ GETTY

Bats harbour many unknown coronaviruses.

An important goal is to learn which models work well, and why. There are models that merely classify according to patterns in the data, and those that infer the reasons for those patterns, but it can be difficult to tell them apart. "There's this question: are we just teaching machines to reiterate things they already know, or are they learning principles that carry into new space?" says Carlson.

To make progress, the process of validating models will be crucial. For instance, several studies have tried to predict which species host zoonotic viruses, with mixed results, but there has been little systematic comparison, making it difficult to know which approaches work. To address this, in early 2020, Verena researchers used predictions of which bat species might host betacoronaviruses as a case study[8]. They created eight statistical models and used them to generate a list of suspected hosts. In the following 16 months, 47 new bat hosts were discovered. When the researchers compared these with their predictions, they found that half of the models performed significantly better than chance. These models included traits such as the species' lifespan or size. The other four models did not take such features into account and performed poorly.

Data developments

Any artificial intelligence (AI) algorithm is fundamentally limited by the data it is fed. "AI works when the algorithm is trained on large amounts of quality data," says Sawyer. "But only a small number of spillovers occur each year, and data on viruses tend to be dirty, with a lot of missing information." Most researchers agree that the data are currently insufficient. "We don't have enough high-quality data to do a good job at prediction," says Mazet.

To some extent, modelling relies on scientists gathering fresh data, but viral-discovery efforts so far have been motivated by considerations such as the highest-risk places and situations. What modellers actually need is sampling aimed at improving geographical and taxonomic coverage, Carlson says. Supplying models with more data of this kind changes the horizon of what questions can be asked. "With a million data points, you can show how deforestation increases viral prevalence in bats," Carlson says. "With a trillion points, you could predict spillover like the weather."

To get anywhere close to that would require global cooperation, with open data sharing as the norm and data standards that everyone adheres to. The obstacles to this are more political, cultural and ethical than scientific. Academic incentives around publications, for example, are an obstacle to rapid data sharing. Guaranteeing that countries that share genetic data benefit from doing so is also crucial. "That's the key issue and dealing with it involves building trust," says Olival. "Making sure you're giving back, not only with vaccines, but with training, capacity building and co-authorship on papers."

The Nagoya Protocol, an international treaty that came into effect in 2014, enshrines countries' sovereignty over natural resources, including biological samples, and allows them to require benefit-sharing agreements in return for access to such samples. However, some labs can now synthesize pathogens or begin to develop vaccines using just genetic sequencing data. "We don't have anything set up in international law that deals with sequence data," says Carlson. "Nagoya isn't made for that world." Similar issues might some day apply to zoonotic risk prediction. "We're using data collected by researchers in the global south," says Carlson. "There are legitimate questions about what it means to take that data and make a technology."

Predict and prepare

For modelling to have real-world impact, it must lead to publicly accessible tools that provide actionable, locally relevant information. Modelling also needs to be better integrated with experimental work to interrogate the characteristics of pathogens. Just as a model might flag candidate viruses for further study, so might those investigations produce information that can be used to validate and refine the models. However, interdisciplinary communication is currently limited. "These are communities that don't talk or even read each other's papers much," says Sawyer.

Modellers also need to clearly communicate the uncertainty inherent in their work, and what they mean by prediction so they do not oversell the benefits. "No one says we're going to have the exact time, place and species that will lead to the next pandemic," says Olival. Researchers are dealing with probabilities, and unexpected things can and do happen.

Even at their best, predictive tools are not going to be able to completely prevent outbreaks. "I absolutely do not think we should hinge the world's security on these models," says Carlson. But alongside improved global surveillance systems, targeted vaccine development and efforts to build health-care capacity worldwide, their value is clear. "They let us do two things: understand what's happening around us and prioritize," Carlson says. Ultimately, that might help to reduce the frequency of pandemics. "We can get better at preventing some of them," says Carlson. "But it requires us to get better at what we're doing."

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Q&A

Xavier Rodó: Forecasting disease

XAVIER RODÓ

Numerous studies over more than two decades have demonstrated a robust relationship between climate and the dynamics of human diseases, such as cholera, malaria and dengue. Changes in climate, including both long-term warming trends and short-term climate variability, might affect patterns of disease. Xavier Rodó, a computational ecologist and climate dynamics specialist at the Barcelona Institute for Global Health and the Catalan Institution for Research and Advanced Studies in Spain, spoke to *Nature* about how climate modelling could be used to help prepare for future disease outbreaks — and the obstacles he has faced in implementing such systems.

How does climate affect disease transmission?

Climate impacts the emergence and spread of disease in myriad ways. Some are quite complex. Climatic conditions can have cascading effects on ecosystems that affect the likelihood of zoonotic spillovers, in which pathogens jump from an animal host to humans. We see, for example, that changes in temperature in the Brazilian Atlantic Forest drive waves of yellow fever in howler monkeys (*Alouatta* species) that precede human epidemics in a predictable manner[1].

As climate changes, so too will the spread and intensity of disease outbreaks. The effects will not be the same everywhere, but changes in temperature and rainfall are going to lead to huge changes in the distribution and dynamics of zoonotic and vector-borne diseases. We are already seeing record numbers of mosquitoes carrying West Nile virus in New York City, for example, when it is typically found farther west.

What evidence is there for climate change influencing disease outbreaks?

The first study[2] I was part of that demonstrated this was published in 2002, in collaboration with Mercedes Pascual, a theoretical ecologist now at the University of Chicago, Illinois. In a previous study[3], we had shown that the incidence of cholera in Bangladesh was affected by short-term climate patterns. Cases rose around six months after periods of increased local temperatures brought on by the El Niño Southern Oscillation (ENSO), a recurring climate pattern of warm (El Niño) and cool (La Niña) phases that occur irregularly every 3–7 years in the Pacific Ocean. But since the 1980s, there has been a marked intensification of ENSO, and we thought that this long-term trend might also be affecting cholera incidence. We looked at historical cholera data spanning a 70-year period, and saw that, between 1980 and 2001, incidence was strongly correlated with ENSO[2]. Data from a period before the intensification, however, showed no such correlation. The long-term trend of ENSO intensification, driven by a warming climate, seems to be affecting cholera dynamics.

How might climate modelling be used to predict and prepare for disease outbreaks?

With current tools, it is possible, in some regions, to forecast climatic conditions in the next season, the next summer or even further into the future — some El Niño events can be predicted up to two years in advance. Knowing months ahead of time that there is going to be an anomalous rainy season in a country, and how that is likely to affect disease incidence, makes it possible for public-health authorities to anticipate and plan their response. For example, they could stock up on medicines, or spray insecticides in certain areas to limit the hatching of mosquitoes.

What are the obstacles to developing these predictive models?

Both climate change and infectious-disease epidemiology are complex systems, and we need to bring together scientists from these very different disciplines to work on this problem. Right now, interdisciplinarity is spoken about more than it is seen. We also face difficulty attracting funding for projects of this kind, and opportunities to publish in established journals can be limited.

Availability of epidemiological data with which we can train and test our models is also a problem. For cholera, we have better historical data than we have recent data. It is similar for COVID-19 — reporting has dropped off, so we have much better data for the first two years of the pandemic than we do for now. We need to understand that long-term data collection is fundamental if we want to be prepared for future threats.

What is the state of the development and implementation of such tools?

I have worked with an international team to develop a model that uses El Niño predictions to forecast dengue outbreaks in Ecuador. The model correctly predicted that in 2016, warmer temperatures and excess rainfall would lead to an outbreak in the city of Machala in March — three months earlier than would be expected. It also predicted that there was a 90% chance that incidence would exceed the average for the previous five years, and that a weak El Niño in 2019 would result in a low probability of a dengue outbreak during the typical peak season[4,5].

This model and others have been adapted for use in other regions[6]. But these models have not yet been picked up by public-health authorities. People say they are interesting, but they don't see the immediate economic benefit — unfortunately, saving lives is not valued as it should be. We have tried many times to implement our cholera prediction model in India and Bangladesh — Pascual more times than me — without success. I've also tried to set up a malaria forecast service in Madagascar, Senegal and Ethiopia, because there is a wealth of data the model can rely on there[7]. But we have been unable to convince the stakeholders.

Interview by Laura Vargas-Parada

This interview has been edited for length and clarity.

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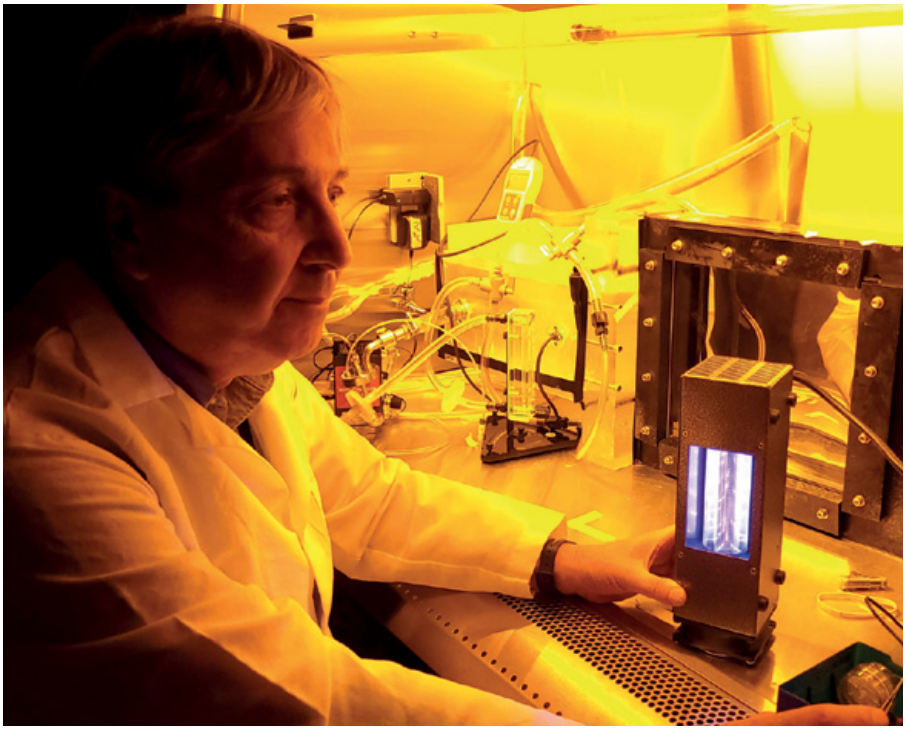


David Brenner studies the effects of far-ultraviolet light.

COLUMBIA UNIV. CENTER FOR RADIOLOGICAL RESEARCH

Safety is in the air

Ultraviolet light to clean the air typically has to be positioned away from people. Devices using shorter UV wavelengths could change this. **By Eric Bender**

The Boston piano bar where Edward Nardell sings cabaret songs would typically be an ideal setting for airborne diseases to spread. But Nardell and his audience are protected from the COVID-19 pandemic by the far-ultraviolet (UV) lights that he had installed to shine down from the ceiling.

Far UV is an emerging form of germicidal UV (GUV) irradiation, a well-established disinfection technology and growing resource in the battle against the virus SARS-CoV-2 and other pathogens that can spread easily through the air in enclosed spaces.

Indoor air safety begins with ventilation but it usually can't end there, says Nardell, a physician and researcher in airborne infection at the Harvard T.H. Chan School of Public Health in Boston, Massachusetts. Ventilation systems that replace air in a room are rarely powerful enough to fully protect against coronaviruses and other easily caught diseases, he explains.

Systems that actively try to clean the air in rooms, such as those using high-efficiency particulate air (HEPA) filters, remove harmful particles more effectively. But they are expensive to install and operate, often noisy, and limited in reach – multiple devices might be needed to cover a room. "That's where the air sanitation with UV comes in," says Donald Milton, an environmental health researcher at the University of Maryland School of Public Health in College Park.

With GUV light, "you can get very high rates of air disinfection with relatively little air movement", says Milton. "And with the newest technology, maybe you don't even have to worry about air movement, because now there are wavelengths that are safer to use and you can use GUV in the whole room." In crowded spaces such as schools, hospitals and restaurants where diseases can easily spread, GUV can operate unnoticed "even before you know that you've got a problem", Milton says. "That's really critical in keeping these things under control."

Gunning for germs

Conventional GUV systems use mercury vapour lamps, which produce light by passing an electrical current through vapourized mercury, and are similar to conventional fluorescent bulbs. The lamps emit radiation in the UVC band, with a wavelength of around 254 nanometres. UVC radiation is filtered by the atmosphere, so life on Earth has not evolved to withstand it. The radiation inflicts photochemical damage that mangles nucleic acids – inactivating pathogenic viruses and bacteria, although not necessarily killing them.

The lamps are widely used to disinfect water, clean fruits and vegetables, and sanitize surfaces in spaces such as operating rooms. But because this wavelength can damage human eyes and skin, the light from these systems is kept away from people. That does not mean, however, that it can't be deployed in public spaces. A clever approach developed decades ago, known as upper-room GUV, places the lamps high in a room, and takes advantage of rising air currents to inactivate pathogens well away from people.

The technique works well, says William Bahnfleth, an architectural engineer at Pennsylvania State University in University Park who focuses on indoor air quality. In a room, air rises from people, equipment and existing ventilation, passes through the radiation zone of the lamps, and then circulates back down into the occupied space.

Although there are no universally accepted and enforced standards for indoor air quality, targets are typically expressed in terms of how often the amount of air in a room is exchanged per hour. The recommendation for examination rooms in US hospitals, for instance, is six air changes per hour. That's a struggle for ventilation systems and typically requires a lot of energy, Bahnfleth says. Whereas, an upper-room GUV system can easily reach the equivalent of two or three times those levels of air exchange for disinfection purposes while using much less energy than a ventilation system."It's mostly impossible for anything but a hospital or special facility to have six air changes," says Nardell. "GUV is the only method that gives you this incredibly high number of equivalent air changes, because you can disinfect such a large volume of air at once."

In an unpublished study that applied various combinations of ventilation, filtration, UV and mask wearing in a variety of buildings, including offices, hotels and schools, "the only technology that routinely got the risks down

to a reasonably acceptable level was UV", says Shelly Miller, a mechanical engineer and specialist in indoor air quality at the University of Colorado Boulder. "To me that says UV is an incredibly powerful air cleaning tool that we just are dropping the ball on."

Riding shorter waves

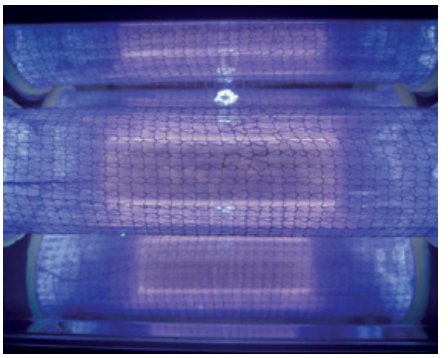
Upper-room GUV was widely adopted in schools and hospitals following studies[1] in the late 1930s and 1940s led by William Wells, a biologist then at the University of Pennsylvania in Philadelphia. Wells and his colleagues showed that upper-room GUV drastically reduced the spread of measles in schools in suburban Philadelphia. Although upper-room GUV is still used in many tuberculosis wards, its use has dropped with the advent of more powerful interventions such as vaccines.

Even though upper-room GUV's conventional UVC light is effective, it is fundamentally limited by the requirement to keep it away from people. Air is cleaned only when it circulates to the top of the room and passes by the GUV light, leaving an opportunity for pathogens to hop to a new host. Shorter wavelengths might help to overcome this limitation.

This is because wavelengths below 254 nm don't penetrate tissues nearly as well, says David Brenner, a physicist specializing in radiological research at Columbia University in New York City. Far-UV light with a wavelength of 222 nm doesn't reach beyond the layer of dead cells on the surface of the skin or the film of tears on the surface of the eye. Because bacteria and viruses are much smaller than those layers, Brenner and his colleagues reasoned that far-UV radiation could destroy the pathogens without damaging the skin and the eyes. The scientists tested their hypothesis with lamps containing krypton chloride gas, molecules of which release UVC radiation mainly in the 222 nm range under electrical excitation.

Originally aiming to improve disinfection in operating rooms, the Columbia team realized that far-UV radiation might also reduce airborne viral transmission. In a 2018 study, the investigators showed that more than 95% of influenza viruses in the air were inactivated when they floated past a low-power far-UV lamp[2]. Brenner's group had already shown that cells in a 3D human skin model and in mice were basically unaffected by such low doses[3], and other researchers found no evidence of eye damage from 222 nm radiation in rats[4].

When COVID-19 hit, the Columbia scientists ran analogous experiments on strains of coronavirus similar to SARS-CoV-2, again with good results[5]. To scale up their tests, the researchers then collaborated with scientists



EWAN EADIE

A krypton chloride excimer lamp.

in the United Kingdom, including a group at Leeds University that had access to a room-size test chamber designed to contain pathogens.

The room-size experiments used *Staphylococcus aureus* bacteria suspended in the air. This microorganism is relatively easy to analyse and is expected to be more robust against UV radiation than coronaviruses, says Ewan Eadie, a medical physicist at the University of Dundee, UK, and the lead author of a paper[6] that outlines the team's findings. "We really had no idea of what was going to come out at the end," he says.

The results were excellent. "We got really rapid reduction in the level of pathogens in the room," says Brenner. "Our equivalent air changes per hour were really big, well over 100 equivalent changes per hour."

On the safety side, Brenner and colleagues reported in May that they had exposed hairless mice to the radiation for 66 weeks without detecting any skin cancer[7]. Their upcoming research will focus on the risk to the eyes, and further investigate the mechanisms of how 222 nm radiation damages pathogens.

"We got really rapid reduction in the level of pathogens in the room."

Despite the promising laboratory tests of far-UV disinfection, there are questions about how well the technology will translate into busy public indoor spaces such as hospitals, schools and restaurants. "The laboratories are pretty sterile clean conditions," Eadie says. "I'd like to see some real-world data."

One real-world clinical trial already under way in Nova Scotia, Canada, is examining the use of far-UV light in nursing homes, where it's difficult to prevent the spread of airborne diseases. The controlled study will track the incidence of COVID-19 and other respiratory viral infections among 200 residents, half of whom will use common areas fitted with far-UV lamps. The other half will have placebo lights, identical in appearance but lacking the far-UV output. The trial began in October 2021 and the results are expected in early 2023.

Nardell, meanwhile, has started to use an airborne-infection research facility in Emalahleni, South Africa, to study COVID-19. Originally designed to analyse tuberculosis infection, the facility includes a three-bed ward, the air from which is transferred to exposure rooms holding animals that easily become sick with the disease being studied — in this case, hamsters. "Hamsters are the experimental animal of choice for COVID," Nardell says. The facility will test the efficacy of far-UV radiation compared with upper-room GUV systems, by monitoring the hamsters for signs of sickness.

But companies aren't waiting on peer-reviewed research. Far-UV lamp fixtures are already on the market, and being installed around the world — not just in buildings, but also on buses and in other infection hotspots. Some devices are even marketed for home use, although Brenner warns consumers to proceed with caution — an appliance delivering the wrong wavelengths can do damage.

Although costs of the fixtures vary widely, Nardell says that US$2,000 is a ballpark retail price for a lamp installed by specialists, and the lamps have an expected lifetime of around 15 months if they run continuously. There's hope that far-UV lamps based on light-emitting diodes (LEDs) will eventually provide cheaper and longer-lived alternatives to the gas lamps currently being used, but prototype LED far-UV lamps are currently restricted to impractically low levels of power, says Eadie.

In the meantime, Nardell says that in the piano bar where he performs, the far-UV lamps provide the equivalent of 35 air exchanges per hour, probably making it one of the safest venues for singing on the planet. When he invited Brenner and his colleagues to the bar, they enjoyed an evening of cabaret without masks, hoping that they would be protected by the invisible light shining on them. "I was pretty nervous and took lots and lots of COVID tests over the next week, but I was fine," Brenner says.

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Eradicating the next pandemic disease

When infections go global, what chance do we have of ridding the world of the pathogen responsible? By Sam Jones

ILLUSTRATION BY SAM FALCONER

In early 2021, Nick Wilson was feeling hopeful. For months, New Zealand had been reporting zero or just a few daily cases of COVID-19. To Wilson, a public-health physician and researcher at the University of Otago in Wellington, eliminating the disease in New Zealand — and possibly across the globe — didn't feel out of reach. "The success of public-health and social measures without the vaccine gave us confidence that when the vaccine became available — if it had sustained high efficacy and was rolled out everywhere — and was combined with public-health and social measures, we could eradicate COVID-19," he says. In July 2021, he and his colleagues wrote a commentary saying just that (N. Wilson *et al. BMJ Glob. Health* **6**, e006810; 2021).

But around the same time, the Delta variant of the coronavirus SARS-CoV-2 started upending the world once again. Within a few months, the New Zealand government abandoned its idea of eliminating COVID-19, at least in the near term.

Today, New Zealand is a microcosm of much of the rest of the world, where rapidly evolving variants of the virus continue to spread, causing illness and death. Wilson's hopes for a future free of COVID-19 aren't dashed completely, but they certainly aren't as high as they were in mid-2021. "It's disappointing," he says. He maintains that eradication is still possible, but it would require that almost everyone on the planet receives a highly effective vaccine that could provide more or less lifelong immunity. "So yeah, basically it's looking very unlikely," he says.

For an infectious disease to be considered eradicated, there cannot be a single case of it worldwide. So far, the only human infectious disease to be eradicated is smallpox, in 1980. Other diseases, such as polio and the parasitic disease dracunculiasis teeter on the edge of eradication — two of the three strains of wild poliovirus have been eradicated, with the third eliminated from most of the world (although vaccine-derived poliovirus has, in the past year, been detected in a number of countries, including the United States).

Ridding the world of any infectious disease is a difficult task. Societal factors and the intrinsic characteristics of a given pathogen can conspire to make it harder still. Understanding those factors, and how they should affect the response to a pandemic, could make it easier to eradicate the next pandemic-causing pathogen.

Stroke of luck

Before its eradication in 1980, smallpox had been around for thousands of years. It killed more than 300 million people in the 1900s alone, and left many survivors with severe scarring and blindness. Smallpox was by no means easy to do away with, but a variety of factors made its eradication possible.

One such stroke of luck was that smallpox passes only between people — there is no animal reservoir in which the virus can hide. This is not the case for many diseases. SARS-CoV-2 probably made its way into people from animals at a market where wildlife was being sold. Now, SARS-CoV-2 has been detected in a range of species in the wild, as well as in household pets and zoo animals. Influenza viruses also reside in non-human hosts, including birds, cats, dogs, bats and sea lions. And malaria is shuttled between people by mosquitoes infected with the parasite responsible for the

disease; dracunculiasis is similarly transmitted by parasite-infected water fleas.

As well as being points of potential spread to people, animal reservoirs can be breeding grounds for mutations, giving rise to variants that might evade the immune protection provided by vaccines or previous infection. Whether animal reservoirs are responsible for the more-recent SARS-CoV-2 variants is debated, but it is clear that current vaccines are less effective against these variants than against earlier forms.

The rate at which a virus accrues mutations can also affect efforts to eradicate it. Although many pharmaceutical companies are able to pivot and adapt their vaccines to target emerging variants, there's always the chance that a virus will move faster and that the pathogen can spread unhindered once again. SARS-CoV-2 mutates faster than many viruses, including smallpox, says Rhea Coler, an infectious-disease researcher at the Center for Global Infectious Disease Research at Seattle Children's Hospital in Washington. However, it still mutates more slowly than do many other infectious diseases, including influenza. Because of this, Coler says, she wouldn't be surprised if an influenza virus were responsible for the next pandemic.

Another variable is how easy it is to tell that someone is infected. "From a microbiologist standpoint, you always ask, 'Is the disease really easily recognizable?,'" says Coler. If a disease can be diagnosed by eye, she says, then that makes tracking its spread simpler, and measures such as quarantining more likely to succeed. "The more sophisticated the methods that are necessary for diagnosing a disease, quite frankly, the less likely it is that the disease will be eradicated," Coler says.

The symptoms of smallpox were impossible to miss. They began with a fever and body aches, followed by a distinct rash on the tongue and mouth that turned into sores. Then, a couple of days later, a similar rash and sores would appear on the face, before spreading to a person's limbs. COVID-19 symptoms, by comparison, can seem similar to those of pneumonia or influenza, or hardly be present at all, meaning that someone can know if they are infected only by getting tested.

A person infected with SARS-CoV-2 can also be contagious even though they are asymptomatic, whereas smallpox was spread only by people with symptoms. This meant health workers could quickly deploy a ring vaccination strategy, in which anyone in close contact with a person showing smallpox symptoms — and therefore more likely to spread it to other people — was immediately vaccinated. This targeted delivery of vaccines was crucial to eradicating smallpox in places where mass vaccination — as used against COVID-19 — was falling short.

Team effort

The eradication of smallpox would not have been possible without a global effort. The same will be true of future campaigns to eradicate disease, Coler says. If political support within and between countries falters, these efforts will not succeed.

In the initial period of COVID-19, many countries formed a united front. "I was impressed that, very early on in the pandemic, there was a lot of sharing of information and collaboration," says Coler. "We would not have gotten the sequences for the virus, for example, if scientists in Asia weren't willing to share them with us." Those genetic sequences allowed researchers around the world to begin developing vaccines immediately.

But as time went on, many of those international collaborations broke down, which harmed the chances of eradicating the pathogen. "With smallpox there were US and Soviet scientists working together. You had that level of cooperation," says Wilson. "I just don't think that's feasible, unfortunately, in the current climate."

A rise in vaccine nationalism over the course of the pandemic has also had a negative effect, Wilson says, with some countries hoarding vaccines, and so limiting vaccination efforts elsewhere. He's also disappointed by the alleged actions of some nations to spread disinformation, discrediting highly effective vaccines developed by other countries. Behaviour such as this could undermine the use of these vaccines across the globe.

"You always ask, 'Is the disease really easily recognizable?'"

The spread of disinformation that has damaged efforts to eradicate COVID-19 has been aided, in part, by the lack of adequate funding for pandemic response. According to one report (see go.nature.com/3ddkg05), in the United States, thousands of public-health departments continue to be underfunded and understaffed. Emily Gee, a health-policy advocate at the Center for American Progress in Washington DC, says that not only does this make it more difficult to implement health measures that could aid eradication, such as contact tracing, vaccination and testing, but it also puts pressure on officials' ability to engage with the public.

To react swiftly and effectively enough to eradicate a future pandemic-causing pathogen, Gee says, it will be important to consider not just how to manufacture and deliver vaccines to where they are needed, but also how to build the trust required for people to have them. She thinks that being more transparent — for example, about how scientists' understanding of a virus will evolve as more research is done, and why certain public-health measures are being used — is an important tool to combat disinformation during a pandemic, as well as more generally.

Tougher tasks ahead

The possibility of eradicating COVID-19 might now be considered slim, but it could be the catalyst to do better the next time a pandemic strikes. Passing legislation such as the PREVENT Pandemics Act in the United States — a bill focused on improving public health, medical preparedness and pandemic-response systems — could put countries in a better position to eradicate future pathogens, Gee says.

Studying where we went wrong over the past two years is also important, Wilson adds. "We should be learning everything we can about every intervention that was tried on COVID-19 and how to optimize it for a much more severe pandemic," he says. His concern that the next threat could be worse than SARS-CoV-2 is shared by Coler. "Even though it has been so devastating, we have been lucky," she says.

"When you think about the viruses that infect humans, a lot of them are less well understood, and harder to control, than coronaviruses," Coler says. The severe acute respiratory syndrome (SARS) outbreak in 2002, and the Middle East respiratory syndrome (MERS) outbreak in 2012, were both caused by coronaviruses. And although SARS and MERS research efforts pale in comparison with those of the past two years, by the time COVID-19 hit, scientists had already studied some essential components of coronaviruses. For example, valuable information about the spike protein allowed for the rapid development of vaccines and insight about key enzymes led to antiviral treatments.

The next pandemic threat might be less well understood and pose an even greater challenge than SARS-CoV-2. Simply preparing to deal with another pandemic of a similar threat level to COVID-19 might not be enough. "We have to be forward thinking," Coler says. "While there are a lot of lessons to be learned from COVID-19, we can't fall into the trap of being prepared for yesterday's disaster."

Sam Jones is a science journalist and audio producer based in Washington, DC.

Learn from past pandemics

COVID-19 shows us how we should prepare for future outbreaks to mount a stronger response, says Devi Sridhar.

The emergency phase of COVID-19 might have passed, but it remains fresh in the minds of politicians and the public.

This is a unique moment to learn from the global response. More outbreaks of infectious disease are inevitable. But it is possible to stop many of them turning into pandemics. The past 20 years of outbreaks — not only of COVID-19, but also Zika, Ebola, swine flu, Middle Eastern respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS) — can teach us how to improve global health security. Preparing for future pandemics involves strengthening the entire chain of the outbreak response, from identifying a pathogen through to mass vaccination.

Monitor zoonoses

The biggest risk comes from pathogens that circulate in animals making the jump into humans. As COVID-19 has demonstrated, once someone is infected in one part of the world, trade and travel will rapidly carry the virus nearly everywhere else. Assessing which pathogens are most likely to make the jump enables us to prepare vaccines and treatments. The World Health Organization has identified several priority diseases with pandemic potential, including Crimean–Congo haemorrhagic fever, Ebola, Marburg, Lassa fever, MERS, SARS, Nipah virus infection and Zika.

However, there are many pathogens with pandemic potential circulating in animals that we do not know about. It is crucial to identify hotspots where humans and animals come into contact and take steps to reduce risk. For example, hygiene standards at markets where animals are slaughtered and sold could be more closely regulated.

Sequence globally

To develop the tools required to tackle a pandemic, such as diagnostic tests, vaccines and therapeutics, we must know what we are fighting. It is crucial that we quickly obtain and share the genetic sequences of viruses as they emerge.

This was done remarkably well with SARS-CoV-2 — not only for the original sequencing in China, but also for subsequent variants detected elsewhere. But not all countries have this capability. If a virus emerges in a country without the ability to sequence it then it could spread silently for weeks, as happened when Ebola surged in Guinea in 2014. To avoid delaying responses that could be crucial to stopping a pandemic, such as reformulating vaccines, there must be investment in genetic-sequencing capability everywhere.

ALAN INGLIS

"Vaccination is essential to beating viral pandemics".

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Strengthen manufacturing

Swine flu, COVID-19 and monkeypox have shown that the model of charitable donations of vaccines from wealthier countries does not work. This leads to vaccine inequality: high-income countries control access to the bulk of supply, and low-income countries get very little. COVID-19 revealed the fragility of vaccine production. The world is heavily dependent on just a few manufacturers, such as the Serum Institute of India in Pune. The manufacture of vaccines and therapeutics needs to be spread more equitably, with regional hubs ready to mass produce high-quality medical products in an emergency. Building local manufacturing capacity requires waiving intellectual-property rights, building factories and training people to work in them — often in low-resource settings. This necessitates the participation of the private sector alongside governments, given its role in vaccine research, production and distribution.

Prepare vaccines for rapid production

Vaccination is essential to beating viral pandemics. If vaccines are ready in advance, they can be quickly deployed when threats emerge to help contain the spread. For pathogens with known pandemic potential, such as influenza, governments should invest in vaccines that can protect against a wide variety of variants. Clinical trials of universal flu vaccines, which mix flu strains to promote a broad-based immune response, are under way. To protect against threats that we have no knowledge of before an outbreak, scientists are creating plug-and-play technical platforms, such as mRNA technology or adenovirus vectors, that can be quickly modified to combat a specific emerging threat.

Stop the spread

Finally, governments must abandon the idea that spread of a respiratory pathogen is inevitable. During the COVID-19 pandemic, countries such as Sweden and the United Kingdom dismissed the idea of a vaccine being ready quickly enough to protect the bulk of the population from infection. Yet multiple vaccines were created, trialled and approved in roughly a year. How many people would have lived if governments had worked to stop transmission until mass vaccination campaigns rolled out? All reasonable efforts should be made to delay the spread of a virus until medical interventions are available. This includes enacting emergency mask mandates in public settings, such as shops and transport hubs, and making plans to keep schools open by moving classes to stadiums, museums and other large spaces that can provide a safer environment.

These five steps can help us respond to pandemic threats better than before. Some progress has been made: the 100 Days Mission, presented to leaders of the G7 group of the world's biggest economies in 2021, includes each of these points in its roadmap for moving from sequencing to vaccines within 100 days. It is of utmost importance that gains are maintained and more investments in pandemic preparation are made, even as the memory of the COVID-19 crisis fades from politicians' minds. We have identified solutions for the future — now we must act on them.

Pandemic preparedness

outlook

nature.com/collections/pandemic-preparedness-outlook
Nature 27 October 2022

Why Social Media Makes People Unhappy

Apps make us upset with ourselves, but there are ways to fix that

By Daisy Yuhas

Disrupted sleep, lower life satisfaction and poor self-esteem are just a few of the negative mental health consequences that researchers have linked to social media. Somehow the same platforms that can help people feel more connected and knowledgeable also contribute to loneliness and disinformation. What succeeds and fails, scientists say, is a function of how these platforms are designed. Amanda Baughan, a graduate student specializing in human-computer interaction at the University of Washington, studies how social media triggers what psychologists call dissociation, or a state of reduced self-reflection and narrowed attention. She presented results at the 2022 Association for Computing Machinery Computer-Human Interaction Conference on Human Factors in Computing Systems. Baughan spoke with Mind Matters editor Daisy Yuhas to explain how and why apps need to change to give the people who use them greater power.

[*An edited transcript of the interview follows.*]

You've shown how changing social media cues and presentations could improve well-being, even when people strongly disagree on issues. Can you give an example?

The design of social media can have a lot of power in how people interact with one another and how they feel about their online experiences. For example, we've found that social media design can actually help people feel more supportive and kind in moments of online conflict, provided there's a little bit of a nudge to behave that way. In one study, we designed an intervention that encouraged people who start talking about something contentious in a comment thread to switch to direct messaging. People really liked it. It helped to resolve their conflict and replicated a solution we use in-person: people having a public argument move to a private space to work things out.

You've also tackled a different problem coming out of social media usage called the 30-Minute Ick Factor. What is that?

We very quickly lose ourselves on social media. When people encounter a platform where they can infinitely scroll for more information, it can trigger a similar neurocognitive reward system as in anticipating a winning lottery ticket or getting food. It's a powerful way that these apps are designed to keep us checking and scrolling.

The 30-Minute Ick Factor is when people mean to check their social media briefly but then find that 30 minutes have passed, and when they realize how much time they have spent, they have this sense of disgust and disappointment in themselves. Research has shown that people are dissatisfied with this habitual social media use. A lot of people frame it as meaningless, unproductive or addictive.

You've argued this experience is less a matter of addiction and more an issue of dissociation. Why?

Dissociation is a psychological process that comes in many forms. In the most common, everyday dissociation, your mind is so absorbed that you are disconnected from your actions. You could be doing the dishes, start daydreaming and not pay attention to how you are doing the dishes. Or you might seek immersive experiences—watching a movie, reading a book or playing a game—that pass the time and cause you to forget where you are.

During these activities, your sense of reflective self-consciousness and the passage of time is reduced. People only realize that they dissociated in hindsight. Attention is restored with the sense of "What just happened?" or "My leg fell asleep while we were watching that movie!"

Dissociation can be a positive thing, especially if it's an absorbing experience, meaningful activity or a needed break. But it can also be harmful in certain cases, as in gambling, or come in conflict with people's time-management goals, as with social media scrolling.

How do you measure people's dissociation on social media?

We worked with 43 participants who used a custom mobile app that we created called Chirp to access their Twitter accounts. The app let people interact with Twitter content while allowing us to ask them questions and test interventions. So when people were using Chirp, after a given number of minutes, we would send them a questionnaire based on a psychological scale for measuring dissociation. We asked how much they agreed with the statement "I am currently using Chirp without really paying attention to what I'm doing" on a scale of 1 to 5. We also did interviews with 11 people to learn more. The results showed dissociation occurred in 42 percent of our participants, and they regularly reported losing track of time or feeling "all-consumed."

You designed four interventions that modified people's Twitter experience on Chirp to reduce dissociation. What worked?

The most successful were custom lists and reading history labels. In custom lists, we forced users to categorize the content they followed, such as "sports" or "news" or "friends." Then, instead of interacting with Twitter's main feed, they engaged only with content on these lists. This approach was coupled with a

Daisy Yuhas edits the *Scientific American* column Mind Matters. She is a freelance science journalist and editor based in Austin, Tex.

reading history intervention in which people received a message when they were caught up on the newest tweets. Rather than continuing to scroll, they were alerted to what they had already seen, and so they focused on just the newest content. Those interventions reduced dissociation, and when we did interviews, people said they felt safer checking their social media accounts when these modifications were present.

In another design, people received timed messages letting them know how long they had been on Chirp and suggesting they leave. They also had the option of viewing a usage page that showed them statistics such as how much time they'd spent on Chirp in the past seven days. These two solutions were effective if people opted to use them. Many people ignored them, however. Also, they thought the timed messages were annoying. Those findings are interesting because a lot of the popular time-management tools available to people look like these time-out and usage notifications.

So what could social media companies be doing differently? And is there any incentive for them to change?

Right now there is a lot working against people who use social media. It's impossible to ever fully catch up on a social media feed, especially when you consider the algorithmically inserted content such as Twitter's trending tweets or TikTok's "For You" page. But I think that there is hope that relatively simple tweaks to social media design, such as custom lists, can make a difference. It's important to note that the custom lists significantly reduced dissociation for people—but they did *not* significantly affect time spent using the app. To me, that points out that reducing people's dissociation may not be as antithetical to social media companies' revenue goals as we might intuitively think.

What's most important for people using social media now to know?

First, don't pile a bunch of shame onto your social media habits. Thousands of people are employed to make you swipe your thumb up on that screen and keep you doing what you're doing. Let's shift the responsibility of designing safe and fulfilling experiences from users to the companies.

Second, get familiar with the well-being tools that are already offered. TikTok has a feature that, every hour, will tell you that you've been scrolling for a while and should consider a break. On Twitter, custom lists are a feature that already exists; it's just not the default option. If more people start using these tools, it could convince these companies to refine them.

Most important, vote for people who are interested in regulating technology because I think that's where we're going to see the biggest changes made. SA

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Illustration by Matthew Holland

NONFICTION

A Busy History

How beavers shaped America—and not just its ecology

Review by Ben Goldfarb

Beavers, you may have noticed, are having a moment. These tireless engineers build woody dams that form ponds, which in turn filter out water pollution, sequester carbon, furnish wildlife habitat and avert drought. The *Los Angeles Times* recently called the beaver a "superhero," and the *New York Times* has deemed them "furry weapons of climate resilience." Wetlands with beavers are so good at fighting megafires that some researchers have urged the U.S. Forest Service to switch mammal mascots from Smokey Bear to Smokey Beaver.

In truth, western science is merely relearning what North America's Indigenous peoples have known for millennia. The Blackfeet so venerated beavers' water-creating abilities that they forbade killing them, and some Algonquian tribes consider the Great Beaver responsible for molding the Connecticut River Valley. Beavers fascinate people not only because of their landscaping skills but because of their anatomical oddities—their scaly tails, burnt-orange teeth, webbed hind feet and dexterous hands. "[T]here is an element of the sacred in the beaver, if only in its deep weirdness …" writes Leila Philip in her engaging new book, *Beaverland*. "Is it any surprise that beavers have fired the human imagination in every continent that they are found?"

As Philip reveals, humankind and castorkind have always been intimately acquainted. Medieval Europeans prized beavers' fatty tail meat as "forest cod," and some Indigenous tribes fashioned their teeth into dice and used their scapulae as digging tools. Especially coveted were "castor sacs," the scent glands with which beavers mark their territories (and which Aesop confused for testicles in one of his fables). The Romans believed castoreum capable of curing ailments from constipation to gout, and the substance still scents perfumes and occasionally flavors some foods today, although its culinary use has dwindled dramatically in recent decades. "If you like raspberry, strawberry, or vanilla ice cream and vanilla pudding," Philip notes, you may have eaten beaver castoreum.

Beaverland: How One Weird Rodent Made America
by Leila Philip.
Twelve, 2022 ($30)

Of course, the most valuable beaver-based commodities were their pelts. *Beaverland*'s subtitle, *How One Weird Rodent Made America,* is no exaggeration. The industrial fur trade drove westward colonization, hurled tribes into centuries of resource war, and lined the pockets of John Jacob Astor, the country's first multimillionaire, who parlayed pelts into a New York real estate empire. By destroying beaver ponds and wetlands, the fur trade also distorted ecosystems. "Before 1600, all of the continent from west to east, save a few desert sections, had stretched out as one great Beaverland," Philip writes—a lush, wet world whose waterways were "diffuse, messy, spread out, flexible at times, and most of all incredibly dynamic … hydrating everything like a great wand of moving water."

Although Beaverland may never fully return to its former grandeur, the rodents have made a remarkable recovery. Philip's odyssey takes her to many sites integral to their comeback, such as the farmhouse in upstate New York where conservationist Dorothy Richards once kept colonies of semidomestic beavers. (They sometimes chewed the legs off mahogany dressers.) She also visits a forest in New Hampshire where contemporary scientists are studying the hydrology of rebuilt beaver meadows: "giant underground sponges that can soak up and hold large stores of water," thus saving watersheds from drought.

Philip spends a lot of time with contemporary fur trappers. Pelts rarely fetch more than $20 these days, but some trappers still make a half-decent living killing beavers at the behest of agencies and landowners, who fret that expanding ponds will damage roads and private property. Philip admirably negotiates these complex interactions: she's respectful of trappers' hard-won knowledge of beaver behavior yet rightly skeptical about whether lethal control is the best way to solve conflicts (although she could have more forcefully refuted the self-serving claim that we need trappers to prevent beaver populations from running amok). Rather than resorting to traps, it's better to use "pond levelers"—pipe systems that partially drain impoundments, thereby balancing human needs with rodents' instincts.

Among the challenges of writing about beavers is that they're seemingly linked to *everything*—the rise of capitalism, the transformation of American landscapes and the fight against climate change, to name a few enormous themes. "Beavers," Philip admits, "were leading me astray." Indeed, we're treated to lengthy digressions about coyote ecology, the history of New England's stone walls and a documentary about naked mole rats.

Perhaps it's only fitting that a book about beavers sometimes spills beyond its banks. Beavers, after all, are some of Animalia's most unruly members: they compel rivers to overflow, transform single-channel streams into braided ones and ingeniously sabotage our precious infrastructure. It's long past time that we again learn to embrace their glorious chaos.

Near *Beaverland*'s end, Philip travels to Maryland, where a stream restorationist named Scott McGill collaborates with beavers to capture pollutants that would otherwise flow into Chesapeake Bay. "To build a stormwater management pond with that kind of water retention would cost one to two million dollars," McGill says, nodding to a beaver compound. The rodents, of course, built it for free.

Ben Goldfarb is a journalist and author of *Eager: The Surprising, Secret Life of Beavers and Why They Matter,* winner of the 2019 PEN/E. O. Wilson Literary Science Writing Award.

Illustration by London Ladd

FICTION

Drumbeat of Climate Chaos

Building tension but lacking empathy

Review by Michael Welch

Expect Me Tomorrow by Christopher Priest. Mobius, 2022 ($26.99)

Acclaimed science-fiction writer Christopher Priest has a long history of creating high-concept thrillers, including *The Separation, The Islanders* and the World Fantasy Award–winning *The Prestige.* His ambitious new epic, *Expect Me Tomorrow,* foretells our climate future by following three interconnected lives that span both generations and continents. There's glaciologist Adler Beck, who struggles to study the shifts in Earth's climate amid increasingly debilitating seizurelike events in the late 1800s; a petty thief known as John Smith, who was arrested in 1877 for defrauding women; and former police profiler Charles Ramsey, who has an experimental chip implanted in his brain in the year 2050.

Priest is an expert at seamlessly adjusting his writing style to meet the topic. Beck's sections, for instance, have the sensibility and linguistic creativity of a Charles Dickens novel, whereas Ramsey's sections exhibit the paranoia and tension of a sci-fi thriller. Binding these various narrative threads together is a gripping mystery about the characters' shared histories and the ever present (and growing) danger of a changing climate.

Although the approaching ecological catastrophe serves as a steady drumbeat throughout the novel, it most often remains strangely distant from the lives of the characters. Readers learn about future water wars, refugee crises and worsening storm cells primarily through passing conversations and news reports. Rarely do they experience the ways climate change is felt in the lives of the characters, beyond a train delay caused by rail lines warping in the heat. Ultimately this disconnect prompts questions about the purpose of eco-fiction in our modern era. Is the goal simply to assert the existence of our world's most pressing problem, or does the genre bear responsibility to build empathy for the people who will suffer the most from this coming disaster? The novel certainly informs—Priest offers pages of scientific explanations of glaciology and the Year Without a Summer in 1816—but it doesn't develop an emotional core.

Without attention to the true human cost of the events Priest portrays, *Expect Me Tomorrow* too often finds itself in danger of using climate change merely as a plot hook—despite how compelling it is to read.

IN BRIEF

How Far the Light Reaches: A Life in Ten Sea Creatures

by Sabrina Imbler. Little, Brown, 2022 ($27)

Journalist Sabrina Imbler's latest book mingles memoir and marine biology in a tender, lucid look at the author's life refracted through the deep sea. Their essays' mesmerizing descriptions of the often mysterious lives of aquatic animals also serve as portals of inquiry into Imbler's life on land. The purple octopus's maternal sacrifice, the yeti crab's vibrant but transient seafloor communities and the cuttlefish's continual transformations are not forced anthropomorphic metaphors but starting points for a visceral exploration of Imbler's family, sexuality, gender, race and relationships. These graceful cross-species analyses illuminate the joys and responsibilities we have as "creatures with a complex brain."

—Dana Dunham

Birth Figures: Early Modern Prints and the Pregnant Body

by Rebecca Whiteley. University of Chicago Press, 2022 ($49)

In this fascinating porthole into English pregnancy culture in the 16th to 18th centuries, cherubic representations of fetuses in transparent wombs greet bewildered readers who, like me, had never heard of "birth figures" before encountering medical historian Rebecca Whiteley's book—part anthropological analysis, part scientific critique. These formulaic illustrations appeared in midwife manuals—and as Whiteley tells it, they were woefully inaccurate depictions of anatomy and conveyed baffling assumptions about female autonomy. By recasting birth figures as evolving feminist iconography, Whiteley places these artifacts in the context of contemporary debates over reproductive rights.

—Maddie Bender

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Enabling rapid responses to infectious diseases

AstraZeneca

The COVID-19 pandemic has been met with an unparalleled response by the global scientific community and its stakeholders, who have developed vaccines and therapeutic antibodies in an unprecedented timescale. These new therapies for preventing and treating COVID-19 have altered the course of the pandemic to an extent that has never before been seen for an infectious disease in terms of the numbers of lives saved, with vaccines alone being estimated to have helped to save 19.8 million lives within their first year of deployment[1] and therapeutic antibodies providing additional protection to the most vulnerable populations[2].

As was recently outlined by the National Institute of Allergy and Infectious Diseases (NIAID) in their pandemic-preparedness plan (P3), research into new technologies is a cornerstone of future pandemic-prevention strategies[3]. To overcome the ongoing challenges posed by COVID-19 and to minimize the impact of future pandemics, AstraZeneca is researching new technologies to support the rapid development of novel vaccines and long-acting monoclonal antibodies (LAABs) for vulnerable populations.

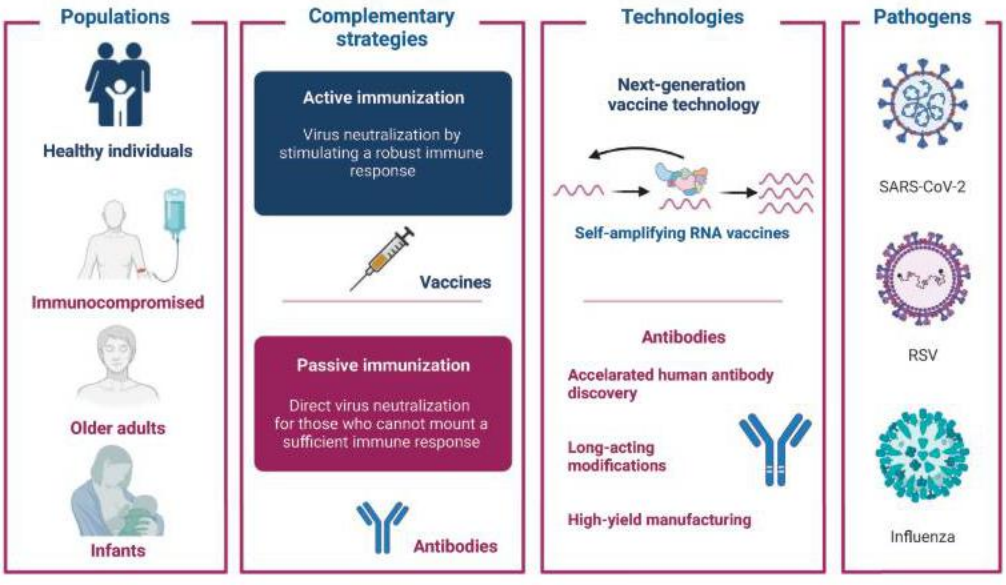

Figure 1. Complementary strategies for infectious disease prevention and treatment. AstraZeneca is committed to developing therapies for the benefit of all individuals, including vulnerable populations in which the burden of disease is the greatest. Research into new vaccine and antibody-discovery technologies will facilitate the rapid development of new vaccines and long-acting monoclonal antibodies (LAABs) that could provide effective and long-lasting immunity for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), respiratory syncytial virus (RSV), influenza and pathogens with pandemic potential.

COMPLEMENTARY STRATEGIES TO PROTECT ALL

At AstraZeneca, our approach to tackling the most challenging infectious diseases and future pandemics encompasses two complementary strategies — active and passive immunization — so that 'no one will be left behind' (**Fig. 1**).

Active immunization is the generation of B-cell-mediated antibody and T-cell-mediated cellular immune responses to antigens from pathogens through vaccination. Vaccines are critical to disease prevention and infection control at both the individual and the population level via herd immunity.

However, other strategies are needed to protect those unable to fully generate an immune response following vaccination, such as individuals who are immunocompromised following organ transplantation or are receiving treatment for certain cancers or immunosuppressive therapies. The administration of exogenous antibodies by injection or intravenous infusion can provide additional protection for vulnerable individuals — a process known as passive immunization or immunoprophylaxis. Examples of passive immunization include the transfer of antibodies from mother to infant via the placenta during pregnancy or via breast milk, and the clinical administration of monoclonal antibodies (mAbs).

TRANSFORMING VACCINE DEVELOPMENT

Investment in novel vaccine-development platforms that are adaptable, reliable, and scalable is necessary to ensure that sufficient doses can be produced to rapidly respond in a pandemic setting. The need for this flexibility has been exemplified by the emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants-of-concern that can be more transmissible and/or can evade antibodies elicited by the currently authorized COVID-19 vaccines, thereby causing an increase in breakthrough infections. Innovative approaches to vaccine development are also needed to develop pan-variant vaccines that could provide protection against multiple viral variants.

AstraZeneca is addressing these types of challenges by researching self-amplifying RNA (saRNA) and novel antigen-design technologies.

saRNA is a novel vaccine platform that has been observed to elicit robust immune responses and could play a vital role in future pandemic responses due to the speed and scalability of its production. saRNA vaccines are delivered by lipid nanoparticles and have the same chemical properties as messenger RNA (mRNA)-based vaccines[4]. However, while mRNA vaccines contain the RNA genetic code for a single antigen, saRNA vaccines comprise the RNA of their target antigen and four additional alphavirus proteins that form the RNA-dependent replicase. This additional component allows for more target antigen mRNA to be produced within a vaccine-recipient's cells on a per-microgram basis. This enables saRNA to be delivered at lower overall concentrations than other RNA-based vaccine platforms, which may offer reduced reactogenicity while improving immunogenicity. Additionally, saRNA vaccines have the same benefits as mRNA vaccines: they can be produced at scale in small bioreactors capable of producing hundreds of millions of doses; they can be quickly adapted for emerging viral variants; and the platform can be applied to novel viruses.

ACCELERATING LAAB DISCOVERY

Prophylaxis with mAbs has a demonstrated history of curbing infectious diseases[2]. More recently, innovations in protein engineering led to the discovery of the YTE modification — a set of three amino-acid changes to the antibody fragment crystallizable (Fc) 'tail' region — which increases an antibody's half-life in serum by threefold to fourfold. These changes allow LAABs to be derived from naturally produced mAbs and enable long-term protection against infectious disease[2]. This approach is being used to develop LAABs for COVID-19 and other pathogens including respiratory syncytial virus (RSV)[2,5]. LAABs are critical for providing passive immunity to protect against viral disease in vulnerable individuals. By mimicking neutralizing antibodies induced by infection or vaccination, LAABs can restrict the ability of a virus to engage with host-cell receptors and prevent host-cell entry[2]. LAABs can be used as prophylaxes to prevent disease or as early treatments following infection[2,6].

In line with the P3 goal of producing an antibody to stop a novel virus in less than 60 days, we challenged ourselves to condense our antibody discovery timeline from years to weeks. We and others developed new technologies from flow-cytometry-based single-cell sorting of antigen-specific B cells to single-cell DNA sequencing that revolutionized how we discovered ultra-potent neutralizing antibodies. These technologies were employed to discover new therapeutic antibodies in the fight against COVID-19[6,7].

LAABs are produced in large-scale, batch-fed, 15,000-liter bioreactors using immortalized cells. AstraZeneca is developing perfusion-based manufacturing capabilities to continuously produce LAABs more efficiently at an even greater scale. Perfusion-based approaches use a cell-retention device to achieve and maintain high cell-culture densities, coupled with continuous media exchange to remove waste products and old culture media, and to capture the desired antibody products. As a result, yields are higher compared with traditional batch and fed-batch cell-culture processing approaches[8]. Collectively, these technologies will allow us to quickly identify and rapidly produce LAABs for novel emerging pathogens.

ASTRAZENECA'S ONGOING COMMITMENT TO VACCINES AND IMMUNE THERAPIES

AstraZeneca supports broad and equitable vaccine access. With a commitment to increase investment in vaccines and immune therapies, AstraZeneca is looking to identify global needs for vaccines against other infectious agents including influenza — a leading cause of respiratory illness and death, and a serious future pandemic threat — and other NIAID P3 priority and prototype pathogens with future pandemic potential. Until we can come up with countermeasures to protect everyone, including the most vulnerable, our work will not be done.

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The Puzzle of Vanishing Lakes

Arctic lakes are disappearing fast, and scientists are just learning why

By Naomi Oreskes

Research sometimes proves, with data, what we more or less already know. Exercise is good for you, and polluted air isn't. Still, sometimes our intuitions are incorrect, and scientific findings surprise researchers, along with the rest of us. A recent example is the phenomenon of disappearing lakes in the Arctic tundra.

You might think these lakes would be expanding, not vanishing. As climate change warms the tundra—melting surface snow and ice and thawing the permafrost—there should be more surface water. Existing lakes should grow because of the extra water, and new ones might appear. Recently, however, scientists have observed not just shrinking lakes but lakes that have completely gone away. A paper published this year in *Nature Climate Change,* based on satellite imagery, found widespread lake loss across the Arctic over the past 20 years. Led by University of Florida postdoctoral researcher Elizabeth Webb, the scientific team found that lakes have shrunk or disappeared completely across 82 percent of the Arctic's lake-rich regions.

Scientists have long recognized that global warming would thaw permafrost, and like many climate effects, that one appears to be happening faster than predicted. But the surprise is really about the bodies of water in the permafrost environment.

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).

Many scientists shared the commonsense expectation that as permafrost thawed, lakes would at first expand because of increased meltwater flowing into them. Eventually, researchers projected, progressive warming during the 21st and 22nd centuries would dry out the Arctic enough that lakes would begin to shrink. But now it looks as if Arctic lakes are disappearing a century or more sooner than predicted.

There is a big difference between a lake gradually dwindling during a hotter climate and a lake vanishing from sight in less than a year. At the end of the summer of 2018, following the warmest and wettest winter on record at that time, 192 lakes in northwestern Alaska had completely or partly drained away. Some large lakes, believed to have existed for millennia, shrank drastically in what appears to have been a matter of months. Scientists have labeled this phenomenon "catastrophic lake drainage."

What caused this? Basically, the ground is becoming more permeable. We talk about "solid ground," but its particles of rock, mineral and organic matter actually have spaces between them. Outside the Arctic, those spaces are filled with air or water; surface water drains into them. (You see this after it rains, when after a few hours the puddles have disappeared.) Arctic landscapes are different. In permafrost, the pore spaces are filled with solid ice, so liquid water cannot readily penetrate. But when the permafrost thaws, water can flow downward. So these far northern lakes are disappearing because surface water can drain rapidly into the subsurface as the permafrost warms up.

Why did scientists miss this? One reason, offered by Webb and her colleagues, is that most climate models assume that permafrost thaw is driven only by warming air. New evidence suggests that rainfall—particularly increasing autumn rain—is now contributing substantially to permafrost loss. The rainfall carries heat into the ground. Yet none of the models in the large Coupled Model Intercomparison Projects (CMIPs) includes such processes. This is a good example of why—no matter how sophisticated our models are or may one day be—we need direct observation of the natural world.

Lakes make up as much as 40 percent of Arctic lowlands, where they provide crucial freshwater for Indigenous communities and critical habitat for a wide range of plant and animal life. The loss of marshy areas that accompany these lakes can also lead to an increase in wildfires, which, in a troubling feedback loop, melts more permafrost. This permafrost holds a huge amount of methane, a greenhouse gas that can create 80 times as much atmospheric warming as carbon dioxide in the short term. Rapid release of this methane could accelerate global warming dramatically.

There is, of course, a clear path to saving Arctic lakes: stop the carbon pollution that is driving global climate change. SA

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Illustration by Jay Bendt

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1972 Nobel Prize Repeat

"The 1972 Nobel prizes in science and economics have been awarded to 10 investigators. For the first time in history a prize has been given a second time in the same field to one individual. Marie Curie and Linus Pauling had previously won two Nobel prizes but in different fields. The new double winner is John Bardeen, who shared the 1956 Nobel prize in physics for discoveries leading to the transistor. Bardeen now shares the prize with Leon N. Cooper and John R. Schrieffer 'for their jointly developed theory of superconductivity, usually called the BCS theory.'"

1922 Fingerprints by Radio

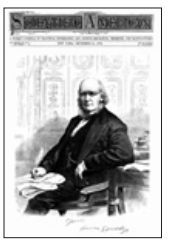
"The latest obstacle placed in the path of the wrong-doer is the long arm of radio, which not only serves to ensure rapid intercommunication between the various police forces of the world, but also transmits photographs and fingerprints for instantaneous identification. An image of a fingerprint is converted into a relief image and wrapped about a cylinder of the transmitting device. As the image turns, in absolute synchronism with the turning of a receiving cylinder at the distant point, the high and low spots of the relief image are brought under a point or stylus. The stylus is connected to a simple device, which makes and breaks a current according to the raised or the lowered portions of the image."

A Need to Reseed

"According to the president of the American Forestry Association, Charles L. Pack, statistics show that there is 11 percent more timber in the Black Forests of Germany today than in 1914. He has sent millions of tree seeds to Europe to help reforest the areas ruined by the war, 'in the hope that the people of [the U.S.] would see the great value of maintaining that backbone of all industry, forest products.' The commercial exploitation of [U.S.] forests has been that the standing timber throughout the country represents today but a fraction of the glorious forests which were found by the early settlers. The power of the government [should] be employed to demand that where someone cuts down the old timber he shall plant the beginnings of the new."

1972

1922



1872

Psychic Reward

"We are unable to reach a definite conclusion as to the validity of psychic claims. In the effort to clear up this confusion, the SCIENTIFIC AMERICAN will pay $2,500 to the first person who produces a psychic photograph under its test conditions and to the full satisfaction of the judges. The SCIENTIFIC AMERICAN will also pay $2,500 to the first person who produces a visible psychic manifestation of other character, under these conditions. Purely mental phenomena like telepathy, or purely auditory ones like rappings, will not be eligible."

1872 Quick Spark

"The extremely short duration of the spark was shown by causing it to illuminate a rapidly revolving disk of paper containing a number of slots. Although it was moving so rapidly that the slots could no longer be seen, it seemed to stand still every time the spark flashed. Professor Rood, of Columbia College, has shown by his beautiful researches that the duration of a single spark is less than ninety-four billionths of a second, a quantity which is entirely inconceivable."

Fertilized Luxuriance

"M. Jeannel, says *Les Mondes,* has made a series of experiments, in the use of chemical fertilizers. It has been found that plants can receive, in solution with the irrigation water, the mineral constituents necessary to their organism. The following results are given of potted plants cultivated in sand watered with ordinary water; plants cultivated in mold similarly irrigated; and plants cultivated in sand supplied with common water and receiving weekly mineral manure in solution. The latter became doubly developed, more green, and flowered far more profusely than the plants raised in mold. The plants cultivated in sand without fertilizer proved puny and miserable. The ingredients include nitrate of ammonia, biphosphate of ammonia, nitrate of potash, chlorhydrate of ammonia, sulphate of lime and sulphate of iron."

1972, DESERT SEA: "The Mediterranean must have looked something like this six million years ago, when the basin was a great interior desert lying 10,000 feet below sea level. Some 5.5 million years ago, an opening was breached at the Strait of Gibraltar. The inrushing Atlantic water constituted a great waterfall. Within a few thousand years the desiccated Mediterranean would be filled to the brim."

Scientific American, Vol. 227, No. 6, December 1972

HOW TO BUILD AN MRNA ARSENAL FOR PANDEMIC PREVENTION

Through in-house research, academic collaborations and global team building, MODERNA CREATES AN ECOSYSTEM for innovation and manufacturing.

The current COVID-19 pandemic has claimed an estimated 18.2 million lives globally[1], but it could have been worse. Without vaccines, the death toll could have been closer to 40 million[2]. A future pandemic, set off by a putative 'Disease X', could be even worse, and health-care experts want to be prepared.

Disease X, in this instance, is the unknown pathogen, as designated by the World Health Organization (WHO), with potential to cause a serious international epidemic. And it's probably not far away. One study[3] estimated up to a 2% chance per year of another pandemic at least as bad as COVID-19, which means a one in five chance over the next ten years. That's why scientists at Moderna are planning for Disease X today.

The company's plan views global health in a broad way. "It's about looking at overall disease burden," says Shannon Klinger, chief legal officer at Moderna, and president of the Moderna Foundation in Cambridge, Massachusetts. "We see that people living in low-income countries are far more likely to die of a communicable disease than a non-communicable disease."

The technology behind Moderna's COVID-19 vaccine — mRNA packaged in lipid nanoparticles — has the potential to reduce disparities in global health and help fight future pandemics. "We think that our mRNA platform is uniquely situated to address some of these challenges, challenges that our industry has been trying to fight for decades," Klinger says. "Part of our global public health strategy is aimed at advancing our mRNA vaccines for the prevention of infectious diseases and investing in the next generation of mRNA innovation."

▲ Messenger RNA technology makes it easier to translate information into a vaccine and do it faster.

Moderna's current pipeline includes numerous programmes relevant to public health, including new vaccines for respiratory threats like COVID variants, influenza and respiratory syncytial virus. In early 2022, the company announced a portfolio of programmes aimed at tackling emerging pathogens, in preparation for Disease X threats. The company selected 15 diseases based on global burden and declaration of priority pathogens from the WHO and the Coalition for Epidemic Preparedness Innovations (CEPI). "They have issued calls to action to develop vaccines against particular pathogens," Klinger says. "Our portfolio already included four of those: SARS-CoV-2, HIV, Nipah and Zika." Now, Moderna will deploy its mRNA technology to research vaccine approaches for the remaining 11 pathogens, and one of its first objectives is to gather as much data as it can.

Prototypes against pathogens

Given the uncertainty of what Disease X could be, Moderna speeds up the development of new vaccines based on prototype pathogens. "We take examples from different viral families," says Andrea Carfi, Moderna's chief scientific officer, infectious disease. "This gives us a starting point to develop a new vaccine against a related pathogen." That starting point includes knowledge about viral structure, cell entry and the parts of the virus that might be the best targets for a vaccine.

Not only does a prototype pathogen suggest potential antigens to target, it also helps Moderna's scientists and their collaborators develop assays and models for testing a new vaccine's impact. "Testing is really fundamental to the development of a vaccine," Carfi says.

For COVID-19, Moderna used its knowledge from work on other coronaviruses to speed up development of its vaccine. Other tools also accelerate the creation of more vaccines. As an example, Carfi says, "The advances in applying structural biology to antigen design — really understanding the atomic details of these proteins and how to stabilize them — helps us engineer better vaccines." Plus, he points out that mRNA technology makes it easier to translate that antigen information into a vaccine and do it faster. "With mRNA approaches, you don't have to grow the virus to make a vaccine," he says. "Instead, you can use available sequence information and draw similarities to other viruses."

Many of the advances in structural biology arise from computation. "Ten years ago, we didn't think it would be possible to use artificial intelligence (AI), but it provides a very good starting point in terms of understanding the structure of viral proteins, especially on the surface of viruses," Carfi says. "It's a little tricky because those are very unstable products." He adds that expanding the database of structures will improve the AI-based training that allows algorithms to explore new viruses.

Together, these analytical tools transform the development of vaccines. "There's no old vaccinology; we combine structural biology, virology, immunology — bringing together all the different aspects of science," Carfi says.

▲ Vaccines that use mRNA technology have the potential to reduce disparities in global health and help fight future pandemics.

"There is no vaccine without understanding how the virus enters cells as infection develops and how to neutralize it."

A case in point is Moderna's work on a vaccine against Nipah virus. Nipah is a zoonotic disease, which the WHO estimates has a fatality rate as high as 75%. "From other paramyxoviruses, where we know the structure of the antigens and how to stabilize them, we can apply that directly to Nipah," he says. "This work suggests the best antigen to target, but then we need to demonstrate that targeting the antigen provides protection," which requires the development of assays and animal models.

For global health, the best prototype pathogen to pick depends on which infections pose the highest risk. "It takes surveillance," Carfi says. "You need to really understand epidemiology and where there are outbreaks of infection." From those outbreaks, Moderna picks a prototype pathogen that is likely to provide the most information about a new infection.

Creating complex vaccines

To battle some diseases, a vaccine must take on a target composed of a multiprotein complex or several pathogens at once. "That's been very difficult with previous technologies," says Melissa Moore, Moderna's chief scientific officer, scientific affairs.

Latent viruses often express many antigens that trigger the production of antibodies. A key antigen for cytomegalovirus, for example, consists of a complex made of five subunits. Targeting that antigen requires a vaccine that recognizes all five subunits. "That really wasn't able to be made using standard biologics — making the proteins in cell culture and then trying to administer them," Moore says. Moderna is investigating a potential vaccine that can put the five needed mRNAs in one lipid nanoparticle to make a vaccine that targets all subunits.

Other combinations can also be created in mRNA vaccines. For example, a multi-valent vaccine can attack multiple strains of the same disease or even different diseases. Moderna's most recent COVID vaccine, authorized or approved by the United States Food and Drug Administration, European Medicines Agency and others, includes mRNA encoding the original strain of the virus plus several variants, including Omicron. In addition, Moore says that Moderna is "working on mixing together mRNAs targeting important respiratory viruses in order to make a combination vaccine". Although other examples of combination vaccines exist, such as the one for measles, mumps and rubella (MMR), making them with mRNA simplifies the manufacturing process — instead of growing multiple cultures of cells, just make the mRNAs and put them together.

Building community science

Beyond its in-house expertise, Moderna collaborates with the broader research community. Today's vaccines based on mRNA arose from years of research in academia and industry. "We could not have developed our mRNA vaccines without the decades of curiosity-based research into

▲ mRNA vaccinology combines structural biology, virology, immunology — bringing together all the different aspects of science.

▲ Moderna collaborates with scientists across academia and industry to advance medicines for Disease X.

understanding the molecular biology of mRNA," Moore says. "It was a cast of hundreds of thousands of people who enabled us to be able to do this."

For tomorrow's mRNA-based vaccines, Moderna has developed a programme that encourages collaborations between academic and industrial scientists. "Internally, we cannot generate all of the preclinical data for investigating all of the possible vaccines," says Moore. So, the company developed its mRNA Access programme, which provides tools for researchers to design novel vaccines for emerging and neglected infectious diseases.

Participating researchers can use Moderna's mRNA Design Studio. With this cloud-based tool, researchers can create mRNAs that might target emerging diseases or existing diseases in new ways. "This allows academic investigators to figure out new antigen designs, and we provide them with the formulated mRNA that targets that antigen," Moore says. "This is amazing technology, and we saw an opportunity to share it with researchers exploring vaccine-preventable diseases."

In fact, defeating future outbreaks of infectious diseases will require spreading vaccine manufacturing around the world. "What these outbreaks tell us is that, even when there is an approved vaccine, it's not always available in sufficient quantities to meet demand and be accessible to the populations most at risk," Klinger says. "That's why one of the things we announced as part of our public health strategy was manufacturing in Kenya." Compared with traditional vaccines, mRNA-based vaccines can be made in smaller facilities that cost less than traditional vaccine facilities[4], which makes it easier to build plants where the vaccines are needed. She adds that the Kenyan plant is expected to produce up to 500 million doses of vaccines a year.

During the COVID-19 pandemic, people around the world learned the value of collaboration. "We understand that pandemic preparedness requires public and private collaboration," Klinger says. "So while our platform enables us to move quickly, we must work with governments, health-care practitioners and other stakeholders to meet the challenges of future pathogens." And when it comes to tackling Disease X, Klinger says, "We are building an ecosystem to be better prepared moving forward."

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moderna

Text by Clara Moskowitz | Graphic by Nadieh Bremer

Milky Way Census

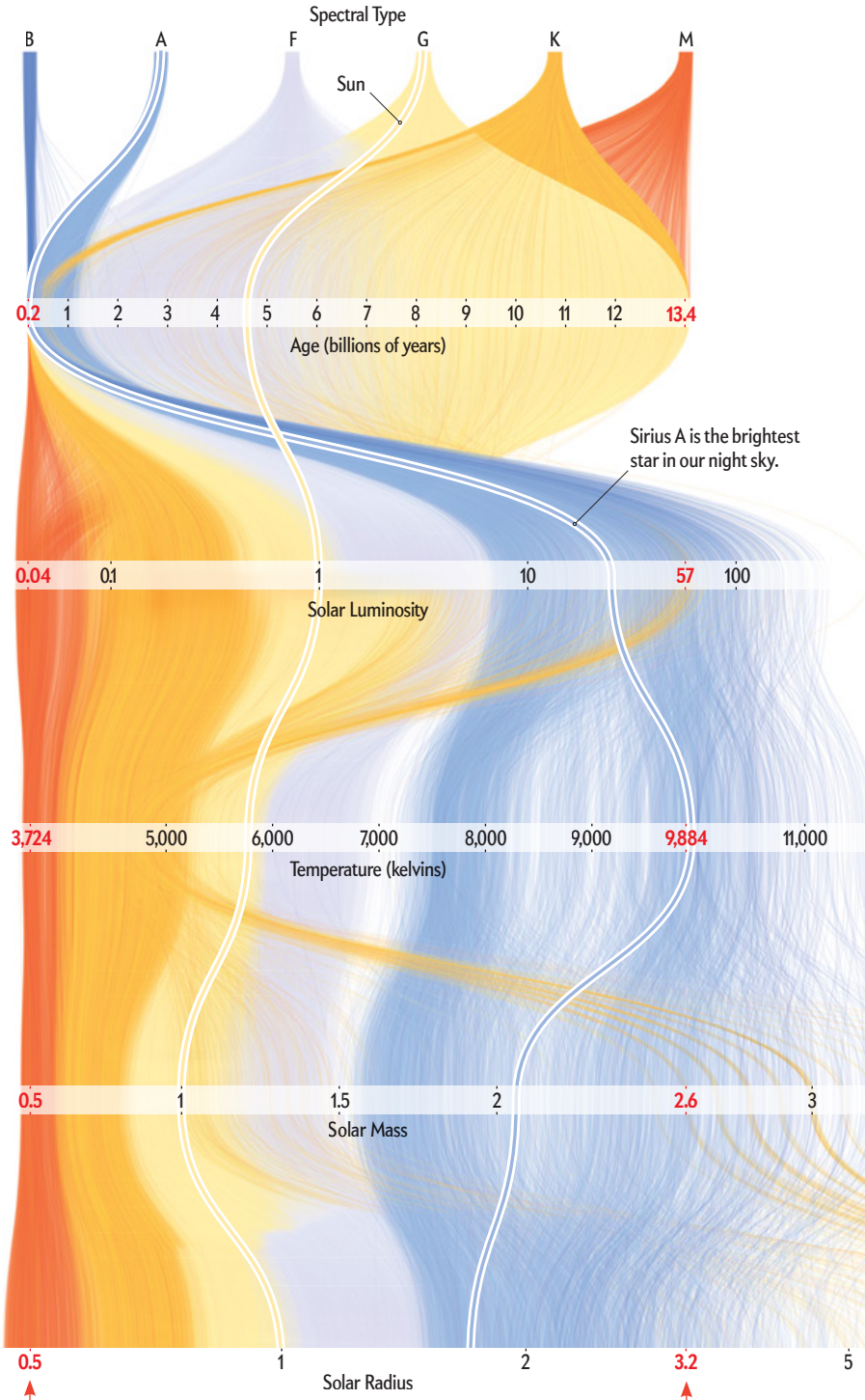
The Gaia satellite is making the most detailed and complete map of the stars in our galaxy

After launching to space in 2013, the European Space Agency's Gaia telescope has been spinning in full circles every six hours, mapping all the stars it can see in every direction. Scientists recently released a new catalog of the mission's latest data, which includes measurements of the chemical compositions, temperatures, colors, masses, ages and speeds of almost two billion stars in the Milky Way. These data reveal typical trends for stars: The massive stars tend to be hot and young. Because they don't live for long, the older massive stars will have died out by now. The smaller stars with lower masses live much longer, so we find them at every age, and they tend to be cooler and redder.

Gaia's observations help astronomers piece together our galaxy's history and understand how it compares with others across the universe. "We are sitting inside the Milky Way," says Timo Prusti, Gaia's project scientist. "It's like a forest: you see lots of trees, but you don't know what the forest looks like because you are inside. With Gaia, we are trying to measure all the trees so we can figure out what it looks like."

Tracing Star Trends

Each line represents a single star, color coded by spectral type. Spectral type is a stellar classification system based on a star's temperature, which roughly correlates to color—hotter stars are blue, and cooler stars are red. The pathway each line takes shows where the star falls on measurements of various stellar characteristics.



A subsample of about 85,000 of Gaia's nearest measured stars are shown here.

Labels in red define the lower and upper 1–99 percent boundary:

Values that fall out of that statistically common range are outliers; they zoom off to the left and right.

Some very massive stars that are at the end of their evolution expand in radius and become cooler, yet they remain quite massive and luminous.

Source: "Gaia Data Release 3: A Golden Sample of Astrophysical Parameters," by Gaia Collaboration, arXiv, 2022 (*data*)

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