

SCIENTIFIC AMERICAN



Did Dark
Energy Change?

Leap Seconds

The Staggering
Success of
Vaccines

Learning from Lucy

The famous fossil is still
teaching us about human origins
50 years after its discovery

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ON THE COVER

Fifty years ago an extraordinary fossil skeleton was discovered in Ethiopia. Nicknamed Lucy, the skeleton came from a small-brained, upright-walking human ancestor who lived nearly 3.2 million years ago. Today Lucy's species, *Australopithecus afarensis*, is the best-known early human ancestor on record, thanks to the wealth of additional fossils that have been recovered.

Illustration by
John Gurche/
Created for the Institute
of Human Origins/
Arizona State University

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Tomekbudjedomek/Getty Images

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Credit: Chris Wren and Kenn Brown/mondoworks

Understanding Our Origins

SOMETHING STRANGE is happening with dark energy. What little we know about it is strange enough: “Dark energy” is the name for an unknown force that is causing the universe to expand faster all the time. Nobody has been able to detect dark energy directly; we can only measure its effects. And one of those measurements is a little . . . off. The Hubble constant describes how quickly the universe is expanding. Physicists estimate its value in the nearby universe by measuring distances to supernovae.

The problem is that these estimates for the Hubble constant don’t match what the standard model of cosmology predicts based on patterns in the cosmic microwave background, the glow left over from the early universe. The discrepancy has gotten more pronounced (and less likely to be a measurement error) in the past few years with more precise observations from the James Webb Space Telescope, building on those from the Hubble Space Telescope.

So has dark energy changed over the course of the universe? Did an additional “early dark energy” force give the universe some extra oomph immediately after the big bang? Theoretical physicist Marc Kamionkowski and astrophysicist Adam G. Riess have been working on this “Hubble tension” problem from the beginning. On page 42, they explain the problem and possible solutions as clearly and entertainingly as I’ve ever seen (as always, great graphics help).

The *Australopithecus afarensis* fossil fondly known as Lucy is one of the most important discoveries in the study of human origins. She was found 50 years ago and quickly changed our understanding of how we

became human. On page 22, her discoverer, Donald C. Johanson, and paleoanthropologist Yohannes Haile-Selassie, who has discovered many other crucial hominin ancestors, share what we’ve learned about the evolution of human brains, gait, habitats and diets by studying these precious fossils.

Earth’s daily rotation has slowed down over time; when dinosaurs roamed the planet, a day lasted just 23.5 hours. This consistent slowing is mostly because of friction. The gravitational pull of the moon causes ocean tides, and the friction of the oceans sliding across the seafloor slows the entire system. Inside the planet, currents in the liquid outer core are now slightly increasing our rotational speed. And global warming is changing the dynamics of Earth’s rotation as well, as water from melting ice moves from the poles toward the equator. It’s a mess. We have added “leap seconds” over the years to synchronize atomic clocks with Earth’s changing rotation. Senior editor Mark Fischetti, working with infographic designer Matthew Twombly, asks on page 50 if it’s time to just let clock time and planetary time drift apart.

Vaccines delivered through a puff up the nose or into the mouth could be even more effective than shots at protecting people from respiratory diseases (plus, no needles). Science journalist Stephani Sutherland on page 34 covers the progress that is being made on nasal vaccines and the reasons scientists are so hopeful about them.

We’re publishing our third annual special package on health equity in this issue, starting on page S1, with a focus on solutions. Here are some highlights: Vaccines are among the most lifesaving interventions in the history of humanity. People working in rural areas have come up with innovations that have improved medical care for all. Disaggregating data improperly lumped together can save lives. Medical devices and algorithms are being corrected for historical biases. And we talked to several experts in global health about what gives them hope for the future. We hope the collection is inspiring—it has been for us at *Scientific American*. ●

Laura Helmuth
is editor in chief
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DUNCAN GEERE AND MIRIAM QUICK GRAPHIC SCIENCE, PAGE 74

On their podcast, *Loud Numbers*, Miriam Quick and Duncan Geere (*above*) turn data into music. There's a techno track charting climate change, a fugue about European bureaucracy, an experimental epic about beer tasting, and more. "You get to ride the waves of the data, moment to moment, in a much more emotionally resonant way" than looking at a graph, Geere says.

As data journalists and storytellers, they use both sonification and visualization to make complex information understandable to our ears and eyes. For this issue's column on music evolution, with text by associate news editor Allison Parshall, Quick and Geere were challenged to represent a song as a visual graph. Quick studied music-performance styles for her Ph.D. in musicology, so she has experience using data to "understand the music in a different way," as she puts it. Geere, who came to data journalism from an earth sciences background, is also passionate about music; he DJs and plays in bands.

Their graphic uncovers and maps key similarities among pieces of traditional music from all over the planet. "It suggests that music, or song specifically, occupies a stable position across cultures," Quick says—that is, we humans sing for a common reason.

LUISA JUNG SOLUTIONS FOR HEALTH EQUITY, PAGE S1

Early in her career as an architect, Luisa Jung realized something was missing. "The world of ideas, of images," was what she loved the most, she says—but not so much turning those ideas into buildings. Jung had moved from Argentina to Germany and was captivated by the illustrations in her new country's newspapers. So she began building a portfolio of her work. "At first I was kind of afraid to draw, so my style was collage," she says, but soon she was dabbling in watercolor and then wood-block printing.

Now an illustrator, Jung lives happily in the world of ideas and metaphor. In this issue's special report on innovations in health equity, her illustrations give form to concepts that can be hard to visualize, such as cultural competency and data disaggregation, but that nonetheless have real consequences for people's health. These kinds of visual metaphors—representations such as an hourglass of mpox and data as a curtain that can obscure reality—come to her naturally. "It's the way my brain works," she says. Jung aims to "represent complex topics in a way that is also kind of poetic."

JYOTI MADHUSOODANAN DEFOGGING DATA, PAGE S21

Nineteen years ago Jyoti Madhusoodanan moved from Ahmedabad, India, to Buffalo, N.Y., to complete a Ph.D. in microbiology. That was when she started having to check a box on forms to indicate her race—and found that the entirety of Asia and the Pacific Islands was lumped into a single category. She recalls thinking, "Asia is massive! How is this helpful to anyone?" The issue remained on her mind for years as she moved from New York to the West Coast and began her career as a science journalist covering health.

As Madhusoodanan lays out in her article for our special report on innovations in health equity, this giant category is used all the time in medicine and health research—and not only is it unhelpful, as she initially suspected, but it does harm. This pooling of data hides important signals that could be used to save lives. In recent years this practice has finally begun to change, a mark of progress that "has been painfully won by people of these communities that have been invisible," Madhusoodanan says. Everyone she spoke with for the story "had a deep, deep personal connection to fixing this."

STEPHANI SUTHERLAND NO MORE NEEDLES, PAGE 34

Health journalist Stephani Sutherland has long been fascinated by pain; it was the subject of her Ph.D. research. "You can't survive very well without it, but if you have chronic pain, it can become really debilitating," she says. So when COVID began causing painful, long-term illness and neurological symptoms, she paid close attention. This condition, called long COVID, is an example of something scientists began to fully understand only in the past few decades. "The nervous system and the immune system are not separate like we were once taught," Sutherland says.

The connection between chronic pain and the immune system has since sparked her interest in immunology. Sutherland's feature in this issue explores a type of needleless vaccine that goes in the nose, not the arm, and could one day provide better immunity to infectious diseases. Nasal vaccines aren't a reality for everyone yet—"we're in early days," Sutherland says. But they could be safer to administer in places with poorer access to medical equipment and even at home. And because they provide immunology inside the nose itself, "you can nip the virus in the bud right where your body encounters it," she says. "That seems really powerful to me."

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BEAR IN MIND

“A Grizzly Question,” by Benjamin Cassidy, reports on plans to reintroduce grizzly bears to the North Cascades and on concerns people have raised about their communities’ safety. The situations presented in the article are common to many reintroduction activities. One part of this is fear of change. Another might be shortsighted self-concern. The reaction is understandable but questionable.

I’ve watched many people going into the Yellowstone backcountry, and the common theme has been trepidation. The environment creates an uncomfortable awareness that one, as a person, is not top dog. To have close encounters with formidable creatures is a serious education in one’s position in the wilderness—a lesson that most people cannot abide. This was a factor in the near extinction of grizzlies in the lower 48 states and is a factor in human resistance to their presence.

DIRK WINDOLF VIA E-MAIL

RNA WORLD

“The New Code of Life,” by Philip Ball, describes some of the types and functions of noncoding RNAs (ncRNAs) found in human cells and notes that “ncRNAs seem to point to a fuzzier, more collective, logic to life.” One possible connection was not mentioned, however: the “RNA world” hypothesis.

Under this concept, an early proto-life-form used RNA both for its enzymatic activities and as its genetic material. Even after evolution replaced this diverse use of RNAs with the specialist molecules of DNA and proteins, RNAs might still retain many functions as a remnant of their earlier roles. So the many ncRNAs that carry out diverse functions could reflect some aspect of an earlier RNA world.

SCOTT T. MEISSNER VIA E-MAIL

HISTORICAL ELEMENTS

“Superheavies,” Stephanie Pappas’s article about superheavy elements, reminded me of a series of articles on “The Synthetic Elements,” by Glenn T. Seaborg and his associates, that were published in *Scientific American* in April 1950, December 1956, April 1963 and April 1969. In the first



June 2024

article, Seaborg and his co-author started with the synthesis of four elements that had been “missing” from the periodic table and then continued with accounts of how five elements beyond uranium were produced in the laboratory. The series updated every few years as the number of synthesized elements grew. Seaborg paid particular attention to the difficulty in obtaining large enough samples to assess their chemical properties. He shared the 1951 Nobel Prize in Chemistry for his work on synthetic elements, and element 106 was named seaborgium in his honor during his lifetime.

I wasn’t around when the original articles were published in the 1950s, but my high school physics teacher had a file of old *SciAm* material that he shared with me. It included articles by Erwin Schrödinger, Albert Einstein, George Gamow, Fred Hoyle and other notables. My teacher said I could take whatever I wanted, so I took the whole file and still have it in my library.

BRUCE A. BOYD ST. LOUIS, MO.

COOL ALLUSION

“Alien Ice,” by Elise Cutts [Advances; April], reports on experiments performed

by physical chemist Christina Tonauer and her colleagues that involved ice XIV, a type of “ordered ice” with ordered hydrogen atoms that can be created within days. I’m curious: Did the researchers skip ice IX? I guess avoiding the name would be like skipping floor 13 in a hotel, given the destructive power of the fictional substance “ice-nine” in Kurt Vonnegut’s 1963 *Cat’s Cradle*. I have no desire for all the liquid in my body to become solid, as happened to characters who got ice-nine in their mouth in the novel, so I hope these scientists are up on their literature.

COLIN MILDE MAHWAH, N.J.

TONAUER REPLIES: There is a real ordered ice called ice IX that we didn’t include in our study. We didn’t skip it for the fear of the effects of the fictitious ice-nine envisioned by Vonnegut. In fact, there was a scientific reason. The formation process of most ordered ices has a significant kinetic barrier: even though the ordered ice structure should be favored, according to thermodynamics, the process is very slow compared with laboratory timescales. Our study reported new synthesis strategies for overcoming that barrier and ordering ices faster. Real ice IX, on the other hand, is an outlier of that rule because it starts ordering at the relatively high temperature of 208 kelvins. In Olympic terms, it wins a gold medal in the “ordering race” of ice polymorphs, so we did not consider it in our study.

HELPING TEENS COPE

“Treating the Anxious Teen,” by BJ Casey and Heidi Meyer, shines a light on advances in the basic clinical science work on addressing fear conditioning. Although this work is important, as respectively current and retired professors of psychology, we would like to note that such optimism is not uniform in the field. In a 2023 review in the journal

“The environment creates an uncomfortable awareness that one, as a person, is not top dog.”

—DIRK WINDOLF VIA E-MAIL

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Behavior Research and Therapy, psychologist Ronald M. Rapee and his colleagues state that when it comes to the effectiveness of cognitive-behavioral therapy in children and adolescents, “there remains substantial room for improvement.”

One of the issues is that children’s needs are different from those of adults. When children and adolescents are being treated, their developmental status regarding emotional self-regulation and cognition must be taken into account. Therapeutic practices developed with adults can have contradictory effects with children. For example, adults find that fear interferes with their ability to follow through with functional routines. Remove the fear, and adults can resume functionality. Children and teens are still learning what functional routines are, so they need opportunities to practice healthy, functional behavior patterns tailored to the kinds of experiences they have outside of the therapy office. Novel interventions that are quite different from standard cognitive-behavioral therapy have shown promise.

ERICA KLEINKNECHT O’SHEA

FOREST GROVE, ORE.

RONALD KLEINKNECHT

BELLINGHAM, WASH.

ERRATA

“Homeschooling Needs More Uniform Oversight,” by the Editors [Science Agenda], incorrectly described the 11-year-old boy who was found dead in 2020 as located in Michigan. His family had moved from that state to California a few months prior.

“The End of the Lab Rat?,” by Rachel Nuwer [September], should have said that outside researchers have used Emulate’s chips to create more than 30 additional models with cells from their labs, not about 70 such models.

In “What If We Never Find Dark Matter?,” by Tracy R. Slatyer and Tim M. P. Tait [September], the opening illustration should have been credited to Olena Shmahalo.

“Nobel Connections,” by Sarah Lewin Frasier and Jen Christiansen [Graphic Science; October], should have referred to Nobel laureate Giorgio Parisi.

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ADVANCES

CHEMISTRY

Productive Pressure

Earthquakes may forge large gold nuggets

SOLID GOLD BARS stacked in bank vaults, plating on the summer's Olympic medals, or even your own pieces of gold jewelry could owe their existence to earthquakes. The stress and strain produced by moving tectonic plates during such an event may trigger a chemical reaction that causes minuscule particles of gold to coalesce into larger nuggets, a new study proposes.

"The biggest finding is showing a new gold-forming process and providing an explanation for how really large gold nuggets might form," says Christopher Voisey, a co-author of the study and a geologist at Monash University in Australia. "This was always a bit of a conundrum, especially when there isn't field evidence supporting the alternative gold-forming processes."

An estimated 75 percent of all mined gold comes from deposits nestled in cracks inside hunks of quartz, one of the most abundant minerals in Earth's crust. Geochemists have known that dissolved gold existed in fluids in the middle to lower levels of the planet's crust and that the fluids could seep into quartz cracks. But the amount of fluid involved seemed to limit how much gold could dissolve and thus the size of the gold chunks that formed. Larger nuggets were hard to explain: experts had theorized that gold nanoparticles within the fluid might aggregate into those bigger chunks within the quartz, yet it was unclear how. Unlike dissolved gold, nanoparticles typically wouldn't have enough chemical energy to start the necessary reaction to build up on the cracks' surface and form a nugget.

The new study, published in *Nature*



Geoscience, suggests that the geological stress caused by earthquakes might activate a peculiar geochemical property called piezoelectricity—and that such activation makes the formation of larger gold nuggets possible.

The piezoelectric effect, which has been known since the 1880s, is essentially

the ability of a material to generate an electric charge when placed under mechanical stress. Many everyday items including microphones, musical greeting cards and inkjet printers take advantage of piezoelectricity, and it occurs naturally in substances from cane sugar to bone.

Quartz can produce this effect because

Tomekbudjedomek/Getty Images

DISPATCHES FROM THE FRONTIERS OF SCIENCE, TECHNOLOGY AND MEDICINE



Gold forms nuggets as it aggregates within quartz underground.

of its structure: it is built from a repeating pattern of positively charged silicon and negatively charged oxygen atoms. When it's stretched or compressed, the arrangement of these atoms changes, and the charges are dispersed asymmetrically. Negative and positive charges build up in different areas of the quartz, creating an

electric field and changing the material's electric state.

Voisey and his colleagues at Monash—located in the historically gold-rich area of Melbourne—thought that this changed state could lower the energy needed for gold nanoparticles in the fluid to interact with the quartz surface, causing a previ-

ously unviable chemical reaction to occur and allowing the nanoparticles to stick and accumulate.

To test their idea, the researchers virtually modeled the electric field that quartz could produce when subjected to earthquake-like forces. They then placed quartz

Continued on page 12

Continued from page 11

mineral crystals in a fluid containing dissolved gold nanoparticles and other gold compounds and found that, when under seismic wavelike forces, the quartz was able to produce enough voltage to jump-start a buildup of nanoparticles.

The study findings point to an intriguing mechanism that could be responsible for forming at least some of the larger gold nuggets in Earth's crust—especially “orogenic” deposits where colliding tectonic plates have folded onto one another to create a mountain range.

“It appears to be a certainty that episodic earthquakes are important in help-

ing form these important orogenic gold nugget deposits,” says James Saunders, a consultant geologist who was not involved in the study. He says he would like to see future research look more into the specifics of this process. This could include investigating how long piezoelectricity-causing earthquake forces have to last to produce such deposits and why large gold nugget deposits might develop in only some cracks in quartz in a given area, despite an earthquake theoretically inducing similar stress and strain on all the cracks. “I think it is a great idea/hypothesis,” Saunders says. “I’ll be interested if it stands up on further evaluation.”

Studying piezoelectricity at a very large scale may be difficult, says Colgate University geologist Aubrey Adams, who was also not involved in the study. “Geoscientists are currently working very hard to quantify how stress (or pressure) varies in 3D with time and location,” she says, “something that is easily measured in a lab but much harder to quantify in the crust.”

Voisey and his team plan to extend experimental parameters by testing different pressures or temperatures, for example, to explore their theory further. “This is very much the pilot study for this technique,” he says, “so I’m excited to see where it can go.” —*Kate Graham-Shaw*

Chemical Chow Down

A microbe family breaks down certain “forever chemicals”

MICROBIOLOGY

A group of bacteria has proved adept at destroying the ultratough carbon-fluorine bonds that give “forever chemicals” their name. This finding boosts hopes that microbes might someday help remove these notoriously pervasive pollutants from the environment.

Nearly 15,000 chemicals commonly found in everyday consumer products such as pizza boxes, rain jackets and sunscreens are recognized as perfluoroalkyl and polyfluoroalkyl substances, or PFASs. These chemicals can enter the body via drinking water or sludge-fertilized crops, and they have already infiltrated the blood of almost every person in the U.S. Scientists have linked even low levels of chronic PFAS exposure to myriad health effects such as kidney cancer, thyroid disease and ulcerative colitis.

Current methods to destroy PFASs require extreme heat or pressure, and they work safely only on filtered-out waste. Researchers have long wondered whether bacteria could break down the chemicals in natural environments, providing a cheaper and more scalable approach. But carbon-fluorine bonds occur mainly in humanmade materials, and PFASs have not existed long enough for bacteria to have specifically evolved the ability to digest them. The new study—though not the first to identify a microbe that destroys carbon-fluorine bonds—provides a step forward, says William Dich-

tel, a chemist at Northwestern University who studies energy-efficient ways to chemically degrade PFASs.

To identify a promising set of bacteria, the study’s authors screened several microbe communities living in wastewater. Four strains from the *Acetobacterium* genus stood out, the team reported in *Science Advances*. Each strain produced an enzyme that can digest caffeate—a naturally occurring plant compound that roughly resembles some PFASs. This enzyme replaced certain fluorine atoms in the PFASs with hydrogen atoms; then a “transporter protein” ferried the fluoride ion by-products out of the single-celled microbes, protecting them from damage. Over three weeks most of the strains split the targeted PFAS molecules into smaller fragments that could be degraded more easily via traditional chemical means.

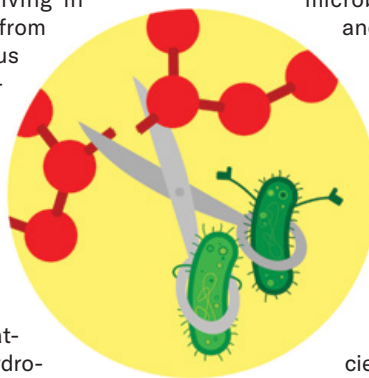
By directly targeting carbon-fluorine bonds, the *Acetobacterium* bacteria partially digested perfluoroalkyls, a type of PFAS that very few microbes can break down. Even so, these *Acetobacterium* strains could work only on perfluoroalkyl molecules that contain carbon-carbon double bonds

adjacent to the carbon-fluorine ones. These “unsaturated” perfluoroalkyl compounds serve as building blocks for most larger PFASs; they are produced by chemical manufacturers and also emerge when PFASs are destroyed via incineration.

Scientists had previously demonstrated that a microbe called *Acidimicrobium* sp. strain A6 could break down carbon-fluorine bonds and completely degrade two of the most ubiquitous perfluoroalkyls. This microbe grows slowly, however, and requires finicky environmental conditions to function. And researchers do not yet fully understand how this bacterial strain does the job.

The *Acetobacterium* lines target a separate group of PFASs, and the team hopes to engineer the microbes to either improve their efficiency or expand their reach—potentially to more perfluoroalkyls. Lead study author Yujie Men of the University of California, Riverside, imagines the microbes would perform best in combination with other approaches to degrade PFASs. The range of chemical structures in these compounds means “a single lab cannot solve this problem.”

Any future commercial use of the microbes would face numerous hurdles, including breakdown speed and replicability outside of the lab, but Men looks forward to seeing how far her team can push the technique. “We’re paving the road as we go,” she says with a laugh. —*Saima S. Iqbal*





ANIMAL COGNITION

Dreaming in Song

Scientists eavesdrop on sleeping birds

SCIENTISTS TELL US that the family dog shuffling its legs while asleep on the floor really is dreaming. And when a bird silently nods off on its perch, it may also dream as its singing muscles twitch. Could it be rehearsing in its sleep?

A substantial proportion of bird species are songbirds with specific brain regions dedicated to learning songs, according to University of Buenos Aires physicist Gabriel B. Mindlin. His research examines connections between birds' dreams and song production—particularly in Zebra Finches, which often learn new sounds and songs, and in Great Kiskadees, which possess a limited, instinctive song-learning capacity.

Scientists had previously observed sleeping birds making movements that resembled lip-syncing. In earlier work, Mindlin and his colleagues implanted electrodes in two Zebra Finches; for a recent study in *Chaos*, they did the same for two Great Kiskadees. This let them record and compare neuron and muscle activity in the sleeping birds.

When awake, Zebra Finches sing a well-regulated line of staccato notes. But their sleeping song movements are fragmented, disjointed and sporadic—“rather like a dream,” Mindlin says. A dozing finch seems to silently practice a few “notes” and then add another, producing a pattern of

muscle activity that reminds Mindlin “of learning a musical instrument.”

Such “rehearsing” appears far less likely in the nonlearning Great Kiskadees, says study co-author Ana Amador, a neuroscientist also at the University of Buenos Aires. For the new research, the scientists ran this species' sensor output through a mathematical model Mindlin recently developed to translate muscle movements into audible sounds. The kiskadees' synthesized sleeping tune comprised quick, identical note syllables that sounded startlingly loud and aggressive—“more like a nightmare than a dream,” Amador says. Slumbering kiskadees frequently combined these movements with a threatening flash of head feathers, which often occurs during their territorial disputes while they are awake.

Listening in on a sleeping songbird to better understand its waking behavior—and to look for a possible link to dreams—is a lot like “cracking a code in a detective novel,” Amador chuckles.

University of Chicago neuroscientist Daniel Margoliash, whose pioneering 1990s work characterized birds' song-learning brain regions, says the new results agree with his own observations of sleeping birds' neurons. But he advises caution in describing this sleep activity as “dreaming.” Future work should more closely examine the sleep states the birds experience during this process, he says—including rapid eye movement (REM) sleep, a sleep stage that is closely associated with dreaming in other animals.

“Is there a distinction between replay patterns formed during non-REM and REM sleep?” Margoliash asks. Such a contrast, he adds, “is one we need to keep in mind when examining what happens when birds sleep.” —David Godkin

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HEALTH

Leap in Time

Aging may happen dramatically in our 40s and 60s

AS A PERSON ENTERS their 60s, the health effects of aging often start to become strikingly clear. Many people begin to use glasses or hearing aids, or their doctors warn them about a sharply increased risk of diabetes or heart disease. But research suggests that our bodies may un-

dergo a dramatic wave of age-related molecular changes not only in our 60s but also in our mid-40s.

For a study in *Nature Aging*, researchers tracked the levels of more than 135,000 molecules and microbes, all reflective of activity in cells and tissues, in 108 healthy volunteers aged 25 to 75. Each volunteer contributed biological specimens, including blood and stool samples, every three to six months for a median of 1.7 years. Results showed that changes in many molecule and microbe levels clustered around two distinct time points: ages 44 and 60. The findings suggest that aging might accelerate around those peri-

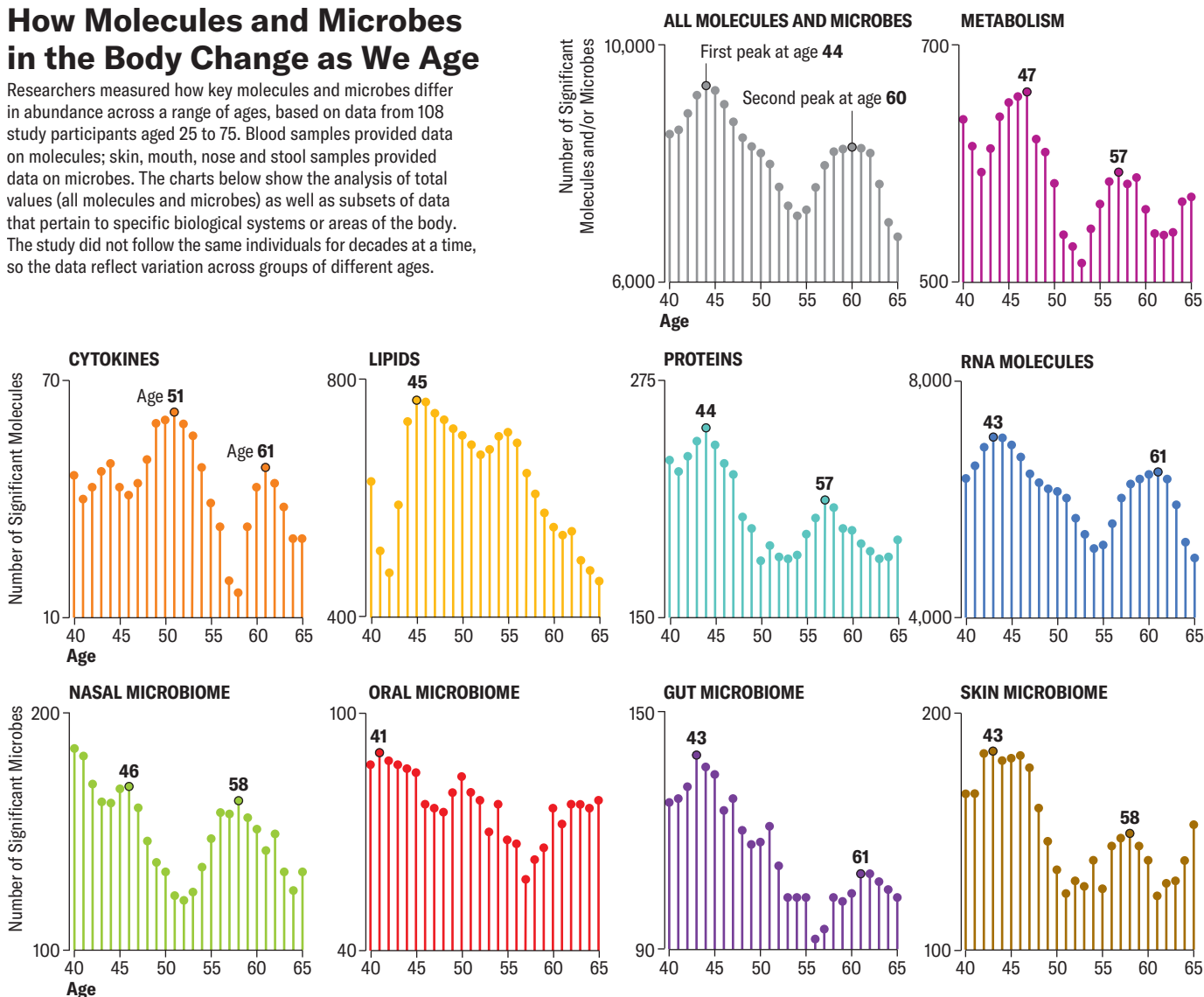
ods—and they signal to experts that our 40s and 50s may be a significant time to closely monitor health.

The study supports many people's anecdotal reports of noticing changes in their 40s that range from more muscle injuries to worse hangovers, and the data give clues as to why, says senior study author Michael P. Snyder, a genetics researcher at Stanford Medicine.

Compared with younger participants, people in their 40s and 60s displayed biological differences that appeared to be linked to muscle weakness and loss, decline in heart health, and inefficient caffeine metabolism. Those in their 40s also

How Molecules and Microbes in the Body Change as We Age

Researchers measured how key molecules and microbes differ in abundance across a range of ages, based on data from 108 study participants aged 25 to 75. Blood samples provided data on molecules; skin, mouth, nose and stool samples provided data on microbes. The charts below show the analysis of total values (all molecules and microbes) as well as subsets of data that pertain to specific biological systems or areas of the body. The study did not follow the same individuals for decades at a time, so the data reflect variation across groups of different ages.



Source: "Nonlinear Dynamics of Multi-omics Profiles during Human Aging," by Xiaotao Shen et al., in *Nature Aging*. Published online August 14, 2024

had reduced activity in cellular pathways responsible for breaking down alcohol and fats—possibly a sign that people start to digest these compounds more slowly around this age. People in their 60s, meanwhile, had lower levels of various immune system molecules, such as inflammatory cytokines, which corresponded to a weakened immune response. They also showed significant differences in levels of certain molecules associated with carbohydrate digestion and heart and kidney function, suggesting that the older participants were more susceptible to type 2 diabetes, cardiovascular disease and kidney issues.

The new study's time points are similar to those identified in a separate 2020 study, in which researchers found that participants' immune systems grew markedly less adept at fighting off pathogens in their late 30s to early 40s and again around age 65. But the latest study's findings are not ironclad; it included a relatively small number of people, all living in California's Palo Alto area. The resulting lack of geographic diversity makes the data less representative of the broader public, notes Aditi Gurkar, who conducts aging-related research at the University of Pittsburgh and was not involved in the recent study. Those sampled likely had some lifestyle factors in common, such as diet, exercise and environmental exposures, which could have swayed the results, she says.

The study also did not follow any individuals for periods longer than about seven years, so scientists cannot be certain that the differences between people in different age groups reflect universal changes. For example, the 40- and 60-year-olds in the study may have aged faster relative to others of the same age in the broader population, Gurkar cautions. She and others say the best way to confirm the results—and to precisely trace age-related biological shifts—would be through a larger study that tracks the same participants over the course of a lifespan. Collecting data on factors such as disease status, physical function or disability could also help researchers better assess the extent to which age-related shifts affect a person's overall health. (The amount of stress that cells and tissues undergo—referred to as

The data give clues to why people often report experiencing more muscle injuries and worse hangovers in their 40s, the study authors say.

biological aging—varies widely between people of different races and socioeconomic classes, and it even differs between individual organs in a person's body.)

The reasons ages 44 and 60 might be turning points in health are not yet apparent, but the study authors hope to probe several hypotheses in future work. Snyder suspects that for people in their 60s, declines in immune system function might precipitate a more widespread organ breakdown. A midlife decline in physical activity, meanwhile, could explain the differences seen among people in their 40s—but so might hormonal changes, including menopause. Menopause alone, however, could not explain the trends in the study, Snyder says: male and female participants appeared to show the same degree of age-related differences at both time points.

Snyder suggests the new data can provide actionable health information. People in their 40s might benefit from getting blood tests that track lipid levels, for instance, or from exercising regularly to maintain heart health. Snyder also underscores the importance of early and regular screenings for heart disease for people in this age range who have existing health conditions.

Limitations aside, Gurkar says, the study is a powerful reminder that lifestyle choices such as diet and exercise can accelerate aging—or slow it down. Few studies on aging focus on middle-aged participants or involve biological sampling as comprehensive as that of this paper, she adds. In addition to identifying potential waves of age-related changes, the work provides a crucial first step toward large-scale disease-prediction models based on biological data.

—Saima S. Iqbal

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Abstract

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BIOLOGY

A Matter of Taste

Flavors are detected outside the mouth, too

IN EASTERN MEXICO'S UNDERGROUND caverns and streams, a blind fish undergoes a peculiar adolescence: as it approaches maturity, taste buds begin to sprout under its chin and on top of its head, creeping toward its back.

"It's a pretty wild amplification of the sensory system of taste," says Josh Gross, an evolutionary geneticist at the University of Cincinnati and a co-author of a recent study on the cave fish in *Nature Communications Biology*. Gross and his team discovered that the new buds blossom around the time when the fish transition from eating larval crustaceans to gobbling up their adulthood staple: bat guano.

Taste buds outside their mouths might be helping the fish detect bat droppings in the utterly dark, "food-starved" caves, Gross says.

Wandering taste buds aren't unheard of elsewhere, especially in other fish. Some damselfish cultivate taste buds on their fins, and channel catfish have them across their midsections. And as alien as it may seem, many cells throughout the human body can taste, too. They're just not sharing the flavors with your brain like taste buds do.

Lora Bankova is a Harvard Medical School respiratory biologist who studies tuft cells, a cell type sprinkled within human mucous tissues like those lining your nostrils, throat and gut. These "rapid responder" cells trigger the immune system if they detect an outside threat, and many of them rely on built-in taste receptors (the same kinds found on taste-bud cells) to do so. Bankova notes that many potentially harmful bacteria communicate via signaling chemicals called lactones—which also happen to activate taste receptors attuned to bitter flavors, prompting tuft cells' immune response. And

it turns out that even environmental allergies may be a matter of taste: dust mites and several mold species can also set off a tuft cell's taste receptors, Bankova says.

"Evolutionarily, taste receptors [have moved around] the body to protect us from the air we inhale and all the attacks we're getting through the orifices," Bankova says. "They're in the inner ear, the urethra, everywhere something can get into your body."

Such "extra" taste receptors aren't just bouncers at the door—they taste test for our internal systems, too. Receptors for sweet tastes help to tune insulin production in the pancreas and make sure neurons in the brain have access to enough glucose. Sweet, bitter and umami receptors in the gut modulate digestion.

Gross says it's still a mystery what taste receptors the bat guano activates in the blind cave fish. "There may be some sugar content if it's a fruit bat, maybe some protein content if it's a carnivorous bat," he says. So far only the cave fish has signed up to sample it. —Elizabeth Anne Brown



Blind cave tetras develop taste buds on their heads.

Hanjo Hellmann/Alamy Stock Photo



NEUROSCIENCE

Smellavision

Odors boost babies' visual learning

BABIES EXPERIENCE a torrent of sensory information from the moment they are born. Knowing nothing about the world, they must learn to sort this deluge into categories of things—*especially* faces. “Faces are one of the most relevant visual signals babies start to learn during the first month,” says Arnaud Leleu, a cognitive neuroscientist at the University of Burgundy in France.

Researchers are still working out how infants use various senses for this recognition: Newborns categorize faces better if the visual image is accompanied by a voice, for example. And evidence suggests babies may also use smell. “We knew babies can combine their senses,” says Tessa Dekker, who studies visual development at University College London. “But it wasn’t clear if this applied to smells, which aren’t as linked to specific events because they operate quite slowly.”

In a recent study in *Child Development*, Leleu and his colleagues confirmed that infants’ face perception is aided by their mother’s body odor—and they found that the influence of smell declines as babies grow. The findings expand scientists’ understanding of the role that multisensory perception plays in early learning.

The team used electroencephalography to record the brain activity of 50 infants be-

tween four and 12 months old while the babies watched a stream of six images per second. Each sixth image was a human face, and the others were animals or objects. The researchers expected that if the babies were devoting special attention to faces, there would be a once-per-second activity spike corresponding to their appearance—a so-called face-selective response—from electrodes placed over brain regions involved in visual processing. They also gave the babies T-shirts that were clean and ones infused with their mother’s body odor.

Overall, face-selective responses increased in strength and complexity with age. But the team also found that the mother’s scent enhanced responses to faces in the youngest infants and observed that the effect progressively decreased in older babies. “This could mean young babies rely more on their mother’s scent because their ability to identify faces using vision alone is still developing,” Dekker says. Visual ability is known to be poor at birth, whereas smell develops relatively early.

The findings highlight the importance of multisensory stimulation early in life. “To help infants learn, we should use all the senses,” Leleu says. “The way we start to recognize things with our senses is the building block to developing concepts, language, memories.” He is continuing to investigate the extent of smell’s effect on perception, including in other age groups. He says he’s finding that if a recognition task is made difficult enough, even adults recruit their noses to help. “It works for faces and other objects,” Leleu adds. “We found an effect using pictures of cars and gasoline odor.”

—Simon Makin

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SCIENCE IN IMAGES

Iron Chompers

Komodo dragons' intimidating grins have a metallic secret

GETTING UP CLOSE with Komodo dragon teeth rarely ends well. The massive lizard's mouth holds 60 serrated teeth at a time, each up to an inch long, peppered with the

remains of previous meals and dozens of feasting bacteria species.

Fortunately, paleontologist Aaron LeBlanc of King's College London got to ex-

amine such teeth divorced from their ferocious owners, and he noticed a strange orange color on the teeth's tips and serrations. The results of closer inspection, published in *Nature Ecology & Evolution*, revealed that the orange came from iron reinforcements rather than from something the creatures ate—marking the first confirmed finding of iron chompers in reptiles. (Some fish and salamanders as well as a handful of mam-

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Alamy Stock Photo



mals, most notably beavers, are also known to have iron in their teeth.)

Reptilian teeth have long been considered simple and “cheap” because they grow quickly and get replaced several times throughout their owner’s life. But research by LeBlanc and his colleagues is helping to change that perception, says University of Manitoba paleontologist Kirstin Brink, who also studies teeth: “Now that we’re starting to actually take a closer look at different reptiles, we’re finding all these really cool adaptations.”

Komodo dragons, which live on a few islands in Indonesia and can grow up to 10 feet long, are “basically tooth factories,” LeBlanc says. The tip of each frequently replaced, pointed tooth curves back into the animal’s mouth, helping it to tear off and swallow large chunks of meat. The iron reinforcement precisely marks a single serration line running down the front

Komodo dragons are “basically tooth factories.”

—Aaron LeBlanc
King’s College London

and back of each tooth—more pronounced on the back—as well as its tip: puncture, pull, swallow, repeat.

LeBlanc was drawn to Komodo teeth because their pointed, curved profile would look at home in dinosaurs’ fearsome smiles. Such comparisons are valuable for paleontologists, Brink notes. “When we’re studying fossils, especially when we’re trying to interpret behaviors that we can no longer observe because the animals are dead, we have to look to modern analogues,” she says.

LeBlanc’s team went on to find signs of iron reinforcement in some other monitor lizard species and crocodilians, as well as in dinosaur teeth—but metallic traces in the latter most likely came from the fossilization process, he says. Still, he and Brink agree, the research suggests scientists should take a closer look at teeth in living reptiles and dinosaurs alike. “We shouldn’t take for granted how complex reptile teeth can be,” LeBlanc says. —Meghan Bartels



The new study's view of *Beorn leggi*

From “Cretaceous Amber Inclusions Illuminate the Evolutionary Origin of Tardigrades,” by M. Mapalo et al., in *Nature Communications Biology*; August 6, 2024

PALEONTOLOGY

Hardy Remnant

Tiny tardigrade fossils suggest when the organisms became ridiculously tough

MICROSCOPIC TARDIGRADES—plump, eight-legged arthropod relatives—are nearly indestructible, and their durability superpower may have helped them weather the deadliest mass extinction in Earth’s history, according to a new fossil analysis.

Tardigrades, also called water bears, can withstand extreme heat, cold, pressure and radiation. Two major tardigrade lines survive hostile environments through a process called cryptobiosis, in which they lose most of their body’s water and enter a suspended metabolic state.

There are only four known tardigrade fossils. All are preserved in amber, including two inside a pebble that was found in Canada in 1940 and dates from 84 million to 72 million years ago. One of the pebble’s tardigrades, representing a species named *Beorn leggi*, was described in 1964. The other was too small to be identified at the time, says Marc Mapalo, a graduate student at Harvard University’s Museum of Comparative Zoology.

For a new study in *Nature Communications Biology*, Mapalo and his colleagues used high-contrast microscopy to uncover previously unseen details in both specimens’ claws, “which are very important taxonomic characteristics in tardigrades,” Mapalo says. Tardigrade body plans have

varied little for millions of years, so the small visible differences in claw shape offered crucial information about where in the tardigrade family tree these amber-trapped fossils belonged, says University of Chicago organismal biologist Jasmine Nirody (whose own work has also examined tardigrade claws).

The authors determined the smaller tardigrade was a new genus and species: *Aerobius dactylus*. They also revised *B. leggi*’s description and classification based on its claw joints. Both species were placed in the same tardigrade superfamily Hypsibiodea, and *B. leggi* was moved into the family Hypsibiidae. Reclassifying *B. leggi* based on previously unseen details clarified its relationship to living tardigrades.

The resulting family tree recalibration allowed the researchers to calculate when the two tardigrade lines that perform cryptobiosis could have diverged—putting a latest date on the likely acquisition of that skill. Their work suggests cryptobiosis appeared in tardigrades during the Carboniferous period (359 million to 299 million years ago), predating a deadly event known as the Permian extinction, or the “Great Dying,” which occurred about 252 million years ago. The authors suggest that cryptobiosis may have helped tardigrades survive the event, which wiped out 96 percent of marine life and 70 percent of life on land.

Cryptobiosis’s evolution is challenging to study, partly because tardigrade fossils are so scarce, Mapalo says. Additional fossil discoveries will help scientists pin down details about the appearance of this unique survival strategy. By sharing this result, he says, “we hope we will entice other people to be aware that fossil tardigrades exist and there are still more to be found.”

—Mindy Weisberger

PSYCHOLOGY

Seasonal Morality

Values may shift with the time of year

AS LEAVES FALL, snow sweeps in or flowers blossom, humans change in measurable ways, too. Research suggests a range of psychological phenomena—such as our emotional state, diet and exercise habits, sexual activity and even color preferences—fluctuate throughout the year. And now a study in the *Proceedings of the National Academy of Sciences USA* demonstrates how moral values can also shift.

For the study, researchers analyzed more than 230,000 online survey responses—a decade’s worth—from people in the U.S., along with smaller groups in Canada and Australia. The questions were based on a standardized framework social scientists use to assess people’s judgments of right and wrong. This framework, called moral foundations theory, sets up a taxonomy of “five pretty fundamental values that shape human social behavior,” says lead author Ian Hohm, a psychology graduate student at the University of British Columbia.

The framework considers loyalty (devotion to one’s own group), authority (re-

spect for leaders and rules), and purity (cleanliness and piety) to be “binding” values that promote group cohesion and conformity. These principles, often associated with political conservatism, consistently received weaker endorsements in summer and winter. And in summer, the more extreme the seasonal weather differences, the more pronounced the effect. (An additional surveyed group in the U.K. showed only the changes in summer.)

Care (preventing harm to others) and fairness (equal treatment) are considered “individualizing” values pertaining to individual rights. These principles showed no consistent seasonal pattern.

One explanation for seasonal swings could be anxiety. Using a 90,000-respondent survey dataset, as well as data on Internet search frequencies, the researchers found that anxiety levels also peak in spring and fall. “There is a close relationship between anxiety and threat,” says University of Nottingham psychologist and study co-author Brian O’Shea. Other studies have shown that people who feel more vulnerable to seasonal illnesses tend to be more distrustful, more xenophobic and more likely to conform to majority opinion. “When you’re threatened,” O’Shea explains, “you then want to get protection from your in-group.” These findings suggest seasonal timing could affect jury decisions, vaccination campaigns—and even election outcomes, the study authors say.



Jasmin Merdan/Getty Images

Howard University psychologist Ivory A. Toldson, whose work involves practical applications of statistics, notes that the study relies on data from “Western, educated, industrialized, rich and democratic (WEIRD)” populations and cautions that generalizing from such results runs the risk of “overlooking the unique moral experiences of marginalized groups.” Hohm agrees that such a pattern wouldn’t affect everyone the same way but emphasizes that the study highlights the seasons’ effect on human psychology.

“One thing that this article is showing is that we are very seasonal creatures,” says Georgetown University School of Medicine psychiatrist Norman Rosenthal, a leading expert on seasonal affective disorder who coined the term in the 1980s. “The internal state definitely affects your behavior.” —Anvita Patwardhan

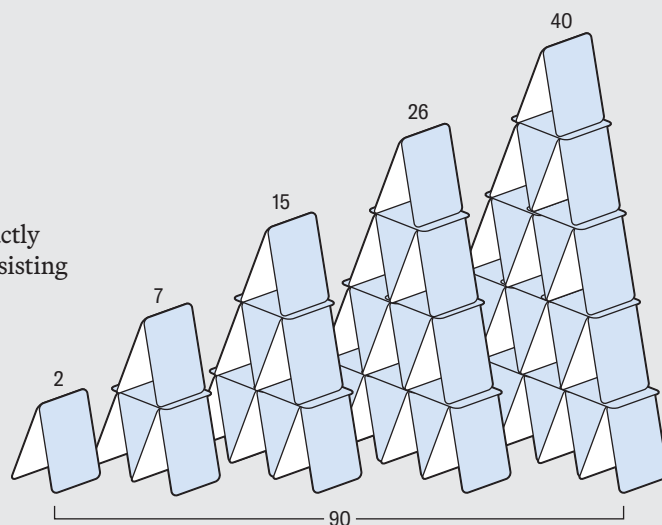
MATH PUZZLE

Playing Architect

By Hans-Karl Eder

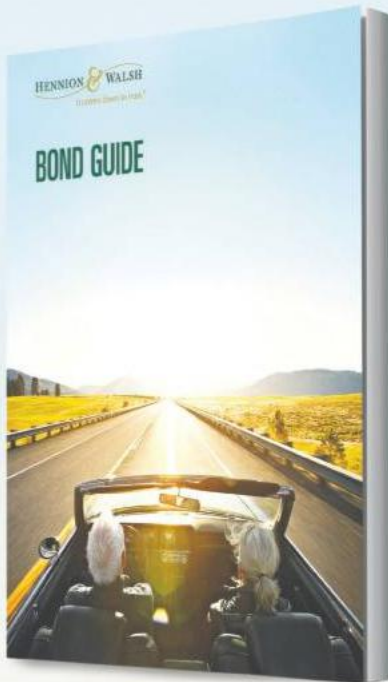
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EVOLUTION

Half a century after its discovery, the iconic fossil remains central to our understanding of human origins

**BY DONALD C. JOHANSON
AND YOHANNES HAILE-SELASSIE
ILLUSTRATION BY JOHN GURCHE
PHOTOGRAPHS BY DAVID L. BRILL**



50



ALL GONE YEARS OF

EVERY ONCE in a great while paleontological fieldwork turns up a fossil so extraordinary that it revolutionizes our understanding of the origin and evolution of

an entire branch of the tree of life. Fifty years ago one of us (Johanson) made just such a discovery on an expedition to the Afar region of Ethiopia. On November 24, 1974, Johanson was out prospecting for fossils of human ancestors with his graduate student Tom Gray, eyes trained on the ground, when he spotted a piece of elbow with humanlike anatomy. Glancing upslope, he saw additional fragments of bone glinting in the noonday sun. In the weeks, months and years that followed, as the expedition team worked to recover and analyze all the ancient

bones eroding out of that hillside, it became clear that Johanson had found a remarkable partial skeleton of a human ancestor who had lived some 3.2 million years ago. She was assigned to a new species, *Australopithecus afarensis*, and given the reference number A.L.288-1, which stands for “Afar locality 288,” the spot where she, the first hominin fossil, was found. But to most people, she is known simply by her nickname, Lucy. With the discovery of Lucy, scientists were forced to reconsider key details of the human story, from when and where humanity got its start to how the various extinct members of the human family were related to one another—and to us. Her combination of apelike and humanlike traits suggested her species occupied a key place in the family tree: ancestral to all later human species, including members of our genus, *Homo*.

It can be precarious to hang such a pivotal argument on a single fossil individual. But in the half a century since Lucy’s unveiling, many more specimens of *Au. afarensis* have been found. Together they provide an exceptionally detailed record of this ancient species, revealing where it roamed, how it lived, how its members differed from one

Donald C. Johanson

is founding director of the Institute of Human Origins at Arizona State University and discoverer of the 3.18-million-year-old human ancestor known as Lucy.

Yohannes Haile-Selassie

is director of the Institute of Human Origins and lead investigator for the Woranso-Mille field site, which has yielded fossil contemporaries of Lucy’s species.





In 1972 researchers traveled to the Afar region of northeastern Ethiopia to look for hominin fossils dating to more than three million years ago. A site called Hadar looked especially promising, its rugged landscape chock-full of mammal fossils that erode out of the hillsides over time (*top left*). The expedition camped along the banks of the Awash River and began a targeted search of the area's fossil-bearing sediments (*right*). On November 24, 1974, Donald C. Johanson discovered the nearly 3.2-million-year-old Lucy skeleton on one of the hillsides. A stake marks the spot where the fossil was found (*bottom left*).

another and how long it endured before going extinct.

We have also learned a lot about Lucy's own predecessors—and her contemporaries. One of the most exciting developments in the field of human origins research since the discovery of Lucy has been the revelation that for most of our prehistory multiple human species, or hominins, roamed the planet. One of us (Haile-Selassie) has found hominins that overlapped in time and space with Lucy's kind. These members of the human family are fascinating in their own right. They also provide vital context for understanding the evolution of the species that may very well have given rise to us all.

TO UNDERSTAND WHY LUCY had such a massive impact on paleoanthropology, we have to look at the state of the science at the time of her discovery. Back in the early 1970s, the oldest hominin fossils on record were thought to be around 2.5 million years old and belonged to a species called *Australopithecus africanus* from South Africa. Younger fossils fell into one of two groups: the so-called robust australopiths, with their giant molars and powerful jaws, and the more delicately built, or “gracile,” forms, which included *Homo*. Although *Au. africanus* was classified as gracile, it didn't particularly resemble either of these later groups. Yet it was the only sufficiently well-documented hominin we had that was old enough to be ancestral to them. There were a few scraps of fossil material from eastern Africa that were older, but there wasn't enough material preserved to get a good sense of the kinds of creatures they came from. And so scientists drew their evolutionary trees with *Au. africanus* as the all-important ancestor of *Homo* and the robust forms. But what they really needed to test that hypothesis about *Au. africanus* were more complete fossils in excess of three million years old.

In the spring of 1972 Johanson journeyed to Ethiopia with French geologist Maurice Taieb in search of hominin fossils from beyond the three-million-year mark. Taieb was keen to take him to the Afar region of northeastern Ethiopia, where he had previously seen pig and elephant fossils that looked to be from the time period Johanson was targeting. Perhaps hominin fossils were there, too, waiting to be discovered. Surveying a bunch of fossil-bearing locations in the region, the team zeroed in on a site called Hadar. Brimming with fossils of rodents, elephants, rhinos, hippos, monkeys, horses, antelopes and carnivores, Hadar must have been a bountiful environment millions of years ago to support so many animals. It seemed like a promising area to search for ancient human ancestors. Johanson knew that if hominin fossils were found there, they could upend our understanding of how humans came to be.

When the expedition team returned to Hadar the following year, Johanson made a tantalizing discovery: a knee joint estimated to be 3.4 million years old. Anatomical details of the knee indicated that it had come from a hominin that walked upright, like us, confirming the fossil hunters' hunch that Hadar had hominins. Johanson suspected the knee belonged to an *Australo-*

pithecus individual, but without more anatomical information to go on, he could not determine whether it came from *Au. africanus* or a new species. What the team needed most was to find remains of skulls and teeth, the body parts that contain the most diagnostic features for distinguishing species in fossil mammals. The researchers could only hope that the next field season would turn up cranial and dental specimens.

Their dream came spectacularly true on that momentous day in 1974. The Lucy fossil preserved skull fragments and a lower jaw with teeth, as well as parts of the arm, leg, pelvis, spine and ribs—47 bones in all representing a whopping 40 percent of the skeleton of a single individual. Her remains promised untold insights into the human past.

Named after the Beatles song “Lucy in the Sky with Diamonds,” which played on the tape deck at camp as the team celebrated, Lucy became an instant sensation. Nothing like her had ever been found before. She was diminutive—her 12-inch-long thigh bone indicated that she stood only three and a half feet tall and weighed 60 to 65 pounds. Like many other animals, early hominins exhibit a condition called sexual dimorphism, wherein males are much larger than females, among other morphological differences. Lucy was too small to be a male. And her erupted wisdom teeth and lack of unfused growth plates in her limb bones confirmed she was an adult.

Other features attested to how she carried herself. After closely inspecting her knee, hip and ankle, as well as conducting extensive biomechanical studies, Johanson and his colleagues concluded that she walked upright—a trait that Charles Darwin argued was a hallmark of humans—with a gait very much like our own. Other scholars interpreted the bones differently, arguing that she walked with her knees and hips bent like chimpanzees do when they occasionally travel on two legs. Final resolution of this debate came in 1978, after researchers discovered a stunning trail of hominin footprints impressed in 3.7-million-year-old volcanic ash at the site of Laetoli in Tanzania. Some of the prints are so detailed that all the characteristics of a modern human footprint left on a beach are visible. They showed that the Laetoli track makers walked like us, not like chimpanzees. And because hominin teeth and jaws similar to those from Hadar had been found at Laetoli, it stood to reason that Lucy's kind left the prints.

Traits such as a receding chin, strongly projecting snout, low and sloping forehead, and very small brain size placed Lucy in the genus *Australopithecus*. But certain aspects of her anatomy hinted that she might be more primitive than other known species in that group. Her first lower premolar was oval in shape and had a single cusp, like an ape's. Likewise, her lower limbs were relatively short, possibly an evolutionary feature left over from her ancestors who lived a more arboreal life. Although only bits of her braincase were recovered, the fragments suggested a brain volume of 388 cubic centimeters. That's very small compared with the modern



When Lucy was discovered 50 years ago, she was the oldest, most complete early member of the human family that had ever been found, with 47 bones representing 40 percent of the skeleton. Features of her hip, knee and ankle indicate that she walked upright on two legs like we do. Yet in other respects she was primitive, with a brain less than a third of the size of our own.

human brain, which averages 1,400 cubic centimeters, and comparable to the average modern chimp brain. Lucy confirmed earlier suspicions that upright walking evolved before large brains.

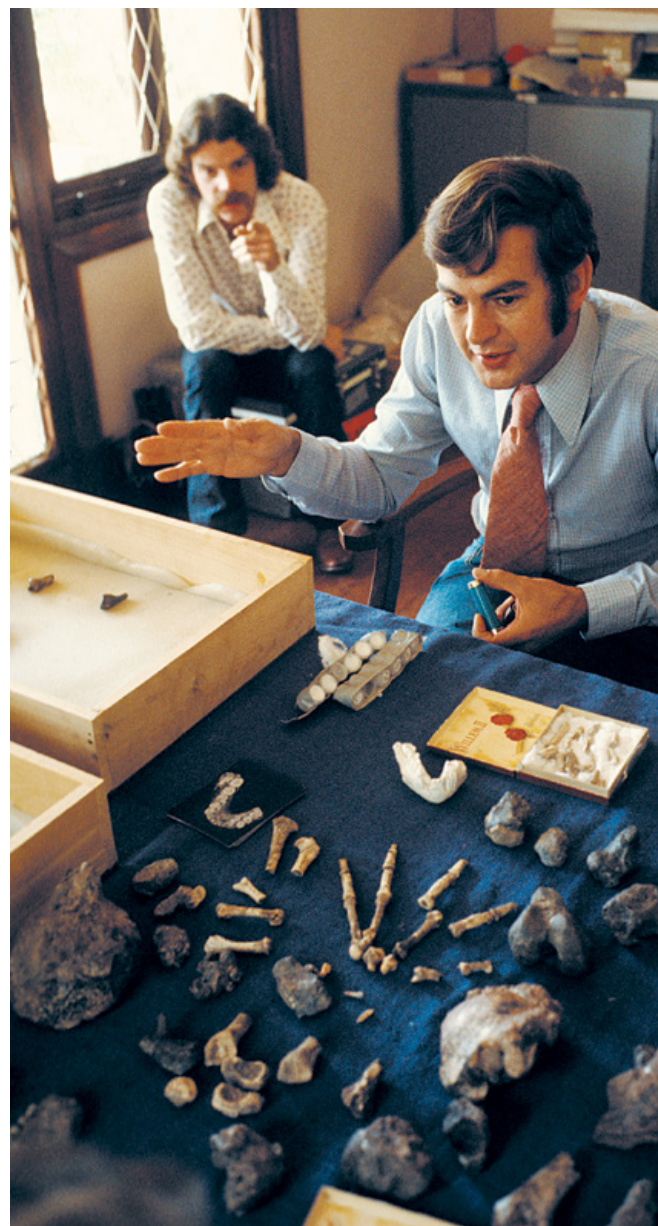
WITH SO MANY PARTS of her skeleton preserved, Lucy was a trove of information. But she was still just one individual. For a deeper understanding of her species, we needed more specimens. To that end, continued fieldwork at Hadar and other sites in the region has yielded a wealth of additional *Au. afarensis* fossils that together provide a detailed portrait of this ancestor.

In 1975, just one year after Lucy was found at Afar Locality 288, the Hadar team discovered more than 200 fossil hominin specimens eroding from a single layer of rock at nearby Afar Locality 333. Dated to a little more than 3.2 million years ago, the sample consisted of male and female adults as well as portions of infants and juveniles estimated to represent at least 17 individuals, all presumably related. The group became known as the “First Family.”

Combining the expanded Hadar collection with Lucy’s Tanzanian counterparts allowed the team to reconstruct the skull of the hominin species found at Hadar and to evaluate the fossils’ taxonomic status and position on the human family tree. In 1978, following a thorough comparative study of all the australopith species then known, Johanson and his colleagues concluded that although some of the dental and cranial features evident in these remains are found in other members of *Australopithecus*, the total morphological package seen in the Hadar and Laetoli fossils was unique and constituted a species new to science: *Australopithecus afarensis*. Furthermore, they proposed, *Au. afarensis* occupied a prominent position on the family tree, replacing *Au. africanus* as the last common ancestor of later hominins, including *Homo* and the robust australopiths.

Not everyone in the paleoanthropological community embraced the naming of this new species. Detractors argued that the hominin record between two million and three million years ago was too sparse to support the claim that *Au. afarensis* was the ancestor of later hominins. The discovery of more fossils from this time period would be crucial for testing this hypothesis.

That additional evidence has since come in. In 1985 researchers working in northern Kenya discovered a 2.5-million-year-old cranium of the robust australopith *Paranthropus aethiopicus*. Dubbed the “Black Skull” for its manganese-tinged color, it possessed a powerful masticatory system, including large crushing and grinding teeth, similar to those of a robust australopith individual sometimes referred to as “Nutcracker Man,” who lived 1.8 million years ago and belonged to the species *Paranthropus boisei*. The Black Skull also shared several traits with *Au. afarensis*, including an extremely projecting lower face. When the three species are considered together, *Au. afarensis* is a compelling ancestor for *P. aethiopicus*, which in turn appears ancestral to *P. boisei*.



Further support for the hypothesis that *Au. afarensis* gave rise to later australopiths in eastern Africa came in 1990, when a cranium the same age as the Black Skull surfaced in Ethiopia’s Middle Awash Valley. The discovery team deemed it a new species, *Australopithecus garhi*, and claimed that it occurred at the right time and place to be ancestral to *Homo*. Like the robust australopiths, this specimen had an impressive masticatory system, with big jaws and a crest atop its head that would have anchored strong chewing muscles. It also had a facial structure similar to that of *Au. afarensis*. Other scientists have surmised that *Au. garhi* descended from *Au. afarensis* and evolved its formidable chewing anatomy in parallel with the robust australopiths but did not itself give rise to later hominin species.

Other fossil finds bolstered the proposed link between *Au. afarensis* and *Homo*. For a long time the oldest known fossils in the genus *Homo* dated only as far back as around two million years ago, leaving a worrying gap of more than a million years between the



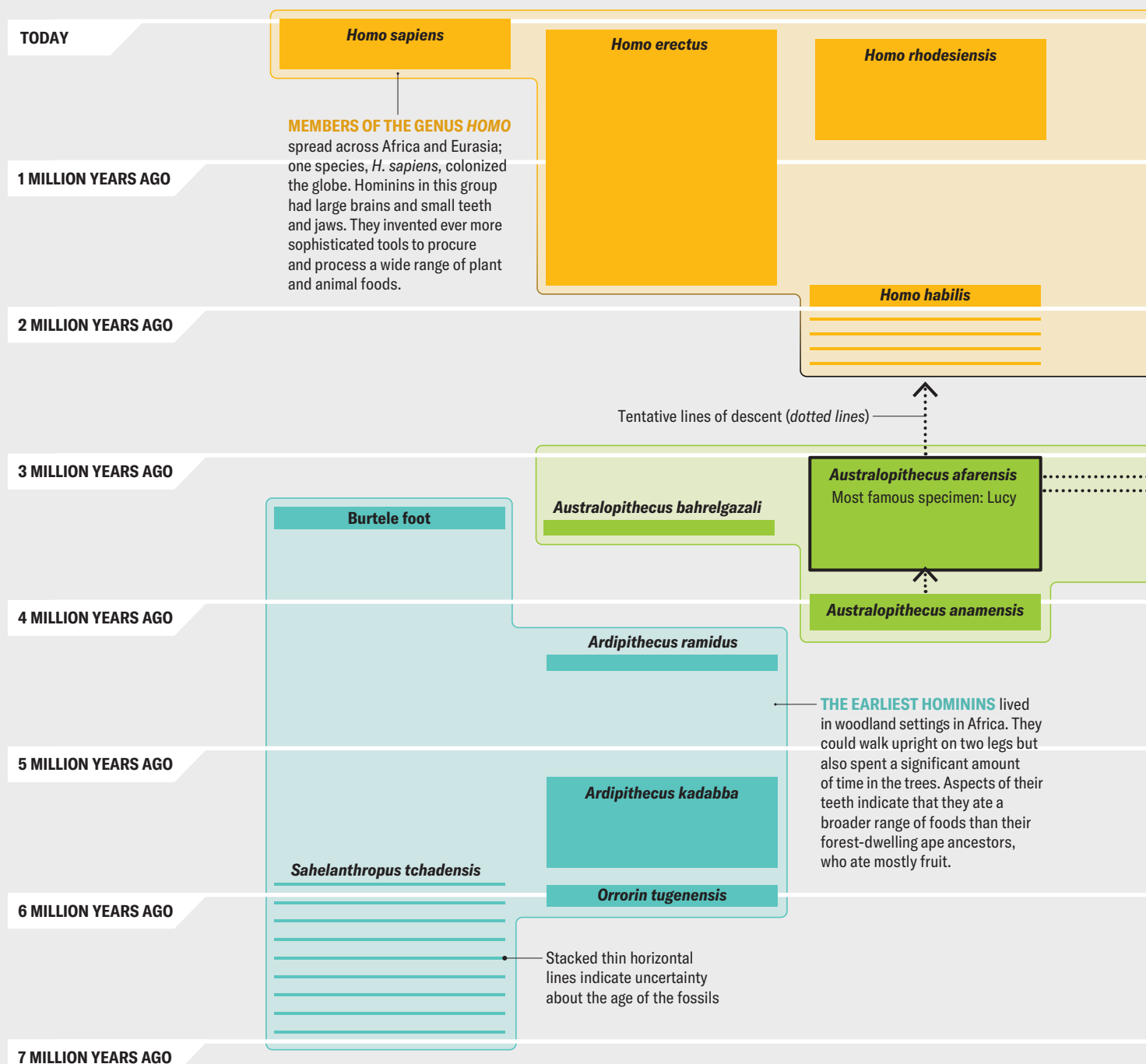
youngest *Au. afarensis* and the oldest *Homo*. In 1994 researchers at Hadar found a 2.33-million-year-old palate—the bone that makes up the roof of the mouth—that shared morphological traits with *Homo habilis*, “Handy Man,” the earliest known member of our genus, narrowing that temporal gap by a few hundred thousand years. And in 2013 a team working at a site northeast of Hadar called Ledi-Geraru recovered the left half of a 2.8-million-year-old mandible bearing a combination of primitive *Au. afarensis* features and characteristics of early *Homo*. The Ledi-Geraru jaw provided another stepping stone between *Au. afarensis* and *Homo* and strengthened the morphological connection between them as well, helping to validate the hypothesis that *Au. afarensis* is the best candidate we have for the ancestor of our own genus.

HUMAN FOSSILS are generally rare, which means that our understanding of the past can change dramatically when new specimens surface. When *Au. afarensis* was

named as a new species in 1978, it was the earliest human ancestor ever documented, with an age range of 3.8 million to 3.0 million years ago. Fossils recovered in the mid-1990s extended the early hominin record back even farther. In 1994 researchers working in the Middle Awash region of Ethiopia’s Afar Rift found hominin fossils dated to 4.4 million years ago. They assigned the remains to a new species, *Ardipithecus ramidus*. The following year another new species was named based on fossil discoveries from Kanapoi and Allia Bay in Kenya’s Turkana Basin: *Australopithecus anamensis*, which lived from 4.3 million to 3.8 million years ago. With the naming of these two species, *Au. afarensis* lost the distinction of being the oldest hominin, but it gained an origin story of its own: *Au. anamensis* is believed to be the direct ancestor of *Au. afarensis*. More recently, discoveries in Chad, Kenya and Ethiopia have pushed the origin of humankind back as far as seven million years.

Other fossil finds have shown that *Au. afarensis* was not the only hominin species around during its

In 1975 Johanson, shown here with graduate student Tom Gray, discovered fossils from a group of hominins—dubbed the First Family—who had died together at another locality in Hadar and belonged to the same species as Lucy (left). Cranial and dental remains from this find allowed researchers to reconstruct the skull of that species, *Australopithecus afarensis* (right).

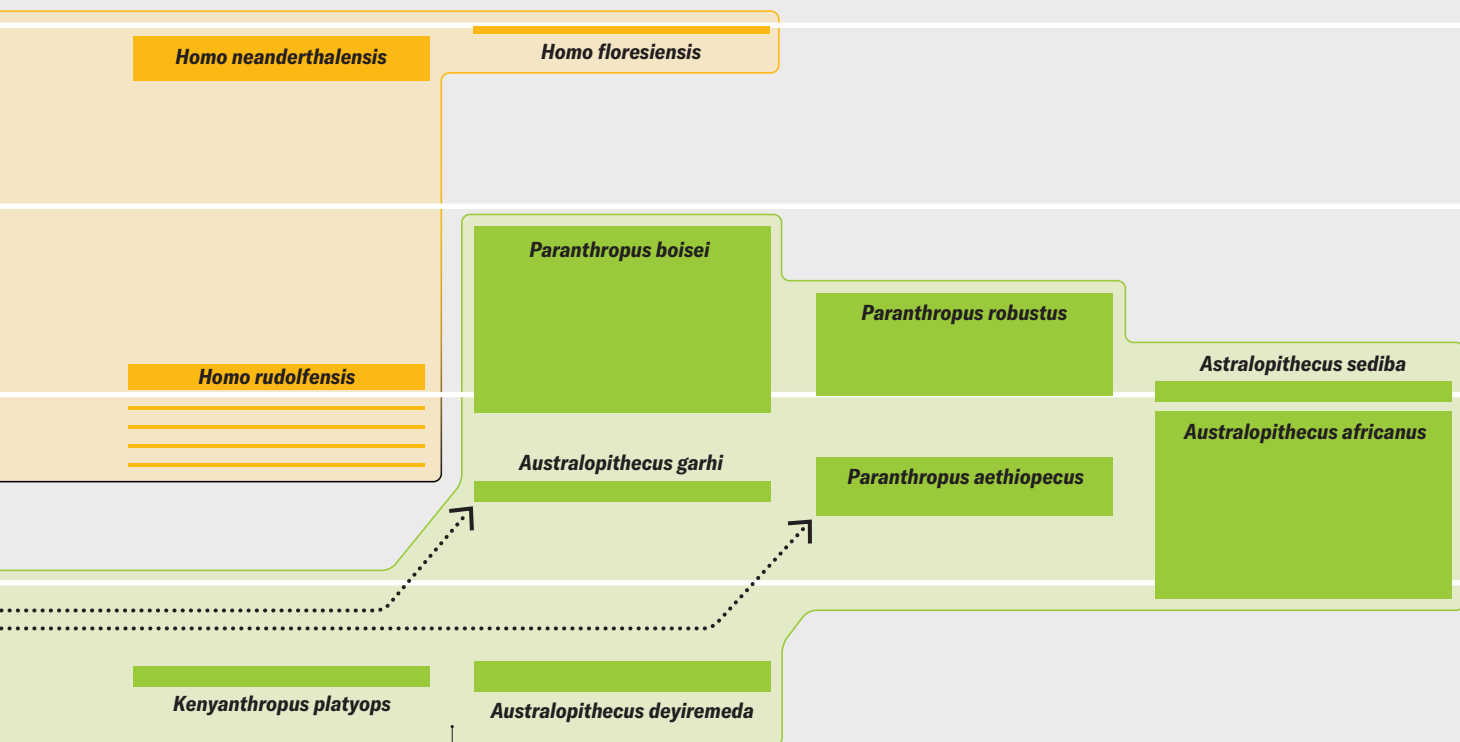


long reign, raising the question of whether *Au. afarensis* or one of these other hominins is the ancestor of *Homo* and *Paranthropus*. Far from diminishing the significance of Lucy's species, these findings enrich its story: we now have many more puzzle pieces from which to reconstruct the evolution of the line that led to us and the factors that shaped it along the way. The picture that is emerging from this work is far more complex—and fascinating—than the one paleoanthropologists traditionally envisioned.

Prior to 1960, human origins researchers thought that only a single hominin species lived at any given time in the past. This notion stemmed from the idea that competition prohibits the coexistence of related species with

similar adaptations, a principle known as competitive exclusion. The fossil record of hominins seemed to support this concept until fossils of two different hominin species were recovered from the same geological layer at sites in Kenya and Tanzania. Still, there was no evidence that another species lived alongside *Au. afarensis*, and because of that, it was considered to be the ancestor of all later hominins.

Eventually, however, challengers turned up from various sites in eastern and central Africa. In 1995 a team lead by paleontologist Michel Brunet discovered a 3.5-million-year-old partial hominin jaw from a site in northern Chad known as Koro-Toro and assigned it to a new species, *Australopithecus bahrelghazali*. This



THE AUSTRALOPITHS lived in a variety of habitats—from woodlands to grasslands—across the African continent. They were fully bipedal and had lost key morphological features that make primates good at climbing trees. Their jaws and teeth were adapted to eating difficult-to-process foods.

Ancestor of Consequence

Back when the Lucy skeleton was discovered in 1974, there were only a few fossil human species on record. A species from South Africa known as *Australopithecus africanus* was the oldest one known, and scientists figured it was ancestral to all later hominins, including our genus, *Homo*. When researchers analyzed Lucy along with similar fossils from other localities in Ethiopia and Kenya in 1978, they concluded that the fossils belonged to a species new to science, *Australopithecus afarensis*, that was older than *Au. africanus* and whose features made it a more compelling ancestor of later hominins. Fossils discovered since then have shown that other hominin species lived at the same time as *Au. afarensis*, raising the question of whether one of these contemporaries might be the all-important ancestor instead. But *Au. afarensis* remains the most compelling candidate for the ancestor of *Homo* and *Paranthropus*.

fossil was significant not only because it was found outside the East African Rift System, where almost all early hominins have been recovered, but also because it overlapped in time with *Au. afarensis*. Not everyone agreed that the jaw was distinctive enough to represent a new species. Nevertheless, it was the first hint that *Au. afarensis* may not have been the only hominin species around 3.5 million years ago.

A second hint came in 2001, when paleontologist Meave Leakey and her team announced their discovery of a 3.5-million-year-old cranium from Lomekwi, a site in northwest Kenya, and assigned it to a new genus and species called *Kenyanthropus platyops*, partly on the basis of what they saw as a distinctive flatness of its

face. Critics also challenged the validity of this species, arguing that the badly crushed skull was too distorted for its true shape to be discernible. Regardless, it was another indication that *Au. afarensis* might not have been alone—even in eastern Africa.

More recently, Haile-Selassie has found the strongest evidence yet that *Au. afarensis* had company. Two decades ago he set out to look for new paleontological sites in the Afar Rift containing hominin fossils between three million and four million years old. His efforts resulted in the discovery of a spectacular new site called Woranso-Mille just 40 kilometers north of Hadar. With fossils spanning the time from 3.8 million to 3.0 million years ago, it has become one of the most important sites



For the past two decades Yohannes Haile-Selassie (right) has been working at a fossil site some 40 kilometers north of Hadar called Woranso-Mille. There he has recovered fossils belonging to contemporaries of *Au. afarensis*, including jawbones belonging to a species called *Australopithecus deyiremeda* (fossil cast, center) and a foot belonging to a yet unidentified species that had a divergent big toe like an ape's (left).

in all of Africa for hominins from the Pliocene epoch.

Perhaps the most remarkable aspect of Woranso-Mille is the diversity of hominins found there. The site has yielded remains of both *Au. anamensis* (including a nearly complete skull that has given us our first look at the face of this ancestor) and its descendant, *Au. afarensis*. It has also produced other hominins. In 2012 Haile-Selassie and his colleagues announced their discovery of an enigmatic hominin foot with a divergent big toe more like an ape's. At 3.4 million years old, it was contemporaneous with *Au. afarensis*. Yet it clearly did not come from that species, whose big toe lined up with the other digits, like ours does. Without any associated skull or tooth remains to guide them, the researchers did not want to assign the foot to a species. But it showed beyond any doubt that Lucy's species shared the landscape with a fundamentally different kind of hominin.

Further evidence that *Au. afarensis* overlapped with other hominins came in 2015, when Haile-Selassie and his colleagues announced their discovery of fossilized upper and lower jaws from a species new to science,

Australopithecus deyiremeda. Dated to 3.3 million to 3.5 million years ago, this species was contemporaneous with both *Au. afarensis* and the owner of the mysterious foot that was recovered from the same site. Whether the foot belongs to *Au. deyiremeda*, given the proximity of the finds, remains to be seen.

The discoveries at Woranso-Mille show that *Au. afarensis* didn't just share the same continent or even the same side of the continent with other hominin species but lived virtually side by side with them. They may have been able to do this by exploiting different ecological niches within the same area. The species with the divergent big toe probably could have climbed trees more efficiently than *Au. afarensis*, for example, and so might have focused on arboreal resources while *Au. afarensis* favored terrestrial ones.

Comparison of the paleoenvironments at the sites where these fossils are found may provide further clues. Hadar and Woranso-Mille are similar in having hosted both *Au. afarensis* and other nonhominin mammals simultaneously. But only Woranso-Mille had more



than one hominin species. Why were there multiple contemporaneous hominin species at Woranso-Mille and not at nearby Hadar? One hypothesis we are testing is that Woranso-Mille encompassed a greater diversity of habitats, which could have supported multiple hominins without substantial direct competition.

THE REALIZATION that *Au. afarensis* might have had as many as three other hominin contemporaries has raised questions about the claim that it was the ancestor of all later hominins, including members of *Homo*. We have to consider whether any of these other species may be a better candidate ancestor than *Au. afarensis*. In practice, it's hard to connect the dots with certainty. One big problem is that the sample sizes of these other species are too small to allow for meaningful comparisons. For example, researchers have argued that *K. platyops* had a flat face like early *Homo* and could thus be considered the ancestor of that genus. But we have only one skull of *K. platyops* to go on, and it's badly crushed. Did this creature actually

have a flat face, or did its poor preservation distort its true features? We would need well-preserved skulls of this species to know. What is more, *K. platyops* is separated from its proposed descendant, *Homo rudolfensis*, by about a million years, making it difficult to link the two. If we had more fossils of *K. platyops* from different time periods to establish how long this species persisted, we might be able to bridge that gap, but we don't.

We simply don't have enough information about *K. platyops* or the other *Au. afarensis* contemporaries to know what kinds of creatures they were and how they are related to the rest of the human family. That leaves *Au. afarensis*—represented by hundreds of fossils from numerous individuals, juvenile and adult, spanning some 800,000 years—as the best candidate ancestor of *Homo* and *Paranthropus*. As additional fossils of these more recently identified hominins come to light, perhaps one of them might emerge as the front-runner. Until then, *Au. afarensis* remains the most likely ancestor and one of the most important species in human evolutionary history. ●

FROM OUR ARCHIVES

Lucy's Baby.

Kate Wong;
December 2006.
[ScientificAmerican.com/archive](https://www.scientificamerican.com/archive)



MEDICINE

No

More

Needles

**Gentle nasal sprays
are being tested as vaccines
against COVID, the flu, RSV,
and more. They may work better
than shots in the arm**

BY STEPHANI SUTHERLAND

ILLUSTRATION BY SAM FALCONER



A

LYSON VELASQUEZ HATES NEEDLES. She never liked getting shots as a kid, and her anxiety only grew as she got older. “It really ballooned in my teens and early 20s,” she says. “It became a full-blown phobia.” She would panic at the sight of a needle being brought into an exam room; more than once she passed out. Velasquez says that she took an antianxiety medication before one appointment yet still ran around the room screaming inconsolably “like I was a small child; I was 22.” After that episode Velasquez, now a 34-year-old financial planner in southern California, quit needles completely. “No vaccinations, no bloodwork. For all of my 20s it was a no-go for me,” she says.

Then COVID showed up. “It finally hit a point where it wasn’t just about me,” Velasquez says. “It felt so selfish not to do this for the greater public health and the safety of our global community.” So she got vaccinated against the SARS-CoV-2 virus in 2021, although she had to sit on her husband’s lap while he held her arms. “It was a spectacle. The poor guy at CVS . . . he did ask me, ‘Are you sure you want to do this?’” She very much did. “I’m very pro-vaccine. I am a rational human. I understand the necessity of [getting] them,” she insists. But today she still struggles with each injection.

Those struggles would end, however, if all her future vaccinations could be delivered by a nasal spray. “Oh, my God, amazing!” Velasquez says.

The amazing appears to be well on its way. Vaccines delivered through the nose are now being tested for several diseases. In the U.S., early clinical trials are showing success. Two of these vaccines have gener-

ated multiple immune system responses against the COVID-causing virus in people who received them through a puff up the nose; earlier this year their makers received nearly \$20 million from Project NextGen, the Biden-Harris administration’s COVID medical initiative. Researchers are optimistic that a nasal spray delivering a COVID vaccine could be ready for the U.S. as soon as 2027. Although recent efforts have focused on inoculations against SARS-CoV-2, nasal vaccines could also protect us against the flu, respiratory syncytial virus (RSV), and more.

A few nasal vaccines have been introduced in the past, but they’ve been beset by problems. The flu inoculation FluMist has not gained popularity because of debates about its effectiveness, and a different vaccine was pulled from the market decades ago because some people had serious side effects. In China and India, nasal vaccines for COVID have been ap-

Stephani Sutherland is a neuroscientist and science journalist based in southern California. She wrote about the causes of long COVID in our March 2023 issue. Follow her on X @SutherlandPhD

proved because those countries prioritized their development during the pandemic, whereas the U.S. and other wealthy nations opted to stick with arm injections. But this new crop of vaccines takes advantage of technology that produces stronger immune responses and is safer than preparations used in the past.

In fact, immunologists say these spritzes up the nose—or inhaled puffs through the mouth—can provide faster, stronger protection against respiratory viruses than a shot in the arm. That is because the new vaccines activate a branch of the immune system that has evolved for robust, rapid responses against airborne germs. “It may be more likely to really prevent infection from getting established,” says Fiona Smaill, an infectious disease researcher at McMaster University in Ontario. Such inoculations may also help reduce the enormous inequities in vaccine access revealed by the pandemic. These formulations should be cheaper and easier to transport to poor regions than current shots.

But nasal vaccines still face technical hurdles, such as how best to deliver them into the body. And unlike injected vaccines, which scientists can measure immune responses to with blood tests alone, testing for immunity that starts in nose cells is more challenging. But researchers working in this field agree that despite the hurdles, nasal formulations are the next step in vaccine evolution.

TRADITIONAL VACCINES injected through the skin and into an arm muscle provide excellent protection against viruses. They coax immune cells into making widely circulated antibodies—special proteins that recognize specific structural features on viruses or other invading pathogens, glom on to them and mark them for destruction. Other immune cells retain a “memory” of that pathogen for future encounters.

Intramuscular injection vaccines are good at preventing a disease from spreading, but they do not stop the initial infection. A nasal spray does a much better job. That’s because sprays are aimed directly at the spot where many viruses first enter the body: the nose and the tissue that lines it, called the mucosa.

Mucosa makes up much of our bodies’ internal surfaces, stretching from the nose, mouth and throat down the respiratory tract to the lungs, through the gastrointestinal tract to the anus, and into the urogenital tract. Mucosa is where our bodies encounter the vast majority of pathogenic threats, Smaill says, be it flu, COVID, or bacterial infections that attack the gut. This tough, triple-layered tissue is specialized to fight off invaders with its thick coating of secretory goo—mucus—and with a cadre of resident immune cells waiting to attack. “Mucosa is really the first line of defense against any infection we’re exposed to,” Smaill says.

Mucosal immunity not only prepares the immune system for the fight where it occurs but also offers three different types of protection—at least one more than a shot does. Nasal vaccines and shots both mobilize im-

Nasal sprays aim directly at the spot where most viruses first enter the body: the nose.

mune messenger cells, which gather the interlopers’ proteins and display them on their surfaces. These cells head to the lymph nodes, where they show off their captured prize to B and T cells, which are members of another part of the immune system called the adaptive arm. B cells, in turn, produce antibodies, molecules that home in on the foreign proteins and flag their owners—the invading microbes—for destruction. Killer T cells directly attack infected cells, eliminating them and the microbes inside. This provides broad protection, but it takes time, during which the virus continues to replicate and spread.

That’s why a second type of protection, offered only by the mucosal tissue, is so important. The mucosa holds cells of the innate immune system, which are the body’s “first responders.” Some of these cells, called macrophages, recognize invasive microbes as foreign and swallow them up. They also trigger inflammation—an alarm sounded to recruit more immune cells.

Another part of this localized response is called tissue-resident immunity. These cells don’t have to detect telltale signs of a pathogen and make a long journey to the infected tissue. They are more like a Special Forces unit dropped behind enemy lines where a skirmish is occurring rather than waiting for the proverbial cavalry to arrive. This localized reaction can be quite potent. Its activation is notoriously difficult to demonstrate, however, so historically it’s been hard for vaccine makers to show they’ve hit the mark. But it turns out that one type of antibody, called IgA, is a good indicator of mucosal immunity because IgAs tend to predominate in the mucosa rather than other parts of the body. In an early trial of CoviLiv, a nasal COVID vaccine produced by Codagenix, about half of participants had detectable IgA responses within several weeks after receiving two doses. That trial also showed the vaccine was safe and led to NextGen funding for a larger trial of the vaccine’s efficacy.

It’s possible an inhaled vaccine may provide yet one more layer of protection, called trained innate immunity. This reaction is a bit of a mystery: although immunologists know it exists and appears also to be produced by intramuscular injections, they can’t quite explain how it works. Immune cells associated with trained innate immunity seem to have memorylike responses, reacting quickly against subsequent infections. They also have been found to respond against pathogens entirely unrelated to the intended vaccine target. Smaill and her colleagues found that when they immunized mice with an inhaled tuberculosis vaccine and then challenged them with pneumococcal bacteria, the mice were protected. In children, there is some evidence that

a tuberculosis vaccine, in the arm, generates this type of broad response against other diseases.

Akiko Iwasaki, an immunologist at Yale University who is working to develop a nasal vaccination for COVID, sees two major potential benefits to nasal immunity in addition to better, faster, more localized protection. First, attacking the virus in the nose could prevent the disease from being transmitted to others by reducing the amount of virus that people breathe out. And second, Iwasaki says, the spray may limit how deeply the infection moves into the body, so “we believe that it will also prevent long COVID.” That debilitating postinfection condition, sometimes marked by signs of entrenched viral particles, disables people with extreme fatigue, chronic pain, a variety of cognitive difficulties, and other symptoms.

MAKING A NEW VACCINE is hard, regardless of how you administer it. It needs to raise an immune response that’s strong enough to protect against future invasions but not so strong that the components of that response—such as inflammation and fever—harm the host.

The lining of the nose puts up its own barriers—literal, physical ones. Because the nasal mucosa is exposed to so many irritants from the air, ranging from pet hair to pollen, the nose has multiple lines of defense against invading pathogens. Nostril hair, mucus, and features called cilia that sweep the nasal surface all aim to trap small foreign objects before they can get deeper into the body—and that includes tiny droplets of vaccine.

And lots of small foreign particles—often harmless—still make it through those defenses. So the nose has developed a way to become less reactive to harmless objects. This dampened reactivity is called immunological tolerance, and it may be the biggest hurdle to successful development of a nasal vaccine. When foreign particles show up in the bloodstream, a space that is ostensibly sterile, immune cells immediately recognize them as invaders. But mucosal surfaces are constantly bombarded by both pathogens and harmless materials. The immune system uses tolerance—a complex series of decisions carried out by specialized cells—to determine whether a substance is harmful. “This is very important because we can’t have our lungs or gastrointestinal tract always responding to nonharmful foreign entities that they encounter,” says Yale infectious disease researcher Benjamin Goldman-Israelow. For example, inflammation in the lungs would make it hard to breathe; in the gut, it would prevent the absorption of water and nutrients.

These barriers may hamper the effectiveness of a nasal flu vaccine that’s been around for a while, called FluMist in the U.S. and Fluenz in Europe. The inoculation is safe, says infectious disease scientist Michael Diamond of Washington University in St. Louis, but it faces a similar problem as do injected flu vaccines: it isn’t very effective at warding off new seasonal flu strains. This might be because flu strains are so com-

mon, and people are frequently infected by the time they are adults. Their immune systems are already primed to recognize and destroy familiar flu particles. FluMist is built from a live flu virus, so immune cells probably treat the vaccine as an invader and demolish it as soon as it shows up in the nose, before it has a chance to do any good. This preexisting immunity isn’t such an issue in children, who are less likely to have had multiple flu infections. Nasal flu vaccines are routinely used to inoculate kids in Europe.

In other vaccines, researchers often use adjuvants, special agents that attract the attention of immune cells, to boost a response. Some nasal vaccines use adjuvants to overcome tolerance, but in the nose, adjuvants can pose unique dangers. In at least one case, a nasal adjuvant led to disastrous consequences. An intranasal vaccine for influenza, licensed in Switzerland for the 2000–2001 season, used a toxin isolated from *Escherichia coli* bacteria as an adjuvant to provoke a reaction to the inactivated virus. No serious side effects were reported during the trial period, but once the vaccine was released, Swiss officials saw a concerning uptick in cases of Bell’s palsy, a disease that causes weakness or paralysis of the facial muscles, often leading to a drooping or disfigured face. Researchers at the University of Zurich estimated that the adjuvanted flu vaccine had increased the risk of contracting Bell’s palsy by about 20 times, and the vaccine was discontinued. “We need to be cautious about using adjuvants like that from known pathogens,” says pharmaceutical formulations scientist Vicky Kett of Queen’s University Belfast in Northern Ireland.

To get around the challenges posed by the nose, some researchers are exploring vaccines inhaled through the mouth. Smaill is working on one of them. She and her McMaster colleagues aerosolized their vaccine for COVID into a fine mist delivered by a nebulizer, from which it rapidly reaches the lungs. Experiments in mice have shown promising results, with mucosal immunity established after administration of the vaccine.

Another vaccine strategy is to use a harmless virus to carry viral genes or proteins. Researchers at the Icahn School of Medicine at Mount Sinai in New York City selected a bird pathogen, Newcastle disease virus (NDV). “It’s naturally a respiratory pathogen,” so it infects nasal cells, says Michael Egan, CEO and chief scientific officer of CastleVax, a company that formed to develop the NDV vaccine for COVID. A small early clinical trial showed the CastleVax vaccine was safe and caused robust immune responses in people. “Those results were very promising,” Egan says. People who received the vaccine also produced antibodies that indicated multitiered mucosal immunity, not simply the adaptive immunity from a shot in the arm.

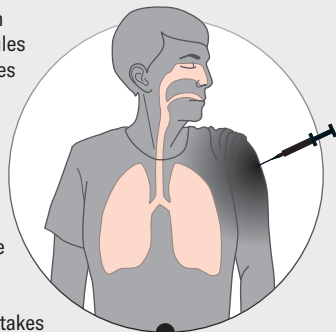
Following that trial, the CastleVax project received NextGen funding, and results from a trial of 10,000 people are expected in 2026. Half of those people will receive a messenger RNA (mRNA) injection, and half

The Vaccine Advantages of a Puff Up the Nose

As kids and adults, we become very familiar with the vaccine needle. Jabs for measles, mumps, COVID, flu, polio, and more protect people against all kinds of diseases. The injection starts in the arm but triggers an immune response that travels the body. It kicks in, however, after an infection starts. A new type of vaccine is emerging, though, for viruses and bacteria that we breathe. It meets the threat at the earliest moment: in the nose and mouth. These nasal or inhaled vaccines could stop pathogens almost before they get started.

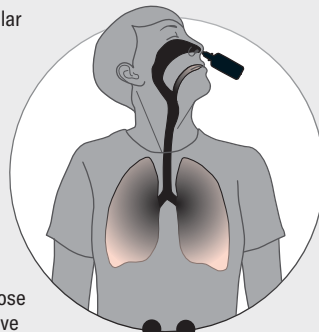
A SHOT IN THE ARM

Traditional vaccines go into an arm muscle. The vaccines carry molecules that are part of a germ or sometimes a badly weakened or killed version of the germ itself. The goal is to introduce these targets to what's called the adaptive immune system. This system essentially trains cells and proteins to recognize the invader. The adaptive system retains a memory of the germ and travels through the body looking to attack it. This response takes time, however.



A SPRAY UP THE NOSE

Nasal vaccines stimulate a particular tissue: the mucosa. It lines the insides of our noses and mouths, stretching down to the lungs and through our gastrointestinal tracts. In addition to adaptive immune cells, the mucosa holds "first responder" cells that immediately attack germs. They are part of what's called the innate immune system. And nasal vaccine sprays contain parts of those germs, to trigger innate and adaptive immune responses.



SYSTEMIC/ADAPTIVE IMMUNITY

- 1 A vaccine is introduced to the body.
- 2 Specialized immune cells take up the vaccine material.
- 3 The aptly named antigen-presenting cells travel to a lymph node via the circulatory system.
- 4 In the lymph node, antigens are presented to helper T cells. Helper T cells engage additional immune cells, priming them for later action.

RESIDENT MUCOSAL IMMUNITY

- 1 Vaccine is introduced to the body—directly into a mucosal area.
- 2 Resident antigen-presenting immune cells take up the vaccine material, then display fragments on their surface to resident helper T cells in the mucosa-associated lymphoid tissue.
- 3 Helper T cells engage additional immune cells already on site, causing them to secrete a mucosal-specific antibody called sIgA, as well as priming the cells for later action.

SUBSEQUENT EXPOSURE TO A VIRUS

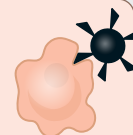
SUBSEQUENT EXPOSURE TO A VIRUS

- 5 When the target virus enters the body—often through the nose—primed immune cells and antibodies released from activated B cells travel from lymph nodes to the site via the circulatory system. Antibodies disable the virus, and killer T cells destroy host cells, preventing further replication.

- 4 When the target virus enters the body via the same mucus-lined route, the primed immune cells and sIgA are already in position, ready to disable the virus and destroy infected cells.

TRAINED INNATE IMMUNITY

Some research indicates that nasal vaccines also prime cells of the innate branch of the immune system—including macrophages—to be more efficient at destroying subsequent viruses unrelated to the target pathogen.



“We’re expecting to see fewer breakthrough infections in people who got the vaccine up the nose.”

—MICHAEL EGAN CASTLEVAX

will get the new NDV nasal spray. The data should show whether the new nasal vaccine can do a better job of preventing infection than the mRNA injections. Egan has high hopes. “We’re expecting to see a lot fewer breakthrough infections in people who got the vaccine up the nose by virtue of having those mucosal immune responses,” he says.

Florian Krammer, one of the Mount Sinai researchers behind the vaccine, engineered NDV particles to display a stabilized version of the spike protein that’s so prominent in SARS-CoV-2. “You end up with a particle that’s covered with spike,” he says. Spike protein in the bloodstream can raise an immune response. But the NDV vaccine works in another way, too. The virus particle can also get into cells, where it can replicate enough times to cause virus particles to emerge from the cells, provoking another immune reaction. Before moving into human trials, however, researchers had to complete clinical trials to establish that the Newcastle virus is truly harmless because the nose is close to the central nervous system—it has neurons that connect to the olfactory bulb, which is part of the brain. Those trials confirmed that it is safe for this use.

This type of caution is one reason a COVID nasal vaccine approved in India hasn’t been adopted by the U.S. or other countries. The inoculation, called iNCO-VACC, uses a harmless simian adenovirus to carry the spike protein into the airway. The research originated in the laboratories of Diamond and some of his colleagues at Washington University at the start of the pandemic, when they tested the formulation on rodents and nonhuman primates. “The preclinical data were outstanding,” Diamond says. Around the time he and his colleagues published initial animal results in *Cell* in 2020, Bharat Biotech in India licensed the idea from the university. In a 2023 phase 3 clinical trial in India, the nasal vaccine produced superior systemic immunity compared with a shot.

Diamond says American drug companies didn’t pursue this approach, because “they wanted to use known quantities,” such as the mRNA vaccines, which were already proving themselves in clinical trials in 2020. As the pandemic took hold, there was little appetite to develop nasal vaccine technology to stimulate mucosal immunity while the tried-and-true route of shots in the arm was available and working. But now, four years later, an inhaled vaccine using technology similar to iNCOVACC’s is being developed for approval in the U.S. by biotech company Ocugen. Both inhaled and nasal forms of the vaccine are set to undergo clinical trials as part of Project NextGen. These new vaccines are using classical vaccine methods

based on the virus rather than using new, mRNA-based technology. The mRNA preparations were developed specifically for intramuscular injections and would have to be significantly modified.

Codagenix, which is developing CoviLiv, sidestepped the need for a new viral vector or an adjuvant by disabling a live SARS-CoV-2 virus. To make it safe, scientists engineered a version of the virus with 283 mutations, alterations to its genetic code that make it hard for the virus to replicate and harm the body. Without all these genetic changes, there would be a chance the virus could revert to a dangerous, pathogenic form. But with hundreds of key mutations, “statistically, it’s basically impossible that this will revert back to a live virus in the population,” says Johanna Kaufmann, who helped to develop the vaccine before leaving Codagenix for another company earlier this year.

BECAUSE MOST PEOPLE on the planet have now been exposed to SARS-CoV-2—in the same way they’re regularly exposed to the flu—some nasal vaccines are being designed as boosters for a preexisting immune response that is starting to wane. For example, Yale researchers Iwasaki and Goldman-Israelow are pursuing a strategy in animals deemed “prime and spike.”

The idea is to start with a vaccine injection—the “prime” that stimulates adaptive immunity—then follow it a few weeks later with a nasal puff that “spikes” the system with more viral protein, leading to mucosal immunity. In a study published in 2022 in *Science*, Iwasaki and her colleagues reported that they primed rodents with the mRNA vaccine developed by Pfizer and BioNTech, the same shot so many of us have received. Two weeks later some of the mice received an intranasal puff of saline containing a fragment of the SARS-CoV-2 spike protein. Because the animals had some preexisting immunity from the shot, the researchers didn’t add any adjuvants to heighten the effects of the nasal puff. Two weeks later researchers detected stronger signs of mucosal immunity in mice that had received this treatment compared with mice that got only the shot.

“Not only can we establish tissue-resident memory T cells” to fight off the virus in the nose, Iwasaki says, but the prime-and-spike method also produces those vigorous IgA antibodies in the mucosal layer. “And that’s much more advantageous because we can prevent the virus from ever infecting the host,” she notes. The study suggests that this approach might also lessen the chances of transmitting the disease to others because of the lower overall viral load. Experiments in hamsters demonstrated that vaccinated animals shed less virus, and they were less likely to contract COVID from infected cage mates that had not been vaccinated themselves.

ALTHOUGH MOST OF THE NEW vaccine strategies are aimed at COVID, nasal vaccines for other diseases

FROM OUR ARCHIVES
Nose Spray Vaccines
Could Quash COVID
Virus Variants.

Marla Broadfoot;
ScientificAmerican.
com, May 3, 2022.
[ScientificAmerican.
com/archive](https://www.ScientificAmerican.com/archive)

are already being planned. Kaufmann, formerly of Codagenix, says the company currently has clinical trials underway for nasal vaccines against flu and RSV. CastleVax's Egan says "we have plans to address other pathogens" such as RSV and human metapneumovirus, another leading cause of respiratory disease in kids.

Vaccines that don't need to be injected could clear many barriers to vaccine access worldwide. "We saw with COVID there was no vaccine equity," Smail says. Many people in low-income countries never received a shot; they are still going without one four years after the vaccines debuted.

In part, this inequity is a consequence of the high cost of delivering a vaccine that needs to stay frozen on a long journey from manufacturing facilities in wealthy countries. Some of the nasal sprays in development don't need deep-cold storage, so they might be easier to store and transport. And a nasal spray or an inhaled puff would be much easier to administer than a shot. No health professional is required, so people could spray it into their noses or mouths at home.

For these reasons, needle-free delivery matters to the World Health Organization. The WHO is using the Codagenix nasal spray in its Solidarity Trial Vaccines program to improve vaccine equity. The CoviLiv spray is now in phase 3 clinical trials around the world as part of this effort. "The fact that the WHO was still interested in a primary vaccination trial in the geographies it's passionate about—that's indicative that there is still a gap," Kaufmann says. CoviLiv was co-developed with the Serum Institute of India, the world's largest maker of vaccines by dose. The partnership enabled production at the high volume required for Solidarity.

The CastleVax vaccine with the NDV vector provides another layer of equity because the facilities required to make it already exist in many low- and middle-income countries. "The cool thing is that NDV is a chicken virus, so it grows very well in embryonated eggs—that's exactly the system used for making flu vaccines," Krammer says. For example, for a clinical trial in Thailand, "we just shipped them the seed virus, and then they produced the vaccine and ran the clinical trials," he says. Many countries around the world have similar facilities, so they will not need to depend on pharma companies based in richer places.

Even high-income countries face barriers to vaccination, although they may be more personal than systemic. For very many people, the needle itself is the problem. Extreme phobia such as Velasquez's is uncommon, but many people have a general fear of needles that makes vaccinations stressful or even impossible for them. For about one in 10 people needle-related fear or pain is a barrier to vaccinations, says C. Meghan McMurtry, a psychologist at the University of Guelph in Ontario. Needle fear "is present in most young kids and in about half of adolescents. And 20 to

30 percent of adults have some level of fear." A review of studies of children showed that "concern around pain and needle fear are barriers to vaccination in about 8 percent of the general population and about 18 percent in the vaccine-hesitant population," McMurtry adds.

Some people are wary of injected vaccines even if they're not afraid of needles, Kett says; they see injections as too invasive even if the needle doesn't bother them. "We're hopeful that something administered by the nasal route would be less likely to come across some of those issues," Kett says.

In the U.S., however, sprays and puffs won't be available until they are approved by the Food and Drug Administration, which requires clear evidence of disease protection. As Diamond points out, standards for such evidence are well established for injections, and vaccine makers can follow the rule book: regulations point to particular antibodies and specific ways to measure them with a simple blood test. But for nasal vaccines, Iwasaki says, "we don't have a standard way to collect nasal mucus or measure antibody titers. All these practical issues have not been worked out."

Iwasaki is also frustrated with a restriction by the U.S. Centers for Disease Control and Prevention that stops researchers from using existing COVID vaccines in basic research to develop new nasal sprays. The rule is a holdover from 2020, when COVID injections had just been developed and were in short supply; people had to wait to get vaccinated until they were eligible based on factors such as age and preexisting conditions. "That made sense back then, but those concerns are years old; things are different now," Iwasaki says. "Now we have excess vaccine being thrown out, and we cannot even get access to the waste, the expired vaccine."

Today scientists want to contrast the effectiveness of nasal formulations with injections already in use. "Those comparisons are really important for convincing the FDA that this is a worthy vaccine to pursue," Iwasaki says. But the restriction has held up studies by her company, Xanadu, slowing down work. (The CDC did not respond to a request for comment.)

Despite the bureaucratic and scientific hurdles, the sheer number of nasal vaccines now in clinical trials encourages Iwasaki and other scientists pursuing the needle-free route. They say it seems like only a matter of time before getting vaccinated will be as simple as a spritz up the nose.

Velasquez, for one, can't wait for that day to arrive. The circumstances that finally forced her to reckon with her fear of needles (a global pandemic, the prospect of parenthood and the numerous blood tests that accompanied her pregnancy) were so much bigger than her. If not for them, she might still be avoiding shots. "So having vaccines without needles—I would get every vaccine any doctor wanted me to get, ever. It would be a complete game changer for me." ●



Cosmic Confusion

Measurements of the universe don't agree on how fast it's expanding. Could an extra ingredient in the early cosmos explain the gap?

BY MARC KAMIONKOWSKI AND ADAM G. RIESS

ILLUSTRATION BY CHRIS GASH



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IFTEEN YEARS AGO COSMOLOGISTS WERE FLYING HIGH.

The simple but wildly successful “standard model of cosmology” could, with just a few ingredients, account for a lot of what we see in the universe. It seemed to explain the distribution of galaxies in space today, the accelerated expansion of the universe and the fluctuations in the brightness of the relic glow from the big bang—called the cosmic microwave background (CMB)—based on a handful of numbers fed into the model. Sure, it contained some unexplained exotic features, such as dark matter and dark energy, but otherwise everything held together. Cosmologists were (relatively) happy.

Over the past decade, though, a pesky inconsistency has arisen, one that defies easy explanation and may portend significant breaks from the standard model. The problem lies with the question of how fast space is growing. When astronomers measure this expansion rate, known as the Hubble constant, by observing supernovae in the nearby universe, their result disagrees with the rate given by the standard model.

This “Hubble tension” was first noted more than 10 years ago, but it was not clear then whether the discrepancy was real or the result of measurement error. With time, however, the inconsistency has become more firmly entrenched, and it now represents a major thorn in the side of an otherwise capable model. The latest data, from the James Webb Space Telescope (JWST), have made the problem worse.

The two of us have been deeply involved in this saga. One (Riess) is an observer and co-discoverer of dark energy, one of the last pieces of the standard cosmological model. He has also spearheaded efforts to determine the Hubble constant by observing the local universe. The other (Kamionkowski) is a theorist who helped to figure out how to calculate the Hubble constant by measuring the CMB. More recently he helped to develop one of the most promising ideas to explain the discrepancy—a notion called early dark energy.

One possibility is that the Hubble tension is telling us the baby universe was expanding faster than we think. Early dark energy posits that this extra expansion might have resulted from an additional repulsive force that was pushing against space at the time and has since died out.

Marc Kamionkowski

is a theoretical physicist at Johns Hopkins University, where he studies cosmology and particle physics.

Adam G. Riess

is an astrophysicist at Johns Hopkins University and the Space Telescope Science Institute. His research on distant supernovae revealed that the expansion of the universe is accelerating, a discovery for which he shared the 2011 Nobel Prize in Physics.

This suggestion is finally facing real-world tests, as experiments are just now becoming capable of measuring the kinds of signals early dark energy might have produced. So far the results are mixed. But as new data come in over the next few years, we should learn more about whether the expansion of the cosmos is diverging from our predictions and possibly why.

THE IDEA THAT THE UNIVERSE is expanding at all came as a surprise in 1929, when Edwin Hubble used the Mount Wilson Observatory near Pasadena, Calif., to show that galaxies are all moving apart from one another. At the time many scientists, including Albert Einstein, favored the idea of a static universe. But the separating galaxies showed that space is swelling ever larger.

If you take an expanding universe and mentally rewind it, you reach the conclusion that at some finite time in the past, all the matter in space would have been on top of itself—the moment of the big bang. The faster the rate of expansion, the shorter the time between that big bang and today. Hubble used this logic to make the first calculation of the Hubble constant, but his initial estimate was so high that it implied the universe was younger than the solar system. This was the very first “Hubble tension,” which was later resolved when German astronomer Walter Baade discovered that the distant galaxies Hubble used for his estimate contained different kinds of stars than the nearby ones he used to calibrate his numbers.

A second Hubble tension appeared in the 1990s as a result of sharpening observations from the Hubble Space Telescope. The observatory’s measured value of the Hubble constant implied that the universe’s oldest stars were older than stellar-evolution theories suggested. This tension was resolved in 1998 with the discovery that the expansion of the cosmos was accelerating. This shocking revelation led scientists to add dark energy—the energy of empty space—to the standard model of cosmology. Once researchers understood that the universe is expanding faster now than it did when it was young, they realized it had to be several billion years older than previously thought.

Since then, our understanding of the origin and evolution of the universe has changed considerably. We can now measure the CMB—our single greatest piece of evidence about cosmic history—with a precision unimaginable at the turn of the millennium. We have mapped the distribution of galaxies over cosmic volumes hundreds of times larger than we had then. Likewise, the number of supernovae being used to measure the expansion history has reached several thousand.

Yet our estimates of how fast space is growing still disagree. For more than a decade increasingly precise measurements of the Hubble constant based on the local universe, made without reference to the standard model and therefore directly testing its accuracy, have converged around 73 kilometers per second per megaparsec (km/s/Mpc) of space, plus or minus 1. This figure is too large, and its estimated uncertainty too small,

One possible explanation is that the Hubble tension is telling us the baby universe was expanding faster than we think.

to be compatible with the value the standard model predicts based on CMB data: 67.5 ± 0.5 km/s/Mpc.

THE LOCAL MEASUREMENTS are largely based on observations of supernovae in a certain class, type Ia, that all explode with a similar energy output, meaning they all have the same intrinsic brightness, or luminosity. Their apparent luminosity (how bright they appear in the sky) is a proxy for their distance from Earth. And comparing their distance with their speed—which we get by measuring their redshift (how much their light has been shifted toward the red end of the electromagnetic spectrum)—tells us how fast space is expanding.

Astronomers calibrate their type Ia supernova distance measurements by comparing them with values for nearby galaxies that host both a supernova of this type and at least one Cepheid variable star—a pulsating supergiant that flares on a timescale tightly correlated to its luminosity, a fact discovered a century ago by [Henrietta Swan Leavitt](#). Scientists in turn calibrate this period-luminosity relation by observing Cepheids in very nearby galaxies whose distances we can measure geometrically through a method called parallax. This step-by-step calibration is called a distance ladder.

Twenty-five years ago a landmark measurement of this kind came out of the Hubble Key Project, resulting in a Hubble constant measurement of $H_0 = 72 \pm 8$ km/s/Mpc. About a dozen years ago this value improved to 74 ± 2.5 km/s/Mpc, thanks to work by two independent groups (the SHOES team, led by Riess, and the Carnegie Hubble Program, led by Wendy L. Freedman of the University of Chicago). In the past few years these measurements have been replicated by many studies and further refined with the aid of the European Space Agency Gaia parallax observatory to 73 ± 1 . Even if we replace some of the steps in the parallax-Cepheid-supernova calibration sequence with other estimates of stellar distances, the Hubble constant changes little and cannot be brought below about 70 km/s/Mpc without uncomfortable contrivances or jettisoning most of the Hubble Space Telescope data. Even this lowest value, though, is far too large compared with the number inferred from the CMB to be chalked up to bad luck.

Astronomers have worked through a long list of possible problems with the supernova distances and suggested many follow-up tests, but none have revealed a flaw in the measurements. Until recently, one of the remaining concerns involved how we determine Cepheid brightness in crowded fields of view. With the Hubble Space Telescope, some of the light from any given Cephe-

The Hubble Constant Problem

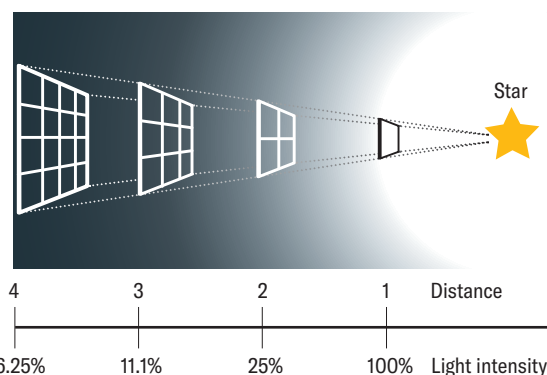
Ever since Edwin Hubble discovered in 1929 that the universe was expanding, scientists have wanted to know how fast. But the latest measurements present a puzzle. One way of calculating the cosmic expansion rate, known as the Hubble constant, is by looking at the relatively nearby objects in the universe using what's called a distance ladder. The other method involves studying the faraway light left over from the big bang, called the cosmic microwave background (CMB), and using the standard model of cosmology to extrapolate the current expansion rate. Over the years the two methods have become increasingly precise, yet they deliver irreconcilable rates.

METHOD 1: DISTANCE LADDERS

To find out how quickly the universe is expanding, scientists need to know two things: how fast galaxies are moving away from us and how far away they are. The first quantity is fairly easy to measure with "redshift"—the amount the galaxy's light has been shifted toward the red end of the electromagnetic spectrum by the Doppler effect. But figuring out distance is trickier.

INVERSE-SQUARE LAW

This rule tells us that when the distance from a light-emitting object is doubled, its brightness decreases by a factor of four. Thus by knowing how luminous something is inherently and comparing that with how bright it appears, we can measure its distance. Special cosmic objects known as standard candles all have the same intrinsic brightness as others in their class. These include periodically brightening stars called Cepheids and so-called type Ia supernova explosions. Scientists calibrate their distance measurements using ladders with three rungs.



FIRST RUNG

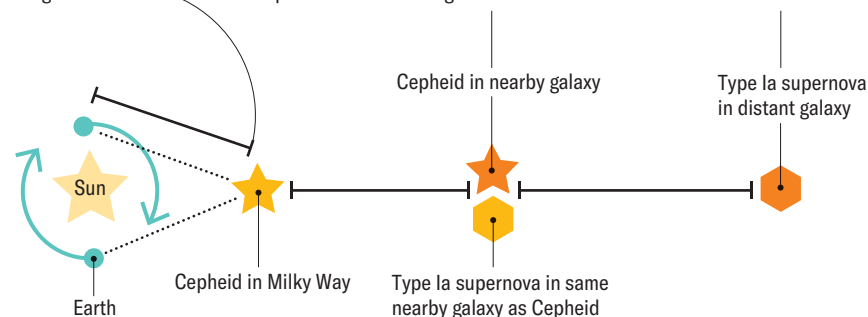
The first starts with Cepheids that are close enough that scientists can triangulate their position by observing them at different points along Earth's orbit.

SECOND RUNG

Astronomers then look at farther Cepheids in other galaxies and compare their apparent brightness with that of the known nearby ones to measure their distances. They can apply these distances to type Ia supernova in the same galaxies.

THIRD RUNG

Researchers can then compare the brightness of even more distant type Ia supernovae to determine their positions. When astronomers combine these with redshifts, they get distance and speed measurements for increasingly faraway galaxies, allowing them to calculate the Hubble constant.



id star overlapped with light from other stars close to it, so scientists had to use statistics to estimate how bright the Cepheid was alone. Recently, however, JWST allowed us to reimage some of these Cepheids with dramatically improved resolution. With JWST, the stars are very cleanly separated with no overlap, and the new measurements are fully consistent with those from Hubble.

THE METHOD FOR INFERRING the Hubble constant from the CMB is a bit more involved but is based on similar principles. The intensity of the CMB light is very nearly the same everywhere in space. Precise measurements show, however, that the intensity varies from one point to another by roughly one part in 100,000. To the eye, this pattern of intensity variations appears fairly random. Yet if we look at two points that are separated by around one degree (about two full moons side by side on the sky), we see a correlation: their intensities (temperatures) are likely to

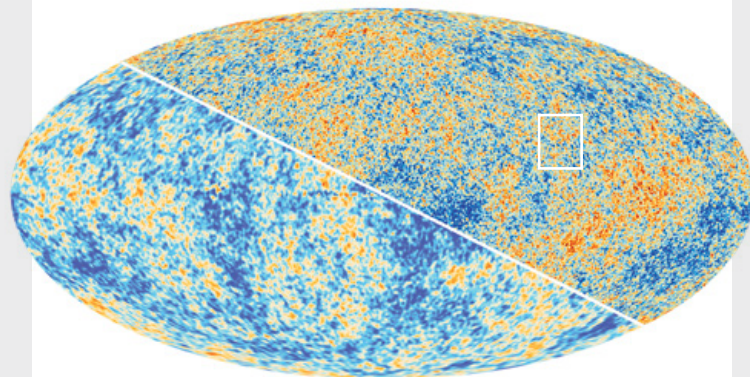
be similar. This pattern is a consequence of how sound spread in the early universe.

During the first roughly 380,000 years after the big bang, space was filled with a plasma of free protons, electrons and light. At around 380,000 years, though, the cosmos cooled enough that electrons could combine with protons to form neutral hydrogen atoms for the first time. Before then electrons had zoomed freely through space, and light couldn't travel far without hitting one. Afterward the electrons were bound up in atoms, and light could flow freely. That initial release of light is what we observe as the CMB today.

During those first 380,000 years, small changes in the density of the electron-proton-light plasma that filled space spread as sound waves, just as sound propagates through the air in a room. The precise origin of these sound waves has to do with quantum fluctuations during the very early universe, but we think of them as noise left over from the big bang. A cosmological sound wave trav-

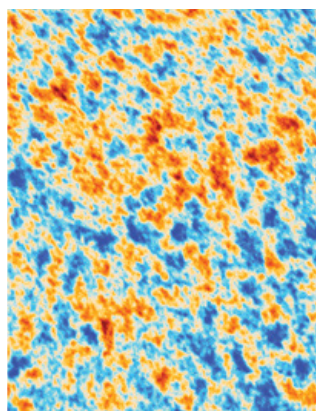
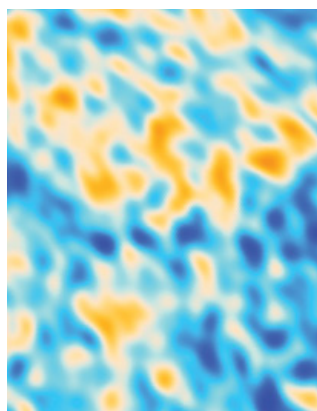
METHOD 2: COSMIC MICROWAVE BACKGROUND MEASUREMENTS

The CMB light is mostly uniform but contains small variations in temperature from point to point. A pattern in these variations reflects how far sound waves could spread when the CMB was created, which in turn can be used to figure out how far the CMB has traveled to reach us. This information, combined with the standard model of cosmology, predicts the Hubble constant. Increasingly sharp observations of the CMB, from the WMAP satellite in 2012 to the Planck spacecraft in 2018, have provided increasingly precise estimates of the constant.



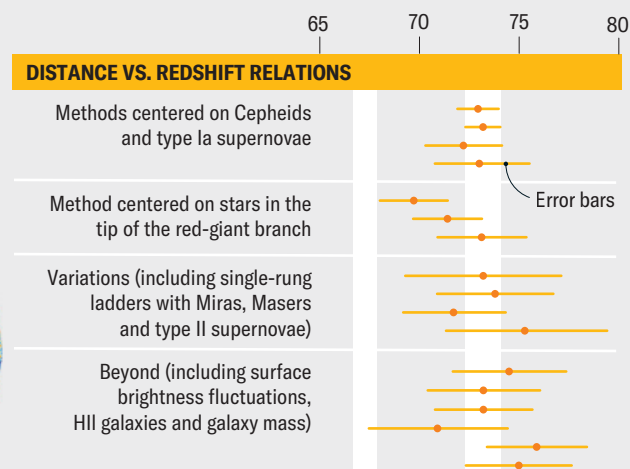
WMAP Census

Planck Census

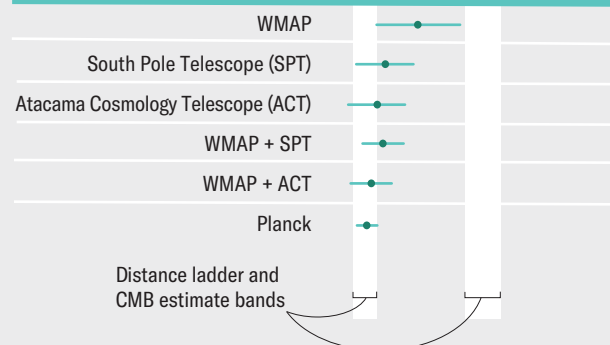


A Sampling of Hubble Constant Estimates, Organized by Measuring Method

Kilometers per second per 3.26 million light-years



COSMIC MICROWAVE BACKGROUND MEASUREMENTS



RESULTS

Over the years the distance ladder measurements of the Hubble constant have converged at a value of 73 ± 1 kilometers per second per megaparsec (km/s/Mpc). The CMB method, on the other hand, gives an estimate of 67.5 ± 0.5 km/s/Mpc. The two values are too far apart to explain. Perhaps there is some overlooked error in the methods, or maybe they are telling us our cosmological model is incomplete.

els a distance determined by the speed of sound in a medium multiplied by the time since the big bang; we call this distance the sound horizon. If there happened to be a particularly “loud” spot somewhere in the universe at the big bang, then it will eventually be “heard” at any point that is a sound horizon away. When the CMB light was released at 380,000 years, it was imprinted with the intensity of the soundscape at that point. The one-degree scale correlation in the CMB intensity thus corresponds to the angular size of the sound horizon at that time.

That scale is determined by the ratio of the sound horizon to the distance to the “surface of last scatter”—essentially, how far light has traveled since it was freed when the CMB was released (the moment electrons were all bound up in atoms, and light could travel freely for the first time). If the expansion rate of the universe is larger, then that distance is smaller, and vice versa.

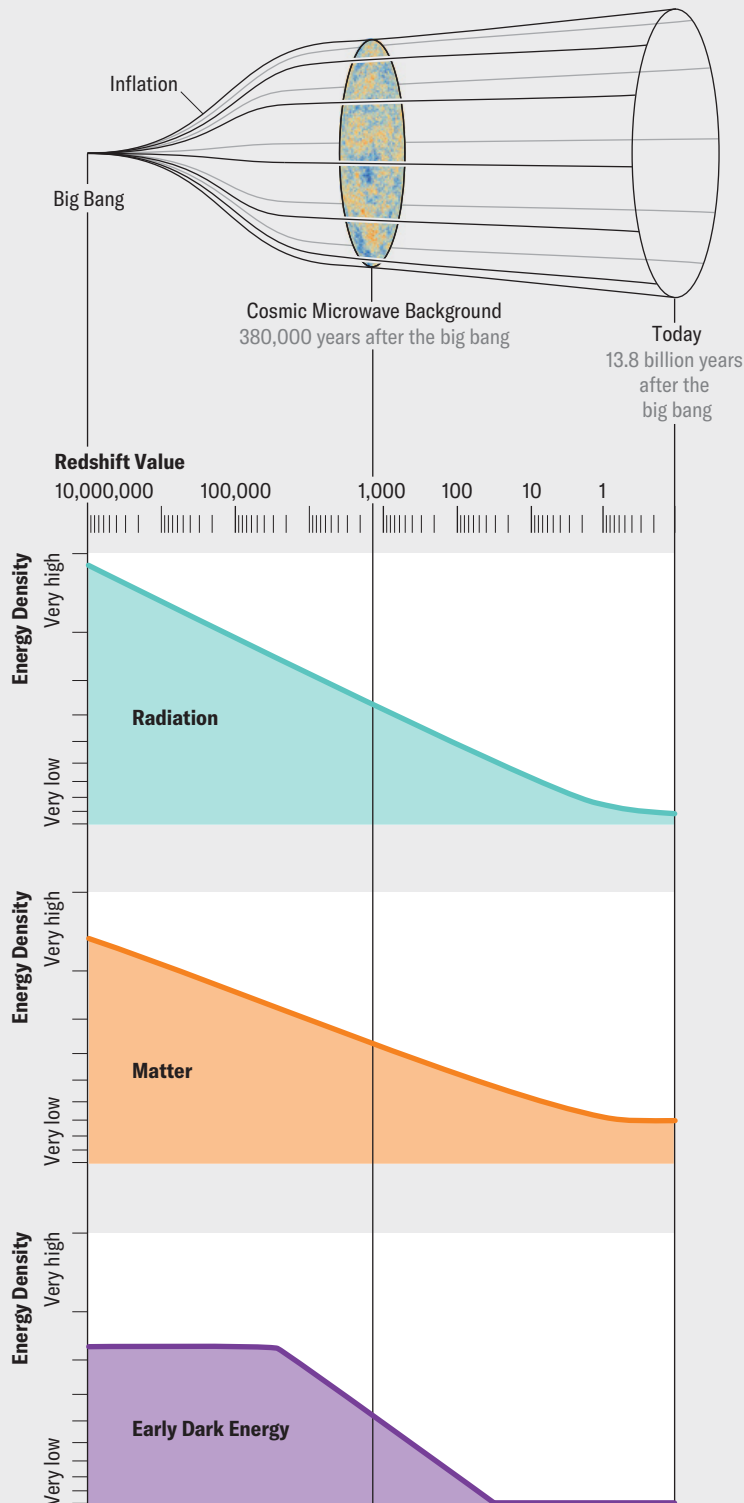
Astronomers can therefore use the measurement of the sound horizon to predict the current rate of the

universe’s expansion—the Hubble constant. The standard model of cosmology predicts a physical length for the sound horizon based on the gravitationally attracting ingredients of the early universe: dark matter, dark energy, neutrinos, photons and atoms. By comparing this length with the measured angular length of the horizon from the CMB (one degree), scientists can infer a value for the Hubble constant. The only problem is that this CMB-inferred value is smaller, by about 9 percent, than the number we obtain by using supernovae.

HAD THE CMB-INFERRED VALUE turned out to be larger than the local value, we would have had a fairly obvious explanation. The distance to the surface of last scatter also depends on the nature of dark energy. If the dark energy density is not precisely constant but decreases slowly with time (as some models, such as one called quintessence, propose), then the distance to the surface of last scatter will be decreased,

Early Dark Energy

One way to reconcile the differing measurements of the Hubble constant is to add an extra component to the universe. One example is “early dark energy,” a hypothetical field spread throughout space. When the universe was young, this field would have had a large energy density and a strong effect on space, causing it to expand faster than it otherwise would have. Today, though, its energy density would be much smaller and its effects negligible.



bringing the CMB-based value of the Hubble constant down to the value observed locally.

Conversely, if the dark energy density were slowly increasing with time, then we would infer from the CMB a larger Hubble constant, and there would be no tension with the supernova measurements. Yet this explanation requires that energy somehow be created out of nothing—a violation of energy conservation, which is a sacred principle in physics. Even if we are perverse enough to imagine models that don't respect energy conservation, we still can't seem to resolve the Hubble tension. The reason has to do with galaxy surveys. The distribution of galaxies in the universe today evolved from the distribution of matter in the early cosmos and thus exhibits the same sound-horizon bump in its correlations. The angular scale of that correlation also allows us to infer distances to the same types of galaxies that host supernovae, and these distances (using the same sound horizon as employed for the CMB) give us a low value of the Hubble constant, consistent with the CMB.

We're left to conclude that “late-time” solutions for the Hubble tension—those that attempt to alter the relation between the Hubble constant and the distance to the CMB surface of last scattering—don't work or at least are not the whole story. The alternative, then, is to surmise that there may be something missing in our understanding of the early universe that leads to a smaller sound horizon. Early dark energy is one possibility.

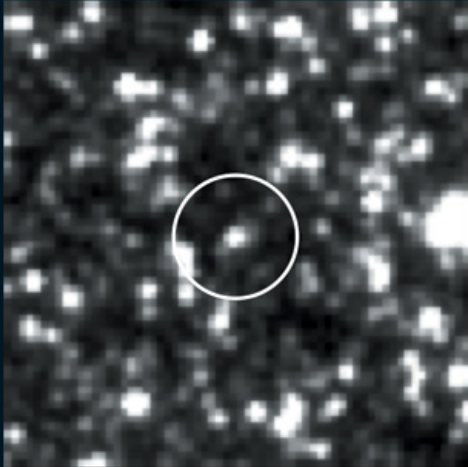
KAMIONKOWSKI AND HIS THEN GRADUATE student Tanvi Karwal were the first to explore this idea in 2016. The expansion rate in the early universe is determined by the density of all the matter in the cosmos at the time. In the standard cosmological model, this includes photons, dark energy, dark matter, neutrinos, protons, electrons and helium nuclei. But what if there were some new component of matter—early dark energy—that had a density roughly 10 percent of the value for everything else at the time and then later decayed away?

The most obvious form for early dark energy to take is a field, similar to an electromagnetic field, that fills space. This field would have added a negative-pressure energy density to space when the universe was young, with the effect of pushing against gravity and propelling space toward a faster expansion. There are two types of fields that could fit the bill. The simplest option is what's called a slowly rolling scalar field. This field would start off with its energy density in the form of potential energy—picture it resting on top of a hill. Over time the field would roll down the hill, and its potential energy would be converted to kinetic energy. Kinetic energy wouldn't affect the universe's expansion the way the potential energy did, so its effects wouldn't be observable as time went on.

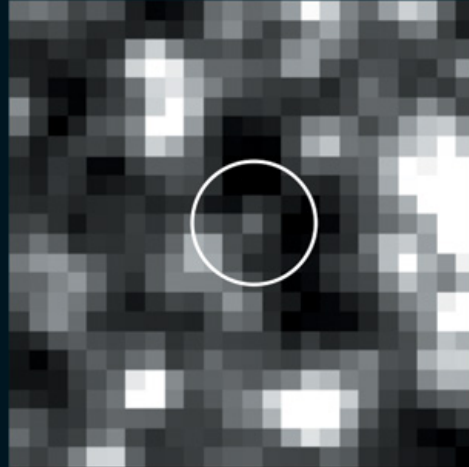
A second option is for the early dark energy field to oscillate rapidly. This field would quickly move from potential to kinetic energy and back again, as if the field were rolling down a hill, into a valley, up another hill and then back down again over and over. If the starting

ESA and the Planck Collaboration (CMB image)

Webb Near-IR



Hubble Near-IR



Side-by-side photographs of a Cepheid star in NGC 5468, a galaxy at the far end of the Hubble Space Telescope's range, as taken by the James Webb Space Telescope (JWST) and the Hubble, show how much sharper the new observatory's imaging is. The JWST data confirmed that distance measurements from Hubble were accurate, despite the blurring of Cepheids with surrounding stars in the Hubble data.

potential is chosen correctly, then the average leads to an overall energy density with more potential energy than kinetic energy—in other words, a situation that produces negative pressure against the universe (as dark energy does) rather than positive pressure (as ordinary matter does). This more complicated oscillating scenario is not required, but it can lead to a variety of interesting physical consequences. For instance, an oscillating early dark energy field might give rise to particles that could be new dark matter candidates or might provide additional seeds for the growth of a large cosmic structure that could show up in the later universe.

After their initial suggestion of early dark energy in 2016, Kamionkowski and Karwal, along with Vivian Poulin of the French National Center for Scientific Research (CNRS) and Tristan L. Smith of Swarthmore College, developed tools to compare the model's predictions with CMB data. It's hard to depart much from the standard cosmological model when we have such precise measurements of the CMB that so far match the model very well. We figured it was a long shot that early dark energy would actually work. To our surprise, though, the analysis identified classes of models that would allow a higher Hubble constant and still fit the CMB data well.

This promising start led others to create a proliferation of variants of early dark energy models. In 2018 these models fared about as well as the standard model in matching CMB measurements. But by 2021 new, higher-resolution CMB data from the Atacama Cosmology Telescope (ACT) seemed to favor early dark energy over the standard model, which drew even more scientists toward the idea. In the past three years, however, more measurements and analysis from ACT, as well as from the South Pole Telescope, the Dark Energy Survey and the Dark Energy Spectroscopic Instrument, led to more nuanced conclusions. Although some analyses keep early dark energy in the running,

most of the results seem to be converging toward the standard cosmological model. Even so, the jury is still out: a broad array of imaginable early dark energy models remain viable.

Many theorists think it may be time to explore other ideas. The problem is that there aren't any particularly compelling new ideas that seem viable. We need something that can increase the expansion of the young universe and shrink the sound horizon to raise the Hubble constant. Perhaps protons and electrons somehow combined differently to form atoms at that time than they do now, or maybe we're missing some effects of early magnetic fields, funny dark matter properties or subtleties in the initial conditions of the early universe. Cosmologists will agree that simple explanations continue to elude us even as the Hubble tension becomes more firmly embedded in the data.

To progress, we must continue to find ways to scrutinize, check and test both local and CMB-inferred values of the Hubble constant. Astronomers are developing strategies for gauging local distances to augment the supernova-based approaches. Measurements of distances to quasars based on radio-interferometric techniques, for instance, are advancing, and there are prospects for using fluctuations in galaxy-surface brightness. Others are trying to use type II supernovae and different kinds of red giant stars to measure distances. There are even proposals to use gravitational-wave signals from merging black holes and neutron stars. We are also intrigued by the potential to determine cosmic distances with gravitational lensing.

Although current results are not yet precise enough to weigh in on the Hubble tension, we expect to see great progress when the Vera C. Rubin Observatory and the Nancy Grace Roman Space Telescope come online. For now we have no good answers, but lots of great questions and experiments are underway. ●

FROM OUR ARCHIVES
The Puzzle of Dark Energy. Adam G. Riess and Mario Livio; March 2016. [Scientific American.com/archive](https://www.scientificamerican.com/archive)



Should We Abandon the Leap Second?

We have been adding “leap seconds” to time kept by our atomic clocks, but soon we may have to subtract one. Are the tiny adjustments worth the bother?

TEXT BY MARK FISCHETTI

ILLUSTRATION AND GRAPHICS BY MATTHEW TWOMBLY

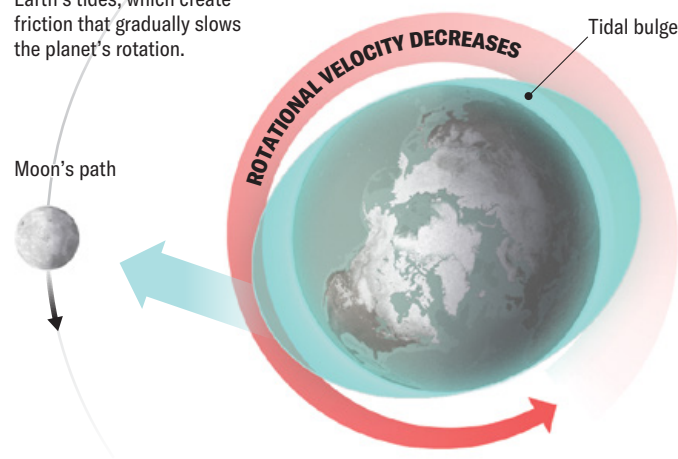
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and infographic designer
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clocks are off by a second or even off by one minute, which they are estimated to be a century from now if we do nothing until then? In our highly digitized world, does the exact length of the rotational day even matter?

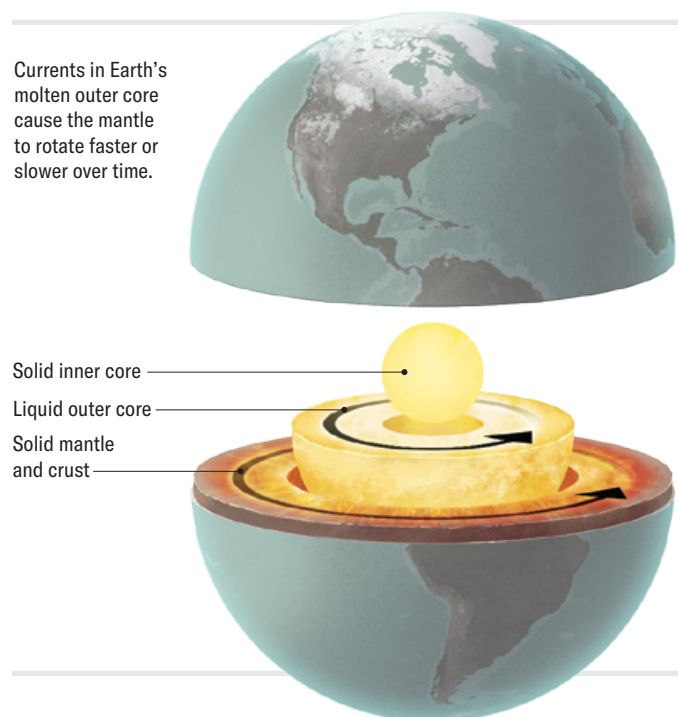
Earth rotates because our solar system condensed from a rotating cloud of gas and dust. Outer space provides virtually zero drag, so the planets, including Earth, just keep spinning. As Earth turns, the gravitational pull between it and the moon, and to a lesser degree the sun, creates ocean tides. As tides grind across the seafloor, they create friction, which gradually slows the planet's rotation. Back in the dinosaur era, a day was about 23.5 hours long; since then, tidal friction has extended it.

The gravitational pull of the moon and sun generates Earth's tides, which create friction that gradually slows the planet's rotation.



Studies of seismic waves show that Earth has a solid inner core and a liquid outer core, which are wrapped by a solid mantle and crust. Currents in the outer core cause the mantle to rotate faster or slower in any given year, but over centuries the changes tend to cancel out, making tidal slowing the prevailing trend.

Currents in Earth's molten outer core cause the mantle to rotate faster or slower over time.



LONG AGO WE HUMANS defined a day as the time it takes Earth to make one rotation about its axis, with one sunrise and one sunset. Our predecessors partitioned that day into 24 hours. But if Earth's rotation slows down a little, it takes a bit longer than one day to complete it. That has been happening for many years. Because the atomic clocks we use to pace everything from Internet communications to GPS apps to automated stock trades never slow down, global time-keepers periodically have added a leap second to the clocks to keep them in sync with Earth. Since 1972 we have made this awkward addition 27 times.

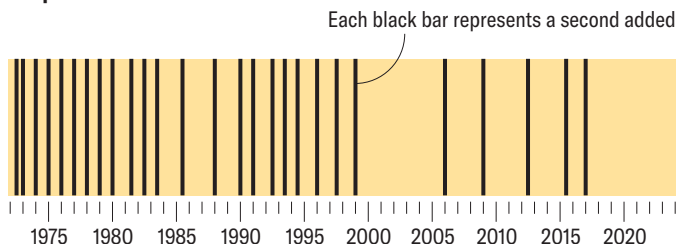
For the first time, however, we may have to subtract a leap second because since around 1990 Earth's rotation has been speeding up, counteracting the slowdown and shortening the day. There are two explanations for why, which I'll explain ... in a second.

The reversal has many people asking why we should bother with leap seconds at all. Each time an adjustment is needed, a mind-boggling number of computers and telecom operations have to be changed. On a regular day, the National Institute of Standards and Technology, which keeps atomic time for the U.S. and synchronizes most of the world's computers, receives more than 100 billion time-coordination requests from up to a billion computers. And leap-second adjustments can create problems. An addition in 2012 was blamed for Reddit suddenly going dark and for foiling operational systems at Qantas Airways, leading to long flight delays across Australia.

What if we just ignored the fact that Earth's rotation and atomic

Tidal slowing is consistent, but Earth's rotational speedup has been counteracting that trend, and the time between added leap seconds has been getting longer, from about a year in the 1970s to three or four years in the 2010s.

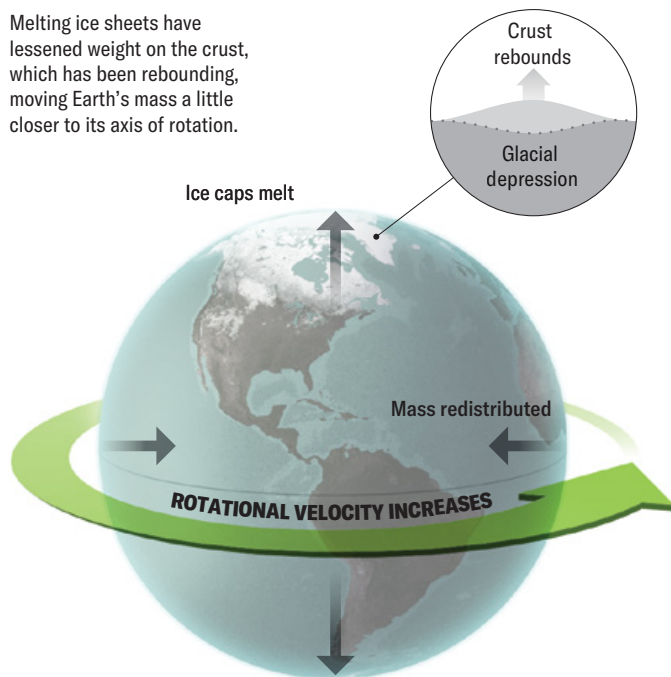
Leap Seconds Added Since 1972



Calculations indicated that by 2026 the ongoing speedup would overtake the slowdown, and we would have to subtract a leap second.

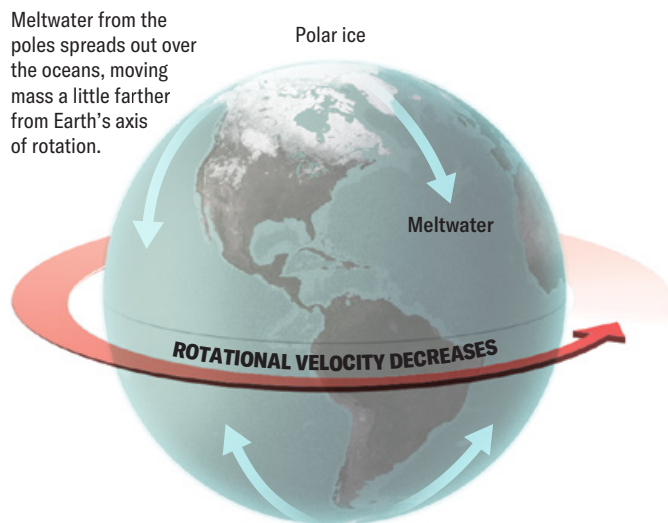
But now global warming is complicating that projection. As the massive ice sheets across the North and South Poles melted at the end of the most recent ice age, the weight of that ice decreased, and the crust that had been compressed underneath it began to rebound, which it is still doing today. That has made Earth more spherical. (The planet is not a perfect sphere; it's slightly wider around the equator.) The change in shape means Earth's overall mass is distributed a little closer to its axis of rotation, speeding its movement in the same way that ice skaters spin faster when pulling in their outstretched arms.

Melting ice sheets have lessened weight on the crust, which has been rebounding, moving Earth's mass a little closer to its axis of rotation.



As ice sheets warm, however, the meltwater spreads out across the global ocean, and most of the ocean is at lower latitudes, farther from the rotation axis than the ice caps are. That slows the spin (the skaters extending their arms outward). For now this effect is stronger, delaying how soon the rotational

speedup will overtake the tidal slowdown. According to a recent study, this counterforce means we won't have to subtract a leap second until 2029.



Given so many vagaries, it's reasonable to ask if we should add or subtract leap seconds at all. And because tidal slowing will always be the long-term trend, we may never again need to subtract a second, so why go through the trouble one time? Few computer programs are written to allow for a negative leap second.

Reverence for the rotational day may be the only reason to keep atomic time in sync with it. If the two time stamps diverge, "for most people, there are no real ramifications," says Duncan Carr Agnew, a geophysicist at the Scripps Institution of Oceanography, who wrote the 2024 *Nature* paper projecting a negative leap second in 2029. Rather than advocating for frequent and random adjustments of a second, Agnew favors the idea of waiting a century, then making one big adjustment because preparations could be made well ahead of time.

This idea has had support for a while. In 2022 parties to the international General Conference on Weights and Measures voted to stop making leap-second adjustments by 2035. After that, time-keepers might agree to a fix every 20 years or perhaps every 100. Whatever the choice, "we want consistency," says physicist Elizabeth Donley, chief of the time and frequency division at NIST. "Time is the most important unit in the international system of units; a lot of other standards depend on it."

Some large Internet providers already follow their own protocols. Rather than waiting for any leaps, Google "smears" its clocks by thousandths of a second once every day. Such independent efforts don't seem to cause any global discontinuities, but if more and more large entities start winging it, "that becomes anarchy," Donley says.

Waiting decades for a well-planned adjustment means astronomical (rotational) time, known as UT1, will diverge more widely from the coordinated universal time (UTC) that is based on atomic clocks. But Donley doesn't think problems will arise. "Computer networks," she says, "don't care where the sun is in the sky." ●

FROM OUR ARCHIVES

How Measuring Time Shaped History. Clara Moskowitz; ScientificAmerican.com, January 28, 2022. [ScientificAmerican.com/archive](https://www.scientificamerican.com/archive)

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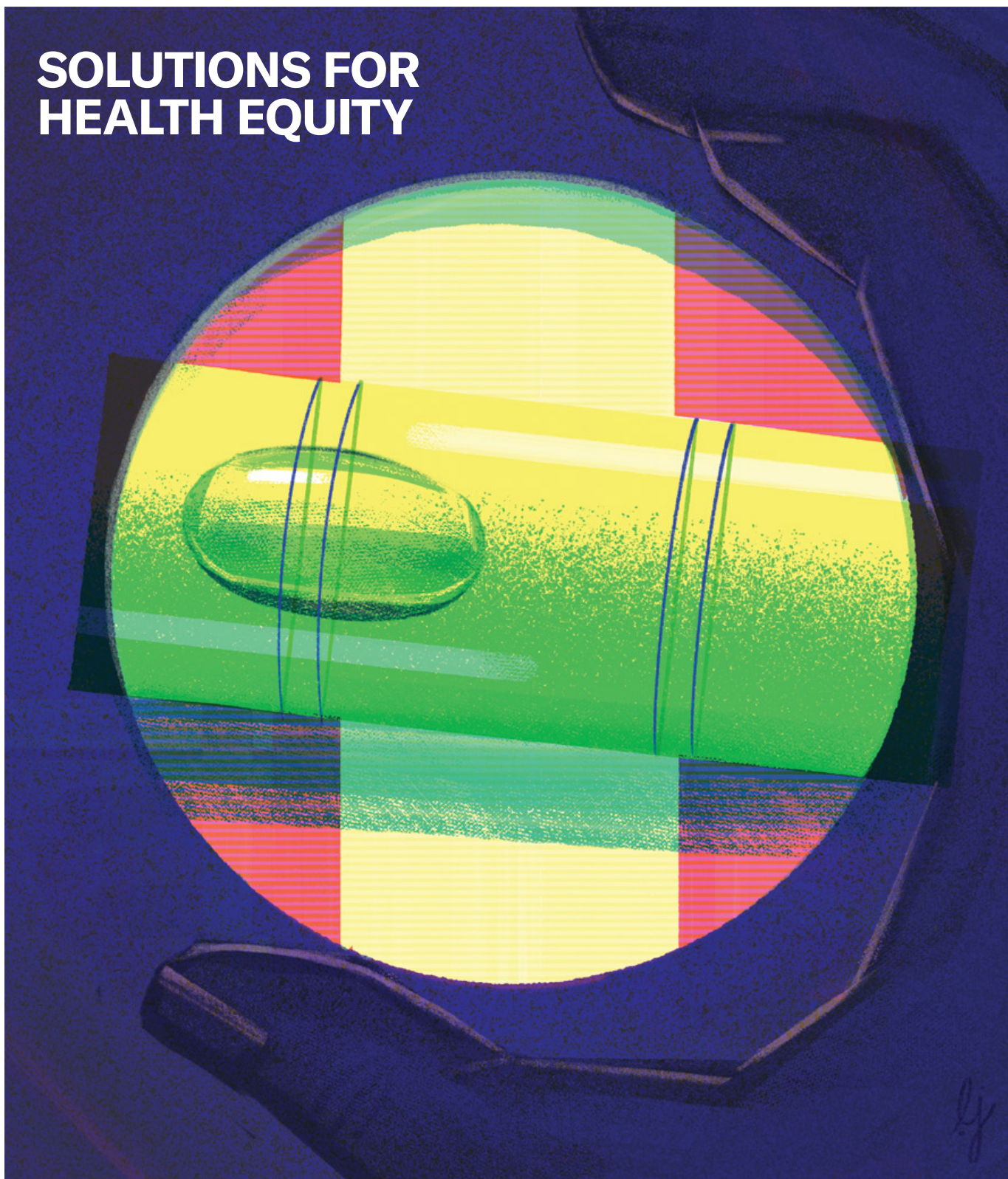
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INNOVATIONS IN

SOLUTIONS FOR HEALTH EQUITY



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SPECIAL REPORT

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BY CHARLES EBKEME

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Health Equity Progress

THE COUNTRY SOMEONE IS BORN INTO has a lifelong effect on their health. So does the neighborhood they live in, the color of their skin, their income and their level of social support. It's unjust. After centuries of persistent health disparities, researchers, advocates, clinicians and public health experts are finding ways to improve health for everyone.

New advances sometimes exaggerate inequities before helping reduce them. But there are reasons for optimism, which journalist Anil Oza shares on page S16. More than almost any other development, vaccines have advanced health equity around the world. They have averted 154 million deaths over the past 50 years, a life saved every 10 seconds, as health writer Tara Haelle explains on page S10, with graphics on pages S12–S13. Collaborative campaigns have brought this powerful preventive health care to children in even the most impoverished regions. Writer Carrie Arnold on page S6 shows how rural areas around the world are benefiting from other inventive and resourceful ways to deliver needed care—from telemedicine to micro clinics to a traveling dialysis bus.

Researchers are working to remove racial bias that has been built into diagnostics, and by doing so they're changing not just tools and algorithms but lives. As journalist Cassandra Willyard writes on page S3, some Black patients once deemed ineligible for new kidneys, despite having the same laboratory results as white patients, are now moving up the wait list for transplant; others with respiratory issues might be able to file for disability after previously being judged unqualified. Epidemiologists and other public health scientists are discovering that prior assumptions about race have lumped together disparate groups with different needs and health risks, particularly within Asian American communities [*see graphic on page S23*]. Now, by teasing apart the data, they are able to better diagnose, treat and even prevent disease. Health writer Jyoti Madhusoodanan on page S21 reveals how this data-driven approach is already saving lives.

Certain diseases and conditions have been used to justify discrimination, especially when the disease is more prevalent in a group that's already marginalized. The people most at risk for mpox, for instance, are men who have sex with men—a community already hit hard by HIV/AIDS. But as global health expert Charles Ebikeme writes on page S25, researchers, clinicians and community members have learned from past experiences and are building up existing networks and clinics that cater specifically to this stigmatized population. Even health-care communication is improving, writer Rod McCullom shares on page S18, as the movement toward culturally sensitive care helps clinicians better understand and empathize with their patients.

Improving health equity requires rethinking our global health infrastructure, and we are still at the beginning. But each solution adds support and begins to build a path toward justice.

—LAUREN GRAVITZ,
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Better Measures

New devices, formulas and tools are removing historical bias from medical diagnoses BY CASSANDRA WILLYARD

MELANIE HOENIG WAS TEACHING first-year medical students how to estimate kidney function when one of them, Cameron Nutt, raised his hand. Why, he asked, did the diagnostic algorithm include an adjustment for Black patients? In the U.S., Black people have higher rates of kidney disease and kidney failure and are less likely to get

a kidney transplant than white people, but the adjustment makes it seem as though Black people have *better* kidney function than people of other races who have the same test results.

Good question, thought Hoenig, a kidney specialist at Beth Israel Deaconess Medical Center in Boston. She had never

wondered why this might be. “I said, ‘You’re right. That doesn’t make any sense,’” Hoenig recalls of the 2016 classroom conversation.

This value for kidney function, called the estimated glomerular filtration rate (eGFR), helps doctors figure out when to send patients to a specialist, when to start dialysis, when they are eligible to join the wait list for a kidney transplant, and where their name lands on that list. Adjusting the algorithm for Black patients decreased their chances for treatment and transplant.

The equations and instruments doctors

rely on are infused with historical bias. Medicine has long treated race as though it provides important information about the underlying biology and genetics of disease, a strategy that has had an enormous impact on diagnosis and treatments. People have been passed over for kidney transplants, denied therapies and diagnosed with diseases later than necessary simply because of the color of their skin.

Race is a social construct that reveals little about ancestry. There is more genetic variation within racial groups than between them. “The racial differences found in large datasets most likely often reflect effects of racism—that is, the experience of being Black in America rather than being Black itself,” researchers wrote in a 2020 *New England Journal of Medicine* article outlining the dangers of race-adjusted algorithms.

To undo this bias, researchers are changing the algorithms and instruments and finding new models to reduce disparities.

KIDNEYS FILTER WASTE and excess water from the blood through tiny structures called glomeruli. Directly measuring how well these glomeruli are functioning is possible but cumbersome, so instead doctors rely on blood levels of a protein called creatinine, a waste product produced by muscles and a by-product of protein metabolism, to estimate the glomerular filtration rate (GFR). When kidneys are working well, they filter out creatinine; if the kidneys start to fail, creatinine levels rise. The protein is easy and inexpensive for laboratories to measure.

The first equation to assess kidney function, developed in the 1970s, relied on age, sex, weight and creatinine levels in the blood. But the formula wasn’t precise. So, in the late 1990s, a team of researchers set out to develop a more accurate one. They used existing data from a study of creatinine and GFR in more than 1,600 people, then correlated the two measurements. The team looked at 16 different factors that might influence the relationship. (We tend to lose muscle mass as we age, for example, so older people have lower creatinine levels than younger people.) The authors noted that for any given GFR, creatinine was higher in Black people than in white people. Why that might be wasn’t clear. Maybe it was because Black people had higher muscle mass, they

speculated. The study population was only 12 percent Black, yet the difference felt too substantial to ignore.

To account for this difference, the researchers added an adjustment for Black patients: a multiplication factor of up to 1.21, which essentially inflated their estimated kidney function by as much as 21 percent. In 2009 the researchers published an updated equation, but the Black correction factor remained, albeit lower, up to 1.16. “We always recognized that race was not the biological process by which African Americans differed from non-African Americans in the relationship between GFR and creatinine,” Andrew Levey, who worked to develop both equations, later explained. But “it stood in for something that was important.”

“The way the lab report was written was, if your creatinine is a 4.0, your kidney function is 19 percent. Oh, unless you’re African American; then it’s 22 percent,” says Martha Pavlakis, a nephrologist at Beth Israel Deaconess. “It makes no sense.” In people with healthy kidneys, small differences don’t matter. But when kidney function declines, eGFR, which decreases as blood creatinine levels rise, becomes crucial. That number helps to determine whether a patient is referred to a nephrologist, diagnosed with kidney disease or deemed eligible to join the wait list for a kidney transplant.

Hoening began working with a small group of students from Harvard Medical School’s Racial Justice Coalition to lobby to eliminate the correction factor, and in 2017 Beth Israel Deaconess became the first medical center to do so. Efforts elsewhere largely stalled until the deaths of George Floyd, Ahmaud Arbery and Breonna Taylor, three Black Americans whose deaths made national news. In the wake of their killings, conversations about race rippled throughout the medical community, Pavlakis says.

As protests erupted across the country, medical students and faculty at many major universities began to circulate petitions calling for an end to the use of the racial correction in eGFR. Some major academic health systems began removing race from the equation, but their approaches were inconsistent. Neil Powe, chief of medicine at Zuckerberg San Francisco General Hospital and Trauma Center, and other experts watched the changes unfold with concern. There was no

unified way of diagnosing kidney disease. “You could be at one hospital and have a diagnosis of kidney disease. You go down the street [to another hospital], and you wouldn’t have kidney disease,” Powe says. “That was just chaos.”

In the summer of 2020 the National Kidney Foundation and the American Society of Nephrology formed a task force to assess how best to move forward. “They thought we’d solve it overnight, but it took us about 10 to 11 months to churn through this,” says Powe, who co-led the task force. Ultimately they chose an equation that used the same 2009 data but eliminated race as a variable, then refit the curve to the whole dataset.

A conversation about race was also happening at the Organ Procurement and Transplantation Network (OPTN), which manages transplants from deceased donors. The wait list for a kidney is long. Patients aren’t eligible to join until they meet certain criteria; these can vary at different transplant centers, but all candidates must have an eGFR of 20 percent or less. And because of the eGFR correction factor, Black patients needed higher creatinine levels than people of other races to pass that threshold. “Nobody who came up with the formula was like, let’s keep Black people off the list. But that, in fact, was the result,” Pavlakis says.

In July 2022 the race variable was explicitly forbidden in organ allocation. Pavlakis saw that as just the first step. She wanted to help Black patients already on the list and those who had previously been denied entry because of their kidney function numbers.

In January 2023 the OPTN decided that transplant centers should look back at the lab reports of Black patients on the list and recalculate their eGFR using the race-neutral equation to see whether they should have been referred for transplant. “Basically, half the Black patients on the transplant list got extra priority added to their standing because of this project,” Pavlakis says.

Pavlakis acknowledged that this change doesn’t fix every disparity in kidney allocation. But she also sees it as restorative justice. “It’s not perfect,” she says, but “I think it’s probably the largest example of fixing a race disparity that is out there.”

PULMONOLOGISTS have been grappling with a similar problem. To assess lung function, doctors ask patients to blow into a de-

vice called a spirometer, which measures the maximum amount of air a person can exhale and how much they can force out of their lungs in a single second. The spirometer compares those numbers with reference values for “normal” lung function. The results help doctors diagnose diseases such as emphysema and chronic obstructive pulmonary disease, assess severity of those conditions and monitor declines in lung function.

What constitutes “normal” varies by age, sex, height and, until recently, race. Why race? Data collected in the late 1800s and early 1900s suggested different races have different lung capacities, a phenomenon researchers ascribed to innate biology rather than social, economic or environmental factors. By the early 20th century the idea that lung capacity varied among racial groups was “an ostensible fact,” wrote Brown University researcher Lundy Braun in a 2015 article on the historical use of race in spirometry. What experts missed was that race was probably a proxy for other factors, such as air quality, nutrition, and other exposures, that affect lung health and development.

When the European Respiratory Society’s Global Lung Function Initiative developed reference values for spirometry in 2012, it used more than 160,000 spirometry results from 33 countries. Researchers observed “proportional differences in pulmonary function between ethnic groups” and decided to develop separate values for four groups: Caucasian, African American, North Asian and Southeast Asian. They also used an “other” category for people who didn’t fit elsewhere. The model assumes that, compared with white adults, Black adults have about 10 to 15 percent smaller lung capacity and that adults of Asian ancestry have 4 to 6 percent smaller lung capacity. So the same spirometry results in Black, Asian and white people led to different interpretations of health. As a result, lung diseases in certain populations have gone undiagnosed and untreated.

The division of reference values by race is problematic for many reasons. “We’re a big melting pot,” says Alexander Niven, a pulmonologist at the Mayo Clinic in Minnesota. So even if there were “a specific cluster of genes that predispose people to greater or less lung function, that’s highly unlikely to remain a pure cluster in this global world.”

What’s more, lungs are in constant con-

“Half the Black patients on the transplant list got extra priority added to their standing because of this project.”

—Martha Pavlakis *Beth Israel Deaconess Medical Center*

tact with the outside world and continue developing throughout childhood and into early adulthood, Niven says. “It’s impossible to separate race from all of these other factors that unfortunately are inexplicably linked to different populations within our society, many of which are likely coloring the changes in lung function that we see in different social groups.”

In practice, the race-based model doesn’t seem to improve predictions when it comes to outcomes that matter. “You can’t tell any better who’s going to go to the hospital. You can’t tell any better who’s going to die. You can’t tell any better who has severe symptoms and who doesn’t. And in some of those cases, you actually worsen your ability to predict by adding race,” says Aaron Baugh, a pulmonary and critical care physician at the University of California, San Francisco.

In 2023 the Global Lung Function Initiative replaced race-based equations with a race-neutral equation. That same year the American Thoracic Society and the European Respiratory Society recommended all health-care providers switch to the new formula.

That shift is happening now, and researchers are just beginning to uncover the broad impact of this change. “Long story short, it’s profound,” says Arjun Manrai, a bioinformatics researcher at Harvard Medical School. Lung function helps to determine disability payments, candidacy for some professions, priority for lung transplants, and more. Manrai and his colleagues found that some 10 million people in the U.S. would have their diagnosis or the severity of their disease reclassified. Disability payments could increase by more than \$1 billion. Such changes are not always beneficial. A new diagnosis can make someone ineligible for certain jobs, such as firefighting. And a Black person with lung cancer might not be identified as a good candidate for surgery because their lung function may be too poor to allow for removal of part of their lung. “There are trade-offs essentially attached to these reclassifications,” Manrai says.

The new equation comes from the same 2012 data as the original formula, and it isn’t perfect. “We kind of settled on the race-neutral equations we have now as the best current option, knowing that in the future, something better might arise,” Baugh says.

MANRAI THINKS A LOT about how traditional algorithms operationalize race, adjusting what constitutes “normal” for any particular patient, and how lessons from those algorithms can be incorporated into producing more sophisticated machine-learning algorithms. “They can be biased, and they can propagate the very same sort of race-based medicine,” he says. “But they’re a tool, and the tool can also be used in the reverse direction: to mitigate existing disparities and to potentially reduce existing biases in the health-care system.”

One example of how AI might help improve health equity is evident in research on disparities in knee pain. Previous studies have shown that Black people routinely report more intense knee pain from arthritis than people of other races. But often that pain can’t be explained by the structural damage visible in x-rays. As a result, it is often dismissed or attributed to external factors such as psychological stress.

Emma Pierson, who studies machine learning and health-care inequities at Cornell University, and her colleagues wanted to understand whether there might be physical signs in the knee itself that could explain this pain disparity. They used knee radiographs and patient pain scores from more than 4,000 people who had osteoarthritis or were at risk of developing it to train a machine-learning model.

Surprisingly, the model predicted pain better than the traditional arthritis scoring system. Specifically, Pierson says, “it seems to be picking up on factors that disproportionately affect underserved patients.” What those factors might be isn’t clear, and Pierson emphasizes a need for caution. “In general, the capabilities of these models tend to out-

strip our ability to understand how they're achieving those capabilities," she says.

SOMETIMES DIAGNOSTIC INSTRUMENTS introduce bias. The fingertip clamps doctors use to measure oxygen levels in the blood, for example, work by measuring the absorption of different wavelengths of light to estimate the blood oxygen level. But the device, called a pulse oximeter, tends to overestimate oxygen saturation in people with darker skin tones.

Researchers have known about this problem for decades, but manufacturers didn't feel much pressure to fix the problem. The effect was relatively minor, and it was most prominent at low oxygen saturations. "That difference was probably correctly assumed to not be physiologically relevant," says Michael Lipnick, an anesthesiologist at the University of California, San Francisco, who leads a research project to assess pulse oximeter performance. "If somebody's oxygen saturation is really 1 percent or even 2 percent higher or lower than the real value, there's no harm."

When the COVID pandemic sickened millions of people, however, small biases had an outsize effect. "Clinical decisions were being made based on that number," Lipnick says. In 2023 a team of researchers looked at health records from more than 24,000 people hospitalized with COVID during the first 19 months of the pandemic. They zeroed in on those who had both a pulse oximeter reading and an arterial blood gas test, the gold standard for measuring oxygen saturation in the blood. Pulse oximeter readings consistently overestimated oxygen levels in Black and Hispanic patients. Black patients were also more likely than white patients to have their need for COVID therapy underestimated because of inaccurate pulse oximeter readings. Such oversight has clinical consequences: being passed over for COVID treatment resulted in an hour's delay in care on average and a higher risk of readmission.

Lipnick is part of the Open Oximetry Project, which has been testing different pulse oximeters in diverse groups to get a sense of their real-world performance. He and his colleagues have seen a range of variability. Most devices tended to perform worse when used on people with darker skin pigment, but some performed better.

Researchers are working to develop more accurate tools, and regulators are considering larger test populations with a variety of skin tones. Lipnick wants better pulse oximeters but worries that some of the fixes may increase costs. "It's a big concern, especially in low- and middle-income countries, where the majority of the world's people with darker skin pigment live," he says.

In the short term, Lipnick says, clinicians should rethink how they use data from pulse oximeters. "It gives a number, and we assume that that number is truth." In reality, the number might be off by as much as 5 percent. If doctors recognize the error rate, they can make decisions that aim to minimize health-care disparities. "I think a lot of the solution will lie

in how we use the technology," he says.

Pavakis also sees a need for more critical thinking on the part of clinicians. She is dismayed at the number of years that she relied on the eGFR equation without stopping to carefully consider the rationale for its race correction. "When we were taught this formula, we were like, 'This is data-driven. This is from a research study. This must be accurate,'" she says. Evidence-based, however, doesn't always mean equitable, and that's the real goal. Hoenig's students and other people who recognized bias are making health care better for all.

Cassandra Willyard is a science journalist based in Madison, Wis. She covers public health, medicine, and more.

Rural Prescriptions

Some of the most innovative solutions for health care come from rural regions around the world BY CARRIE ARNOLD

ON A FRIGID WINTER EVENING about five years ago, a desperately ill young woman walked through the doors of the Sanford Bemidji Medical Center in rural Minnesota. Several weeks before, she had labored alone for hours in her tiny mobile home to bring a new baby into the world. The woman had received no prenatal care and no medical attention at delivery—the kind of situation that has made maternal mortality rates for Native American women in rural areas twice as high as those of white women. The only reason she was showing up now was that the baby wasn't eating. She had no running water to make formula. The hospital was her only option. Johnna Nynas, the obstetrician on call, quickly diagnosed her patient with postpartum preeclampsia, a rare condition that affects people after pregnancy and can be deadly if untreated.

For Nynas's pregnant patients, the hospital in Bemidji is the only option between Duluth, Minn. (three hours away), and Fargo, N.D. (2.5 hours away). The surrounding area is one of the poorest in Minnesota. Some residents of the nearby Leech Lake, Red Lake and White Earth Indian Reservations don't have reliable access to running water. With so many pressing un-

met needs, people find it difficult to get prenatal care. Transportation (especially in winter) and child care for medical visits that require a several-hour car ride and possibly an overnight hotel stay are often unaffordable, even if Medicaid covers the cost of the health care. Nynas, who was born and raised in rural Minnesota, says that by the time an expectant parent arrives in her office, they may have a list of health concerns that have gone untreated for years. She links this lack of care directly to the elevated risk of pregnancy-related deaths and complications in the region.

"When we first meet patients, it's probably the first contact they've had with the health-care system in quite some time," Nynas says. Haunted by her patient's preeclampsia emergency, she set out to remove barriers to needed care. Loaned blood pressure cuffs and bathroom scales let many of her low-risk patients receive checkups over the phone. This communication made it easier to schedule in-person visits for ultrasounds and blood tests.

David Driscoll, director of the Healthy Appalachia Institute at the University of Virginia, isn't surprised that the impetus for change began in a rural area. The regions

that face staggering health inequalities are developing innovative solutions to enhance well-being for everyone. Rural communities' perpetual need to do more with less and to overcome obstacles not found elsewhere has led to modernized care delivery. Although many of the innovations are tech-centric, not all require Internet access to work. These shifts are helping doctors bring world-class medical care to even the most far-flung patients.

ONE CHALLENGE for rural health experts is to ensure solutions don't exacerbate existing disparities. Doctor visits via a video call won't help someone without an adequate Internet connection, for example. But advocates say thoughtful action paired with infrastructure investment will broaden access to services.

Simple equipment sent home with low-risk pregnant patients helped Nynas's northern Minnesota families deliver healthy infants. Nynas's success with home devices such as bathroom scales, blood pressure cuffs and fetal heart-rate monitors convinced her to expand her reach. Collaborating with several local community groups, Nynas applied for a grant from the federal government's Rural Maternity and Obstetric Management Strategies program. With this funding, Nynas was able to not only expand patients' virtual care but also provide additional local resources, such as an in-hospital food pantry, transportation services and a visiting-nurses program. She is setting up a satellite clinic at an Indian Health Service facility, which typically has limited prenatal services. This approach will let patients without home Internet or phones upload their data and connect with nearby providers in consultation with remote experts for complex pregnancies.

Health-care micro sites such as these act as a bridge between major medical centers and small communities and are showing huge promise in rural health, says Michael Carney, interim provost at the University of Wisconsin-Eau Claire, because they combine the best of telemedicine and in-person care. Patients without broadband Internet can go to a local clinic and talk to a specialist online. Nurses and other providers at the local clinic can do bloodwork, measure vital signs and nurture the doctor-patient relationship. These micro sites are the flagship

of the University of Wisconsin's ongoing rural health partnership with the Mayo Clinic, Carney says, and are intended to bolster the health of his hometown. Carney says practitioners worldwide are asking, "How do we deliver health care in a cost-effective way to people who can't come to a traditional clinic?"

IN SOUTHWESTERN VIRGINIA, where Driscoll grew up, the distances between two points aren't that far as the crow flies. But the residents of the area's tiny towns and hollers aren't crows. The narrow, winding roads mean even seemingly short drives can take hours. Without public transportation, many of the area's older adults can't travel to medical appointments. Driscoll's first job, in the 1990s, was with a community organization that drove local patients to clinics and hospitals.

Driscoll chatted with his passengers, listening to their problems. Many said the doctor's visit they were headed to was their first in years because they had been physically unable to get to appointments. Multiple, untreated chronic diseases such as asthma, diabetes and hypertension were the rule, not the exception. With poverty rates high and grocery stores few and far between, most of his passengers experienced food insecurity, and their diets lacked fresh fruits and vegetables. The few people who had home Internet relied on dial-up because broadband wasn't available yet.

Rural communities in Virginia and around the world face many of the same challenges—lack of clean drinking water, unreliable transportation, lagging investments in infrastructure and technology, and hospital and clinic closures. Driscoll's conversations revealed precisely how those challenges contribute to health disparities. It sparked his lifelong interest in rural health and ultimately brought him back home to the rugged hills where Virginia disappears into Tennessee and Kentucky.

Today, with a \$5.1-million federal grant, Driscoll is addressing problems that have been amplified by the COVID pandemic. According to one study, so-called diseases of despair, including opiate misuse and overdose, suicide and alcohol-related liver disease, spiked by 40 percent in central Appalachia during the beginning of the pandemic. As a result, the number of prema-

ture deaths in Appalachia is 25 percent higher than in the rest of the U.S.

Like many rural health programs, the efforts at the University of Virginia rely extensively on telehealth. That's largely because in the mid-1980s, awareness of these kinds of health disparities (and their origins) dovetailed with emerging technological breakthroughs. As a policy analyst at the Virginia Department of Health, Kathy Wiberly was tasked with helping to address deficits in health-care access in rural parts of the state. One of the solutions that emerged was the potential for telemedicine. Many of the region's small, rural hospitals didn't have the patient volume to warrant hiring, say, a neurologist or a neonatologist. Very sick newborns or people experiencing a potential stroke would have to be sent by ambulance or helicopter to a large medical center, often hours away. Such delays in care can prove deadly. "With stroke, time is precious. You're saving the brain," Wiberly says.

Instead of moving patients, Wiberly began working to connect small hospitals with their large, urban counterparts via videoconferencing and other technologies. Rural physicians could consult with on-call specialists in distant parts of the state to stabilize or manage fragile patients. This approach, she says, "saved lives and saved brains and saved disability further down the road." In 2019 [more than one quarter of U.S. hospitals](#) had the capacity for telehealth-based stroke care.

After some initial success, Wiberly began trying to expand telehealth access. Her biggest problem, however, wasn't related to technology. It was convincing patients, insurers and especially physicians that the approach could work. Few doctors have received telemedicine training during their residencies and internships, then or now, Wiberly says. They learn to see patients in person—that's the model they're trained with and used to.

"Yet at the same time, the landscape has changed," Wiberly says. Medicine is no longer strictly an in-office practice. COVID accelerated the adoption and acceptance of telemedicine, and it has become a mainstay of rural health care, she says, especially in behavioral health care and psychiatry.

Telehealth alone can't fix all the health problems facing rural areas. Limited broadband access means not everyone can

set up a video chat with their doctor. And a lot of medical care requires in-person visits and readily available providers—things that aren't guaranteed as rural hospitals continue to shrink or close. To tackle these issues, providers have gotten creative.

A DIAGNOSIS OF KIDNEY FAILURE is life-altering. For residents of the remote Australian outback, it can be doubly so. The Pintubi people returned to Kintore, around 500 kilometers west of Alice Springs in the Northern Territory, in the 1980s after forced displacement by the Australian government starting in the 1940s. Those who needed dialysis had to leave again to receive care at the nearest clinics in Alice Springs or Darwin. Indigenous peoples such as the Pintubi make up almost 4 percent of Australia's population and more than 14 percent of people on dialysis in the country. In 2016 research showed that Aboriginal people's kidneys reached end-stage failure decades sooner than the kidneys of non-Indigenous Australians and New Zealanders, and an earlier study had found they were 1.5 times more likely to die on dialysis. For those who survived, quality of life was low.

Aboriginal Australians wanted to be “on country”—to live in their ancestral homelands with loved ones—while on dialysis. When the Australian government rebuffed their requests, Indigenous artists auctioned their work to raise more than \$1 million (AUD) to build a nonprofit dialysis clinic, Purple House, in Kintore.

But bringing dialysis to an area where sheep overwhelmingly outnumbered people wasn't an easy proposal. What's more, dialysis is a thirsty procedure, using hundreds of liters of water for a single week's treatment. Such a water-intensive therapy is ill-suited to the outback, which contains some of the driest biomes in the world. Purple House CEO Sarah Brown, who was tapped to lead the organization after a long career as a bush nurse, needed a therapy she could bring to her patients that merely sipped from the region's scarce water supply.

To make matters worse, what limited water does exist in the area's deep wells has too much fluoride and other contaminants to be drinkable, let alone used in dialysis. To address the problem, a team of engineers

developed a way to filter the water so it could be used for dialysis. Then, rather than discarding it, the clinic devised a setup that let it reuse the water to provide pressure for the system. Brown knew they also needed to work with community leaders to integrate traditional Aboriginal beliefs and healing into dialysis treatments.

Over the next 20 years the Purple House transformed dialysis in Australia. In recognition of its efforts, the government created a special billing code to allow more nurses to deliver dialysis in remote communities. “We have gone from the worst survival rates in the country to the best,” Brown says.

Brown's group also built a traveling dialysis bus known as the Purple Truck. The bus visits communities not served by the clinics and allows residents of Alice Springs and Darwin to visit family. Both survival and quality of life have improved. Now densely populated regions such as Sydney and Melbourne have built their own dialysis buses. The approach not only brings access to the life-saving therapy but allows Australians to travel without missing crucial dialysis sessions.

Brown remade dialysis from the ground up. “We're disruptors,” she says. “You don't have to assume that something is going to stay the same. You can work together, and you can change the system.”

A MATERNAL MENTAL health program has had a similar impact in parts of rural Pakistan. To address growing global mental health needs, Atif Rahman, a researcher at the University of Liverpool in England, has developed short-term interventions that can be delivered by peers and other nonspecialists. The idea, he says, is to bolster access to behavioral health care, especially where treatment is virtually nonexistent.

Many of Rahman's efforts have focused on perinatal health in Pakistan, where he is originally from. His team trained rural community members there to deliver coaching sessions to decrease the mental health struggles of new moms. “It's a powerful combination,” Rahman says. “We are freeing the peer to be more of a human support.”

With a worldwide shortage of mental health workers, especially in the Global South, being able to rely on nonprofessionals opens doors to those most in need. Rahman

says the community members in his program “are doing as good a job as trained therapists who spend years and years training.” He is now expanding the perinatal mental health program to parts of other low- and middle-income countries.

Not all these experiments in rural health will prove successful or be transferable to other communities, says Lauren Eberly of the University of Pennsylvania, a cardiologist who developed a phone-based treatment program for people with heart failure who live in the Navajo Nation. Different rural communities have different needs and barriers, she says, and scientists must gain local input and insight to determine what help people need and what they will accept. Researchers have to start by asking questions and listening to feedback rather than assuming they know how to solve long-standing, deep-seated problems, Eberly says.

“The traditional health-care system really benefits those who are fluent and those who are white. It's really marginalized a lot of other groups,” Eberly says. “We really need to rethink how we can deliver health care in a way that makes sense for our communities and our patients.” The point, she says, is to use successful interventions as creative inspiration for solving other issues in health care and health equity.

Transportation issues aren't limited to rural settings; they can affect urban areas, too. So can lack of broadband access, food insecurity, and other disparities. Because many innovations developed in rural areas target these broad problems, urban and suburban areas can also benefit from them. Telehealth is a prime example, Wibberly says. The advantages of telemedicine first appeared most obvious for rural areas, but the approach has gone mainstream. She is confident that other rural health programs will become standard medical practice.

To Wibberly, the reason so much innovation occurs in rural health is simple. “It's a smaller community. People know one another. They know who the trusted entities are,” she says. “Let them figure out what will work for them because it's a whole lot easier to fix access to care issues for a city of 20,000 than it is for one of 20 million.”

Carrie Arnold is an independent public health journalist in Virginia.

Photograph by Nia MacKnight

For Eliza Scott, who lives on a farm 2.5 hours away from the Bemidji clinic in rural Minnesota, virtual prenatal care with a clinic-provided home-monitoring kit has meant the difference between getting care or no care at all.



The Staggering Success of Vaccines

Vaccines have been aiding health equity for 200 years, and today they are poised to save even more lives from more diseases BY TARA HAELE

ONCE A WEEK, early in the morning, community health worker Kiden Josephine Francis Laja mounts her bicycle and pedals as far as 10 miles away from her small village in South Sudan. Some weeks Laja is doing outreach, spending her day educating a community about which vaccines she can provide and what diseases they prevent. “It’s my responsibility to tell the mothers to bring the children for vaccination,” she says. She answers their questions and lets them know she’ll be back, usually the following week, to vaccinate their children. Late in the evening she mounts her bike and heads home.

When Laja returns with the vaccines, kept in a cooler with ice packs, she will spend the day immunizing anywhere from a few to 200 children against a range of diseases: polio, tetanus, diphtheria, pertussis, hepatitis B, influenza, bacterial meningitis, tuberculosis and, more recently, COVID. Most people in high-income countries haven’t seen these diseases in decades, but the people of South Sudan know them well. Many have seen family and friends die from them.

During the rest of the week Laja works at the community health center in her village of Pure, monitoring the solar-powered refrigerator and the vials inside. She vaccinates anyone who comes to the facility and metes out drugs for a few maladies such as ulcers, malaria and typhoid. But the village doesn’t have antibiotics—or electricity. Villagers grow their own food, raise goats and chickens, and get their water from wells in the ground.

It’s not easy work for just \$102 a month, especially when it sometimes takes three months for the 25-year-old mother of two

to get her pay. When it rains on travel days, she and her outreach pamphlets get soaked. She must regularly check the temperature of the vials in the cooler and replace the ice packs at just the right time to ensure the vaccines don’t go bad.

People in South Sudan don’t have much, but they have this program. “Vaccines are very important to me and my community and even to my country,” Laja says. During a large outbreak of measles that began in 2022 in the country, thousands of children suffered from the disease, and many died, leading to a nationwide vaccination campaign in 2023. “Now in our community you cannot find cases of measles,” she says.

Around the globe the measles vaccine has saved nearly 94 million lives over the past 50 years. This and other vaccinations have revolutionized global health. “Immunization is the most universal innovation that we have across humankind,” says [Orin Levine](#), a fellow at the Center for Global Development in Washington, D.C. He notes that there are people around the world without access to telephones or even toilets, but they find ways to get their children immunized. “It’s the innovation that demonstrates what is possible in terms of delivery of service to everyone everywhere.”

A [May study](#) in the *Lancet* estimated that vaccines against 14 common pathogens have saved 154 million lives over the past five decades—at a rate of six lives every minute. They have cut infant mortality by 40 percent globally and by more than 50 percent in Africa. Throughout history vaccines have saved more lives than almost any other intervention. And vaccines’ promotion of

health equity goes far beyond preventing death. The *Lancet* study found that each life saved through immunization resulted in an average 66 years of full health, without the long-term problems that many diseases cause. Vaccines play a role in nearly every measurement of health equity, from improving access to care, to reducing disability and long-term morbidity, to preventing loss of labor and the death of caretakers.

“We say vaccines are one of humanity’s great achievements in terms of having furthered the lifespan and life quality for humanity in the past 50 years,” says [Aurélia Nguyen](#), chief program officer at Gavi, the Vaccine Alliance, a public-private partnership that works to ensure low- and middle-income countries have access to vaccines against more than 20 infectious diseases. Of all the different health interventions that exist, she says, “vaccines have the widest reach across the world.” The clearest evidence of vaccines’ impact on equity is that they are often the first intervention introduced into a community with no other health-care resources.

“When you don’t have a health worker or health system, there’s nothing. If you have no money, then you want the best bang for the buck, and it’s going to be immunization,” says [Seth Berkley](#), former CEO of Gavi. “For every dollar you invest in immunization, you get \$54 of benefit. From a cost-effectiveness point of view, it’s the best investment, so it tends to be the intervention that gets out to those communities first. And once you do that, you have a health worker who’s visiting those communities on a regular basis, and then that begins to start the conversation toward more primary health care, and that leads to getting a basic clinic set up. Immunization is the vanguard of the health system.”

Every country in the world has an immunization program thanks to the World Health Organization’s [Expanded Program on Immunization](#), which was established in 1974. “Every single country and territory” has access to at least some vaccines,



says Kate O'Brien, director of the WHO's immunization, vaccines and biologicals department. Poverty, malnutrition, underlying health conditions, overcrowding, human conflict, displacement, and lack of access to medical care, hygiene or sanitation—all of these are risk factors for infectious disease, O'Brien says. Vaccines' ability to reduce disease in the settings most plagued by these problems gives them disproportionate power to improve equity.

THERE MAY BE NO GREATER demonstration of vaccines' power to deliver health equity than their success with smallpox. "The mag-

nitude of the accomplishment of having eradicated smallpox, where absolutely nobody on this earth gets the disease," O'Brien says, "that's the ultimate in the issue of equity."

A version of a smallpox vaccine was developed in 1796, and in 1959 global health experts decided to pursue full eradication. In the decade that followed, it became clear that such an ambitious goal would require more than political will. Although smallpox had been eliminated from North America and Europe, frequent outbreaks continued in South America, Africa and Asia.

In 1967 the WHO started its Intensified Eradication Program, which prompted a

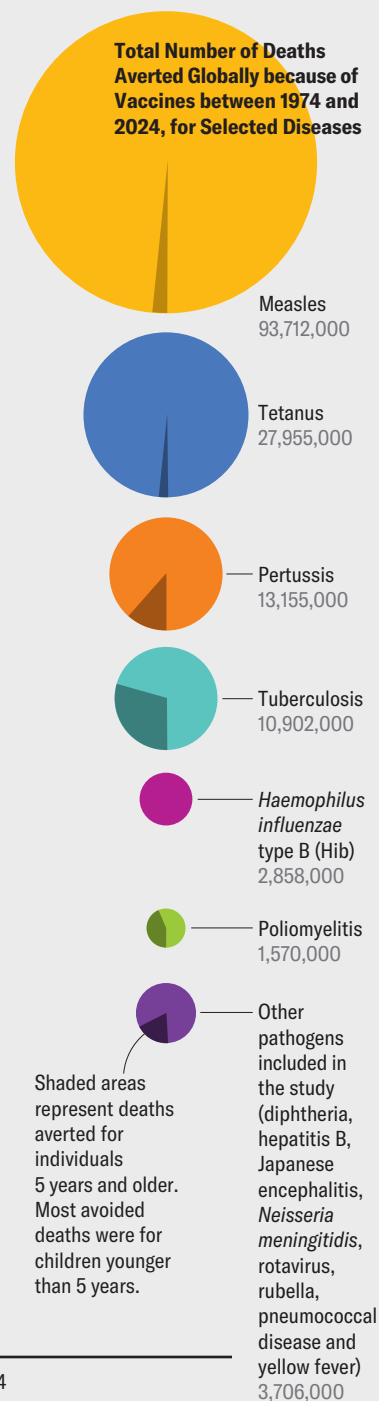
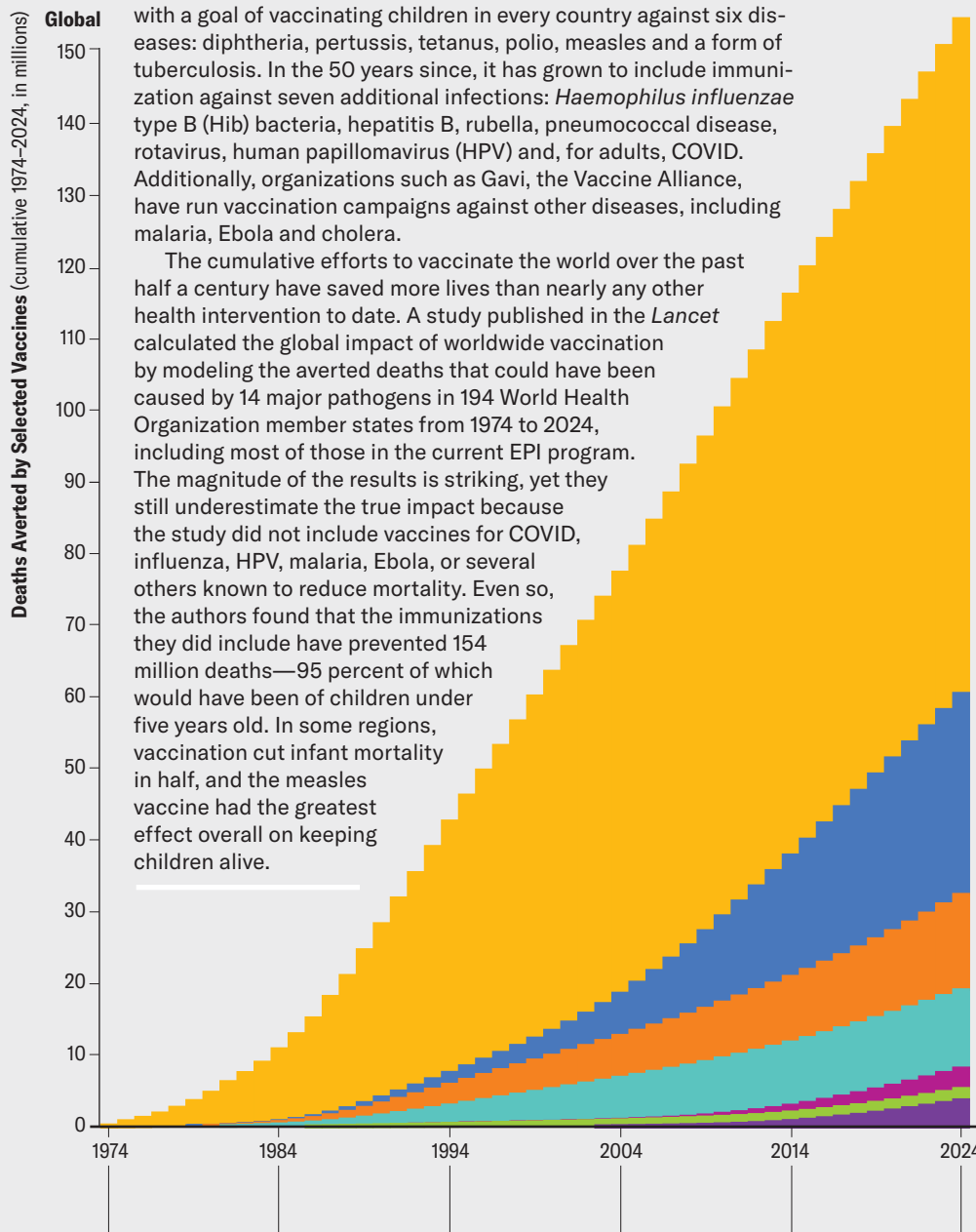
series of innovations. The bifurcated needle, which was developed around that time, allowed for smaller doses and required less user expertise for vaccine delivery than the previously favored jet injector. Researchers created a surveillance system to better track disease and vaccinate close contacts of infected people, making mass vaccination campaigns more effective. The last documented case of smallpox occurred in Somalia in 1977, and the WHO declared smallpox officially eradicated three years later.

That success inspired a similarly lofty goal in 1988 that has proved far more challenging: eradicating polio. Since the estab-

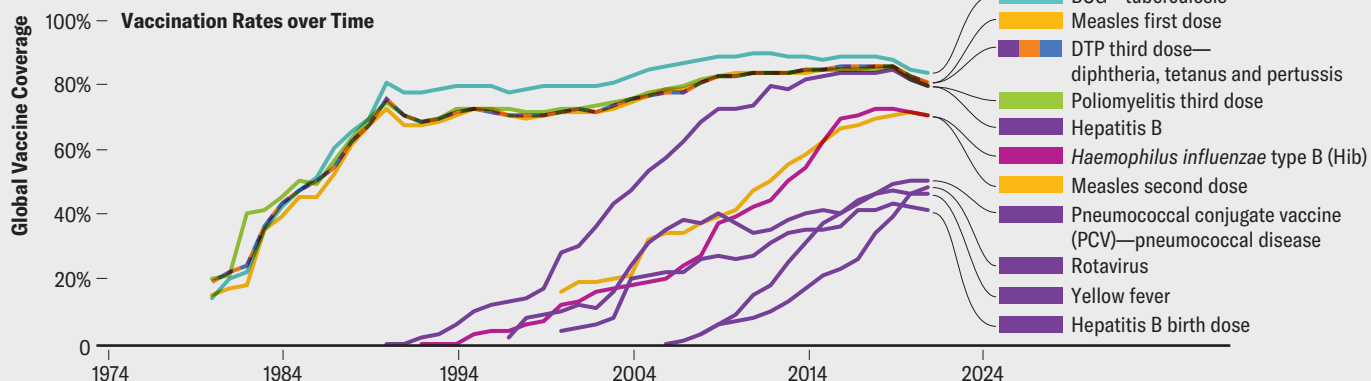
Millions and Millions Saved

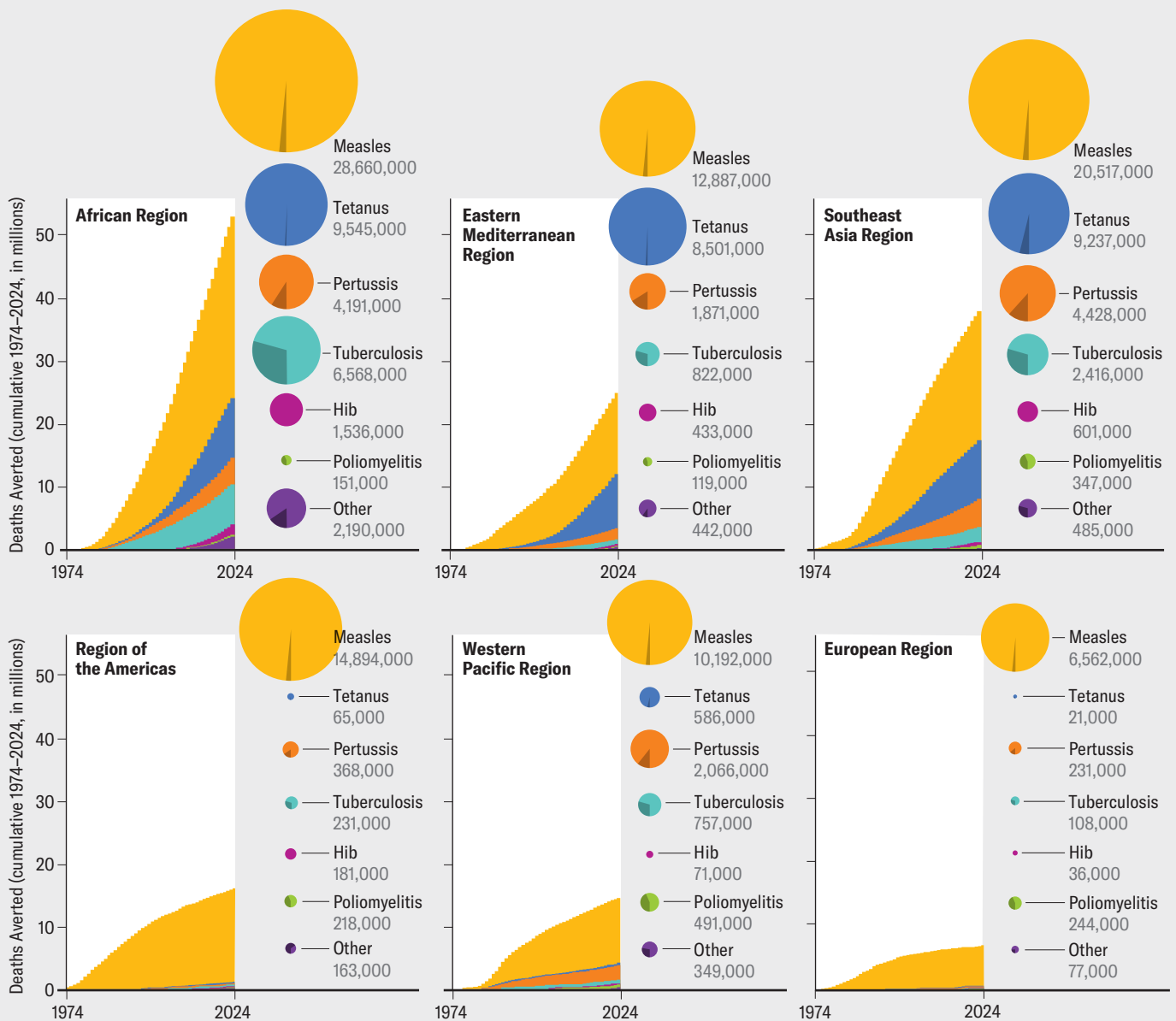
The Essential Program on Immunization (EPI) was developed in 1974 with a goal of vaccinating children in every country against six diseases: diphtheria, pertussis, tetanus, polio, measles and a form of tuberculosis. In the 50 years since, it has grown to include immunization against seven additional infections: *Haemophilus influenzae* type B (Hib) bacteria, hepatitis B, rubella, pneumococcal disease, rotavirus, human papillomavirus (HPV) and, for adults, COVID. Additionally, organizations such as Gavi, the Vaccine Alliance, have run vaccination campaigns against other diseases, including malaria, Ebola and cholera.

The cumulative efforts to vaccinate the world over the past half a century have saved more lives than nearly any other health intervention to date. A study published in the *Lancet* calculated the global impact of worldwide vaccination by modeling the averted deaths that could have been caused by 14 major pathogens in 194 World Health Organization member states from 1974 to 2024, including most of those in the current EPI program. The magnitude of the results is striking, yet they still underestimate the true impact because the study did not include vaccines for COVID, influenza, HPV, malaria, Ebola, or several others known to reduce mortality. Even so, the authors found that the immunizations they did include have prevented 154 million deaths—95 percent of which would have been of children under five years old. In some regions, vaccination cut infant mortality in half, and the measles vaccine had the greatest effect overall on keeping children alive.



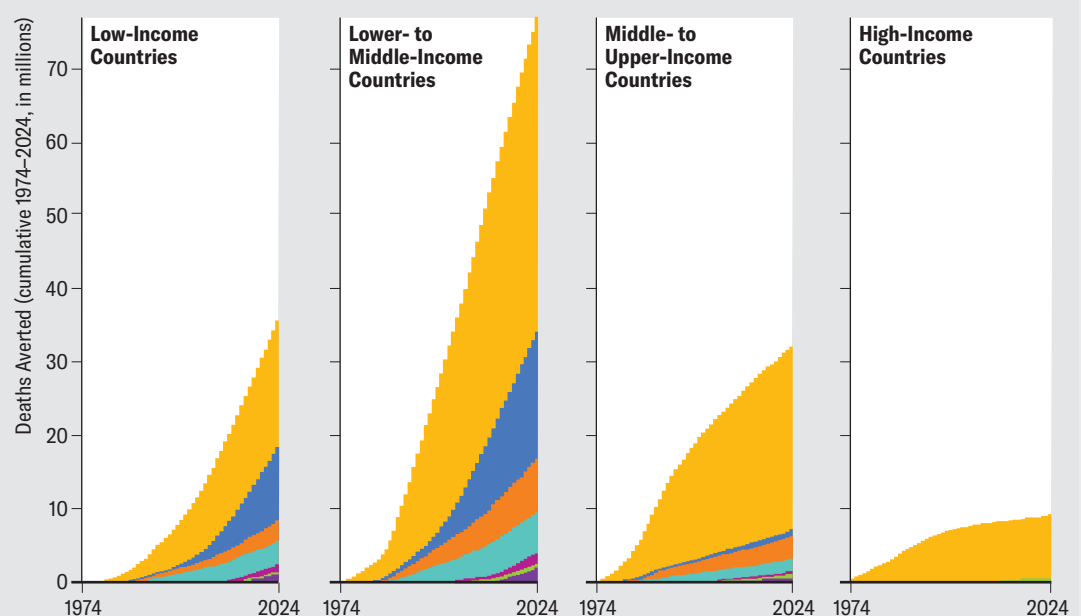
Shaded areas represent deaths averted for individuals 5 years and older. Most avoided deaths were for children younger than 5 years.





WHERE IT MATTERS MOST

Vaccines' relative impact on mortality varies by country depending on how affected that country already is by a particular disease and the other major causes of disease there. Vaccine-preventable diseases cause far fewer deaths in high-income countries, where sanitation, hygiene, nutrition, medical infrastructure and health-care access have already substantially improved survival. Meanwhile, vaccines have an outsized impact on preventing deaths in low- and middle-income countries where infectious disease remains a top killer. In short, as the *Lancet* study authors write, "Vaccines promote equity by saving more lives in places where more deaths occur."



“Vaccines level the playing field.... But frankly, it was a really long road to get to that kind of equity.”

—Nicole Lurie *Coalition for Epidemic Preparedness Innovations*

lishment of the Global Polio Eradication Initiative, cases have fallen 99 percent worldwide, but that last 1 percent is taking decades longer than planned. Public health experts now recognize that very few diseases can be completely eradicated through immunizations. Even so, they aim to decrease vaccine-preventable diseases to such low levels that severe morbidity and mortality are negligible. The WHO's renamed Essential Program on Immunization initially focused on six childhood diseases: polio; measles; disseminated tuberculosis, the form of the disease most common in children; and diphtheria, tetanus and pertussis, for which children receive the combined DTP vaccine. It has now expanded to include vaccines against 13 diseases.

“We have to look backward, in some ways, to realize how far we've really gone,” says Lois Privor-Dumm of Johns Hopkins University, who recently retired from her role as a senior research associate. “There has been tremendous progress over the past 50 years, and what is really left is making sure the equity agenda is really a focus.”

Now the question is how best to do it. A raft of technological and policy innovations aim to help. Before the WHO's current vaccination program began, fewer than 5 percent of the world's babies had access to routine immunizations. Today 84 percent of infants have received three doses of the DTP vaccine, the metric used to assess global immunization coverage.

“[Vaccines] level the playing field in terms of who gets these diseases and who doesn't,” says Nicole Lurie, U.S. director of the Coalition for Epidemic Preparedness Innovations (CEPI), a foundation formed specifically to develop and improve access to vaccines for diseases that lack strong market demand. “But frankly, it was a really long road to get to that kind of equity.”

Setbacks through the 1990s led global health leaders to rethink their approach, and in 2000 Gavi was founded collaboratively by the WHO, UNICEF, the World

Bank and the Gates Foundation. Thanks to Gavi, says Violaine Mitchell, director of immunization at the Gates Foundation, “now countries not only assume but demand that when a vaccine is introduced in the developed world, it's also made available in the developing world.”

Gavi has vaccinated more than one billion children with a routine suite of shots and given a total of 1.8 billion immunizations to people of all ages through campaigns for illnesses such as measles in Ethiopia, Afghanistan and Somalia and yellow fever in Congo, averting more than 17 million deaths through 2022. Since Gavi was established, there has been a 70 percent reduction in deaths from vaccine-preventable diseases in children living in the lower-income countries the alliance supports, and mortality among children younger than five years in those countries has been halved. The pneumococcal and rotavirus vaccines have been particularly significant—pneumonia and diarrhea are among the top global killers of children under five.

But even those impressive numbers don't fully capture the dramatic ways vaccines advance health equity. For example, epidemics of meningococcal meningitis were common in the “meningitis belt,” a stretch of 26 countries just south of the Sahara desert that has the highest rates of meningococcal disease in the world. Up to half of those infected die without treatment; even with treatment, one in 10 people dies. Since the development and distribution of a vaccine against meningitis A, this form of the disease has been nearly eliminated. The vaccine has not only saved lives but prevented long-term effects that meningitis survivors often suffer, including hearing loss, seizures, limb amputations or weakness, scarring, vision problems and cognitive difficulties.

Another example is the human papillomavirus (HPV) vaccine, which can prevent up to 90 percent of HPV-related cancers, including nearly all cervical cancer. Because

high-income countries implemented cervical cancer screening programs decades ago, 94 percent of global deaths from cervical cancer in 2022 were in low- and middle-income countries. Gavi programs have vaccinated more than 16 million girls worldwide against HPV, and the organization aims to vaccinate 86 million by 2025. The physical benefits won't be seen for years—it takes up to two decades for an HPV infection to develop into cancer—but the ripple effects of prevention go far beyond saving a single person's life. A death from cervical cancer may mean loss of a family caretaker, loss of income and difficulty meeting children's continuing health needs. “The tsunami effect of losing a mother to children, especially for those who are not economically stable, is devastating to a family,” O'Brien says. “Their lives are entirely dependent on the survival of that person.”

VACCINATION CAN BE A KEY entry point to additional health care. William Foege, a former director of the U.S. Centers for Disease Control and Prevention, who was instrumental in leading smallpox eradication and in setting up Gavi, called vaccines “the tugboat” for preventive care.

When health workers arrive to vaccinate children in a community, they can assess other children's growth trajectories and nutritional issues, provide vitamin A supplements where there are deficiencies, distribute deworming tablets, monitor mosquito-borne diseases and check on additional needs. “If you manage to reach a child and give them a measles vaccine, then you may be able to give their mother maternal services,” Nguyen says. “It's a perfect time to say: Are you sleeping under a bed net? Do you need a bed net? What are you doing for family planning?” Mitchell says. “All those conversations can come about because of the contact between the caregiver and the health worker that wouldn't [otherwise] happen.”

In 1985 Rotary International launched its PolioPlus program, which used vaccination campaigns as an opening for other health interventions. “When Rotary and its partners added other things to improve the health systems of countries, it was a game changer,” says Stella Anyangwe, a Rotary International EndPolioNow coordinator and former WHO official. By

strengthening laboratory systems, the cold-chain network of refrigerated storage necessary for transporting the vaccine, and overall disease surveillance, she says, improving systems for polio eradication “strengthened the health systems in general.” In short, Levine says, “immunization is an innovation that is pulling other innovations along.”

It can also free up valuable time and resources in health care. As infectious disease incidence falls, health workers and hospital beds become available for people with other conditions. This may already be happening with malaria. In Burkina Faso, about two out of every five visits to a health-care provider are for malaria, which historically accounts for more than 60 percent of the country’s hospitalizations. Similarly, malaria cases make up about half of hospitalizations in Cameroon; most of those patients are children under five who are eligible for the malaria vaccine. Although current malaria vaccines don’t prevent infection altogether, they reduce severe disease by 30 percent and all-cause mortality by 13 percent. Gavi began rolling out vaccination campaigns against malaria last year, providing 18 million doses to a dozen African countries, and malaria deaths have already begun falling. “You can imagine how much that’s going to free up capacity for health-care workers to focus on other [issues],” Nguyen says.

Vaccines help countries with fewer resources protect themselves from disease. Outbreaks disproportionately affect poorer areas: the 2014–2016 Ebola epidemic in West Africa, for example, devastated the region’s health-care infrastructure. Since the development of an Ebola vaccine in the late 2010s, subsequent outbreaks have remained comparatively small. And the current outbreak of mpox [see “History Lessons,” by Charles Ebikeme, on page S25], which led the WHO to declare a global public health emergency in August, is being managed with vaccines that became available only in the past few years.

Gavi now supports stockpiles of outbreak-specific vaccines for cholera, yellow fever, meningococcal disease and Ebola so the countries most affected can focus their health-care resources on chronic disease, snakebites, cancer and HIV, among other conditions.

IN LATE 2019, when a novel coronavirus detected in Wuhan, China, kicked off one of the largest, deadliest pandemics in a century, everyone looked to the same solution: a vaccine. COVID’s devastation hit poorer countries with less developed health-care systems particularly hard, and in wealthier countries people from underserved and low-income communities suffered higher rates of illness, death and economic hardship. It was clear that a COVID vaccine would be the most equitable solution.

The U.S. quickly directed \$10 billion toward vaccine development, and dozens of other countries allocated what they could. The effort broke every record for the fastest vaccine development. The Chinese CDC released the sequence of SARS-CoV-2 on January 10, 2020, and just 11 months later, on December 8, 2020, the first COVID vaccine was administered outside of a clinical trial.

Officials at Gavi, UNICEF, WHO and CEPI quickly organized Covax, an international effort to accelerate COVID vaccine development and “to guarantee fair and equitable access for every country in the world,” according to the WHO. Covax delivered nearly two billion vaccines to more than 140 countries in the two years after the vaccines’ introduction, “by far the fastest, largest and most effective public health rollout in history,” a Gavi spokesperson says. A 2022 study in the *Lancet Infectious Diseases* estimates that COVID vaccination worldwide prevented 19.8 million excess deaths, 7.4 million of those in Covax countries.

The challenges were steep and vaccine distribution contentious. “At no point did a richer country with access to vaccine doses choose to slow down its rollout to make doses available for people at higher risk in lower-income countries,” Levine says. “That’s vaccine nationalism, and it undermined the success of hardworking folks at Covax.”

Those problems have prompted a lot of reflection and a lot of new action. The organizations behind Covax have now set their sights on improving vaccine equity during future pandemics. Because Africa lacked vaccine access and had few manufacturing capabilities of its own, the new efforts are particularly focused on boosting the continent’s vaccine-manufacturing capabilities. The Africa CDC has partnered with other organizations to create the Partnerships for African Vaccine Manufactur-

ing with a goal of making 60 percent of its needed vaccines by 2040. In June 2024 Gavi launched the African Vaccine Manufacturing Accelerator, a financing program developed with the Africa CDC and African Union to put up to \$1.2 billion over the next decade toward building up the continent’s vaccine-manufacturing capacity.

In the almost 25 years since Gavi was launched, it has made substantial progress in advancing equity in vaccine manufacturing. In 2000 four of its five vaccine suppliers were in wealthy countries. Today most of its 20 or so suppliers are in developing countries. “It opened up a marketplace for large-scale, low-cost manufacturing in India, in Brazil, in China and in Indonesia,” says Berkley, former Gavi CEO.

It will still be immensely challenging to get vaccines into the arms and mouths of people who need them most. Health workers must find and immunize zero-dose children—children who have yet to receive vaccines of any kind, like the ones Laja sees in South Sudan. And low-income countries must acquire the financing and build the infrastructure to facilitate that process. Then Laja and her peers must educate people so fear does not become a barrier to access.

Workers such as Laja are part of the global workforce that the WHO, Gavi, UNICEF, the Gates Foundation, Rotary, and other organizations have trained to use vaccines against disease and health disparities. Earlier this year Laja completed training in preparation for South Sudan’s malaria-vaccine rollout. In 2022 there were almost 7,000 malaria deaths in South Sudan, and the disease is the top killer of young children in the country. The previous year South Sudan’s malaria fatalities accounted for more than 1.2 percent of the total worldwide.

Laja is eager to see the vaccines’ impact on her community and in the villages she visits, where parents will walk for miles from outlying areas to meet her. “There are very few things women and caretakers will walk hours and hours for, but vaccines are still one of them,” says Mitchell of the Gates Foundation. “People will literally drop everything to come and vaccinate their child.”

Tara Haelle is a Dallas-based science journalist whose specialties include infectious disease, medical research and health disparities.

Of Hope and Justice

AS TOLD TO ANIL OZA

The journey toward health equity can, at times, feel endless. But it can also be exciting and inspiring. SCIENTIFIC AMERICAN asked some of the researchers, physicians, advocates, and others working on health equity what they are most hopeful about. Each had numerous concerns but also reasons for optimism. They pointed to progress in widening access to health care, making science more inclusive, and reducing the health burden of systemic racism and other biases. They are also emboldened by the energy and enthusiasm of their colleagues working to advance health equity.

“Any level of justice work has to be rooted in a context of hope, right?” says Aletha Maybank, chief health equity officer at the American Medical Association. “A hope and faith that we will all be able to have an experience of optimal health.”

The following interviews have been edited for length and clarity.



MADHUKAR PAI

CHAIR, EPIDEMIOLOGY AND GLOBAL HEALTH, MCGILL UNIVERSITY

My biggest source of hope is young people. It's the youngest people who are shining a clear light on why climate change is devastating and why leaders are not acting on what has been obvious for many years. It's the youngest people who are doing great work in the U.S. on gun control, even as they're getting slaughtered in schools. It's the young people who are alarmed about the rollback of reproductive rights in the U.S., in Afghanistan, you name it.

I feel like their moral clarity is the clearest because, unlike older people who already bought into something or were worried about their next paycheck or position or winning awards, young people are devastatingly clear in terms of what's wrong. Their problem statements are spectacularly accurate and on point, and so they give me a huge amount of hope. That's partly why I still teach global health to young people.

Just fanning their energy, their passion, might well be the biggest source of hope for all of humankind. But we need to go beyond that because although their diagnosis is perfect, their ability to act is limited. They're not in power; they often are not voting. They're usually given two minutes to speak at the front end of the meeting and shown out of the door while the adults are making big decisions. So how do we potentiate them to go beyond just sound bites or nice photo ops to action and give them empowered ways of doing things?



SEYE ABIMBOLA

ASSOCIATE PROFESSOR, HEALTH SYSTEMS, UNIVERSITY OF SYDNEY

One of the things about which I'm hopeful is a growing confidence and restlessness and disquiet from global health professionals and academics from and in the Global South about how the field itself works and needs to change. Historically the field was premised on this idea that the West—or the Global North, as we refer to it today—has a right and a duty to impose itself on the rest of the world.

For example, if someone wanted to do a study in Nigeria and the people who are going to lead it come from London, they would rely on a lot of the infrastructure in Nigeria but disregard that the local collaborators know anything. Then they go home and write this paper and publish it in the *BMJ* or in the *Lancet*. Now, for me, what I think has changed, what I see changing more and more, is the push-back on that. That's just the tip of the iceberg. But that physically measurable, countable phenomenon of partnership research sits on a whole bed of assumptions and normalized practices that we took from the colonial experience.



RACHEL HARDEMAN

DIRECTOR, CENTER FOR ANTIRACISM RESEARCH FOR HEALTH EQUITY, UNIVERSITY OF MINNESOTA SCHOOL OF PUBLIC HEALTH

One of the things that gives me hope is the work that I'm doing, along with many other incredibly brilliant scholars across the country, around measuring racism. In my work and within our research center, we have to be able to make the invisible visible. Racism is so often passed off as this insidious thing that is baked into the system, and it's so hard to identify, especially when it's not an explicit interaction with someone.

In a lot of my work and in what I'm seeing across the country with other scholars—incredibly brilliant Black scholars in particular—is an investment and interest in figuring out how we leverage data to measure structural and other forms of racism and then how to use that to inform policy change. We're coalescing around the need to understand that health policy and social policy go hand in hand. We can't, for example, talk about historical redlining and racial covenants and birth outcomes in those communities without having the data, without understanding the history as well as what's happening currently. And then using that to inform housing policy just as much as we might use that evidence to inform health policy.



WAFAA EL-SADR

DIRECTOR, GLOBAL HEALTH INITIATIVE, COLUMBIA UNIVERSITY MAILMAN SCHOOL OF PUBLIC HEALTH

When I think back to what things looked like 25 years ago, compared with today, it's night and day. Investments in health systems, largely driven by the HIV epidemic, have borne fruit in amazing ways. No services were available, or those that did exist were fractured. There were no resources; there was no access to medicines or lab tests. It's just been an enormous transformation in only a couple of decades, so that gives me hope for the future.

More than 20 years ago I remember going to a clinic very far away from the capital city in one of the provinces in South Africa. There was nothing available for HIV testing or for treatment, and, I remember this vividly, this nurse very proudly opened a notebook that she had in a drawer in her very rickety desk and said, "I have a list of people here who need treatment." And then she pulled out another sheet of paper, and she said, "Look at this. I have a certificate. I've been trained. I'm ready. I want to save my people." And I remember walking away thinking, "This gives me hope. There are people who care about their communities. They're ready, they're willing." And I'll never forget that, and I'll never forget the look on her face of "I can't wait anymore."



BARNEY GRAHAM

FOUNDING DIRECTOR, DAVID SATCHER GLOBAL HEALTH EQUITY INSTITUTE, MOREHOUSE SCHOOL OF MEDICINE

Hopefulness comes from a faith and belief that things have a way of evolving toward the good. The moral arc of the universe bends toward the good. But it may take a long time. Helping to diversify the public health workforce through creating more opportunities and knowledge for students is a multigenerational process.

Four African American students did almost all the bench work that was needed to get the Moderna COVID vaccine into that first phase 1 trial in March 2020. We're very proud of them for getting that whole vaccine program launched.

We must change the narrative of what people can do and what they are able to do and start asking, Who gets to be trained? Who gets to have the knowledge? Who gets to make the decisions? Who gets to decide what to make and where it goes? All those decisions happen at some level of leadership. If you diversify that leadership, you will have a better, more balanced opinion about how things should be done. That's how you start moving toward equity.



ALETHA MAYBANK

CHIEF HEALTH EQUITY OFFICER, AMERICAN MEDICAL ASSOCIATION

It's helpful looking at progress. The past four years, since the public murder of George Floyd, there is now the ability to mention racism where you couldn't before. Prior to the public murder of George Floyd, folks would never have expected the AMA to make a statement about racism being a public health threat. And then the AMA's House of Delegates passed a policy that really reaffirms ridding medicine of medical essentialism and ridding medicine of the use of race as a proxy for biology. That has been aligned with a movement around getting rid of racist algorithms, clinical algorithms [see "Better Measures," by Cassandra Willyard, on page S3]. That would have never started without this national and collective movement to name racism and the exposure of inequities during COVID. That response and that collective response do provide hope.

Anil Oza is a Boston-based science journalist focused on health inequity and neuroscience.

Cultural Competency

A movement, which aims to help providers better understand their patients' culture and language, is gaining traction and hopes to improve care and save lives BY ROD MCCULLOM

CALIFORNIA'S INLAND EMPIRE is a broad swath of land east of Los Angeles, about five times the size of Connecticut, stretching through desert and surrounded by mountains. It's one of the state's fastest-growing regions, but it's underresourced, with incomes and education levels lower than the state average. It is also medically underserved, with too few primary care physicians and specialists to adequately tend to the area's increasing population. In the region's many Spanish-speaking communities, finding a doctor who speaks the same language is difficult. And whether people can communicate well with their health-care providers affects patient outcomes.

Three years ago the Inland Empire Free Clinic opened in Colton, Calif., to provide free health and medical care and social services. Its clinic is staffed by physicians and medical students from the nearby California University of Science and Medicine. Many are proficient in Spanish, and those who aren't work through interpreters. "The moment I talk in Spanish to patients, they change their attitude and are more open to tell me how they actually feel," says Alexandra Lopez Vera, director of C.U.S.M.'s medical Spanish program, who coordinates interpreters for the clinic. "If I talk to

a Latina who comes to see a doctor because they have a problem related to the reproductive system, they may feel like, 'I feel embarrassed to tell this white guy who doesn't speak my language about this situation that I'm having.' They request for me to be with them."

Research has shown that in the U.S., patients with limited English proficiency have a higher risk of hospital readmission and greater difficulty adhering to medication regimens. More than 25 million people who live in the U.S. have limited English proficiency. Because the majority of those are Spanish speakers, many medical schools now offer medical Spanish. C.U.S.M., which was founded in 2018, has made it mandatory. Finding a common language is just one way in which medical schools, clinics, hospitals and health-care networks are working to address health disparities as part of an increasingly visible movement known as culturally sensitive or concordant care.

When patients don't trust the providers caring for them or when they feel dismissed or misunderstood, they're less likely to share relevant information. And when providers don't understand a patient's life experiences and culture or don't speak their language, they may be less like-

ly to ask relevant questions. Culturally sensitive care starts with the premise that people come from diverse cultural, ethnic, religious and socioeconomic backgrounds and that understanding these differences is crucial for proper health care. Hospitals and medical schools are now adding tools to help their providers improve sensitivity around language, traditions and cultural expectations. The strategy is already advancing health equity. A growing body of research shows that by addressing bias and stigma directly in a rapidly diversifying patient population, culturally concordant care results in better health outcomes across a person's lifespan—from prenatal and maternal health to pediatrics to end-of-life decisions.

MATERNAL MORTALITY RATES in the U.S. are higher than in any other high-income nation in the world. In 2022 that rate was about 22 deaths per 100,000 live births, according to the Centers for Disease Control and Prevention's National Center for Health Statistics, down from almost 33 deaths per 100,000 live births in 2021.

The death rates are the worst in Black communities. Data from the Chicago Department of Public Health revealed that in 2019, Black women in Chicago were almost



six times more likely than white women to die during pregnancy or within one year of giving birth. To try to reduce this number, the University of Illinois Hospital and Health Sciences System (UIHealth) introduced a new initiative in 2022: its Melanated Group Midwifery Care program.

The midwifery group was born out of Karie Stewart's frustration with a system that was failing Black and brown families.

"The Black population is experiencing the most deadly outcomes when it comes to pregnancy," says Stewart, a certified nurse-midwife at UIHealth and one of the investigators leading the Melanated Group Midwifery Care program's research. The patients she serves are predominantly Black and live on the west and south sides of Chicago, where a number of hospitals shut down their labor and delivery units

during the worst of the COVID pandemic. "There is a lack of care for those already disadvantaged," she says. Stewart approached Kylea Laina Liese and Stacie Geller of the University of Illinois Chicago, who study risk factors associated with maternal health, and together they made a plan, secured a \$7.1-million research grant and got to work.

The research project includes people at

“Folks are using the health-care system more. They’re not running from it. They’re empowered from their maternity experience.” —Karie Stewart *Melanated Group Midwifery Care*

all stages of pregnancy, from the first trimester to 12 months after birth. It matches Black pregnant people with Black midwives and is expanding prenatal care in communities with limited maternal health services. The program provides group education to support people in different stages of pregnancy, offers breastfeeding resources, helps participants with family planning after their babies are born, and ultimately reframes maternal and postpartum care in a way that respects Black patients’ needs and experiences in a health-care system still recovering from historical and systemic racism.

Today Stewart and her team are four years into the five-year grant, and they can point to qualitative changes in the community they serve. (The team expects to share quantitative data after the research period ends in 2025.) “We’re seeing folks use the health-care system more. They’re not running from it,” Stewart says. “They’re empowered from their maternity experience. They’re empowered to share what’s going on.” Given that many of these patients had previously avoided the health-care system, she sees this as a big win. “We want them to be engaged in their health care not just when they’re pregnant but after having a child and to seek care for anything else they have going on.”

IN MEDICAL SCHOOLS ACROSS the country, clinicians, faculty, administrators and students are reviewing their curricula to identify existing biases and teach cultural sensitivity to the next generation of physicians. When schools integrated information on racial disparities into their teachings, according to a 2019 study in *Academic Medicine*, students were more motivated to work in diverse communities.

In 2021 Temple University’s Lewis Katz School of Medicine in Philadelphia formed a task force of students and faculty to identify potential problems in the school’s course curricula, says Abiona Berkeley, an

anesthesiologist and interim associate dean of the school’s diversity, equity and inclusion office. There were 346 instances in the curriculum, she says, “where we had an opportunity for development and growth.” These included dozens of examples of racial or ethnic stereotypes, as well as symptoms that had never been studied in groups representing a range of human skin tones. Berkeley says several members of the faculty have told her, “It’s changed the way I look at some of my patients and how I engage with them.”

Hillel Maresky, a cardiothoracic radiologist, arrived at Temple University in 2019, before the cultural sensitivity task force was assembled. He soon noticed an odd phenomenon. Many of his Black female patients had chest x-rays, computed tomography scans and magnetic resonance imaging (MRI) that seemed to include shadows or squiggly lines known as artifacts. He discovered that these artifacts were being caused by the women’s hair braids, locs and twists and the hair bands that held them in place. Certain hair oils and conditioners used by Black women also presented problems: the oils occasionally contain trace amounts of metals that interfere with MRI machines’ powerful magnets. “As I was compiling these cases, I learned that there really was a hole in the medical literature on this topic,” Maresky says.

When images are unclear or contain artifacts, patients must be scanned again. And additional testing means additional radiation exposure, as well as logistical challenges such as transportation or loss of hours at work. The lack of familiarity with these hairstyles and the lack of data regarding their effect on imaging present problems not only for radiologists but for clinicians in a wide range of medical fields.

Maresky began collecting a dataset that now includes more than 100 images of such artifacts that mirrored disease, and Angela Udongwo, a fourth-year medical

student in his laboratory, has now presented their findings at a couple of conferences and to other medical schools in the Philadelphia area. They have also completed a pilot study on physicians’ awareness of and familiarity with Black hairstyles. “We found the length of your career correlated with how familiar and comfortable you are with identifying these hairstyles in imaging,” Udongwo says. But these are skills that can be taught. “There is no curriculum developed around teaching this.”

Udongwo is Nigerian American and has worn braids for years. While collecting research for the project, she heard one story after another about patients who encountered radiologists with little cultural sensitivity or understanding. It just doesn’t make sense, she says, that radiologists in 2024 aren’t familiar with these hairstyles.

MEDICAL SCHOOLS ARE BEGINNING to catch up. In 1991–1992, researchers surveyed all 126 medical schools in the U.S. about whether they had implemented cultural-sensitivity training or had plans to do so in the future. Their results were published in 1994 in *Academic Medicine*. Of the 98 schools that responded, only 13 provided a cultural-sensitivity course, and only one of those was a requirement. Today medical schools, governments and hospitals across the U.S. have guidelines for cultural-sensitivity training. They’re expanding their sensitivity around communication, too: as of 2019, almost 80 percent of the nation’s medical schools offered medical Spanish.

Not only does language concordance improve outcomes, but it can also enhance patients’ experiences. A small study by Lopez Vera assessed patient satisfaction at the Spanish-friendly Inland Empire Free Clinic and found that those treated by a doctor who spoke their language had the highest satisfaction scores. These days, between technology and artificial intelligence, some people assume they don’t need to learn a new language, Lopez Vera says. But the evidence shows that the human-to-human approach is not just more empathetic but more effective.

Rod McCullom is a science writer whose work has appeared in *Undark*, *Nature*, the *Atlantic* and *M.I.T. Technology Review*, among other magazines.

Defogging Data

As researchers separate out health data from culturally distinct groups, they're finding ways to reduce health disparities BY JYOTI MADHUSOODANAN

MANY OF THE PATIENTS who come to Eugene Yang's cardiology clinic trace their origins back to India, China, Korea, and multiple parts of Southeast Asia. His clinic is in Seattle, a hub for the tech industry and home to thousands of immigrant workers. Yang had seen firsthand how people from each of these groups were at risk of heart disease and how their typical lifestyles differ.

Yet despite differences in their cultures and backgrounds, these patients have been lumped together with people from other communities in a single category: Asian American, Native Hawaiian and Pacific Islander, or AANHPI. So Yang and his colleagues created a study looking at how social stress factors affect heart health in the Asian American communities he treats. The researchers analyzed stressors such as food insecurity, delays in medical care and living in a neighborhood that didn't feel close-knit or safe. Then they correlated these issues with risk factors for heart disease among Chinese, Filipino and Asian Indian adults. Other Asian communities were grouped together into a single category.

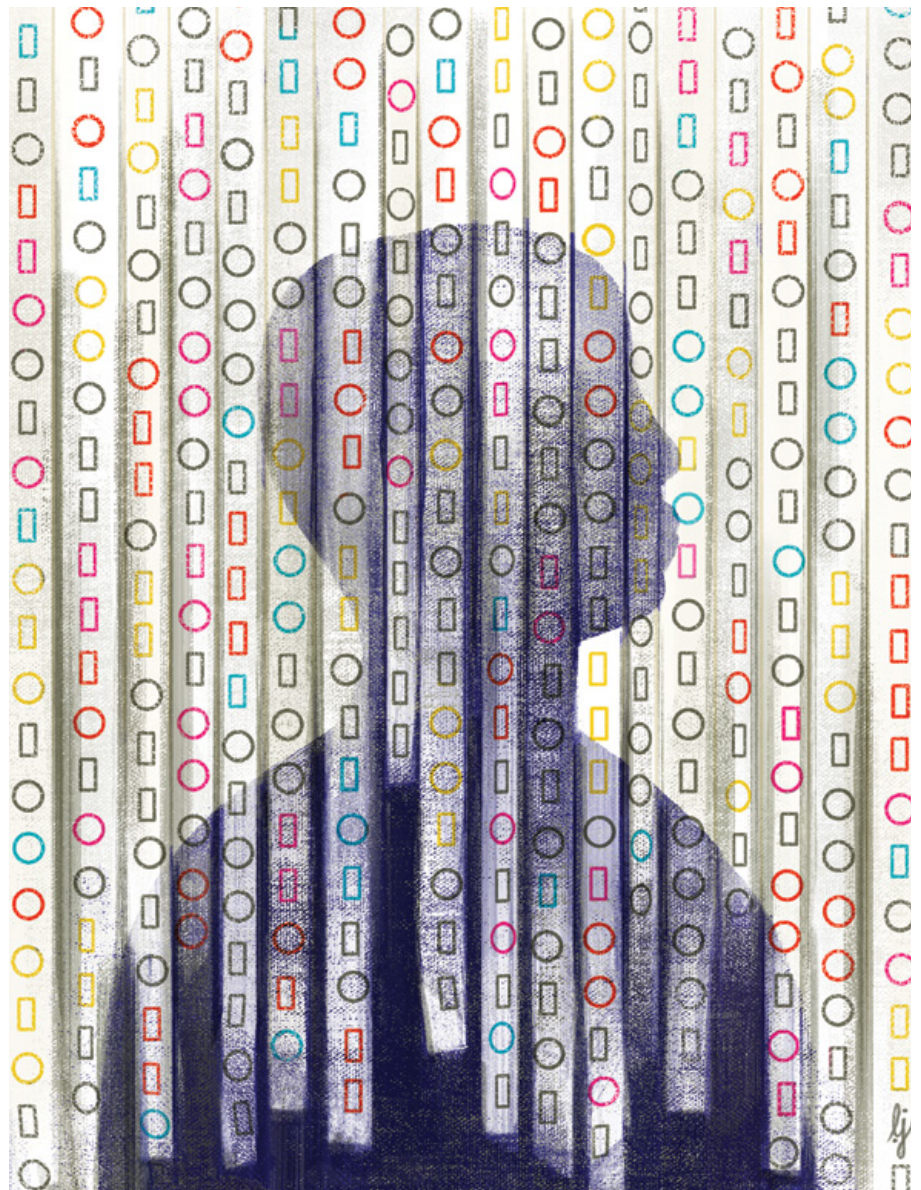
The recently completed study showed that the same stressors manifest differently in people of different ethnicities. Across the board, those who experienced more social stress had poorer sleep, struggled to exercise and used more nicotine—all factors associated with higher rates of heart disease. But differences emerged between groups. In Chinese Americans high stress was associated with an increased risk of diabetes, whereas in Filipino adults it was linked to high blood pressure. Asian Indians were most likely to experience poor sleep and physical inactivity when bearing the brunt of social stress. "There are significant differences in how social determinants of health impact the different Asian subgroups," Yang says. Recognizing this variation is a first step toward helping physicians tai-

lor interventions more appropriately.

For decades such nuance had been all but invisible to scientists, clinicians and policymakers. The single AANHPI category, which was defined in the 1997 U.S. Census, is still used widely by hospitals, as well as by state and national health databases. Researchers and policymakers use these data to assess disease rates and peo-

ple's health needs and to decide how to allocate resources.

But the AANHPI category masks rich diversity. People in this group have ancestral links to more than 50 countries. They collectively speak more than 100 different languages, have widely variable ways of life that differentially affect their health risks and represent a diversity of genetic backgrounds. They're also the fastest-growing racial and ethnic minority in the U.S. By pooling their data, researchers end up with a potpourri that obscures population-specific health needs or health risks. "When you lump everybody together, you don't see that maybe there are important differences," Yang says.



Now efforts led by advocates, researchers and community organizers—most of them from AANHPI communities—are paving the way to data equity and better health.

Spurred in part by the realization that aggregated data masked stark health disparities during the COVID pandemic, researchers began studying disease risk in specific AANHPI cohorts such as Pacific Islander, South Asian and Vietnamese populations. They're finding that teasing apart data in community-specific ways lets them use race and ethnicity information without conflating it with biology. Policymakers are catching up, too, using data specific to individual communities to better understand how to allocate resources and communicate more effectively.

These efforts are improving AANHPI health outcomes, says epidemiologist Stella Yi of New York University Langone Health. In recent years disaggregating AANHPI data has helped health-care professionals improve hepatitis B vaccination rates, reduce the devastation that has been caused by COVID and wildfires among Hawaiian communities, and identify better diet strategies to help South Asian communities reduce their risk of heart disease. "It's been really exciting to watch," Yi says.

TELLIE (CHANTELLE) MATAGI was a 20-inch, eight-pound, six-ounce bundle of newborn joy in a Utah hospital nursery when her identity vanished into the health system. On hospital forms Matagi, who is of Samoan ancestry, had been labeled Asian, a category that blurred racial lines so completely it rendered them meaningless. Matagi, a community health leader who managed the Pacific Islander Task Force within the Hawaii State Department of Health during the early days of the COVID pandemic, says the record bothered her parents. It also troubled Asian staff at the hospital, who recognized the incongruity of so many people being lumped together. Matagi ended up quitting her job in 2022 to address her own health. She had diabetes and high blood pressure, and her doctors suggested she just lose weight. But because she was familiar with the science and knew aggregated data were masking her Samoan ancestry, she realized they

couldn't understand her true health risks. "I knew I wasn't being seen," she says.

Grouping too much data blurs the reality of people's lives. For example, in the aggregate, the risk of cancer death among Asian Americans is about 40 percent lower than that for white people. But disaggregating data reveals important patterns. Within the AANHPI group, lung cancer is the leading cancer diagnosis among Vietnamese, Laotian and Chamorro (those with ancestry in the Mariana Islands) men, and colorectal cancer is highest among Laotian, Hmong and Cambodian men.

When data are pooled, these nuances vanish. "One group looks better than they really are, the other group looks worse than they really are, and you can't rely on those estimates anymore," says Joseph Kaholokula, a physician at the University of Hawai'i at Mānoa. "It's nonsense. It's not good science, yet people have been doing this for decades."

That's because for decades federal and state health databases have offered researchers only a high-altitude view. Early attempts to break population data down with greater granularity failed because there simply weren't enough people in each group. The effort sparked concerns that, although the people included in these health-related data samples should remain anonymous, there were so few they could be easily identified. And funding to look at AANHPI health has been limited—a 2019 study reported that over the previous 25 years, only 0.17 percent of all National Institutes of Health funding for clinical research supported projects focused on AANHPI communities.

This is in part the result of broader stereotyping of Asian Americans as a "model minority," a category in which everyone is assumed to be well educated, financially secure and generally healthy. The model-minority trope illustrates how race-based assumptions can bias scientific research, says Tina Kauh, a program manager at the Robert Wood Johnson Foundation. "It's important for people to recognize that systemic racism is really what's driving the fact that we don't disaggregate data." With so little NIH funding to support their work, scientists have struggled to dispel the model-mi-

nority myth. "It's like this hamster wheel you get stuck on," Kauh says.

KAUH FIRST BUMPED into that cycle in college during an undergraduate psychology class about how culture and ethnicity shape someone's behaviors and perceptions of social norms. Fascinated, she tried to dig deeper into the experiences of Asian Americans, yet she couldn't find the data. Kauh persisted, revisiting the topic in graduate school but says she found it "basically impossible" to get funders interested. Since then, she says, "it's been this mission of mine to try to push for collecting data about Asian Americans."

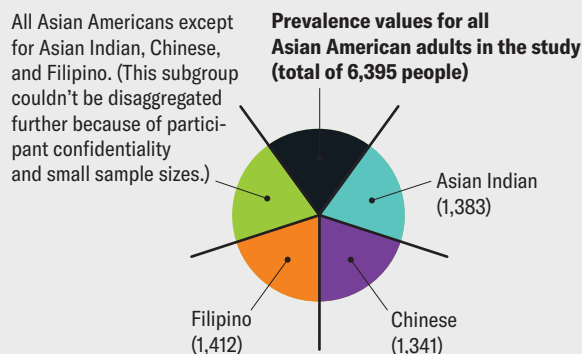
Kauh's parents were Korean immigrants who owned a convenience store in Philadelphia. Even as a teen, Kauh could tell that their grueling schedules, language issues and social isolation took a physical and mental toll. Their lives were hardly those of a model minority. "I could see the challenges they experienced on a daily basis, but no one ever really talked about that except to frame it as 'look how hardworking they are,'" she says.

The social stressors Kauh's parents experienced were financial and cultural, both of which can affect a person's health. Language barriers, racism, changes in diet with the move to a new country and the circumstances of that move—whether someone migrates to pursue a graduate degree or to flee from conflict—can add up. None of these factors are related to the biological basis of disease, but they determine what resources a person or community might need to achieve good health.

When researchers understand the links between social factors and people's health, they can begin to design tailored solutions. Food is one clear example. In the U.S., South Asian communities have disproportionately high rates of heart disease—an observation often explained by diet, says Alka Kanaya, a clinician who studies diabetes at the University of California, San Francisco. Researchers typically gather details about food habits using a list of standard questions based on Western diets that don't represent global cuisines. Advice about what constitutes a "healthy" food is also based on studies conducted with Western diets. "You have to be specific to what people may be eating

Heart Health across Asian American Communities

Food insecurity, living in an unsafe neighborhood, exposure to nicotine, and other social factors can increase risk of heart disease. But not everyone is affected the same way. Grouping data from diverse groups together hides the differences. A 2024 analysis by Eugene Yang and his colleagues found that Filipino, Chinese and Asian Indian adults experience different health outcomes in response to social and environmental stress.



Prevalence of Cardiovascular Risk Factors, by Asian American Subgroup (age standardized, self-reported)



and how they may be cooking it. Having nonaccurate ways of measurement just gives you useless data,” Kanaya says.

For the past decade Kanaya and other researchers have run a study of heart health among South Asians living in the U.S. called Mediators of Atherosclerosis in South Asians Living in America (MAS-ALA). It includes a food-frequency questionnaire that lists many South Asian foods, such as dhokla (a savory cake), sambar (lentil stew), steamed fish, lamb curry and popular snacks. Last year the researchers analyzed the diets of nearly 900 people from the study and identified

foods correlated with a “South Asian Mediterranean-style diet”—one rich in fresh vegetables, fruit, fish, beans and legumes. They found that people who ate more of these foods had a lower risk of heart disease and diabetes than other people in the cohort.

Data such as these can help clinicians advise patients more effectively by offering dietary solutions that may be easier for them to follow rather than forcing a more Western lifestyle on them, Kanaya explains.

GETTING GRANULAR with community data proved to be a lifesaving strategy in

Hawaii during the worst of the COVID pandemic. The state health department’s infectious disease team was heavily focused on controlling the spread of the virus at the start in 2020. But the scientists were “thinking of it in terms of a purely biological system versus understanding what puts people at risk,” says Joshua Quint, an epidemiologist at the Hawaii State Department of Health. “Accurate measurement of social factors is so important.”

To gather those data, Quint teamed up with Matagi and Kaholokula, the University of Hawai‘i physician, to form a COVID investigation team. The group quickly

When researchers understand the links between social factors and health, they can begin to design tailored solutions.

discovered there was no way to figure out which of the Native Hawaiian and 20 or more Pacific Islander communities needed resources or what those resources were. The data at hand were simply too sparse to base any estimates on. So the team began recording COVID deaths with more specific demographic details. When counts were low enough that they risked making individuals identifiable, the team noted these details in a separate section of the database to ensure that information from smaller communities was not lost in an aggregate, Matagi says.

The team members didn't just gather information—they shared it with the communities through hours of virtual visits and phone calls. As they talked, the carefully gathered and stored details helped communities see their own losses amid the sea of numbers. No one could deny the devastation they'd experienced, nor could their experiences be minimized by a database that didn't represent them and their needs. The strategy was especially effective among the Samoan, Marshallese and Chuuk (people originally from part of Micronesia), Matagi says, because they were the three Pacific Islander communities most affected by the disease.

The researchers worked with each community to identify specific requirements. Some needed a safe place to keep healthy family members distanced from those with COVID, others wanted more resources allocated to food or medical care, and still others sought a way to maintain social connections or attend religious gatherings virtually while observing COVID precautions.

The same approach helped the team customize care after the Maui wildfires by recognizing specific needs such as food, shelter and medicine. Its methods have since been highlighted by the World Health Organization as an effective way to reduce health disparities.

Identifying a community's needs and meeting them appropriately can make a range of infectious diseases more man-

ageable. In New York City in the early 2000s, routine hepatitis B vaccination was available only to children. Among adults the virus was typically seen as a sexually transmitted infection (STI), and testing and treatment were offered primarily at HIV clinics.

But the infection was common among Asian American immigrants because of high endemic rates in their countries of origin. In families the virus passed between married partners, from person to person through household contact such as the sharing of utensils, and from mother to child during childbirth. These adults were unlikely to seek care at an STI clinic. At the time, researchers reported rates of hepatitis B among Asian Americans that were about 50 times higher than those among non-Hispanic white people, as well as rates of liver cancer, a common consequence of infection, that were several times higher. In 2003 researchers at New York University teamed up with community organizers, politicians and clinicians in the city to help address the disparity.

The coalition's work helped to establish that the problem would not be stemmed by STI clinic screenings, because that "was not somewhere that we knew Asian American immigrant adults would feel comfortable going," says epidemiologist Simona Kwon of N.Y.U. Langone Health, who joined the effort a few years after it began. "The communities are very different," Kwon says, "and the health priorities are different." Western social norms and biased perceptions had been unintentionally driving health outcomes for hepatitis B.

The N.Y.U. team helped city officials implement community-based programs and offer adult vaccinations at primary care clinics and through community-based organizations. Recognizing that not just viral infection rates but social conventions guide people's choices about care was the key to driving down hepatitis B transmission.

Quint warns that in efforts to apply race and ethnicity data, researchers and policymakers should be careful not to conflate a person's health with these factors alone. Aggregated or not, race and ethnicity are always simple representations of broader social and cultural factors that affect health. But disaggregation, he says, can "help us get beyond race and talk about ethnicity in ways that are more meaningful and helpful."

EFFORTS TO CREATE community-specific solutions are what "actually move the disparities dial," Matagi says. Now, after the success of state- and community-level studies, policymakers are launching larger studies and investing more money in the hopes of better understanding the health of different groups under the AANHPI umbrella.

Last year the White House announced a national effort to prioritize equity for AANHPI communities, and earlier this year the National Heart, Lung, and Blood Institute launched a large epidemiological study to understand health trends in these populations. This seven-year project, named the Multi-ethnic Observational Study in American Asian and Pacific Islander Communities (MOSAIC), aims to track the health of 10,000 people who identify with various AANHPI subgroups. One challenge, Kanaya says, will be to find out how granular they can get—keeping the data anonymized but with sufficient detail to identify meaningful trends, yet without adding so many checkboxes that a long list leaves participants exhausted.

Establishing new categories of race and ethnicity may seem to contradict efforts to make medicine and health care equitable and free of racial bias. But done right, these endeavors can be complementary. "There's a push to avoid talking about race, and I think there are big risks associated with that if it's coming from a place of wanting to ignore problems," Quint says. "We need statistics that cut across all ranges of demographic factors so we can find out if we're building a more just and fair society."

Jyoti Madhusoodanan is a science journalist based in Portland, Ore. She covers health, medicine and the life sciences.

History Lessons

Clinics and public health researchers are taking direct aim at the mpox outbreak by starting in local clinics and using tools that were developed to tackle HIV/AIDS

BY CHARLES EBIKEME

THE ABANDONED BUILDINGS behind the New Somerset hospital in Cape Town, South Africa, are prime real estate along the waterfront, so guards patrol the area day and night to protect against squatters. But squatters aren't the only visitors. Tucked in among the empty facades is the Ivan Toms Center for Health, one of the first clinics in South Africa for men who have sex with men. It was launched in 2009 to provide comprehensive, free and sensitive health care. These days a new concern is on the minds of its visitors: mpox.

The first human case of mpox, formerly known as monkeypox, was described in the 1970s. The disease is thought to be caused by a virus that jumped from animals to humans and causes symptoms similar to smallpox. This past August the World Health Organization designated mpox a public health emergency of international concern for the second time in two years. Although the risk of mpox is not limited to men who have sex with men, the transmission dynamics of the 2022 outbreak led researchers and public health officials to identify them as a high-risk group. During 2022 more than 90 percent of known cases were among gay, bisexual, and other men who have sex with men. As the outbreak builds, Ivan Toms and similar clinics have seen an increase in patients wanting information.

Epidemics begin and end in communities. Today people around the world understand and respond to outbreaks differently than they did before the COVID pandemic. They appreciate concepts of transmission, protection and vaccine availability at a deeply personal level and are hungry for information. They want to know if a case has appeared locally and, if so, how to protect themselves. And the community most affected by mpox is one that has suffered multiple other outbreaks—most notably, the HIV/AIDS crisis. Critically, that means it's a community that clinicians and public health researchers know, understand and collaborate with.

Dimie Ogoina, a Nigerian infectious disease physician-scientist, and his team were the first to describe sexual transmission of mpox in Nigeria in 2017. He believes that what makes the disease so challenging is the comorbidities that exist in Africa, especially co-infection with HIV. His team noticed that those with the most severe cases of mpox also had HIV infections. "Most of them had advanced HIV ... and [were] not on treatment," Ogoina says.

People with HIV accounted for around 40 percent of those diagnosed with mpox in the 2022 outbreak, and recent studies suggest that people who have more advanced HIV have worse clinical outcomes and higher mortality from mpox. How the two diseases interact is still a mystery, however. Researchers have yet to tease apart whether HIV infection raises the risk of acquiring mpox or increases its severity or whether people living with HIV simply might be more likely to be diagnosed because they're already receiving better care. Better understanding this connection could be critically important. As the outbreak spreads to more nonendemic countries, effective treatment of HIV could hold one key to bringing the outbreak to an end.

MPOX'S PRESENT ECHOES HIV's past—it's a disease that has the potential to affect everyone and is more dangerous within a specific community. The comparison is etched in the brick and mortar of the clinic on the waterfront: Ivan Toms, the man, was both an anti-Apartheid and a gay rights activist.

The challenge with both diseases is how to get information to an already stigmatized group of people in a timely enough manner to halt the ongoing outbreak without making that stigma even worse. The 2022 outbreak showed that our first attempts failed: an article in *PLOS Global Health* was simply entitled "Monkeypox Is Not a Gay Disease," recognizing that stigma had quickly emerged around the virus, echoing the early days of the HIV pandemic.

The advantage today is that those dealing with mpox have lessons from HIV/AIDS to follow. One small but meaningful way this has already been addressed is its name: monkeypox was renamed in 2022 to mitigate against racist and stigmatizing language. And as a result of the 2022 global emergency and lessons learned from the HIV/AIDS pandemic, public health officials are better equipped to build coordinated messaging and meet patients where they are.

"[Our] clients overall are now familiar with mpox, as we had the 2022 outbreak and did extensive education," says Johan Hugo, an HIV clinician at the Ivan Toms Center. The center has integrated mpox services into its HIV care as recommended by the WHO and is part of a network of clinics and government agencies, including the South African Department of Health, that are using common messaging and strategies for mpox. "We work closely with organizations that support key populations to ensure we remain in line with one another," he says. Such coordination in messaging helps to combat stigma around a disease that is not yet fully understood.

Despite significant improvements in access to HIV/AIDS treatment, gaps persist because patients are worried about their diagnosis creating stigma related to sexual and reproductive health. It is no different with mpox. The stigma associated with mpox can adversely affect prevention and treatment, with people less likely to disclose symptoms or seek care—they may even hide their condition for fear of being diagnosed. There is no specific treatment for mpox, and its symptoms are similar to those of other viruses such as chicken pox. But rapid, accurate diagnosis is the only way to prevent transmission and end outbreaks.

To achieve this, public health officials are taking everything they've learned from HIV and using it to attack mpox outbreaks. For instance, Ivan Toms and other clinics have developed approaches for delivering health services that allow for discretion and



privacy. In addition to onsite testing and health checks, the center also packages and dispenses medications for its clients, eliminating the need to visit a general pharmacy. The approach has been so successful that after becoming the first clinic to run demonstration projects for HIV Pre-Exposure Prophylaxis (PrEP) in Africa in 2015, Ivan Toms is now one of the largest providers of PrEP in South Africa and a key train-

ing institution for service providers across 11 African countries.

PrEP reduces HIV risk by preventing HIV from entering the body and replicating. But protection requires that users maintain high levels of the medication in their bodies. Because adherence is crucial, practitioners aim for frictionless care that removes any social barriers. To that end, the clinic runs a WhatsApp service, smart lockers that safely

store patients' medicines, and mobile units that go directly into communities. Across the entire Cape Metro area, mobile units provide comprehensive HIV testing, treatment and prevention services, including self-screening, PrEP, antiretroviral drug initiation and follow-up, viral load testing, and screening for sexually transmitted infections. "Our mobile units are an extension of our facility and seek to provide the same



formation online and then to ensure that every client who comes through our services is provided direct information about the current situation,” Hugo says. Most days, that’s as many as 120 to 150 people.

THERE ARE TWO VARIANTS of mpox virus: clade I is endemic to central Africa and has killed up to 10 percent of the people it has infected during previous outbreaks, making it far deadlier than clade II, the type responsible for the 2022 outbreak. Both are circulating today in different countries in Africa. And unlike the 2022 outbreak, this one—which is tearing through the Democratic Republic of Congo (DRC)—has largely spread through men seeing women who are sex workers. “We are not dealing with one outbreak of one clade—we are dealing with several outbreaks of different clades in different countries with different modes of transmission and different levels of risk,” said Tedros Adhanom Ghebreyesus, WHO’s director general, during his opening remarks at the emergency committee meeting where the global health emergency was declared. “Stopping these outbreaks will require a tailored and comprehensive response, with communities at the center.”

In July 2024 South Africa notified the WHO of 20 confirmed mpox cases between May 8 and July 2, including three deaths—the first reported in the country since 2022. Cases occurred in three of South Africa’s nine provinces, including the Western Cape, where the Ivan Toms Center for Health resides. How the outbreak evolves from here will depend heavily on case identification and treatment management.

There is one internationally approved vaccine for mpox (another is approved in Japan with emergency approval in the DRC), which can act as both preexposure and postexposure prophylaxis for people at high risk. But although the vaccine is available in numerous high-income nations, current access in South Africa is limited to nonexistent. “The vaccine was originally made for smallpox, with U.S. funding,” says Mohga Kamal-Yanni, a senior policy adviser to the People’s Medicines Alliance, a global coalition with the goal of creating equitable access to vaccines and other medical technology. The companies that make these vaccines hold their patents, she says, “and when the mpox outbreak started, there was

no discussion on technology transfer to another potential manufacturer.”

During the COVID pandemic, African countries surpassed all expectations despite challenges in vaccine access. Tanzania emerged as one of the best-performing African countries for COVID vaccination rates: Between January 2022 and April 2023 the country managed to bump its total population vaccination rate from 2.8 to 51 percent. This happened in part because COVID-specific vaccinations were integrated with other routine health services, allowing for effective delivery.

The COVID pandemic forever changed Africa’s policy, regulatory and vaccine landscapes. Low-income countries have learned to push through regulatory red tape, advocate for their people and work with high-income nations to get vaccines distributed more equitably. After putting a vaccination plan in place, Nigeria received the first donation of 10,000 vaccines from the U.S. just a few days after the global mpox emergency was declared. Other donations are aimed at countries across the African continent: Spain promised 500,000 doses from its stockpile, the U.S. committed to sending another 50,000 doses to the DRC, and Japan pledged millions of doses. Some of those vaccines have already arrived in Africa.

Citing lessons learned from COVID, global health institutions are also mobilizing resources. Gavi, the Vaccine Alliance, has mobilized resources for mpox, the rollout of which will be an early test of Gavi’s First Response Fund. The fund aims to make resources immediately available for a vaccine response to a public health emergency and includes a \$500-million fund aimed at ensuring early access to vaccines within days of an emergency declaration. This, according to Gavi director of development finance David Kinder, was one of the big lessons learned from COVID.

The 2022 mpox outbreak was deemed to be over about nine months after the WHO declared an emergency. The 2024 outbreak could be larger and longer. If it is going to be extinguished as quickly, lessons learned from previous pandemics hold the key.

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level of care,” Hugo says. “Each of our teams provides comprehensive HIV testing, treatment and prevention.”

Because so many men who have acquired mpox are using PrEP, researchers think HIV may simply be another marker of higher-risk behaviors facilitating infection. The goal will be for mpox services to follow the same community outreach. “Our strategy for mpox currently is to provide broader in-

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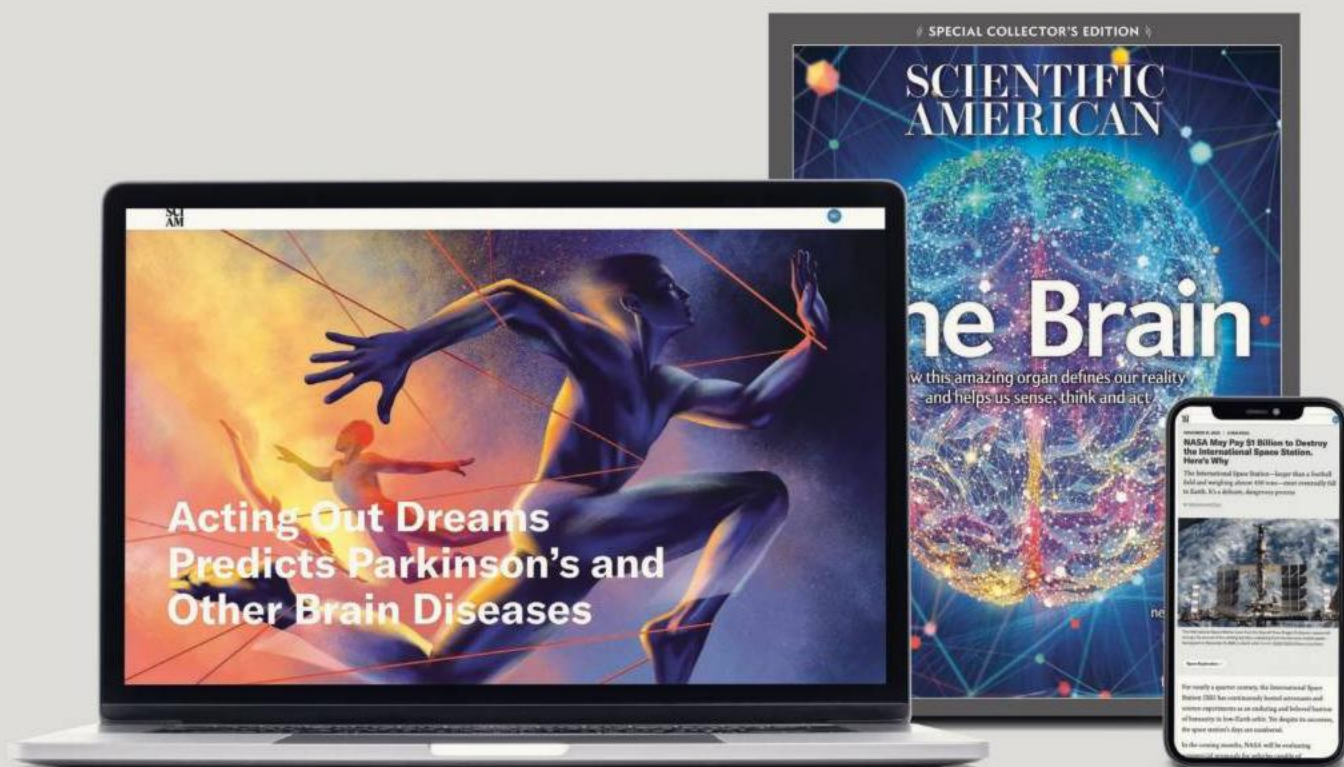
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Vote in November for Science

Kamala Harris has plans to improve health, boost the economy and mitigate climate change. Donald Trump has threats and a dangerous record **BY THE EDITORS**

IN THE NOVEMBER ELECTION, the U.S. faces two futures. In one, the new president offers the country better prospects, relying on science, solid evidence and the willingness to learn from experience. She pushes policies that boost good jobs nationwide by embracing technology and clean energy. She supports education, public health and reproductive rights. She treats the climate crisis as the emergency it is and seeks to mitigate its catastrophic storms, fires and droughts.

In the other future, the new president endangers public health and safety and rejects evidence, preferring instead nonsensical conspiracy fantasies. He ignores the climate crisis in favor of more pollution. He requires that federal officials show personal loyalty to him rather than upholding U.S. laws. He fills positions in federal science and other agencies with unqualified ideologues. He goads people into hate and division, and he inspires extremists at state and local levels to pass laws that disrupt education and make it harder to earn a living.

Only one of these futures will improve the fate of this country and the world. That is why, for only the second time in our magazine's 179-year history, the editors of *Scientific American* are endorsing a candidate for president. That person is Kamala Harris.

Before making this endorsement, we evaluated Harris's record as a U.S. senator and as vice president under Joe Biden, as well as policy proposals she's made as a presidential candidate. Her opponent, Donald Trump, who was president from 2017 to 2021, also has a record—a disastrous one. Let's compare.

HEALTH CARE. The Biden-Harris administration shored up the popular Affordable Care Act (ACA), giving more people access to health insurance through subsidies. During Harris's September 10 debate with Trump, she said one of her goals as president would be to expand it. Scores of studies have shown that people with insurance stay healthier and live longer because they

can afford to see doctors for preventive and acute care. Harris supports expansion of Medicaid, the U.S. health-care program for low-income people. States that have expanded this program have seen health gains in their populations, whereas states that continue to restrict eligibility have not. To pay for Medicare, the health insurance program primarily for older Americans, Harris supports a tax increase on people who earn \$400,000 or more a year. And the Biden-Harris administration succeeded in passing the Inflation Reduction Act (IRA), which caps the costs of several expensive drugs, including insulin, for Medicare enrollees. Harris's vice presidential pick, Tim Walz, signed into law a prohibition against excessive price hikes on generic drugs as governor of Minnesota.

When in office, Trump proposed cuts to Medicare and Medicaid. He also pushed for a work requirement as a condition for Medicaid eligibility, making it harder for people to qualify for the program. As a candidate, both in 2016 and this year, he pledged to repeal the ACA, but it's not clear what he would replace it with. When prodded during the September debate, he said, "I have concepts of a plan" but didn't elaborate. Like Harris, however, he has voiced concern about drug prices, and in 2020 he signed an executive order designed to lower prices of drugs covered by Medicare.

The COVID pandemic has been the greatest test of the American health-care system in modern history. Harris was vice president of an administration that boosted widespread distribution of COVID vaccines and created a program for free mail-order COVID tests. Wastewater surveillance for viruses has improved, allowing public health officials to respond more quickly when levels are high. Bird flu now poses a new threat, highlighting the importance of the Biden-Harris administration's Office of Pandemic Preparedness and Response Policy.

Trump touted his pandemic efforts during his first debate with Harris, but in 2020 he encouraged resistance to basic pub-

lic health measures, spread misinformation about treatments and suggested injections of bleach could cure the disease. By the end of that year about 350,000 people in the U.S. had died of COVID; the current national total is well over a million. Trump and his staff had one great success: Operation Warp Speed, which developed effective COVID vaccines extremely quickly. Yet Trump plans billion-dollar budget cuts to the Centers for Disease Control and Prevention and the National Institutes of Health, which started the COVID-vaccine research program. These steps are in line with the guidance of Project 2025, an extreme conservative blueprint for the next presidency drawn up by many former Trump staffers. He's also talked about ending the Office of Pandemic Preparedness and Response Policy.

REPRODUCTIVE RIGHTS. Harris is a staunch supporter of reproductive rights. During the September debate, she spoke plainly about her desire to reinstate "the protections of *Roe v. Wade*" and added, "I think the American people believe that certain freedoms, in particular the freedom to make decisions about one's own body, should not be made by the government." She has vowed to improve access to abortion. She has defended the right to order the abortion pill mifepristone through the mail under authorization by the U.S. Food and Drug Administration, even as MAGA Republican state officials have tried—so far unsuccessfully—to revoke that right. As a senator, she co-sponsored a package of bills to reduce rising rates of maternal mortality.

Trump said he would vote against a ballot measure expanding access to abortions in Florida, where he lives. The current Florida law makes most abortions illegal after six weeks of pregnancy, before many people even know they are pregnant.

Trump appointed the conservative U.S. Supreme Court justices who overturned *Roe v. Wade*, removing the constitutional right to a basic health-care procedure. He spreads misinformation about abortion—



during the September debate, he said some states support abortion into the ninth month and beyond, calling it “execution after birth.” No state allows this. He also refused to answer the question of whether he would veto a federal abortion ban, saying Congress would never approve such a ban in the first place. He made no mention of an executive order and praised the Supreme Court, three justices of which he placed, for sending abortion back to states to decide. This ruling led to a patchwork of laws and entire sections of the country where abortion is dangerously limited.

GUN SAFETY. The Biden-Harris administration closed the gun-show loophole, which had allowed people to buy guns without a license. The evidence is clear that easy access to guns in the U.S. has increased the risk of suicides, murder and firearm accidents. Harris supports a program that temporarily removes guns from people deemed dangerous by a court.

Trump promised the National Rifle Association that he would get rid of all Biden-Harris gun measures. Even after Trump was injured and a supporter was killed in an attempted assassination, the former president remained silent on gun safety. His running mate, J. D. Vance, said the increased number of school shootings was

an unhappy “fact of life” and the solution was stronger school security.

ENVIRONMENT AND CLIMATE. Harris said pointedly during the September debate that climate change was real. She would continue the responsible leadership shown by Biden, who has undertaken the most substantial climate action of any president. The Biden-Harris administration restored U.S. membership in the Paris Agreement on coping with climate change. Harris’s election would continue IRA tax credits for clean energy, as well as regulations to reduce power-plant emissions and coal use. This approach puts the country on course to cut U.S. carbon emissions in half by 2030. The IRA also includes a commitment to broadening electric vehicle technology.

Trump has said climate change is a hoax, and he dodged the question “What would you do to fight climate change?” during the September debate. He pulled the U.S. out of the Paris Agreement. Under his direction, the Environmental Protection Agency and other federal agencies abandoned more than 100 environmental policies and rules, many designed to ensure clean air and water, restrict the dangers of toxic chemicals and protect wildlife. He has also tried to revoke funding for satellite-based climate-research projects.

TECHNOLOGY. The Biden-Harris administration’s 2023 Executive Order on Safe, Secure and Trustworthy Development and Use of Artificial Intelligence requires that AI-based products be safe for consumers and national security. The CHIPS and Science Act invigorates the chipmaking industry and semiconductor research while growing the workforce. A new Trump administration would undo all of this work and quickly. Under the devious and divisive Project 2025 framework, technology safeguards on AI would be overturned. AI influences our criminal justice, labor and health-care systems. As is the rightful complaint now, there would be no knowing how these programs are developed, how they are tested or whether they even work.

THE 2024 U.S. BALLOTS are also about Congress and local officials—people who make decisions that affect our communities and families. Extremist state legislators in Ohio, for instance, have given politicians the right to revoke any rule from the state health department designed to limit the spread of contagious disease. Other states have passed similar measures. In education, many states now forbid lessons about racial bias. But research has shown such lessons reduce stereotypes and do not prompt schoolchildren to view one another negatively, regardless of their race. This is the kind of science MAGA politicians ignore, and such people do not deserve our votes.

Harris does deserve our vote. She offers us a way forward lit by rationality and respect for all. Economically, the renewable-energy projects she supports will create new jobs in rural America. Her platform also increases tax deductions for new small businesses from \$5,000 to \$50,000, making it easier for them to turn a profit. Trump, a convicted felon who was also found liable for sexual abuse in a civil trial, offers a return to his dark fantasies and demagoguery, whether it’s denying the reality of climate change or the election results of 2020 that were confirmed by more than 60 court cases, including some overseen by judges appointed by Trump.

One of two futures will materialize according to our choices in this election. Only one is a vote for reality and integrity. We urge you to vote for Kamala Harris. ●

How Science Upstaged Climate Denial

A play celebrates the agreement that opened nations worldwide to accepting the science of climate change

BY BEN SANTER

IT'S A VERY STRANGE experience to watch a play in which you are a character—and to shake hands with the person who plays you. I did both this past July while attending a performance of *Kyoto* at the Swan Theater in Stratford-upon-Avon in England. The moment meant more, of course, than just a glimpse of oneself on history's stage. The play shows how science won out over climate denial in a critical face-off between scientists and industry over the future of the planet.

Kyoto is about the Kyoto Protocol, an agreement made more than 25 years ago that, as summarized by the United Nations, committed “industrialized countries and economies in transition to limit and reduce greenhouse gases (GHG) emissions in accordance with agreed individual targets.” Written by Joe Murphy and Joe Robertson, the play provides a dramatic retelling of a historic meeting in December 1997 in Kyoto, Japan, where the protocol was finalized.

At this meeting, a key Intergovernmental Panel on Climate Change (IPCC) scientific assessment helped to inform the international emissions-reduction negotiations—the Working Group I part of the IPCC Second Assessment Report, which was completed in 1995 and published in early 1996. I was convening lead author of chapter eight, “Detection of Climate Change and Attribution of Causes.” The role of the IPCC, back in 1995 and today, was to advise the governments of the world on the science and negative impacts of climate change, as well as on strategies for mitigating and adapting to those impacts.

In 1990 the first IPCC scientific assessment had concluded that the jury was still out on

whether a human-caused climate change signal could be identified in real-world climate data. The 1995 assessment's chapter reached a very different conclusion, encapsulated in 12 simple words: “The balance of evidence suggests a discernible human influence on global climate.” This was a momentous statement from cautious scientists and a rather conservative organization.

Multiple factors contributed to this dramatic transition. Advances in the science of climate fingerprinting, for example, made a big difference in climate research during the five years between the two reports. Fingerprinting seeks to identify the unique signatures of different human and natural influences on Earth's climate. This uniqueness becomes apparent if we probe beyond a single number—such as the average temperature of Earth's surface, including land and oceans—and look instead at complex patterns of climate change. Patterns have discriminatory power and allow scientists to separate the signature of human-caused fossil-fuel burning from the signatures of purely natural phenomena (such as El Niño and La Niña climate patterns, changes in the sun's energy output, and effects of volcanic eruptions).

Kyoto describes some of the fingerprint evidence that was presented during a key meeting in Madrid in November 1995, ahead of the Kyoto face-off dramatized in the performance. The “discernible human influence on global climate” conclusion was finalized in Madrid, where the participants included 177 delegates from 96 countries, representatives from 14 nongovernmental organizations, and 28 lead authors of the IPCC Second Assessment Report.

Ben Santer

is a climate scientist and a John D. and Catherine T. MacArthur Fellow. From 1992 until his retirement in 2021, Santer pursued research in climate fingerprinting at Lawrence Livermore National Laboratory in California. He was a contributor to all six of the Intergovernmental Panel on Climate Change's completed scientific assessments.

As a lead author of the evidence chapter, I was there among them in that Madrid plenary room. So were several of the other characters in *Kyoto*, including the play's central one: Donald Pearlman, who was a lawyer and lobbyist for the Climate Council, a consortium of energy interests.

Pearlman and I were on opposite sides of the Madrid chessboard. My efforts were directed toward synthesizing and assessing complex science and ensuring that the science was accurately represented in the IPCC report. His were directed toward delaying international efforts to reduce emissions of heat-trapping greenhouse gases. Such reductions were bad for the business interests he represented and for the revenues of oil-producing countries such as Saudi Arabia and Kuwait.

Pearlman, who died in 2005, understood the singular importance of the Madrid “discernible human influence” conclusion. He knew it was the scientific writing on the wall. The jury was no longer out. Human-caused fingerprints had been identified in records of Earth's surface and atmospheric temperatures. Humans were not innocent bystanders in the climate system; they were active participants. Burning fossil fuels had changed the chemistry of Earth's atmosphere, thereby warming the planet and sending Earth's vital signs into concerning territory. The Madrid conclusion meant the days of unfettered fossil-fuel use and carbon pollution were numbered.

It also made Pearlman's lobbying job more difficult. His response was to attack the science and the scientists as part of a rear-guard action to delay international agreement on reducing greenhouse gas emissions. As Pearlman's character explains in *Kyoto*, it was a deliberate “scorched-Earth” strategy: torch the science and the scientists.

I experienced this strategy firsthand in a memorable personal meeting with Pearlman in Washington, D.C., on May 21, 1996. After I spoke at the U.S. Congress's Rayburn House Office Building about the scientific evidence for human fingerprints on global climate, Pearlman confronted me and started screaming at me—literally screaming. He expressed outrage at what he claimed were unauthorized changes to the chapter I had been responsible for. The changes had in fact been authorized by the



Getting *Kyoto* ready for its world premiere in London this past summer.

IPCC, as Pearlman knew very well. He had been present at the Madrid meeting where the changes were discussed.

Ultimately he lost. Despite tremendous differences among countries in terms of their national self-interest, culpability for the problem of human-caused climate change, and vulnerability to the effects of climate change, an international agreement was finally reached. The 1997 *Kyoto Protocol* commits participating countries to a common goal: reducing greenhouse gas emissions and avoiding “dangerous anthropogenic interference” in Earth’s climate system. *Kyoto* is the dynamic story of how that agreement was achieved.

In one memorable line in the play, Pearlman’s wife, Shirley, asks him, “Are we on the wrong side?” The question is prompted by an exposé of Pearlman’s lobbying activities in the German news magazine *Der Spiegel*. Shirley wants to know whether her husband’s efforts to cast doubt on the climate-change science—and on the scientists involved in advancing that science—place them on the wrong side of history. The Pearlman character in the play responds, “No, Shirley. We’re not on the wrong side.”

But Pearlman and the industries he represented were on the wrong side of the science. Nearly 30 years after the Madrid IPCC meeting and after Pearlman’s concerted efforts to undercut climate science, human fingerprints on Earth’s climate are now unequivocal and ubiquitous. The cautious 1995 “discernible human influence” finding has been confirmed and strengthened by all four subsequent IPCC assessments. The scientists in Madrid got it right.

Pearlman and his employers were also on the wrong side of history. Today 191 countries have ratified the Kyoto Protocol. Although the U.S. Congress never did ratify it, the protocol helped to pave the way for the 2016 Paris Agreement. The serious consequences of human-caused global warming are now manifest to all, building momentum for real action to cut carbon pollution. The days of climate science denial are numbered.

But they are not quite over yet. Another Donald—former president Donald Trump—has repeatedly denied the reality and seriousness of climate change. It’s no surprise that his backers look a lot like Pearlman’s. There is a very small probability that Trump will ever watch *Kyoto*. There’s an even smaller probability that Trump will consider whether he, too, is on the wrong side of science and history.

Sadly, he is. Trump’s return to the U.S. presidency would reprise Pearlman’s heyday, when manufactured doubt obscured mature scientific understanding. *Kyoto* tells the story of how that scientific understanding evolved and how powerful vested interests tried to destroy it. It is absolutely vital to give that account today, with the bill for climate change coming due all around us.

I hope *Kyoto* reaches audiences I could never dream of reaching through all the scientific papers I’ve ever written. And I hope it provides us with what mathematicians call an existence principle—proof that something difficult is possible. The existence principle in *Kyoto* is that humanity can come together and solve a seemingly intractable problem. ●

Many Adults Don’t Outgrow ADHD

The disorder looks different in grown-ups, but diagnosis is improving

BY LYDIA DENWORTH

KNOW OF SOMEONE who was diagnosed with attention deficit hyperactivity disorder (ADHD) as a child in the 1990s. When he turned 18, his insurance company notified him that his medication—a kind that gives kids with ADHD a better chance to succeed in school and can be quite pricey—was no longer covered. ADHD, the insurer said in effect, was a childhood disorder. What an unfortunate choice: to either struggle financially to pay for your medication or head into college or the workforce without the treatment that helps you.

The idea that ADHD was restricted to kids was deeply ingrained at the time. People thought “it was a developmental lag that just needed to catch up,” says psychologist Stephen Faraone of Upstate Medical University in Syracuse, N.Y.

But ADHD often continues into adulthood, multiple studies have now shown. The current estimated prevalence in adults is around 2.5 to 3 percent, compared with 5 to 6 percent in children. The 2013 edition of the *Diagnostic and Statistical Manual of Mental Disorders (DSM-5)* made it easier to diagnose adults, saying grown-ups can have five symptoms instead of the six required in children and acknowledging that ADHD might look different as people grow older. “They don’t climb on furniture and stuff like that,” Faraone says. (The *DSM-5* still requires that some symptoms be present before the age of 12.) The first guide-

lines for diagnosing and treating ADHD in adults are now being developed by the American Professional Society of ADHD and Related Disorders.

In adults, the disorder can appear rather different than in youngsters. Grown-ups dealing with inattention and hyperactivity may have more difficulty than average completing long reports for work, sitting through meetings or restaurant meals, paying bills on time, or sustaining romantic relationships. “We’re shining a light on what’s probably really going on,” says clinical psychologist Margaret H. Sibley of the University of Washington School of Medicine, who worked on several of the new studies. “People in adult mental health settings just aren’t even being screened for it.”

Because of the lack of screening, many people who could benefit from treatment aren’t getting it, experts say. Also, it is likely that the rate in adults is higher than the 3 percent I mentioned earlier. A 2021 analysis showed that when based on symptoms alone rather than documented childhood onset, the rate in adults ranges from about 9 percent in young adults to more than 4 percent in those older than 60.

Some people do outgrow the disorder, though probably far fewer than previously thought. (It’s unclear whether people’s brains become more neurotypical over time or they learn to compensate.) A 2022 study in the *Journal of American Psychiatry*, led by Sibley, found that slightly more than 9 percent of people diagnosed as children had no sign of the condition as adults. Usually such people had milder symptoms and strong support from parents.

A more common scenario is that the severity of symptoms fluctuates. Previous studies tested people once in adulthood and gave a yes/no diagnosis. Sibley’s study retested teens and young adults multiple times and revealed that 60 percent of those who showed remission later experienced a recurrence. “It appears to be a condition that waxes and wanes,” Sibley says. “There is likely a role of environment in turning up or down the volume of somebody’s difficulties.” In other words, ADHD symptoms may tend

to flare up when life gets stressful and ease when life is calmer.

Although a few studies have suggested it is possible for ADHD to appear for the first time in adulthood, more recent research indicates that adult onset is highly unlikely. Nearly all such cases are probably either misdiagnoses of another condition, such as substance use or anxiety, or instances in which childhood symptoms were missed, Sibley says.

Many parents—and even grandparents—first recognize their own symptoms when their child is diagnosed. This is particularly true of females with the disorder, whose behavior as children tends to be more inattentive than hyperactive like the stereotypical boy with ADHD. As adults, however, females are more likely than males to seek mental health treatment. “When you’re a child, you get mental health treatment if you cause someone else a problem,” Faraone says. “When you’re an adult, you go in because you have a problem.”

Most people who have been diagnosed with ADHD will try medication (usually stimulants such as Ritalin), but within the first year 40 to

50 percent discontinue the pills for at least 180 days, says psychiatric epidemiologist Isabell Brikell of the Karolinska Institute in Sweden. Reasons can include adolescent independence, increased costs and, for adults, providers less trained in treating ADHD. Thanks to parental oversight, children are more likely to maintain treatment, but a large study across eight countries showed that discontinuation rates peak for patients at the age of 18. “The transition from child and adolescent psychiatric care does not work well in many countries,” Brikell says.

The lack of proper treatment can raise other health problems. Brikell says several Swedish-led studies have shown that ADHD is associated with diseases that increase with aging, such as a slightly higher risk of hypertension and other cardiovascular diseases. The disorder has been linked to greater risks of obesity, substance use and sleep problems.

The good news is that because the medical community is increasingly aware of the nuances of adult ADHD, people experiencing difficulties have a better chance of getting a professional diagnosis. For grown-ups, Faraone says, proper treatment can be life-changing. ●



Lydia Denworth is an award-winning science journalist and contributing editor for *Scientific American*. She is author of *Friendship* (W. W. Norton, 2020).

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Putting equity at our core: serving patients, communities and businesses



For more than 240 years, Takeda has understood why putting patients first matters. Fuelled by our purpose to create 'better health for people and a brighter future for the world', we remain committed to achieving equitable healthcare for all. We acknowledge that addressing the multi-faceted global issue of inequity in healthcare is both a pressing social need and a business priority.

We proactively engage in dialogue, drive collaboration and share learnings focused on ways we can all help advance health equity. To facilitate this intricate and nuanced work, Takeda is leveraging its global capabilities and resources to embed health equity across our company. With this approach, our aim is to deliver innovative medicines and products to more of the people and communities that need them.

We recognize there is no one-size-fits-all solution for infusing health equity throughout an organization. Resources, tools and people will (and should) be different. Solutions and services will (and should) be customized and tailored to meet the needs of the patients and communities we're ultimately trying to serve. Our decision-making framework of patient, trust, reputation, business (PTRB) — always in that order — provides an anchor that allows us to embed our health-equity principles into our business operations.



Embedding Health Equity Into Your Work Starts With Asking Important Questions:



Are my teams and tools reflective of the communities we are trying to serve?



Are we including diverse perspectives in our decision making?



How are we listening to and learning from communities?



What approaches and solutions can we develop to address barriers to care?

Takeda

ADVANCING HEALTH EQUITY STARTS WITHIN THE WALLS OF AN ORGANIZATION

Often, when companies think about health equity they simply deem it to be part of diversity, equity and inclusion (DE&I) or corporate social responsibility (CSR) initiatives. Understanding its relevance and the role companies can play may be difficult, but we believe that health equity is both an important social concern and an opportunity to aid our business. For Takeda, health equity can help us excel at holistic value-based healthcare outcomes; inform, improve and enhance clinical research; and support other opportunities to grow our global impact and create a more sustainable business. Embedding

health equity also builds trust with local partners, allowing us to better understand the underlying causes of inequities and how we can co-create solutions with communities to drive change.

As we strive to foster a more inclusive health ecosystem, it has become apparent that this work is not a solo venture. Every contributor has an important and valued role to play — from the convener who can bring the right stakeholders together, to the subject matter expert who intimately understands local community dynamics, to the funder who has the financial means to support a programme.

There is no simple solution to tackling health inequity, but we're confident that infusing health equity principles across our

organization is a strong step in the right direction. Guided by our foundational question — "What more can we do for patients?" — we're constantly evolving. This is where our company's commitment to health equity is key. We're uniquely positioned to incorporate the lens of health equity into our work so it's not a separate initiative, but rather a part of our daily efforts.

PUTTING OUR PATIENTS FIRST THROUGH MEANINGFUL ENGAGEMENT

Integrating health equity considerations into the way we engage with patients continues to ground and guide our value- and outcomes-focused approach. We know that our most innovative medicines and

therapies cannot achieve their potential impact if the people who need them can't access them. Aware of this dynamic, our patient engagement initiatives are designed with a focus on inclusivity and accessibility, ensuring that under-resourced populations have equitable access to healthcare resources and services. Over the last few years, with guidance from several global authority commissions, we've refined our holistic patient engagement approach. This approach helps us engage with patients, collect data and integrate insights throughout the lifecycle — from discovery to delivery.

At Takeda, we're constantly trying to find efficiencies in our governance and operations so we can focus on what matters most to patients. We're using scientifically validated social determinants of health data to better understand patient groups across key markets. This helps our teams uncover insights around the perceptions, behaviours and attitudes that move patients closer to, or away from, healthcare. Our collective patient engagement work reinforces the critical need to not just bring patients to the table, but also to have their voices heard.

ENSURING DIVERSITY IN CLINICAL STUDIES

One such area where we have seen this value operate in practice is through our development programme related to psoriasis. Much of what is known about psoriasis — a chronic skin disease — often does not reflect all skin tones. As a result, these gaps in care can lead to a delayed diagnosis or inadequate care for people of colour with this condition. In fact, individuals with darker skin are historically under-represented in both dermatologic education and research.

We are embedding health equity into the development programme for our investigative



Partnership will look different for every organization and entity – we must cross traditional lines and collaborate between industries and even between the private and public sectors.

oral therapy for psoriasis, ensuring patient diversity is present in our clinical trials and beyond. Guided by our patient-first approach, we are disseminating culturally relatable resources including imagery of psoriasis that reflects the diversity of skin types found within the patient population. We are also providing educational materials aimed at training medical professionals to accurately diagnose psoriasis across different skin types and tones. If we can ensure that clinical trial participant populations, research and educational materials are reflective of the patients who are likely to use the treatment, then we'll have a stronger understanding and confidence that our efforts are supporting many types of patients with psoriasis.

SUPPORTING AND IMPROVING COMMUNITIES BY BUILDING BRIDGES TO CARE

One of the ways that we support patients throughout their journey is through community-based partnerships. By working with our communities, we can help create sustainable change — because when we meet patients where

they are, we often see that the solution probably lies there too. This starts by equipping our teams with the right resources and investments to actively engage with communities. We then listen to the communities and patients to better understand the barriers they face. We take these conversations and glean learnings from their experiences and environment. Together, we co-create solutions that are tailored to the needs of the people they aim to serve across our development, discovery and delivery cycles. This is a long-term commitment because we cannot address any of these issues quickly nor alone — eventually collective efforts will add up and result in tangible, community-oriented change.

Our Oncology Business Unit (OBU) is working to support the Vietnamese American community, a population significantly impacted by lung cancer. We partnered with Gryt Health to convene a community-led advisory committee to uncover the key barriers patients, healthcare providers and the Vietnamese American community faced. We discovered that language and literacy were the biggest hurdles — imagine trying to digest new information

while also having to translate it into your native language.

We asked ourselves: "Would a person actually be able to understand the risks, screening opportunities, treatment options, or how to best navigate the healthcare system in that circumstance?"

Our team gathered existing, culturally-relevant materials about lung cancer and worked with the community advisory board to ensure they were suitable and accessible for the Vietnamese American community. These resources are available on a centralized hub containing information to support the patients at every step along their journey. This reinforces our inclusive approach and commitment to support community-level needs to advance health equity. As the saying goes, nothing is for the community, without the community.

INNOVATIVE DIGITAL APPROACHES CAN HELP ADVANCE HEALTH EQUITY

Takeda is accelerating the use of data, digital and technology (DD&T) to speed the delivery of life-saving medicines, while also easing the burden of diagnosis and treatment for patients, their

Takeda

families and healthcare providers. These technologies are helping us identify areas where health inequities exist and how we may be able to address the gaps in care. We've seen this first-hand in the ways climate change is exacerbating health crises, like in the case of dengue fever.

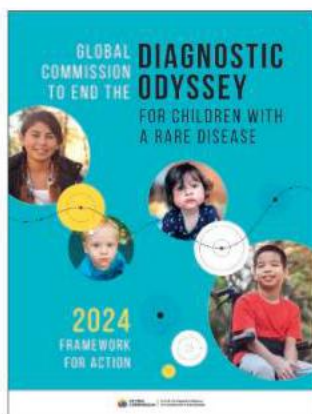
In 2019, dengue was recognized by the World Health Organization (WHO) as one of the top 10 threats to global health. The incidence of dengue has risen 30-fold in the past 50 years, and it is now prevalent in more than 100 countries, in both rural and urban areas¹⁻⁴. Dengue is associated with broad economic and societal burdens, including risks of inequitable health and economic outcomes for vulnerable populations^{1,5}.

Our recent Latin America Dengue Digital Innovation Challenge sparked health innovations and solutions that have the potential to improve dengue prevention, disease education and awareness, and to build further trust in vaccinations. The challenge had a mutually beneficial impact, as it enabled local organizations to access Takeda's global expertise and network, while also providing Takeda with the chance to collaborate with innovative companies focused on fighting dengue fever across the region. The challenge received 50 high-quality ideas across Latin America, with topics ranging from improving disease awareness to generating real-world health data and even

predicting dengue outbreaks. As the threat of dengue grows with climate change, it is increasingly important to work with communities and strengthen the dengue digital innovation ecosystem in Latin America and beyond.

THE POWER OF PURPOSE-DRIVEN COLLABORATION

Takeda is proud to be a founding member and co-chair of the Global Commission to End the Diagnostic Odyssey for Children with a Rare Disease — a multidisciplinary group of rare disease advocates, researchers, physicians and innovators from across the globe who are working to end the long and arduous diagnostic journey. I'm humbled to represent Takeda as a co-chair of the Global Commission, and proud of our work to identify innovative global solutions to tackle today's and tomorrow's challenges in rare disease diagnosis.



Global Commission to End the Diagnostic Odyssey for Children with a Rare Disease

The Global Commission envisions a world where there is equitable support and resources for all children living with a rare disease and their caregivers. That is why the Global Commission has expanded its membership to include more representatives from more countries, including Ghana and the Philippines. The Global Commission has also developed a framework for action in accelerating diagnosis to support global, regional and national efforts to end the diagnostic odyssey. Our goal is to ensure that this framework, and the growing number of case studies being collected globally — including from low- and middle-income countries — which bring it to life, are presented in a way that is both culturally relevant and accessible for countries who may have a less robust healthcare infrastructure. Through this, we hope to accelerate efforts to improve the diagnosis of rare diseases in children.

EMBEDDING HEALTH EQUITY TO BUILD A BRIGHTER FUTURE

Our collective efforts to embed health equity throughout our organization have had a tangible effect on our ability to deliver sustainable impact for patients, our business and future generations to come. I am proud of where Takeda is on this journey right now, and excited about where we will go and the impact I hope we have toward

helping every single individual reach their full health potential. Bringing an organization along on this journey takes time, commitment and investment. Advancing health equity requires us all to play a role.

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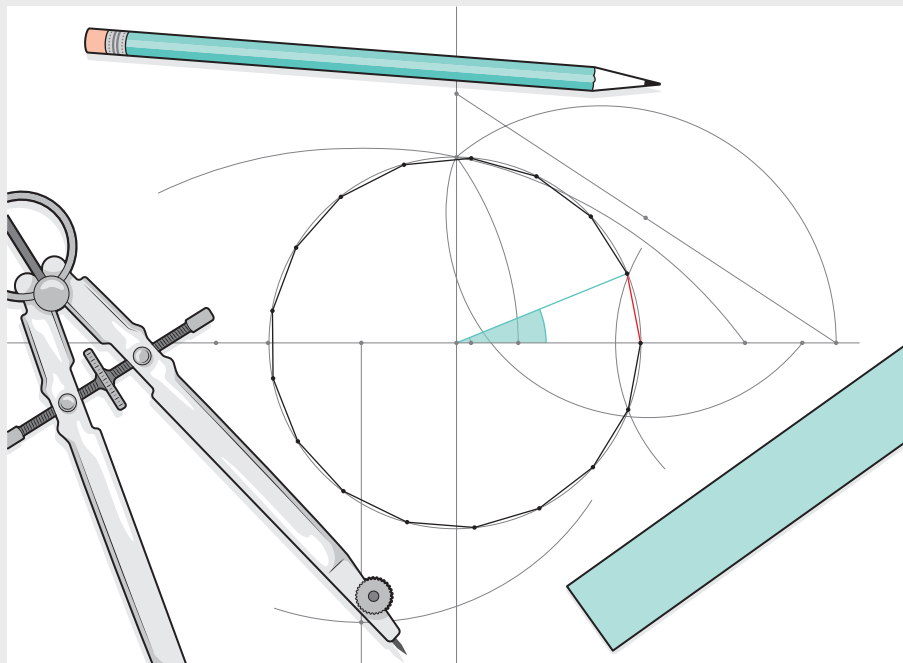
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When Gauss Cracked the Heptadecagon

As a teenager, he solved a 2,100-year-old math problem BY JACK MURTAGH

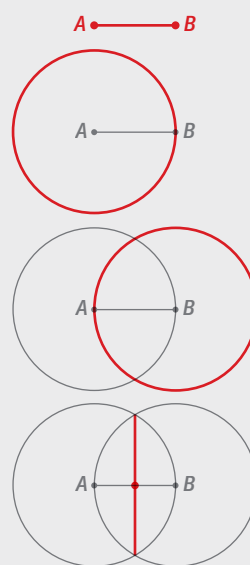
IF YOU HAD TO CHOOSE a few words or symbols to encapsulate your legacy, what would you pick? Johann Carl Friedrich Gauss (1777–1855) left behind a trophy case stocked with mathematical achievements to choose from, but above all, he wanted a “regular heptadecagon” etched on his headstone. The highly symmetrical 17-sided shape starred in a proof that Gauss considered one of his greatest contributions to math. At just 18 years old, Gauss used a heptadecagon to solve a classic problem that had stumped mathematicians for more than 2,000 years. A tour through that history reveals deep connections between the ancient conception of shapes as drawings and a modern perspective of the equations that govern them.

The ancient Greeks excelled at geometry, placing special emphasis on constructions created with a compass and straightedge. Think of these constructions as diagrams with desired geometric properties created solely with a writing utensil and two tools. Given two points, a drawing compass (not to be confused with the navigational device) lets a person create a circle that is centered on either point and passes through the other point. A straightedge can be used to draw straight lines between the points. Neither tool has any markings on it, so people cannot measure distances or angles with them.

The Greeks didn’t impose arbitrary rules just to make math

more challenging. The game of constructing shapes with a compass and straight-edge originates in Euclid’s *Elements* from the third century B.C.E., one of the most important textbooks ever written. Like modern mathematicians, Euclid set out to derive all of geometry from a minimal list of assumptions. Instead of merely asserting the existence of shapes or other geometric objects, Euclid wanted to build them explicitly from the simplest ingredients: lines and circles. To get a feel for these constructions, try one for yourself: find the midpoint of the line segment from *A* to *B* below. Eyeballing won’t suffice; your method must identify the exact midpoint.

First use a compass to draw a circle that is centered at *A* and passing through *B*. Then repeat this step to make a circle that is centered at *B* and passing through *A*. These circles will intersect at two points. Use the straightedge to connect these points. Because of the symmetry in the construction, this vertical line will intersect the original line segment exactly at its midpoint.



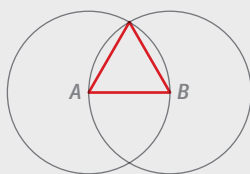
Jack Murtagh

is a freelance math writer and puzzle creator.

He writes a column on mathematical curiosities for *Scientific American* and creates daily puzzles for the Morning Brew newsletter.

He holds a Ph.D. in theoretical computer science from Harvard University. Follow him on X @JackPMurtagh

This exercise does much more than bisect a line segment. It creates a right angle between the two lines, which is not a trivial feat with such a restricted tool set. And by connecting a few more points, you can make an equilateral triangle—one whose sides have equal lengths and whose angles have equal measurements.



Among all the shapes we can construct with a compass and straightedge, regular polygons hold a special cachet.

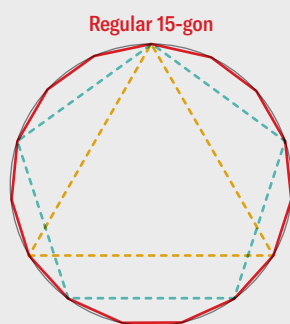
Notice that each edge of the triangle is also a radius of one of the circles. The circles are the same size, and therefore all the triangle's sides have the same length. So equilateral triangles are constructible with a compass and straightedge, QED. Congratulations on persisting through the first proposition in the first book of Euclid's *Elements*. Only 13 more books to go.

Among all the shapes one can construct with a compass and straightedge, regular polygons hold a special cachet. Polygons are enclosed shapes composed of straight-line edges, such as triangles and rectangles (as opposed to curved shapes such as circles or unenclosed shapes such as the letter E). Regular polygons have the most symmetry in that their sides all have equal lengths and their angles all have equal measurements (like squares and equilateral triangles but unlike rectangles and rhombuses). Constructing any old irregular triangle with a compass and straightedge is child's play—just scatter three points on the page and connect them with lines. But constructing our perfectly symmetrical equilateral triangle—a regular polygon—requires some elegant legwork.

Euclid figured out how to construct regular polygons with three, four or five sides—equilateral triangles, squares or regular pentagons, respectively. He squeezed a few more generalizations out of these core constructions; for instance, once you have a regular polygon on the page, a simple maneuver will produce a new regular polygon with double the number of sides.

You can repeat this doubling procedure as many times as you wish. That means

three-, four- and five-sided regular polygons can be transformed into six-, eight- and 10-sided regular polygons, as well as 12-, 16- and 20-sided ones, and so on. Euclid also showed how to “multiply” the three- and five-sided regular polygons to produce a regular 15-gon.

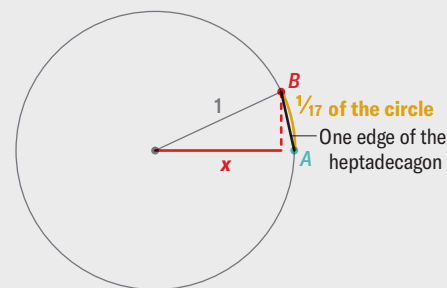


Progress halted there. Somehow Euclid knew a regular 3,072-gon was constructible in principle (a triangle doubled 10 times), but he had no idea how to construct a regular seven-gon (heptagon) or 11-gon (hendecagon). To be clear, regular polygons of any number of sides greater than two do exist and can be constructed with more capable tools. The question Euclid left behind asks which ones are constructible with a compass and straightedge alone. It remained unanswered for two millennia until a certain German teenager picked up a pencil.

By 1796 no new regular polygons had joined the pantheon of constructible shapes, yet mathematicians had acquired a deeper understanding of compass-and-straightedge constructions. Gauss knew

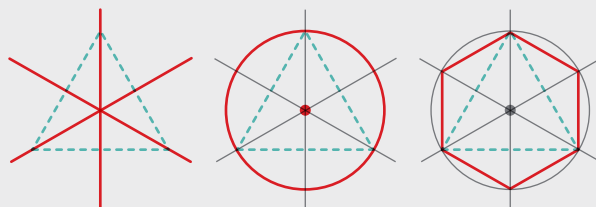
how to reduce the problem of making a regular polygon to that of merely creating a line segment with a very specific length. To create a 17-gon, start with a unit circle (where the radius equals one) and a point *A* on the circle, as in the graphic below. Imagine we could find the red point *B* above *A* exactly one 17th of the way around the circle. If we could construct the red point from the blue point, we could repeat that action all the way around the circle and connect the dots with our straightedge: voilà, a regular heptadecagon.

How do we draw point *B* given point *A*, though? Notice that if we can draw the red line segment labeled *x*, then we can connect that to the red point *B*, and we win. The entire problem of constructing a regular heptadecagon boils down to creating a line segment with the precise length *x*. For the mathematically curious, $x = \cosine(2\pi/17)$.



Can we use a compass and straightedge to construct a line segment of any length? By Gauss's time, mathematicians knew the surprising answer to this question. A length is constructible exactly when it can be expressed with the operations of addition, subtraction, multiplication, division or square roots applied to integers. So some strange numbers, such as the square root of $99/5$, are constructible (99 and 5 are integers, and we're applying division and square root to them), whereas some more familiar numbers such as pi (π) and the cube root of 2 cannot be constructed, because one can never write them

To double the number of sides on a given regular polygon, bisect each side of the polygon, draw a circle centered at the intersection of the bisectors and passing through the vertices of the polygon, and connect the points where the bisectors meet the circle.



in terms of these five operations alone.

Remarkably, the rudimentary tools the ancient Greeks used to draw their geometric diagrams perfectly match the natural operations of modern-day algebra: addition (+), subtraction (−), multiplication (×), division (/) and taking square roots ($\sqrt{}$). The reason stems from the fact that the equations for lines and circles use only these five operations, a perspective Euclid couldn't have envisioned in the prealgebra age.

It might surprise you to learn that Gauss never actually drew a regular heptadecagon. He didn't need to. He proved that the shape is constructible in principle by expressing the special length x [cosine ($\frac{2\pi}{17}$)] solely in terms of the five algebraic operations the compass and straightedge allow. Even if you don't find his equation particularly enlightening, its complexity demonstrates how much work the adolescent must have poured into the problem.

$$\cos \frac{2\pi}{17} = \frac{1}{16} \left(\sqrt{17} + \sqrt{34 - 2\sqrt{17}} - 1 \right) + \frac{1}{8} \left(\sqrt{17 + 3\sqrt{17} - \sqrt{34 - 2\sqrt{17}} - 2\sqrt{34 + 2\sqrt{17}}} \right)$$

Even more impressive, Gauss fully characterized which regular polygons are constructible and which aren't (although it was not until 1837 that Pierre Wantzel provided a rigorous proof showing Gauss's characterization didn't leave out anything). So not only did Gauss describe the form that all constructible regular polygons take, but he and Wantzel vindicated Euclid's frustrations by proving that the elusive regular heptagon (seven sides) and hendecagon (11 sides) are impossible to construct with a compass and straightedge alone, as are infinitely many other shapes.

According to biographer G. Waldo Dunnington, Gauss felt great pride in cracking the millennia-old problem and told a friend that he wanted a regular heptadecagon displayed on his headstone. Sadly, he didn't get it, but a monument in Gauss's birth city of Brunswick, Germany, has a 17-pointed star engraved on the back. The stonemason chose a star because he believed people couldn't distinguish a heptadecagon from a circle. I wonder whether Euclid would agree. ●

Nope—It's Never Aliens

Claims of alien starships visiting Earth always fall short BY PHIL PLAIT

GREW UP BELIEVING IN UFOS.

I watched every TV show about aliens, spaceships, and aliens *in* spaceships. I voraciously read magazines and books on the topic, credulously soaking up everything I saw and believing it wholeheartedly because, after all, if someone published a book saying these things are real, they *must* be real, right?

Right?

Over the years, though, I took up science as a career and critical thinking as a passion. Gradually I looked back at all the information I had taken in as a kid and realized it was overwhelmingly baloney. It was just scads and scads of nonsense: bad photography, sketchy witnesses, wild speculation and evidence-free claims. That was more than 30 years ago. Sadly, nothing's changed.

In this modern age, we don't call them UFOs anymore; now they're UAPs, for unidentified aerial (or anomalous) phenomena. I can't help but think that's to distance the idea from the old "flying saucers" stigma. But no matter what you call them, it's all still just the same breathless headlines and lack of substance behind them. There's no there there. Still, we've been so primed by so many stories of alien visitations over the years that even the thinnest of testimony gets reported far beyond its merit.

One of the more recent blips on the extraterrestrial radar is a collection of videos declassified by the U.S. Department of Defense that contain what are purported to be UAPs—true by semantics if not by implication. Taken from F/A-18 Super Hornet fighter jets using visible light and infrared cameras, three videos in particular—called FLIR, GOFAST and GIMBAL—show small objects moving at terrific speeds, whirling like the spaceships in *Close Encounters of the Third Kind* and apparently following the planes as if piloted. FLIR was filmed in 2004, and GOFAST and GIMBAL are from January 2015.

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These videos made quite a splash in 2017, especially because U.S. Navy officials flatly stated that the objects were unidentified. Certainly the pilots don't seem to know what they're seeing; in the GIMBAL video, one can be heard remarking that the object is going against the direction of the wind, again implying that the UAP was under some kind of control.

So are these objects alien spacecraft? I would bet a lot of money—a *lot*—on "no."

Mick West, a retired computer programmer and prominent UFO skeptic, has examined the videos very carefully and applied trigonometry and physics to what's seen to find far more plausible explanations than interstellar visitors. For example, the object apparently moving against the wind in the GOFAST video is probably a balloon. In a video analysis, West convincingly argues that the object is at low altitude and not moving very quickly; it's the jet's motion that makes the object appear to zip across the sky. This effect, called parallax, is what makes roadside trees whoosh by when you're zooming down a highway while distant buildings seem to move much more slowly. The other UAP videos have similar mundane explanations.

Occam's razor, the well-worn rule of thumb for scientific inquiry, applies well here: the simplest explanation is usually the best. As critical thinkers sometimes say, "if you hear hoofbeats, think horses, not unicorns."

That it was navy pilots who encountered these objects would seemingly enhance the credibility of these reports. Pilots inarguably have more experience looking at things in the sky than the average person, but that doesn't mean they're immune to error. For example, in 2011 an

Air Canada first officer reportedly put a plane in a nosedive because he saw Venus. I've seen countless reports of UFOs that for real and for sure turned out to be Venus, Jupiter, the



A GOFAST video still shows a U.S. Navy F/A-18 jet crew's encounter with an unexplained anomalous phenomenon, or UAP. (The appearance of U.S. Department of Defense visual information does not imply or constitute an endorsement.)

moon, airplanes, satellites, meteors, rocket launches, floating paper bag lanterns or, in one very famous case, military flares.

The fact is, everyone can make mistakes—even experts. There's a reason the term "argument from authority" is considered a logical fallacy.

Astronomers are no exception; we've sometimes been fooled—or at least momentarily baffled—by unexpected observations. Not that long ago some of us got excited by what seemed to be a radio observatory's detection of a new type of astrophysical signal; further investigation showed, however, that the signal was electromagnetic interference from a nearby microwave oven. A different time, an astronomer accidentally discovered Mars. Another discovered the sun.

The important part of all these stories is that the scientists involved didn't immediately run to the media claiming they

had found little green men. Skepticism and careful analysis won the day.

That's not always the case. For example, Avi Loeb is a renowned astrophysicist at the Center for Astrophysics | Harvard & Smithsonian. He is also a vocal proponent of the idea that small spherules of metal he and his collaborators found on the ocean floor are interstellar in origin and may even be from aliens.

This source is, well, unlikely. The idea is that a meteor from interstellar space (determined from its estimated incoming trajectory and high speed) burned up in Earth's atmosphere, dropping debris into the ocean. An expedition led by Loeb dredged some of the seafloor where the researchers expected that debris to be and found tiny metallic balls that they argue are from another star.

Many other experts hold *extremely* dim views of these claims. One of the most out-

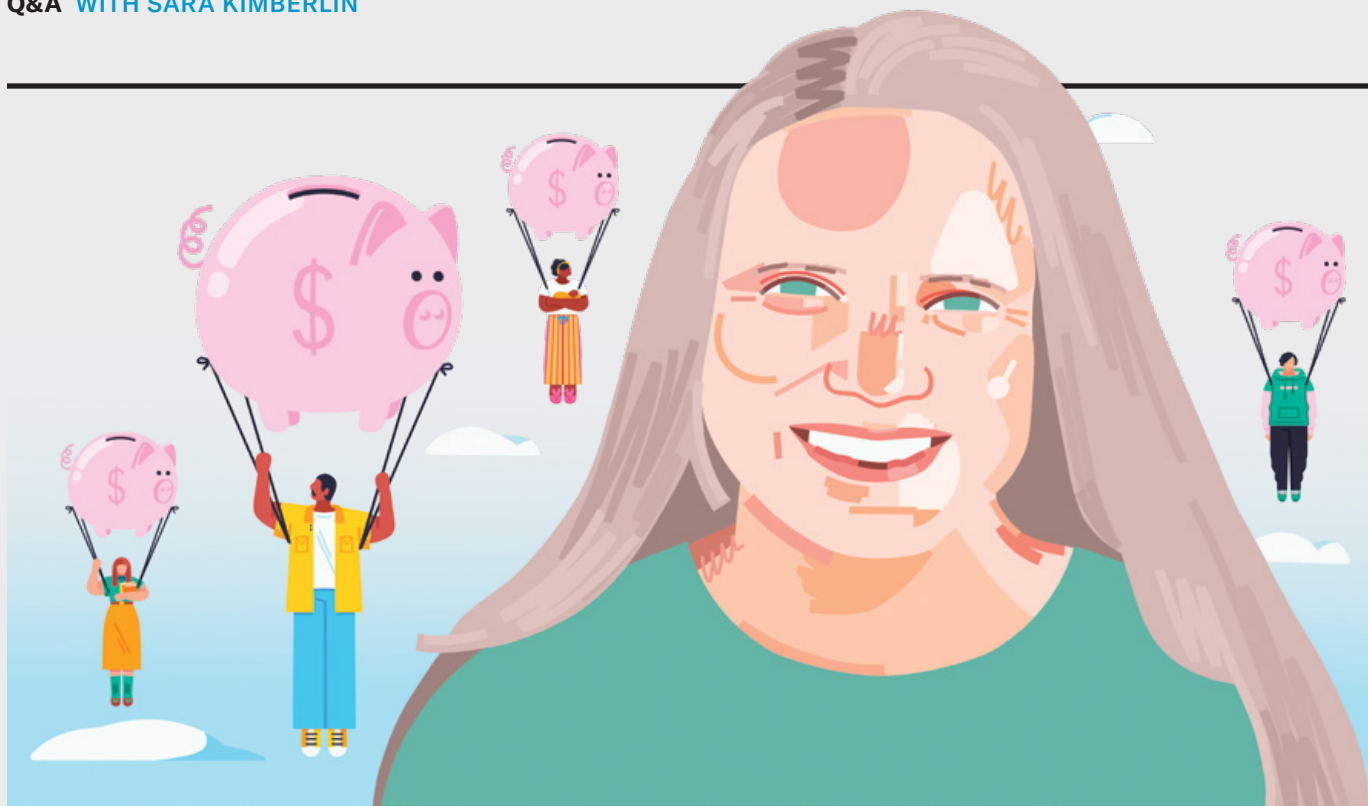
spoken has been astrophysicist and science writer Ethan Siegel, who bluntly calls them "embarrassing." Current consensus is that the meteor's interstellar origin is far from proven, the location where debris might have fallen is quite uncertain, and Loeb's spherules could originate from modern-day coal ash or ancient volcanic eruptions rather than the breakup of some interstellar object in Earth's atmosphere.

Despite this pushback—and many other critiques, some published in reputable peer-reviewed scientific journals—Loeb still maintains that the meteor was interstellar and the spherules are from that very event. He has even co-founded a multimillion-dollar project to investigate his own claims. Of course, Loeb's prestigious status adds an air of authority to his hypothesis, but his claiming something, no matter how strenuously, doesn't make it so.

Should we bother studying unidentified phenomena, aerial or otherwise? Of course! Not all have been explained, although we shouldn't leap to the conclusion that they're unexplainable. NASA itself funded a small project to look into UAPs, if only because they could conceivably be a potential threat to airspace safety and national security. But in the case of UAPs at least, time and again there turn out to be simpler explanations, and at some point we have to admit that in all likelihood, we're throwing good money after bad.

To be clear, none of this means we should abandon our searches for extraterrestrial life. We now know that planets in the Milky Way probably number in the hundreds of billions, and no doubt some may resemble Earth and might even host life. But if our own world is any guide, we should expect few, if any, of these living worlds to harbor much more than microbes, let alone anything capable of building starships or radio telescopes. (Earth has had only single-cellular life for most of its history.) We need to carefully distinguish between the possibility of life's mere existence elsewhere in the cosmos and its even more rare evolution to intelligence and being able to trek among the stars.

Until we get much better and more reliable data, assume those hoofbeats are horses. ●



How Basic Income Works

Recent studies show a universal basic income could improve lives BY ALLISON PARSHALL

IN 2020, AMID WIDESPREAD LAYOFFS and economic turmoil brought on by the COVID pandemic, 1,000 low-income people in Texas and Illinois won something of a lottery. They were selected to receive \$1,000 per month—with no strings attached—for three years as part of a study on guaranteed income by OpenResearch, a nonprofit research organization funded in part by OpenAI and its founder, Sam Altman.

Silicon Valley philanthropists are just one piece of a growing movement for using basic income to improve people's lives. In recent years the Stanford Basic Income Lab and the Center for Guaranteed Income Research have been tracking 30-plus pilot programs that have tested basic income in towns and cities across the U.S.

"There's a long history of interest in basic income in the United States," says Sara Kimberlin, executive director of the Stanford Center on Poverty and Inequality. Founding father Thomas Paine advocated for it in *The Rights of Man*. Martin Luther King, Jr., called it the solution to poverty. Even economist and free-market capitalist Milton Friedman suggested basic income in the form of a "negative income tax."

When people receive unconditional cash, they tend to use the money in ways that increase their financial security and housing stability, Kimberlin says, pointing to a "large body of research." Those

observations line up with the most recent results from OpenResearch, which showed that participants increased spending to meet their basic needs and to help family and friends. A separate study published online in July in the *Journal of the American Medical Association* also found that cash benefits reduced emergency room visits.

Taken as a whole, the evidence suggests that when people's most basic needs are met, they start to build a firmer financial foundation for themselves and their family. SCIENTIFIC AMERICAN spoke with Kimberlin to learn more about these basic-income pilot programs and how this unconditional, guaranteed aid improves people's lives.

An edited transcript of the interview follows.

What is the promise of basic income?

A key problem that basic income or guaranteed income is designed to address is the significant share of people and families who don't have enough resources to be able to meet their essential needs. And we have a lot of research that shows the challenges that arise from struggling to meet your basic needs. For example, if you don't have access to stable, safe housing, health care or food, that interferes with your ability to be a productive worker or to take care of your family. And if you're a child, that interferes with your ability to concentrate in school.

Allison Parshall is an associate news editor at *Scientific American* who often covers biology, health, technology and physics.

On the flip side, there's a lot of research showing the positive things that happen when a policy ensures people's needs can be met. It shows that when food stamps are introduced in a particular area, the outcomes for the families improve. Other research shows that children whose families received the Earned Income Tax Credit when they were young had more positive long-term educational outcomes, which translated to stronger financial security later in life.

Why provide cash, as opposed to food stamps or rent assistance?

Cash is flexible. People can use it to meet whatever their most pressing need may be. It's an efficient way of addressing people's needs, and it also gives people a lot of dignity and autonomy in deciding how they're going to use it. It helps to avoid situations where someone may already have resources designated to pay for food but needs, for example, emergency child care. If they don't get it, then they can't get to their job, which could cause a lot of disruption down the line by making them miss a paycheck, then miss the rent. You can look at unconditional cash as a potentially very promising way of approaching social support because it streamlines the administrative costs and makes it easier for people to access the support they are eligible for.

What stood out for you about the new findings from OpenResearch?

It's a very large study, and it's well designed and well funded. It studied a fairly broad, more representative population, rather than being targeted to a specific group such as parents of young children, which meant there was a lot of variation in the outcomes.

It wasn't surprising that the study found the most common uses of the funds were to cover basic needs such as housing, food and transportation. This is something we see consistently across guaranteed-income pilots that are tracked on the [Guaranteed Income Pilots Dashboard](#) on the Stanford Basic Income Lab website.

Something that stood out for me was the significant increase in people spending money to help their friends and family. That struck me because it means there are some effects of this program that are not

“Cash is flexible. It gives people a lot of dignity and autonomy in deciding how they are going to use it.” —SARA KIMBERLIN

fully captured in the results. If a participant is saying, “Oh, my cousin called me because her husband lost his job, and they can't make their rent this month, and I gave her some money so her family wouldn't get evicted”—outcomes like that wouldn't be fully captured in the participant data. There's a ripple of positive effects that are going out beyond the direct recipient.

People who received the cash worked an average of one hour less per week and were 2 percent less likely to be employed than people in a control group that received \$50. What does that tell you?

People wonder: Does receiving unrestricted cash mean people are going to just stop working? How would that affect the labor market? There have been different findings across different studies. Some have shown somewhat increased employment. You can imagine how that's possible. If receiving a basic income allows you to repair your car so that it's reliable or pay for child care, that might make it more possible for you to get a job. There have also been studies that have shown no significant impact on employment.

And then there have been studies that show some reductions in employment or in number of hours worked compared with a control group. That's what was found in these OpenResearch results.

One important piece of context here is that this study, along with many of the studies in this recent crop of guaranteed-income pilots, took place in the unusual economic setting of the pandemic. Unemployment was very high across the entire U.S. in both the treatment and the control group at the beginning of this study. Over the course of the three years lots of people in both groups went out and got jobs as more jobs became available again—overall, employment and hours worked increased in both groups, but they increased less in the group receiving \$1,000.

Many of the drivers that might cause somebody to work less when they receive a basic income could be seen as positive outcomes in other ways. For example, single parents or parents of young children might work fewer hours to spend more time directly caring for their children.

Is just giving people money really a viable solution to poverty?

Basic income, particularly at this scale that has been studied, is not a cure-all or magical solution to poverty. Access to health care, schooling, child care and affordable housing are still needed. I think it makes sense to think about basic income as a promising intervention that complements other parts of the social safety net. Unrestricted cash has a lot of power to be able to fill in places where the safety net is inadequate.

What are some open questions about the impacts of basic income that you hope more research will answer?

It's really important to study how these programs work for different groups of people. There are different pilots focused on specific populations, such as people aging out of foster care, people experiencing domestic violence or people reentering society after incarceration. Understanding how it works for different groups is helpful for designing programs and policies.

And a critical question is: What are the long-term effects of these programs, in particular on people's health? A three-year study can't address health problems that have developed over people's lifetime. But if you had a long-term program in place, would you see different effects on people's health, such as on chronic health conditions? And studying the potential effects of these programs on children's long-term trajectories is very important. Some of those outcomes are not measurable yet, but they may be quite consequential for the people who receive the money and may ripple out to their families and communities. ●



How to Beat Procrastination

To stop putting off tasks, think about the positives

BY JAVIER GRANADOS SAMAYOA AND RUSSELL FAZIO

BY APRIL 12, 2024—three days before the deadline for filing tax returns in the U.S.—more than a quarter of American taxpayers had yet to do so. Procrastination—delaying something despite an awareness of associated negative consequences, leading to discomfort—is a common experience for many. Unfortunately, procrastination tends to carry significant costs. For instance, completing a task when rushing to finish can affect the quality of one’s work. Moreover, procrastination is by its very definition stressful, and naturally such stress can take its toll.

Chronic procrastinators tend to report more symptoms of illness, more visits to the doctor, lower overall well-being and even greater financial struggles.

So if procrastination is so costly, why do so many people regularly do it? Years of research have provided a reasonably comprehensive list of psychological factors that relate to procrastination. But it’s been unclear what mental processes underlie the decision to start or postpone a task. When faced with an upcoming deadline, how do people decide to initiate a chore or project?

To explore this question, we conducted

a series of studies examining task delay, the behavioral component of procrastination in which people put off completing something despite lacking any objectively strategic reason to do so. We found that people with a negativity bias tend to delay tasks more, especially if they tend to be poor at self-control.

The central idea guiding our work was that as people pursue their goals, the environment nudges them to make specific assessments that can shape their behavior. For example, once a taxpayer has received all the necessary documentation—typically well before the filing deadline—they may ask themselves, “Do I want to do this *now*?” This question should bring to mind some positive outcomes (for instance, the satisfaction of completing a chore and, potentially, receiving a tax refund sooner) and some that are negative (such as the tediousness of the task).

Ultimately the positives must be weighed against the negatives. Notably there are individual differences in how people generally weigh positive and negative signals—a characteristic that psychologists call valence weighting bias. Whereas some people tend to give greater weight to the pros, others give greater weight to the cons. We reasoned that those with a more negative weighting bias should be more likely to procrastinate.

Our first study used surveys to identify people who generally expected to receive a tax refund but tended to submit their taxes either early (during the last two weeks of January or early February) or late in tax season (the first two weeks of April). Some 232 people who met our eligibility criteria participated in a follow-up session, in which we measured their valence weighting bias, using a game affectionately called “BeanFest.”

In this game, people viewed images of beans that varied in shape and number of speckles. Some beans, when selected, yielded points, whereas others led to a loss. We later assessed how participants generalized from these newly learned associations (such as that oblong beans with many speckles were “bad” and that circular beans with few speckles were “good”) to new bean images that had

both positive and negative aspects (such as circular beans with many speckles). The people who leaned more heavily on the negative features when assessing the novel beans had a negative valence weighting bias, whereas those who leaned more on the positive features had a more positive bias.

The decisions that people make in this game reveal something very fundamental: it turns out that people's tendencies to generalize either positive or negative associations on this test can serve as a proxy for their general likelihood of weighing pros or cons when making decisions of any kind. Through this process we found that those people who had reported filing taxes late in the season exhibited a more negative valence weighting bias. They apparently felt more preoccupied by the unpleasant aspects of preparing their tax return.

Having found evidence that this bias predicted task delay, we followed up with a different approach. We asked 147 students enrolled in an introductory psychology course for their record of participation in a research experience program in which completing a predetermined number of hours of experiments earned extra credit. Using these data, we focused on the average date of research participation; broadly speaking, later dates indicated greater task delay. And much like doing taxes, putting off these hours of research participation ultimately led to greater stress because it exacerbated an "end-of-semester crunch."

Then we added one more element to this study. Other research has found that valence weighting bias shapes decision-making even more strongly when people are relatively unmotivated to deliberate beyond their initial impulsive reactions or do not have the cognitive resources and time to do so. So we asked students to rate—on a scale of 1 ("not at all like me") to 5 ("very much like me")—how strongly they agreed with statements such as "I am good at resisting temptation." Not

People who are inclined to see the negatives rather than the positives are more likely to delay tasks, especially if they tend to be poor at self-control.

surprisingly, those who reported better self-control tended to participate earlier in the semester. More to the point, those with a more negative weighting bias tended to delay, as indicated by the average day of earning research hours, and this pattern was *most* evident among those reporting poorer self-control.

Can we disrupt this link between weighting bias and task delay? In our last study, we explored that possibility. We again examined student participation in the research experience program. But instead of recruiting from the general pool of students, we specifically sought out those who had reported struggling with procrastination more generally. These participants, we reasoned, probably had a negative weighting bias.

We then randomly assigned the students who agreed to participate to either a control or an experimental condition. Both groups of participants from the psychology course played BeanFest, but the latter involved a training procedure. Specifically, on each of numerous trials, participants indicated whether a novel bean was helpful or harmful, and then we told them whether their decision was *objectively* correct. That feedback effectively trained participants to better weigh pros versus cons, bringing more balance to their perspective. In the control condition—where we did not attempt to shape students' tendency toward the positive or negative—we provided no additional information.

After this targeted BeanFest intervention, students went back to the semester as usual. Impressively, when we followed up with them two weeks later, those in the experimental group showed

fewer signs of procrastination—that is, greater research participation—than those in the control group. More important, this recalibration procedure, as we call it, does something the real world rarely does: it provides objectively correct feedback about the appropriate weighting of positive and negative signals, and through repetition it shifts valence weighting tendencies toward a more balanced equilibrium. Even though BeanFest may seem utterly unrelated to something like research participation, this training exercise works because the act of weighing the pros and cons of a situation is the same, whether it involves beans or a real-world decision. So when people's bias is changed in BeanFest, that naturally generalizes to situations beyond the lab.

Putting it all together, our research uncovers the processes that lead to procrastination. When faced with a deadline, people seem to ask themselves, "Do I want to do this *now*?" That leads them to weigh the pros and cons involved—and their biases then come into play. Although additional rigorous testing is required, the training procedure used in our last study shows promise as an avenue to assist people who struggle with procrastination. Cognitive training based on this approach—for example, through a smartphone app—could help individuals who struggle with delaying tasks.

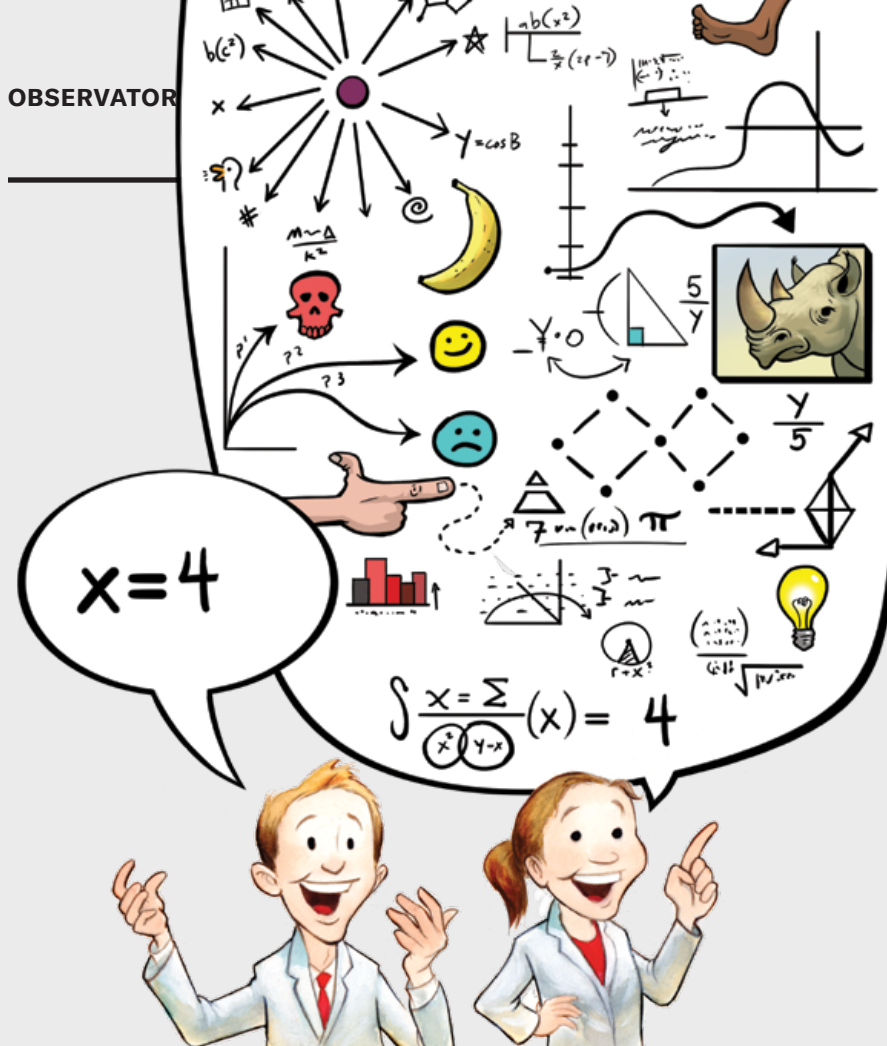
But there are more immediate implications of our work as well. Our research indicates that valence weighting has the biggest influence on people who lack the motivation and cognitive resources to pause and deliberate beyond their initial quick appraisals on whether to tackle a task. In other words, just pushing yourself to think a little bit more before acting may help you generate more positive reasons to get started and to ensure you don't put off until tomorrow what you might best do today. ●

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Russell Fazio

is Harold E. Burt Chair in Psychology at the Ohio State University. His research concerns attitudes, including their formation, their accessibility from memory, and the effect they have on attention, judgment and behavior.



The Dull Edge of Occam's Razor

Contrary to the popular maxim, the simplest explanation is often not the best one

BY NAOMI ORESKES

IF YOU'VE EVER HUNG AROUND scientists, you've most likely at some point heard one of them say "the best explanation is the simplest one." But is it? From the behavior of ants to the occurrence of tornadoes, the natural world is often quite complex. Why should we assume the simplest explanation is closest to the truth?

This idea is known as Occam's (or Ockham's) razor. It's also referred to as the "principle of parsimony" or the "rule of economy." And it bears a family relationship to the "principle of least astonishment," which holds that if an

explanation is too surprising, it's probably not right. But real life is often messy and complicated, and, as every good detective novelist knows, sometimes the killer is the one you least expect.

Let's start with some evidence about the idea itself. The name comes from William of Ockham, a 14th-century scholastic philosopher and theologian who formulated the principle in Latin:

pluralitas non est ponenda sine necessitate, rendered in English as "entities should not be multiplied beyond necessity." The point was an ontological argument dating back at least as far as Aristotle's time about enti-

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ties: What exists in the world? How do we know they exist? The philosophical claim is a form of ontological minimalism: we should not invoke entities unless we have evidence that they exist. Even if we are sure things exist—say, comets—we should not invoke them as causal agents unless we have evidence that they cause the kinds of effects we are assigning to them. In other words: don't make stuff up.

In 1687 Isaac Newton expanded on this notion with his concept of a *vera causa*—a true cause—when he wrote in his best-known work, the *Principia Mathematica*, "We are to admit no more causes of natural things than such as are both true and sufficient to explain their appearances." He continued: "To this purpose, the philosophers say that Nature does nothing in vain, and more is in vain when less will serve; for Nature is pleased with simplicity, and affects not the pomp of superfluous causes."

Newton was one of the greatest scientists of all time, but if we stop to think about it, this claim is a peculiar one. Who is to say what "pleases nature"? And doesn't this guidance assume we know what we are in fact trying to figure out?

Consider the work of astronomer Vera C. Rubin, who found compelling evidence for the existence of dark matter. While studying the motion of spiral galaxies, Rubin discovered that the speed at which stars rotated around the center of their galaxies made sense only if these galaxies contained an additional mass weighing about 10 times more than the visible stars. The claim of a new form of "dark" matter—unseen and unseeable and present in far greater quantities than the visible matter of the universe—was not a simple explanation, but it turned out to be the best explanation.

Physics is filled with explanations that are surprising, unexpected and hard to get your head around. Newton explained light as being made of particles, whereas other scientists of his era explained it as a wave. Quantum mechanics, however, tells us that light is, in some respects, both a wave and a particle. Newton's account was simpler, but modern physics tells us that the more complex model is closer to the truth.

When we turn to biology, things get even more complicated. Imagine two

smokers, both of whom went through a pack a day for 30 years. One gets cancer; the other does not. The simplest explanation? For decades the tobacco industry's answer was that smoking doesn't cause cancer. Simple but false. The correct answer is that disease is complex, and we don't yet understand all the factors involved in carcinogenesis.

And then there's the vexing question of how we define simplicity. Consider the ongoing debate over the origin of the COVID pandemic. On the side of the lab-leak theory—that the SARS-CoV-2 virus escaped from a facility rather than being transmitted from wild animals to humans—some commentators have invoked Occam's razor. But it's not obvious that this theory is *simpler*. One could argue the reverse: given that most past pandemics had a zoonotic origin, the simpler explanation is that this pandemic did, too.

Occam's razor is not a fact or even a theory. It's a metaphysical principle: an idea held independently of empirical evidence. (Think "God is love" or "beauty is truth.") But unless we are prepared to make assumptions about God and nature, there is no good reason that we should prefer a simpler explanation to a complex one. Moreover, in human affairs things are more often than not complex. Human motivations are typically multiple. People can be good and bad at the same time, selfish and selfless, depending on circumstances. The shelves of ethicists are filled with books pondering why good people do bad things, and their answers are rarely short and sweet.

In 1927 British geneticist J.B.S. Haldane wrote in his essay "Possible Worlds" that "the universe is not only queerer than we suppose, but queerer than we *can* suppose." There are, in fact, new things under the sun, and rare events may be rare precisely because they involve a complex confluence of events. Put this way, we can see Occam's razor as simply a failure of imagination.

Our explanations should match the world as best as we can make them. Science is about letting the chips fall, and sometimes this means accepting that the truth is not simple, even if it would make our lives easier if it were. ●



ALFRED WEGENER TO THE WORLD

And yet it moves! Shh—hear the mountains murmur?
Peripatetic prairies slowly creep
across the globe. There is no *terra firma*.
Is that so terra-ble? We'll have to keep
producing new and updated editions
of every atlas. But it's no one's fault
that continents collide, or split in fissions.
On groaning sleds of granite and basalt,
coastlines advance on trans-oceanic missions
like runners in the world's most boring race
(though slow, they never fail to cover ground)
and somehow, *still*, their clip exceeds the pace
a stubborn academic comes around
to evidence, and changes his positions.

Author's note: Wegener was an early proponent of continental drift—a theory initially met with resistance.

Daniel Gafef writes poetry, plays, short stories, and humor. His book *Imaginary Sonnets* contains 70 monologues spoken by historical figures—scientists, artists, saints, murderers, and one fish.

Gifts from the Land

Robin Wall Kimmerer reframed ideas of sustainability. Can she do the same with economics? BY MEERA SUBRAMANIAN



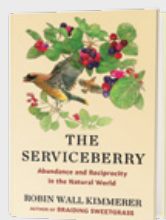
NONFICTION

Nature provides many gifts, but it is easy to take them for granted. It's not just the strawberries you buy at the grocery store but also the plastic container that holds them, made of ancient life-forms transformed into fossils and then feedstock for plastics. How can we better recognize the value of the natural world and build communities—and economies—that acknowledge such abundance?

This is the central question of *The Serviceberry: Abundance and Reciprocity in the Natural World*. It's the third book by Robin Wall Kimmerer, an ecologist, professor at the State University of New York College of Environmental Science and Forestry, and member of the Citizen Potawatomi Nation. For seven sleepy years, her last book, *Braiding Sweetgrass: Indigenous Wisdom, Scientific Knowledge, and the Teachings of Plants*, published in 2013, quietly grew in popularity, until it leaped onto the *New York*

Times bestseller list in 2020, where it has remained. It was as though Kimmerer's concepts about animating nature and respecting nonhuman species as if they were people, told through the personal lens of an Indigenous scientist, struck a chord that was aching to be played. These ideas continue to reverberate: she is routinely invited to be a keynote speaker, her words are emblazoned on museum walls, and in 2022 she received the prestigious MacArthur Foundation "genius" grant.

The Serviceberry, which grew out of a 2022 essay in



The Serviceberry: Abundance and Reciprocity in the Natural World by Robin Wall Kimmerer. Scribner, 2024 (\$20)

Emergence Magazine, is a much slimmer volume than *Braiding Sweetgrass* but is written with the same lyrical, personable voice that invites readers into worlds of possibility. In short chapters punctuated by line drawings from illustrator John Burgoyne, this sweet offering builds on her ideas about the gift economy and how Indigenous wisdom might inform it. She explores ancient guidelines known as the Honorable Harvest, her interpretation a bulleted manifesto for gratitude and how circular economies are a way to put these concepts into practice.

Kimmerer also continues her inquiry into language and what it reveals about worldviews. In the opening chapter, we learn *Bozakmin* is the Potawatomi word for "serviceberry," a native shrub integral in Indigenous foodways that produces a blueberrylike fruit. *Bozakmin* is, literally, the "best of the berries," and the Potawatomi root word for "berry" also means "gift." Languages around the world offer examples that demonstrate the deeper connections we once had to the earth that very literally sustains us. The Greek word *oikos*, Kimmerer writes, is the root for both "ecology" and "economy."

Oh, but how we've forgotten the link! As Kimmerer fills a pail with an abundance of serviceberries in the opening scene, a flock of cedar waxwings joining her in the harvest, she sees the fruit as "a pure gift from the land. I have not earned, paid for, nor labored for them." She urges readers to take note of the small bequests that abound, which remind us we live in a world of reciprocity where giving can be liberated from an artificial market that manufactures scarcity and individual desire: Little Free Libraries on front lawns and free boxes of clothes and the invitation from a neighbor to come pick berries for free.

Kimmerer admits this way of generous living—intimate with both the land and one's

neighbors—works best in small, close-knit communities. Yet more than half the world's population now lives in urban environments, and the flow from country to city continues. Given this context, how do we, as she writes, "reclaim ourselves as neighbors"? If serviceberries were a marketable commodity, I can't help but wonder, would her neighbors have opened their farm to her for a free day of harvesting? I wanted her to wrestle more with the capitalist juggernaut in which nearly all of us are enmeshed, one dominated by the schemes of people untroubled by destroying what others love in the name of profit.

"Recognizing 'enoughness' is a radical act," she writes, "in an economy that is always urging us to consume more." Recognition is one step. Transforming economies is something else altogether. Kimmerer, who donated her book advance to land conservation and social justice work, writes that she knows little of economics or finance. Although she seeks understanding through books and conversations, she seems to struggle the way many of us do with how such ideas would scale.

The answer, Kimmerer writes in the last and strongest chapter, is to look to ecological succession in the natural world, where disturbances cause seemingly intransient systems to transform. Capitalism may not crumble, but we could pursue conditions for economic succession to a space where reciprocity is recognized. Not just by imagining another way to be in the world but by creating it. Many plants and animals go dormant, waiting for the right moment to resurface and come fully alive again. Can ideas and ways of being, like rhizomes reaching through soil, do the same?

Meera Subramanian is an award-winning independent journalist, author of *A River Runs Again* (PublicAffairs, 2015) and a contributing editor at *Orion* magazine.

Time's Arrow

Fifty years after its initial publication, *The Dispossessed* is as relevant as ever

FICTION

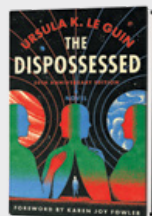
A little more than halfway through *The Dispossessed*, Ursula K. Le Guin's inexhaustibly rich and wise science-fiction novel about a physicist caught between societies, the protagonist, Shevek, born and raised in an anarchist's collective, gets drunk (for the first time) at a fancy soiree in a capitalist society on a planet not his own. There this brilliant but bewildered scientist gets cornered by a plutocrat with impertinent questions. What is the point of Shevek's efforts to create a General Temporal Theory reconciling "aspects or processes of time"?

Shevek explains that time in our perceptions is like an arrow, moving in one direction only. In the cosmos and the atom, however, it moves in circles and cycles, the "infinite repetition" an "atemporal process."

"But what's the good of

this sort of 'understanding,'" the plutocrat asks, "if it doesn't result in practical, technological applications?"

The tensions Le Guin explores here—between the theoretical and the applicable, the scientist and society—have not diminished in the 50 years since *The Dispossessed* swept the Hugo, Locus and Nebula awards. The science in this 1974 novel—now reissued with a celebratory, pained-about-the-present introduction by literary writer Karen Joy



The Dispossessed: A Novel (50th Anniversary Edition)

by Ursula K. Le Guin.
Harper, 2024 (\$35)



Fowler—is vague, a physics explored through metaphor. But Le Guin's depiction of a scientist caught between opposing, utterly convincing worlds remains thrilling in its precision, at times even frightening.

On the collectivist planet Anarres, a desert landscape ravaged by famine, Shevek's search for a General Temporal Theory is thwarted by scientist-bureaucrats who are concerned his discoveries might prove counterrevolutionary. After engineering a diplomatic escape to lush Urras, funded by capitalist plenty, Shevek learns that his work is viewed as proprietary—a product. This per-

spective changes him. Shevek finds himself behaving like the patriarchal "propertarians" of Urras. Drunk and lonely, this gentle man whose language has no possessive pronouns seizes a woman as if she is his. It's an act that later disgusts him—and sets him on a revolutionary course that will affect all the worlds that humanity has reached.

Le Guin, who died in 2018, leaves it to readers to make what they will of this shift. The arrow of time has sped forward since 1974, but the circles and cycles of Le Guin's masterpiece continue to suggest, with urgent humanity, both present and future.

—Alan Scherstuhl

IN BRIEF

Treekeepers: The Race for a Forested Future

by Lauren E. Oakes. Basic Books, 2024 (\$30)



At the start of *Treekeepers*, Lauren E. Oakes recalls the feverish response to a 2019 study published in *Science* that claimed Earth could sustain 1.2 trillion new trees.

Oakes—an ecologist and journalist—had spent more than a decade studying old-growth forests, and as she watched scientists debate the importance of tree planting in mitigating climate change, she found herself wanting to answer that question. *Treekeepers* is an ambitious memoir of Oakes's boots-on-the-ground research under old-growth canopy and a rigorous exploration of forests and climate change. Most of all, it's a hopeful profile of the people working to restore, retain and nurture strong forests. —Lyndsie Bourgon

Power Metal: The Race for the Resources That Will Shape the Future

by Vince Beiser. Riverhead, 2024 (\$32)



In his unflinching follow-up to *The World in a Grain*—a book that turned sand into a riveting story—journalist Vince Beiser reveals the costs of extracting the "titanic quantities" of minerals necessary to

meet the growing demand for our "Electro-Digital Age." Beiser tracks cobalt and lithium from environmentally destructive excavation sites in Chile's Atacama Desert and the deep-sea floor through a geopolitically fraught supply chain to our electric cars and solar panels. With gains in green energy failing to rebalance Mother Nature's scales (as few as one in 10 solar panels are recycled), Beiser urges us to rethink our understanding of sustainability. —Dana Dunham

Citrus: A World History

by David J. Mabberley. Thames and Hudson, 2024 (\$50)



The relationship between people and citrus is a millennia-long balance of push and pull, adaptation and adjustment. Botanist David J. Mabberley skillfully traces this

captivating saga, exploring trade deals that have been forged through these fruits' flavor, extensive art inspired by their beauty, and medical and genetic innovations inspired by their biological properties. Mabberley's vibrant account of citrus, which begins with the Han Dynasty and ends with the modern orange juice industry, will fascinate history enthusiasts as much as it will delight design aficionados in search of the ideal coffee-table book. —Lucy Tu

The Evolution of Music

Songs and speech across cultures hint at why music evolved

TEXT BY ALLISON PARSHALL

GRAPHIC BY DUNCAN GEERE AND

MIRIAM QUICK FROM *LOUD NUMBERS*

HUMANS MUST HAVE LEARNED to sing early in our history because “we can find something we can call music in every society,” says musicologist Yuto Ozaki of Keio University in Tokyo. But did singing evolve as a mere by-product of speaking or with its own unique role in human society? To investigate this question, Ozaki and a large team of collaborators compared samples of songs and speech from around the world. These categories can vary wildly across cultures: songs can be lilting lullabies or rhythmic chants or wailing laments, and some spoken languages have more “musical” qualities, such as tonal languages, which convey meaning through pitch.

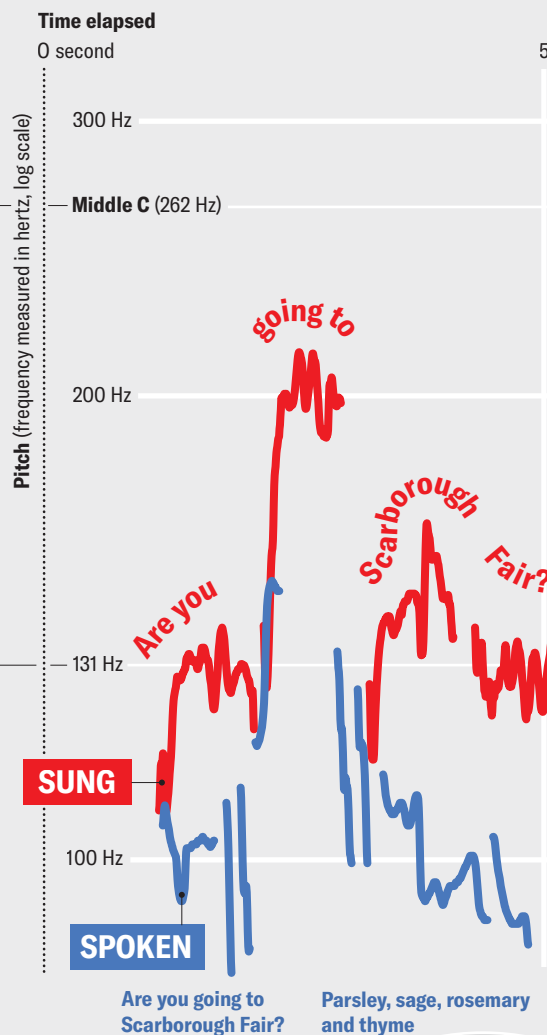
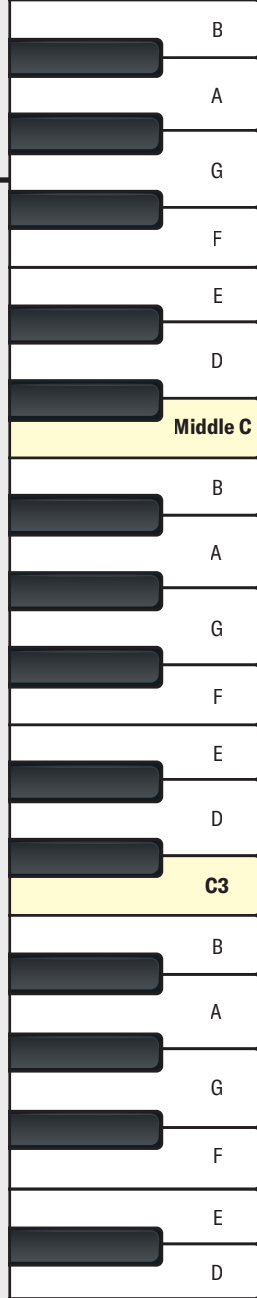
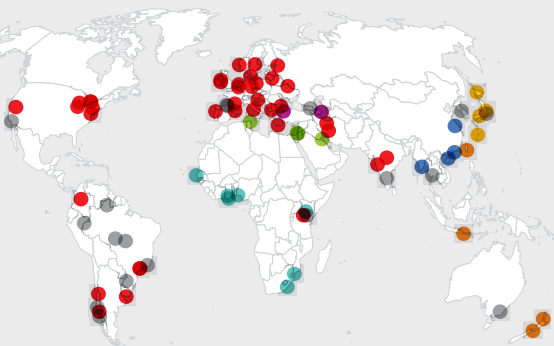
Despite this variation, the researchers found three worldwide trends: songs tend to be slower than speech, with higher and slightly more stable pitches. These consistent differences suggest that singing isn’t just a by-product of speech, yet why it evolved is still unknown. Perhaps it developed to unite people, an idea called the social-bonding hypothesis, says co-author Patrick Savage, a musicologist at the University of Auckland in New Zealand. “Slower, more regular and more predictable melodies may allow us to synchronize and to harmonize,” he says, “and through that, to bring us together in a way that language can’t.”

Language family

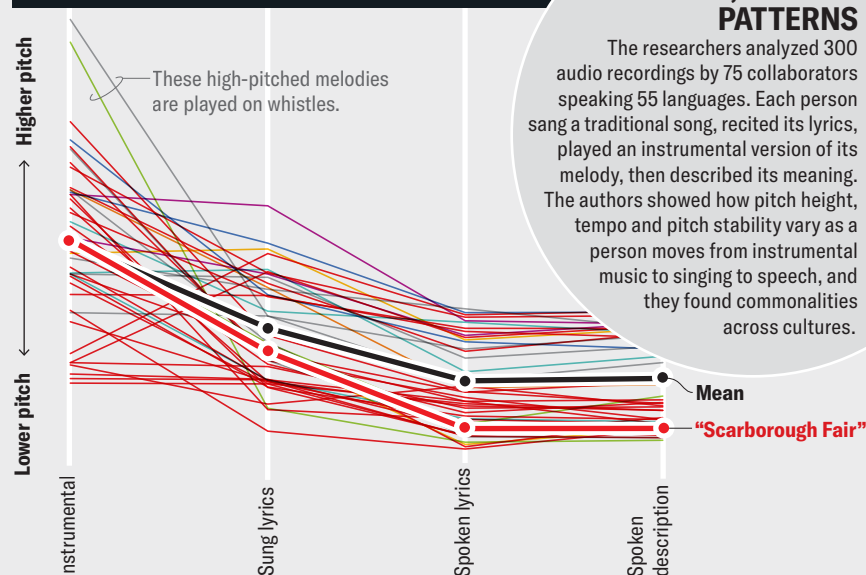
- Indo-European
- Atlantic-Congo
- Japonic

- Sino-Tibetan
- Afro-Asiatic
- Austronesian
- Turkic

- Language families with one representative



Pitch height

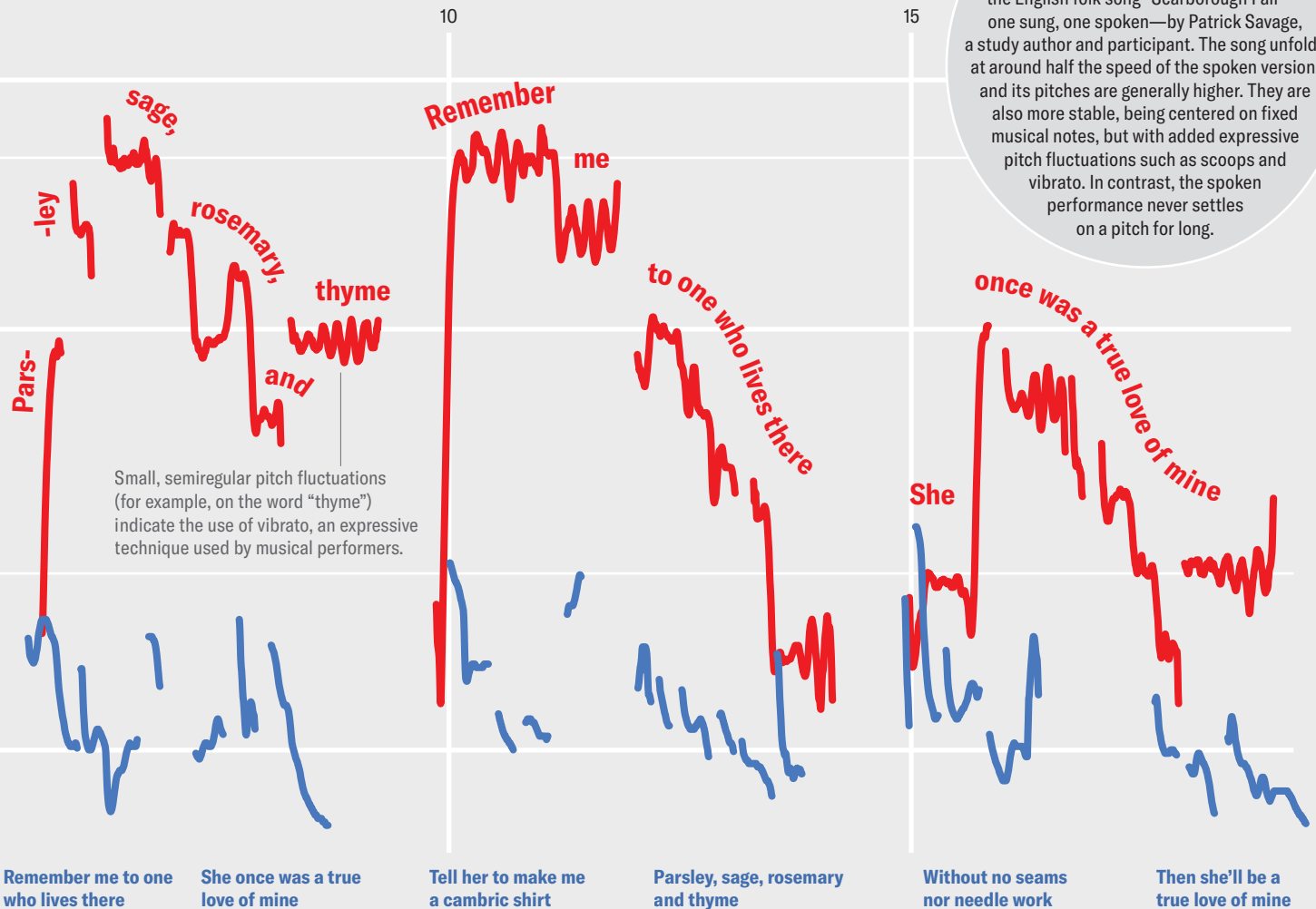


DIFFERENT SONGS, SIMILAR PATTERNS

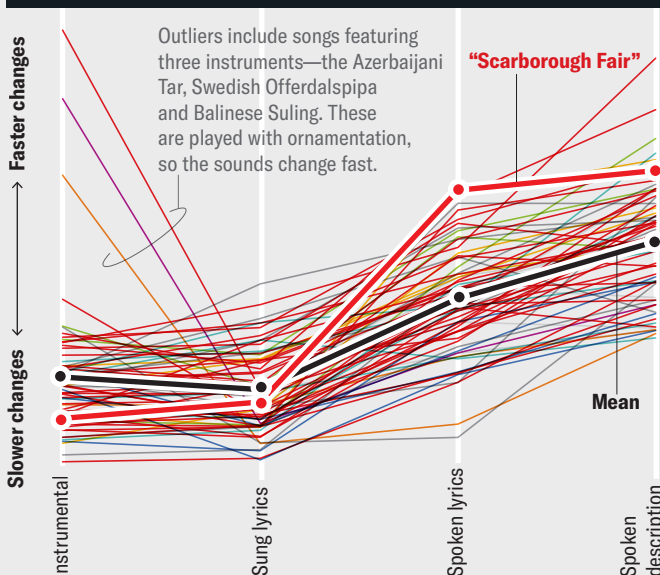
The researchers analyzed 300 audio recordings by 75 collaborators speaking 55 languages. Each person sang a traditional song, recited its lyrics, played an instrumental version of its melody, then described its meaning. The authors showed how pitch height, tempo and pitch stability vary as a person moves from instrumental music to singing to speech, and they found commonalities across cultures.

BREAKING DOWN A SONG

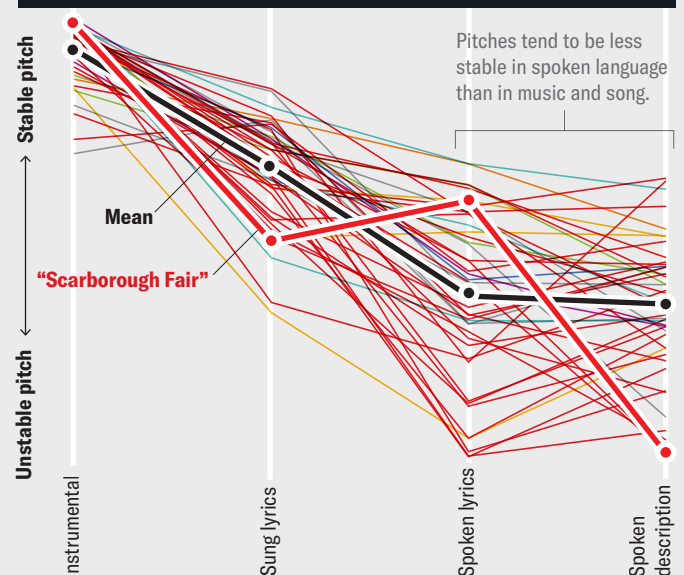
The chart visualizes two recordings of the English folk song “Scarborough Fair”—one sung, one spoken—by Patrick Savage, a study author and participant. The song unfolds at around half the speed of the spoken version, and its pitches are generally higher. They are also more stable, being centered on fixed musical notes, but with added expressive pitch fluctuations such as scoops and vibrato. In contrast, the spoken performance never settles on a pitch for long.



Tempo



Pitch stability



Source: “Globally, Songs and Instrumental Melodies Are Slower and Higher and Use More Stable Pitches than Speech: A Registered Report,” by Yuto Ozaki et al., in *Science Advances*, Vol. 10; May 15, 2024 (data)

50, 100 & 150 Years



SPATIAL RELATIONS IN BOYS AND GIRLS

1974

"A cognitive attribute known as 'spatial ability' can be assessed by specially designed tests. Findings that implied a superior male performance have endured in psychology literature. Jerome Kagan, a Harvard University psychologist concerned with child development, and Ann Karnovsky, then one of Kagan's graduate students, wondered when this supposed superiority first becomes evident. They designed a simple test given to 222 boys and 223 girls in the first, second, third and fourth grades in Lexington, Mass., and the seventh grade in Newton, Mass. The investigators found no sex difference, with one exception: in the low-ability and medium-ability division of the seventh-grade mathematics class, the boys' performance was significantly superior. Karnovsky and Kagan conclude that males and females are potentially of equal competence. The lower scores of some seventh-grade girls Karnovsky attributes to the effect of cultural conditioning."

COMPUTER CHESS CHAMP

"The first world computer chess championship was won in Stockholm by a Russian program called Kaissa, with four victories and no defeats. Three programs each lost one game. The tie was broken based on the fewest total moves and a play-off game. Second place

was awarded to the four-time U.S. national champion, Chess 4.0 from Northwestern University. Third place went to Ribbit, the Canadian champion from the University of Waterloo, and fourth place to Chaos, written by programmers at Sperry Univac. There were 13 entries from eight countries."



PRECIOUS STONES INSIDE PLANTS

1924

"Now and again, substances which closely resemble opals and pearls are discovered in giant tropical bamboos. In the young stages of growth the hollow stems are filled with a jelly-like substance. As time goes on this dries up and an interesting mineral deposit known as tabasheer is formed. Some of this plays a part in making the stems stiff and strong but, at times, an excess settles in more or less rounded lumps at the stem joints. These are pale blue or white. There is a close chemical connection to an opal, and the general color and the manner of light reflection are much the same."

A SWINGING APOLOGY

"One of our readers, G.H. Taber of Pittsburgh, has been good enough to point out an error which crept

into the article on fused quartz in the July issue. On page 59 we said of clocks they run 'faster as the weather gets warmer and the bob (of the pendulum) longer.' Of course, the clock runs slower as the pendulum gets longer. We are obliged to Mr. Taber. We are sorry. We will try not to do it again."



CHLOROFORM KILLS DENTAL PATIENTS

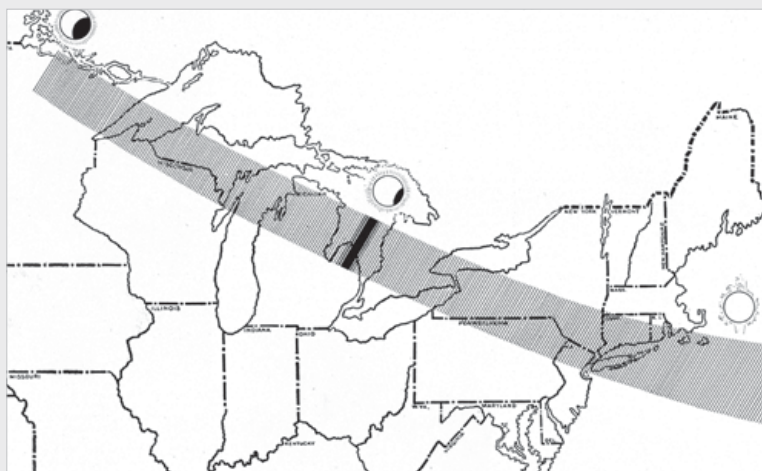
1874

"The death of another patient in the dental chair, while under the influence of chloroform, again attracts public attention. This latest accident occurred in Boston. The jury impaneled at the coroner's inquest notes that owing to our present lack of knowledge, chloroform's use as an anaesthetic is utterly unjustifiable. They also recommend legislative enactments to prevent its administration. That

does not appear needed, however, since the growing tendency of the medical profession is in favor of pure ether as a substitute, or else a mixture of chloroform, ether and alcohol, which we understand produces good results without causing the dangerous depressing effect of the chloroform or the nausea of ether. The employment of nitrous oxide in dental surgery is also greatly extending; and since it is both a harmless as well as an agreeable anaesthetic, it possesses peculiar advantages."

BARN BURST INTO FLAME

"Many farmers have experienced sudden and destructive conflagrations in their hay lofts. Barns have been known to burst into flame, almost without warning. Abbé Moigno, in *Les Monde*, gives the following theory: Hay, when piled damp and in too large masses, ferments and turns dark. In decomposing, sufficient heat is developed and vapors begin to be emitted. The hay becomes carbonized little by little, and then the charred portion, like peat, becomes a kind of pyrophorus. The charcoal becomes concentrated on the surface to such a degree that the mass reaches a temperature which results in its bursting into flames."



1924, Total Eclipse: "The shaded area marks the 'shadow path' in which the total eclipse of the sun, on January 24, 1925, will be visible. At the western end the sun will rise already half eclipsed. At the heavy line midway along the path the eclipse will be just at its beginning as the sun rises. East of this midpoint all the eclipse, from beginning to end, will be visible."

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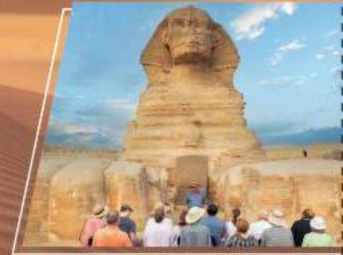
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**SCIENTIFIC AMERICAN,
NOVEMBER 2024: PAGES
S21–S22**

“DEFOGGING DATA,” by Jyoti Madhusoodanan [Innovations in Solutions for Health Equity], should have said that the Office of Management and Budget defined the single Asian or Pacific Islander category in 1977 and that a 1997 revision to the standard required that group to be split into two categories. In addition, the article should have given Joseph Keawe‘aimoku Kaholokula’s full name and described him as a health disparities researcher.

**SCIENTIFIC AMERICAN,
NOVEMBER 2024: PAGE S4**

“BETTER MEASURES,” by Cassandra Willard [Innovations in Solutions for Health Equity], should have described creatinine as a molecule, not a protein.