COSMOLOGY
The Puzzle of Dark Energy

SUSTAINABILITY
Climate Refugees of Syria

NEUROSCIENCE
The Brain's Garbage Disposal

SCIENTIFIC AMERICAN

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MYSTERY HUMAN

Enigmatic bones found in South Africa are stirring a debate about our origins

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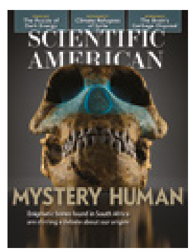

ON THE COVER
Skull of new human species *Homo naledi* was virtually reconstructed from fossil fragments belonging to several individuals. In this artist's conception, which is based on a 3-D image file released to the public by the discovery team in South Africa, blue indicates areas for which fossil material has not been recovered.
Illustration by Bryan Christie.

COVER ILLUSTRATION SOURCE: UNIVERSITY OF THE WITWATERSRAND, HEATHER GAVIN *Mercyhurst University* AND PETER SCHMID *University of Zurich*; FILES WERE DOWNLOADED FROM WWW.MORPHOSOURCE.ORG *Duke University*

Photograph by John Wendle

SCIENTIFIC AMERICAN

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ON THE WEB

Cabinet of the Universe
Scientific American explores astronaut/video game developer Richard Garriott's unique artifact collection documenting the history of the universe.
Go to www.ScientificAmerican.com/mar2016/universe

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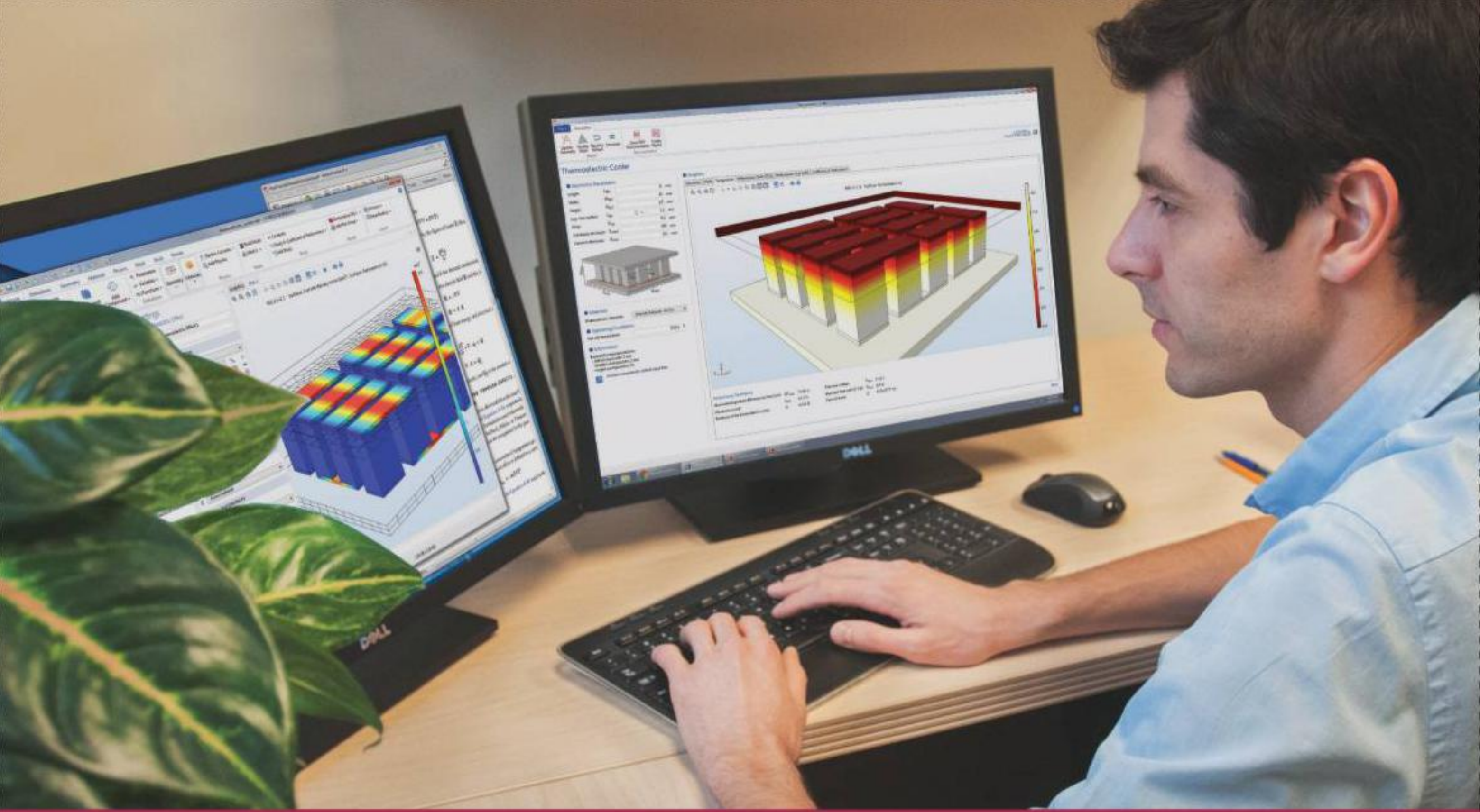

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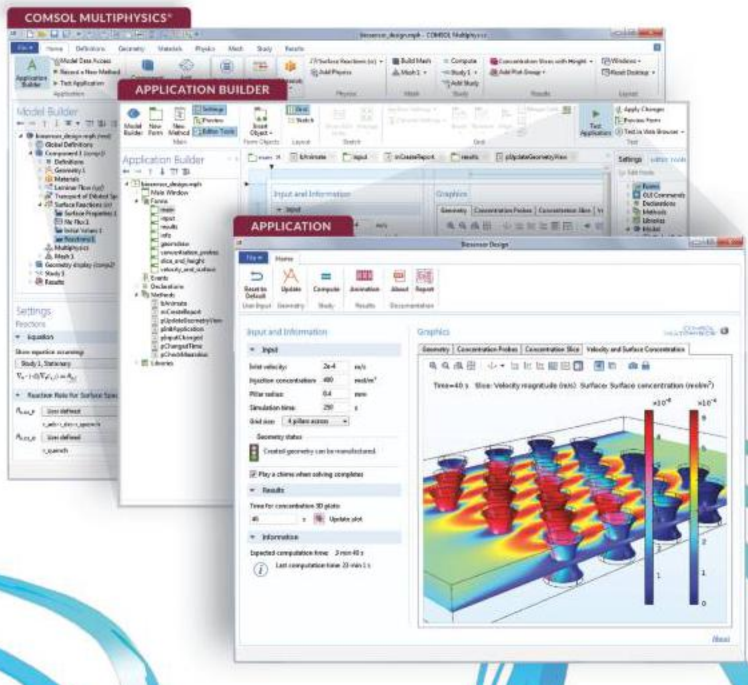

COMSOL

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

Looking to the Rising Star

We humans are many, but we are also one. Species, that is. For much of our evolutionary history, however, members of our family of ancestors, the hominins, trod the planet at the same time. Piecing together how and where these different species arose and lived from fragments of bone has always seemed an astonishing challenge to me.

This issue's cover story, "Mystery Human," by senior editor Kate Wong, explores a recent puzzle from a cache of enigmatic fossils found in a cave in South Africa outside Johannesburg, called Rising Star. The bones of a new species, *Homo naledi,* rested nearly 100 feet below the surface, in the "Dinaledi chamber." The expedition to find them involved steep climbs and squeezing through passages as tight as eight inches across. In total, scientists have recovered more than 1,550 specimens from at least 15 individuals—so far. Tantalizingly, the bones combine primitive and more modern traits. Therein lies a series of provocative claims and debates about the relation of the new species to other ancient members of our human family, as well as what they might mean for *H. naledi's* behavior. For instance, *H. naledi* may have been intentionally disposing of its dead in the cave, a supposition backed up by the lack of sizable animal bones, which would suggest predators or other factors at work. Turn to page 28 to begin a fascinating journey into our intriguing origins. SA

ENTRIES OPEN

With a mission to help foster the young researchers whose work will improve the world through the process we call science, the Google Science Fair opened for entries on February 17. Now in its sixth year, the annual competition is for students around the world ages 13 through 18; each entry can be by one student or up to three as a team. *Scientific American* is a founding partner, and I serve as the chief judge; other partners are Lego Education, *National Geographic* and Virgin Galactic.

The *Scientific American* Innovator Award recognizes work in basic research topics, as well as the behavioral sciences, with a cash prize of $15,000 to be put toward the students' studies, a trip with a guardian on a *Scientific American*/Bright Horizons cruise, a year of mentorship to advance the winning work, and digital access to 170 years of *Scientific American*'s archives for the winners' schools for one year. The submission deadline is May 17. The global finalists will travel to Google headquarters in Mountain View, Calif., for the awards event on September 27.

Read about past winners at www.ScientificAmerican.com/education. For more, go to www.googlesciencefair.com. —*M.D.*

Illustration by Bryan Christie (skull); Illustration by Nick Higgins (DiChristina)

PROMOTION

The Agenda Setters

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Contemporary Jewish Museum | San Francisco, CA | November 5, 2015

As part of an ongoing partnership with Merck KGaA, Darmstadt, Germany, SCIENTIFIC AMERICAN’s Custom Media Group took part in a unique forum, exploring next-generation innovation trends in materials science.

Luiz G. Viera, CEO and Managing Director of EMD Performance Materials, a business unit of Merck KGaA, Darmstadt, Germany, noted that a diversity of thinkers and ideas is what truly empowers technological progress and new products, such as flexible displays.

Learn more at: **125yearssmartertogether.com**

November 2015

DARK ENERGY

"Seeing in the Dark," by Joshua Frieman, discusses the effort to confirm whether the accelerated expansion of the universe is because of dark energy. Is it possible to test the hypothesis that our known universe is part of a much larger, more massive universe that might account for the accelerated expansion?

Jack W. Hakala
via e-mail

Frieman points out that a difficulty with one of the four candidates for dark energy, the quantum-mechanical contribution to the vacuum energy, is that its quantity is not yet determined, because calculations give about 10^{120} times more than what currently appears to exist. This embarrassing miscalculation does not, however, negate the principle that its contribution is likely to be nonnegligible.

David Reid
Haifa, Israel

FRIEMAN REPLIES: In response to Hakala: The notion of a multiverse continues to fascinate theorists. One idea for explaining the smallness of the cosmological constant (why it is not 120 orders of magnitude larger) posits that in different regions of the multiverse, the cosmological constant takes on different values. In most of those regions, it is much too large to enable the conditions for life to form; only in regions where it is small, as we observe it to be, can a 14-billion-year-old universe filled with galaxies and life form. Whether we can test this anthropic selection principle is still open to question.

Reid raises a good point. Whatever dark energy turns out to be, it's likely that we will still be left trying to understand the smallness of the vacuum energy. Whether measurements of the properties of dark energy from the Dark Energy Survey or other projects will help illuminate this problem is as yet unknown.

> **"Babies and young children are capable of acquiring several languages simultaneously if they are provided with the right family and social environment."**
>
> AZZAM QASRAWI *RONDA, SPAIN*

INFOMERCIAL?

As a one-time contributor to *Scientific American* and long-time subscriber, I am surprised to see "Disease Detector," by Shana O. Kelley, presented as a scientific article when it actually is a cleverly disguised advertisement for a commercial enterprise. As stated in the article, despite being a Distinguished Professor of chemistry at the University of Toronto, Kelley also happens to be "director of, and holds equity, in Xagenic, a company that commercializes technology described in this article." This is an "infomercial." I expect more from the most prestigious popular scientific magazine in the U.S.

Leonard A. Cohen
Editor, Nutrition and Cancer

THE EDITORS REPLY: Scientific American *invites leading investigators to write about cutting-edge research. Once in a while, an author is also involved with companies that hope to commercialize the work. In such cases, we disclose relevant financial ties, as we did in Kelley's biography. Her article is based on peer-reviewed scientific literature, cited in her story, and also presents competing technology.*

MULTILINGUAL CHILDREN

"Baby Talk," by Patricia K. Kuhl, discusses a period of about six months to seven years in which children are able to quickly learn "a language or two." In my experience, babies and young children are, in fact, capable of acquiring several languages simultaneously, if they are provided with the right family and social environment.

My wife and I were fortunate to provide such an environment for our four daughters, who acquired German, Arabic, French and English during their early years. My German wife and I, a native Arabic speaker, have communicated in English since we met. We brought up our daughters in France, where they went to a primary school that was taught in French and English and were looked after, for a few hours a week, by a French speaker. We then moved to Spain when they were three to eight years old. They acquired Spanish within three months of starting school.

For this proficiency to be achieved, it is vital that each individual communicate with the children in their own native language. And children should be discouraged from mixing languages when they speak to a person. Young children will associate each person with his or her first language.

Azzam Qasrawi
Ronda, Spain

THE SPEED OF GRAVITY

I'm curious about George Musser's reference to gravity traveling at the speed of light in his article "Where Is Here?" Has this been confirmed?

Watching a gorgeous sunset some years ago, someone piped up, "Of course, you know, this really happened eight minutes ago." While I was showering the next morning, it dawned on me that if gravity traveled at the speed of light, Earth's orbit would be "off" (geometrically with the sun) by eight minutes, multiplied by our orbital velocity.

Is it not reasonable to assume that gravity could be an instantaneous manifestation, sort of like nonlocality?

Syd France
Kirkland, Wash.

In discussing nonlocality, Musser talks about the reshaping of spacetime in terms of the movement of tectonic plates. I think a more apt and universal reference for the point he is trying to make is that Earth is always both spinning on its axis and revolving around the sun, and the solar system itself is revolving around the center of our galaxy, and so on. Therefore, any attempt to define a location on Earth as being "here" in spacetime is an inherently nonsensical concept.

DENNIS COLEMAN
Allendale, N.J.

MUSSER REPLIES: In answer to France's question: Isaac Newton did think that gravity propagated instantaneously, but in our modern understanding, thanks to Albert Einstein, gravity, per se, does not travel: it is a consequence of the curvature of spacetime at the location of an object. Changes in curvature (namely, gravitational waves) do travel, at light speed, as has been confirmed indirectly by observations of the orbits of binary pulsars and, more controversially, by the gravitational lensing caused by Jupiter.

Coleman is right that the universe appears to have no preferred frame of reference, so it's meaningless to talk of "the" position or velocity of, say, a baseball. It is moving at 80 miles an hour relative to the field but far faster relative to the sun or the center of the galaxy. That idea goes back at least as far as Galileo, and Einstein formalized it in special relativity. But the tectonics metaphor was intended to get across a different idea: that even if you decide on a frame of reference, position has no fixed meaning. That is the innovation of general relativity.

FOOD ALLERGIES

I appreciate hearing about any medical research concerning food allergies, such as in "Overreaction," by Ellen Ruppel Shell [The Science of Health]. My son, who is 21, has several well-documented IgE-mediated food allergies.

In discussing a study involving peanut allergies, Shell casually refers to "proteins found in nuts." Peanuts are legumes, not tree nuts.

MARY ELLEN CLARK
via e-mail

LETTERS TO THE EDITOR

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Letters may be edited for length and clarity. We regret that we cannot answer each one. Post a comment on any article at ScientificAmerican.com/mar2016

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A Clear View of Medical Care

U.S. states have a chance to get a handle on health costs—if the Supreme Court doesn't get in the way

By the Editors

In one hospital in Bayonne, N.J., a patient treated for chronic obstructive pulmonary disease, a respiratory ailment, could get a bill for $99,690. Just across the state line in New York, at another hospital in the Bronx, a patient with the same disease would be charged only $7,044. In the Los Angeles area, comparable joint replacement surgeries can cost $297,000 or $84,000, depending on the facility.

Such wild disparities in health care costs are driven, in large part, by the different rates insurance companies negotiate with hospitals. That is why 18 states have passed laws that tell companies to provide data on patient claims, information that is otherwise hidden. It is a valuable attempt to track out-of-control health care costs and improve treatment. Yet in early December members of the U.S. Supreme Court took some serious swipes at the effort. "Burdensome and costly," Justice Ruth Bader Ginsburg called it. "Purely for bureaucratic reasons," said Justice Stephen Breyer.

The court was hearing arguments in a case challenging Vermont's version of the law. Companies have claimed that such requirements are excessive—that 50 states might put in 50 different requests for this claims information and that an existing federal law already covers it. But that law does not, and the court should support efforts like Vermont's when it issues a decision later this spring.

The case, *Gobeille v. Liberty Mutual,* began because Vermont passed a law requiring health insurance plans to turn data about claims over to a state health analysis and regulation unit, the Green Mountain Care Board. Those included Medicare and Medicaid, national plans such as Blue Cross, and those that companies run for their employees, known as self-funded plans. This last category, which covers more than 90 million Americans across the country, caused some trouble. Private companies complained, arguing that they already disclose this kind of information under a federal law called ERISA, which requires firms to submit health plan data to the U.S. Department of Labor. A lower court agreed, saying that state laws duplicate that effort.

They do not. The Labor Department collects information about the financial state of health plans. It does not collect information about the actual costs of care, however, nor does it track the outcomes of that care. Without a new federal statute, which is a political nonstarter, the state laws do ask for such data, and that is why the U.S. solicitor general is supporting Vermont's case. So are many other states and the American Medical Association.

The issue boils down to how to gather the best evidence. Insurance companies negotiate different rates with different hospitals and doctors, and patients get care for a single ailment from multiple providers. "For decades, the prices that hospitals and physicians charge private insurers have been treated as trade secrets," said a recent commentary on the case in the *New England Journal of Medicine.* To understand the actual costs of treatment and the benefits, health care researchers need to be able to see what is happening to an entire population so the data are not biased and to track a patient through an entire course of care. A person with a neck injury from a car accident might be treated first by one hospital, then get follow-up from a doctor in another town, then see a physical therapist for rehabilitation. One provider never has all the information. Yet the patient's insurance company gets all the claims related to the accident. It has the best—sometimes the only—overall view.

Failure to gather this information from the maximum number of patients would result in a skewed picture. For instance, people in self-insured plans tend to be younger and healthier than people in other types of plans. Without laws such as the one Vermont passed, if you want to understand what it costs to treat asthma, you are limited to data about a relatively older and sicker population. That will not help you understand the costs and care of children with this disease.

The U.S. spends more than twice as much on health care, per person, as does the typical developed country. Yet Americans die years sooner than people do in France, Japan or similar nations. The Supreme Court is the legal guardian of the Constitution, whose first sentence instructs government to "promote the general Welfare," so the court should stand with states as they try and rectify this imbalance. SA

SCIENTIFIC AMERICAN ONLINE
COMMENT ON THIS ARTICLE AT
SCIENTIFICAMERICAN.COM/MAR2016

Illustration by Dave Murray

Keeve Nachman is an assistant professor in the department of environmental health sciences at the Johns Hopkins Bloomberg School of Public Health. He directs the Food Production and Public Health Program at the Johns Hopkins Center for a Livable Future.

Pills for Pigs: Just Say No

New guidelines to curb the overuse of drugs in food animals are inadequate to deal with a growing crisis

By Keeve Nachman

In 1945 Alexander Fleming, the man who discovered penicillin, warned that overuse of his miracle drug could make bacteria immune to it. He was right—and not just about penicillin: the Centers for Disease Control and Prevention has estimated that antibiotic-resistant bacteria infect more than two million people a year, at least 23,000 of whom die. A significant part of that overuse, the CDC says, involves feeding the drugs to the animals we eat. Farmers do this not to cure or prevent disease but simply to make livestock grow bigger and faster.

In 2013 the Food and Drug Administration finally stepped in, asking drug companies to stop selling antibiotics for the purpose of promoting the growth of animals by December 2016. The agency still allows the use of these drugs for "disease prevention," however—that is, to fight off infections animals have not yet gotten. In principle, it might sound reasonable. In practice, this loophole may be big enough to allow farmers to continue with what they have been doing all along, raising concerns that the FDA's plan will not amount to much.

To make things worse, the FDA resisted developing a meaningful plan to evaluate the effect of its action. Instead it intends simply to rely on sales data from drug companies to see whether its (nonbinding) guidelines are actually working. These data are far from ideal for this purpose; even the agency acknowledges that sales are not a reliable way to gauge how antibiotics are really being used.

The data offer no sense of whether the plan is working. The agency's recently released antibiotic sales figures for 2014 show a small increase over 2013, which is consistent with trends in previous years. That result is not surprising, given that the drug companies were not asked to comply fully with the new guidelines until the end of this year. We will have more meaningful information when the FDA releases the 2016 data sometime late in 2017.

Unfortunately, we can't wait that long. Despite acknowledging that misuse in animals is a big part of the problem, the CDC can't figure out exactly how big it is. We are also getting disconcerting signals from around the world, including recent news of the emergence and spread of the *mcr-1* gene, which helps bacteria resist even some of our last-resort antibiotics. An infection with bacteria that sport this gene could be fatal, even in the best health care settings. The alarm was sounded late last year, when this gene was discovered in pigs and humans in China, and since then, it has been found in several other countries. It has yet to show up in the U.S., which is reassuring in the short term, but it may be only a matter of time before it finds its way here.

How worried should we be? More than we are, that's for sure, at least until we change the way antibiotics are used. Sadly, not enough is being done. The biggest battles are being fought over proposals for unfunded, voluntary agency initiatives to collect better antibiotic usage data. Such information could be helpful in determining the full extent to which antibiotic misuse is contributing to untreatable bacterial infections in people. No plan has been put on the table that can change the way the drugs are actually used.

The funding situation is not likely to get much better in the near term. In spite of the $375 million proposed in the current congressional budget to combat outbreaks of antibiotic-resistant bacteria, only $8.7 million (or a little more than 2 percent) is earmarked for the FDA to address antibiotic resistance in the first place. The U.S. Department of Agriculture did not receive a line-item allocation of funds for the same purpose.

People born in the past 70 years are fortunate enough to live in a time when major medical and public health advances, including antibiotics, have allowed us to live long enough to die from chronic diseases instead of infectious ones. The misuse of antibiotics in animal agriculture threatens to hurtle us into a postantibiotic world, where even the most routine infections may become deadly. We must take meaningful action—and fast. SA

SCIENTIFIC AMERICAN ONLINE
COMMENT ON THIS ARTICLE AT
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Illustration by Scott Brundage

ADVANCES

Oil prices are falling, falling, falling. But what may be good for car owners is foiling carefully laid plans for reducing carbon dioxide emissions.

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INSIDE

GALLERY STOCK

ENVIRONMENT

Cheap Oil Undermines Climate Cleanup

The fate of what might prove to be the most important technology for solving global warming is floundering

A few months ago at the Paris climate talks, President Barack Obama and a panoply of world leaders talked at length about the importance of reducing carbon dioxide pollution associated with burning coal, the largest source of greenhouse gases. So far there is only one way to do that without pulling the plug on coal altogether: carbon capture and storage (CCS), a process by which CO_2 is pulled from a smokestack before it escapes into the air and is then buried deep underground.

Nearly every plan to mitigate global warming includes CCS, yet few countries have adopted the technology because there is little incentive to make the costly investment. Decades ago, however, the U.S. found a clever way to make the method economically viable: tie CCS to oil recovery. And while the scheme seemed to work, low oil prices now are putting CCS—and therefore almost all climate cleanup plans—in jeopardy.

Oil-field workers first pumped carbon dioxide down into oil wells in 1972. Called enhanced oil recovery (EOR), the tech-

Oil and gas company Denbury Resources (*left*) buys carbon dioxide pollution from a nearby coal power plant (*right*) to recover oil deep below Mississippi.

nique boosts the amount of petroleum that a well yields because the gas eases the flow of the oil, restores pressure underground to force more oil to the surface, and slips into nooks and crannies that other aids, such as water, will simply flow around. During the process, a portion of CO_2 becomes trapped underground like the oil before it. “It will stay there for eternity,” says Richard Esposito, a geologist who has worked to develop CCS at the coal-burning electric utility Southern Company.

This arrangement—using CO_2 to get oil—is one of the few ways to make carbon capture pay, says Julio Friedmann, the principal deputy assistant secretary for fossil energy at the U.S. Department of Energy. “EOR has been the dominant storage mode because it produces revenue,” he explains. In other words, it potentially satisfies oil companies and environmentalists. With money to be made, a handful of EOR projects popped up across the U.S. over the past few decades. For example, at the Tinsley oil field in Mississippi, the oil and natural gas company Denbury Resources began flooding wells with CO_2 in March 2008 and now recycles some 670 million cubic feet (19 million cubic meters) of the gas every day—increasing its oil production from 50 barrels a day to more than 9,000 barrels a day.

In fact, Denbury and several other companies using EOR need so much CO_2 that they recently contracted to buy the pollution from a new coal-fired power plant in Kemper County, Mississippi—the ultimate goal of the scheme. Such so-called anthropogenic CO_2 now makes up roughly a quarter of all the CO_2 used for this type of oil recovery (the rest comes from natural deposits trapped in geologic domes).

The relationship between CCS and EOR is fragile, however. Because the price of oil has dipped so dramatically over the past couple of years, burying CO_2 no longer pays. Plummeting prices have made it difficult for EOR companies to bring in enough money to pay for new machinery, such as pumps, compressors and specialized pipelines, says Dan Cole, Denbury's vice president of commercial development and governmental relations. Already oil-field services giant Schlumberger has shut down its Carbon Services unit, which was supposed to turn CO_2 into a steady business, and others are considering similar moves. Those closures could throw a wrench into the climate cleanup efforts carefully laid out in recent reports by the International Energy Agency and the Intergovernmental Panel on Climate Change.

At the same time, the troubled relation-

COMMENT AT ScientificAmerican.com/mar2016

ROGELIO V. SOLIS *AP Photo*

Because the price of oil has dipped so dramatically over the past couple of years, burying carbon dioxide no longer pays.

ship may highlight the irony of crafting planet-saving scenarios that rely on oil extraction. After all, burning the extra oil produced by pumping CO_2 underground produces more CO_2 that ends up in the atmosphere, causing yet more global warming.

And there are alternative solutions to pay for CCS, although they are far from application. For example, one way to encourage burying CO_2 pollution directly is to provide a $50-per-metric-ton tax credit for such sequestration, says the DOE's Friedmann. He adds, "The harsh mathematics of atmospheric accumulation make it clear that CCS needs to be a climate solution."

—David Biello

HEALTH

Off the Beaten Path

Pacemakers that temporarily disrupt the organ's rhythm may boost its health

Sometimes it pays to be out of sync. A new study shows that intentionally throwing off the timing of a heart's contractions can effectively treat a failure to pump sufficient blood.

In about a quarter of the five million Americans with the condition known as heart failure, the organ's chambers fail to contract in perfect synchrony. When pacemakers are implanted to restore favorable timing—known as cardiac resynchronization therapy—the heart often ends up stronger than in heart failure patients who never had out-of-step contractions. In essence, moving from dyssynchrony to synchrony seems to be beneficial. That observation led David Kass, who directs the Johns Hopkins Center for Molecular Cardiobiology, to a tantalizing question: Could heart failure patients with regular contractions benefit from a little discord?

To answer the question, Kass and his colleagues placed pacemakers into 23 dogs, 17 of which were induced into heart failure. Then, for six hours a day, the pacemaker in eight of the experimental animals forced the right side of the ventricle to contract earlier than the left side. For the rest of each day, the device reverted to synchronized pacing.

After four weeks, key indicators of heart health proved markedly better in the dogs with pacemakers programmed for a period of irregular contractions. Their hearts pumped blood more forcefully, and proteins responsible for contractions and muscle structure were more abundant. The results, published last December in *Science Translational Medicine,* "fly in the face of our conventional thoughts about cardiac resynchronization therapy," says George Thomas, a cardiologist at NewYork-Presbyterian Hospital and Weill Cornell Medical College who was not involved with the study.

Key heart health indicators proved markedly better in the dogs with pacemakers programmed for a period of irregular contractions.

The treatment can be likened to the body's reaction following a vaccination. Just as an injection of a weakened or partial virus triggers a protective immune response, exposing the heart to a "dose" of dyssynchrony fortifies its functioning. Kass plans to study the approach in humans in a year or so, but other cardiologists have already taken notice of the preliminary results. "It's a very thought-provoking, original idea," says David Frankel, who treats heart failure at the University of Pennsylvania. He thinks many patients could benefit from a break in the monotony. *—Jessica Wapner*

SPACE

On the Road Again

The European Space Agency launches part one of a new mission to Mars

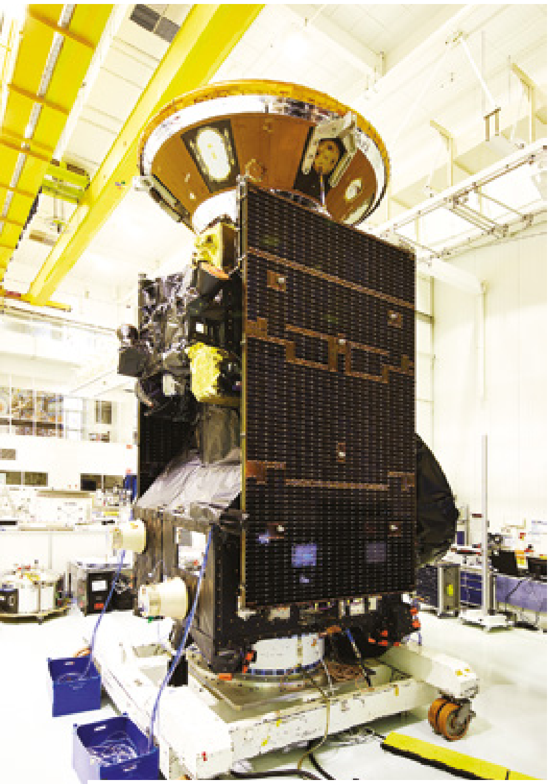
Mars has become both a literal and figurative graveyard for robotic missions: in total, 26 have either failed to reach the Red Planet or did not survive touchdown. Those disappointments have hardly discouraged further attempts, however. So who's next in line? The European Space Agency, which, in partnership with Russia's Roscosmos state corporation, will launch a hugely ambitious mission to Mars this month.

If all goes well, the ExoMars program will encompass two separate journeys. This year's orbiter and landing module, which are set to launch together onboard a Russian Proton rocket from the Baikonur Cosmodrome in Kazakhstan, will serve as interplanetary scouts for the second component: a rover mission in 2018.

To prepare for the rover, the orbiter-module duo will have to complete a

HENRY STEADMAN *Getty Images* (heart); COURTESY OF ESA (*prototype*)

COMMENT AT ScientificAmerican.com/mar2016



If successful, the ESA's orbiter and lander (*above*) will pave the way for a rover mission in 2018 (*prototype, above left*).

long list of objectives. For example, the module will test key landing technologies, such as an onboard computer, radar altimeter and parachute. Meanwhile the orbiter, the largest spacecraft ever sent to Mars, will circle the planet at an altitude of 400 kilometers and sniff for traces of methane and other gases that could signpost past or present life below. It will also scan for water ice hidden under the planet's surface and, just as important, help to transmit data between Earth and the rover when it arrives.

All in all, the ExoMars rover has the potential to hit a "home run" in gathering evidence about whether Mars has ever supported life, says Peter Willis, an investigation scientist for NASA's Mars 2020 mission. The ESA rover will have the capability to drill a record two meters deep and carry the most sensitive instruments yet for detecting biological signatures in the samples it pulls, explains Jorge Vago, a project scientist for ExoMars. "If life ever existed on Mars," he says, "the ExoMars rover will be the first mission that has a real chance of detecting the biological remnants of it." —*Jeremy Hsu*

ENRICO SACCHETTI

For the indeterminable future, bags of contaminated nuclear waste will sit on temporary storage plots in Japan.

ENERGY

Fukushima Today

Half a decade later the nuclear disaster site continues to spill waste

Five years ago this month a devastating tsunami engulfed Japan's northeastern coast, triggering the worst nuclear disaster since Chernobyl. Washing over a 10-meter-high seawall, the waves knocked out electricity at Fukushima Daiichi nuclear power plant, causing cooling systems to fail and half of the facility's uranium cores to overheat and melt through their steel containers. Hydrogen explosions in the next few days damaged three of the reactor buildings, venting radioactive materials into the air. That plume of airborne contamination forced some 160,000 people to evacuate from their homes.

Today the disaster site remains in crisis mode. Former residents will not likely return anytime soon, because levels of radioactivity near their abodes remain high. Even more troublesome, the plant has yet to stop producing dangerous nuclear waste: its operator, the Tokyo Electric Power Company (TEPCO), currently circulates water through the three melted units to keep them cool—generating a relentless supply of radioactive water. To make matters worse, groundwater flowing from a hill behind the crippled plant now mingles with radioactive materials before heading into the sea.

TEPCO collects the contaminated water and stores it all in massive tanks at the rate of up to 400 metric tons a day. Lately the water has been processed to reduce the concentration of radionuclides, but it still retains high concentrations of tritium, a radioactive isotope of hydrogen. Disputes over its final resting place remain unresolved. The same goes for the millions of bags of contaminated topsoil and other solid waste from the disaster, as well as the uranium fuel itself. Health reports, too, are worrisome. Scientists have seen an increase in thyroid cancers among the children who

AP PHOTO (top); GETTY IMAGES (bottom)

COMMENT AT ScientificAmerican.com/mar2016

GETTY IMAGES

BY THE NUMBERS

2020–2021
Projected date for removal of fuel debris from Fukushima Daiichi's reactors

2051–2061
Projected date by which the plant will be fully decommissioned

$100 billion
Cost of the accident thus far, excluding indirect costs to tourism and food exports

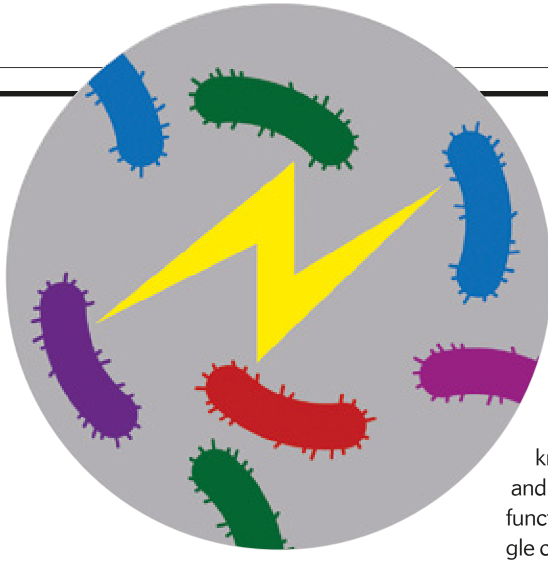
3,200
Deaths from ailments and suicides resulting from the evacuation

1,000
Predicted total deaths from cancers caused by the radioactive leaks

SOURCES: "THE WORLD NUCLEAR INDUSTRY STATUS REPORT 2015," BY MYCLE SCHNEIDER AND ANTONY FROGGATT; JULY 2015 (*first four items*); "ACCOUNTING FOR LONG-TERM DOSES IN 'WORLDWIDE HEALTH EFFECTS OF THE FUKUSHIMA DAIICHI NUCLEAR ACCIDENT,'" BY JAN BEYEA ET AL., IN *ENERGY & ENVIRONMENTAL SCIENCE*, VOL. 6, NO. 3; MARCH 1, 2013 (*last item*)

had lived in Fukushima at the time, although it is too early to tell if those cases can be attributed to the accident.

Nevertheless, Japan's government plans to recommit to nuclear power. Prime Minister Shinzo Abe recently emphasized the urgent need to restart the country's nuclear power plants, which all were taken offline following the Fukushima Daiichi disaster. So far two have been brought back to full operation. —*Madhusree Mukerjee*



BIOLOGY

The Connection Was Electric

Bacteria employ electrical signaling in the same way brain cells do

Bacteria may be ancient organisms, but don't call them primitive. Despite being unicellular, they can behave collectively—sharing nutrients with neighbors, moving in concert with others and even committing suicide for the greater good of their colony. Molecules that travel from cell to cell enable such group behavior in a signaling process called quorum sensing. Now new evidence reveals that bacteria may have another way to "talk" to one another: communication via electrical signaling—a mechanism previously thought to occur only in multicellular organisms.

In 2010 molecular biologist Gürol Süel, now at the University of California, San Diego, set out to understand how a soil bacterium called *Bacillus subtilis* could grow into massive communities of more than a million cells and still thrive. He and his colleagues found that once the colony reaches a critical size, bacteria on the periphery stop reproducing to leave core cells with a sufficient nutrient supply.

But that observation led to the question of how the edge cells receive word to cease dividing. In a recent follow-up study, Süel discovered that the intercellular signals in this case were in fact electrical. The messages travel via ion channels, proteins on a cell's surface that control the flow of charged particles—in this case, potassium ions—into and out of a cell. The opening and closing of these channels can change the charges of neighboring cells, inducing them to release such particles and thereby relaying electrical signals from one cell to the next. "We've known that bacteria had ion channels and people have assigned them different functions, but only in the context of the single cell," Süel says. "Now we're seeing that they're also being used to coordinate behavior over millions of cells." The study appears in the journal *Nature.*

Electrical signaling of this type is also how neurons in our brain pass along information. This and other findings are therefore prompting scientists to reevaluate their assumptions about single-celled life. "Bacteria have been thought of as limited because they are not multicellular," says Steve Lockless, a biologist at Texas A&M University who was not involved in the study. But as unicellular organisms increasingly offer evidence of multifaceted behaviors, that may not be the case for much longer. —*Diana Kwon*

CHEMISTRY

Neither Here nor There

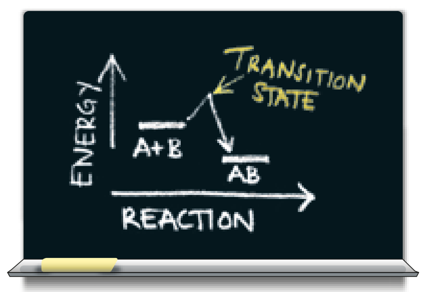
For the first time chemists measure the elusive moment when entities in a reaction convert

Hike from one valley to another via a mountain pass, and eventually you'll come to the highest point of your journey, where you'll probably stop briefly to take in the view before descending. That moment serves as a good analogy to one of chemistry's mysteries: the brief transition state that occurs just as molecules in a reaction are about to transform into new chemical species.

Scientists have long regarded transition states as too unstable and fleeting to be observed. But chemists at the Massachusetts Institute of Technology have now measured the energy of a transition state. Just as the height of a mountain pass constrains how long it will take a hiker to reach the summit, energetic properties of a transition state govern how long it takes for chemical reactants to adopt new conformations.

To make the crucial measurements, Joshua Baraban, then a graduate student at M.I.T., and his colleagues excited acetylene with a laser. In this simple reaction, the molecule twists from a linear to a zigzag conformation. Acetylene vibrated predictably as it absorbed light at greater intensities, but in the instant before it went from straight to zigzag, the vibrations stopped, providing a window into the elusive transition state.

"We found that the frequency of the vibrations dips to zero just as the molecule goes over the hump from one conformation to another," says Baraban, now at the University of Colorado Boulder. By measuring the energy it took until the vibrations paused, the team could characterize the



transition state's energetic properties. The results were published recently in the journal *Science.*

The method also worked to track the transition state of the more complex conversion of hydrogen cyanide to hydrogen isocyanide, found Baraban's colleague Georg Mellau of Justus Liebig University Giessen in Germany. The ability to quantify this brief moment "is important wherever chemistry is important," Baraban says. For instance, better knowledge of transition states in fuel-combustion reactions could allow scientists to engineer cars with better gas mileage. —*Charles Schmidt*

Illustration by Thomas Fuchs (bacteria), Illustration by Jen Christiansen (chalkboard)

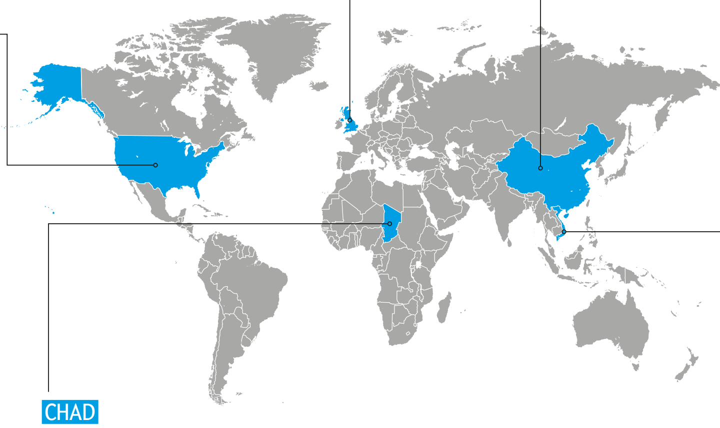
IN THE NEWS

Quick Hits

U.S.
Astronaut Scott Kelly returns to Earth this month after spending a full year in space, the longest mission for any American. Kelly is one half of NASA's Twins Study, an investigation into how life in microgravity affects physiology. His identical twin and fellow astronaut, Mark Kelly, remained on Earth.

U.K.
An e-cigarette manufactured by British American Tobacco has received approval as a doctor-prescribed aid for quitting smoking. National health insurance will cover the vaping device.

CHINA
Xiaoice, an artificially intelligent computer program developed by Microsoft, has become a trainee weather anchor for Dragon TV, one of the country's largest news broadcasting channels. It currently delivers daily forecasts.



VIETNAM
The online video-streaming service Netflix expanded into Vietnam and more than 130 other nations, bringing the total up to 190 countries.

ANTARCTICA
Atmospheric scientists have started to gather information about clouds over Western Antarctica for the first time since 1967. The experiment will run until early 2017 and help climate modelers determine how warming at Earth's poles could change global weather patterns.

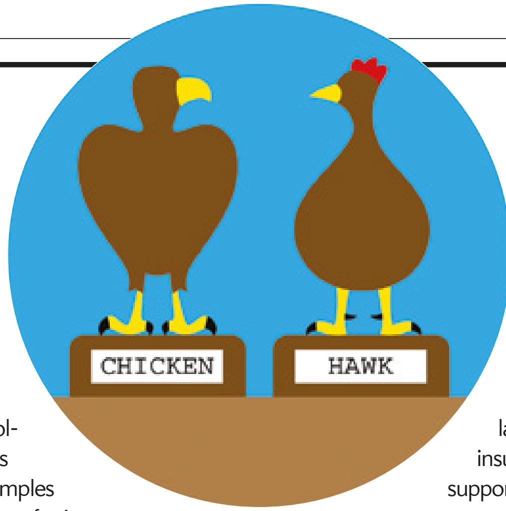
CHAD
An outbreak of Guinea worm disease in dogs could thwart the anticipated eradication of the parasitic infection. Although only 25 human cases were reported globally in 2015, more than 450 infections were reported in dogs in Chad last year. Experts suspect canines are passing the parasites to humans.

For more details, visit www.ScientificAmerican.com/mar2016/advances

TAXONOMY

Classification Conundrum

Scores of museum specimens carry a name that isn't theirs



A certain French rose by any other name may smell as sweet, but fragrance aside, its scientific name is *Rosa gallica*—and that's the name it should bear in botanical collections. Yet more than half of plant specimens tucked away in herbaria may be mislabeled, and the problem could extend to other types of collections, too, according to a study published in *Current Biology*.

To examine how pervasive mislabeling can be, researchers at the University of Oxford and the Royal Botanic Garden Edinburgh analyzed the tags on 4,500 specimens of African ginger and more than 49,000 specimens of morning glories as case studies. "We found at least half of the names associated with those specimens were synonyms or illegitimate names," says botanist Robert Scotland.

The errant nomenclature most likely arises when biologists and collections managers classify samples of a species without conferring with colleagues at other institutions. In other cases, a sample may be designated by its genus alone if its species name initially is unspecified or undetermined—a simplification that Scotland's team counted as incorrect. And although the researchers think the problem is more prevalent in collections of plants than in those of vertebrate animals, they suspect that misplaced monikers run rampant through insect stockpiles as well.

Some experts, including Barbara Thiers, director of New York Botanical Garden's William & Lynda Steere Herbarium, think the one-half estimate for plants is an exaggeration. But both Thiers and Scotland agree that insufficient financial support for collections management makes consistently accurate categorization of thousands on thousands of specimens a daunting task. Group efforts, such as the online databases The Plant List, FishNet and ZooBank, could help tackle the situation.

Why all the fuss? Wrong names can interfere with research on a particular organism and hinder conservation efforts. "If we don't know the right names to use for plants or animals," Thiers says, "there's no way we'll be able to save them."

—Jennifer Hackett

Illustration by Thomas Fuchs

COURTESY OF NIC BENNER *University of Missouri*

GENETICS

You Can Edit a Pig, but It Will Still Be a Pig

Scientists use CRISPR gene-editing tool to prevent devastating swine infection

One of the worst things that can happen to a pig farmer is a pen infected with porcine reproductive and respiratory syndrome virus (PRRSV). It emerged in the 1980s, and the syndrome now afflicts these hoofed animals worldwide, causing illness, death and miscarriage. In fact, it has been designated the most economically significant disease for swine, costing livestock producers in North America $600 million annually from deaths and medical treatments. Vaccinations have mostly failed to prevent the syndrome's spread, but a new approach by biologists at the University of Missouri may mark a turning point. They are one of the first teams to develop a commercial agricultural application for the revolutionary CRISPR/Cas9 gene-editing method—to breed pigs resistant to infection.

CRISPR/Cas9 is a gene-manipulation tool that allows scientists to make changes to DNA with razor-sharp accuracy. The tool has generated excitement in the research community because it allows rapid modification of gene function, replacing older and less efficient methods. For porcine reproductive and respiratory syndrome, Missouri's Randall Prather, Kristen Whitworth and Kevin Wells turned to the technique to breed three piglets that lacked a protein on cells that acts as a doorway for the virus. The edited piglets were grouped together in a pen with seven normal piglets, and then they all were inoculated with PRRSV.

About five days later the normal pigs grew feverish and ill, but the genetically edited pigs did not. Despite sharing close quarters with their sick pen mates, they remained in top health throughout the 35-day study period. Blood testing also revealed that the edited animals did not produce antibodies against the virus—further evidence that they evaded infection entirely. "I expected the pigs would get the virus but not get as sick," Prather says. "But it is just night and day. The pigs are running around with the other pigs coughing on them, but they are just fine." The study's results were published in the journal *Nature Biotechnology*.

This work and other recent experiments demonstrate the promise of CRISPR/Cas9 for the care of domestic animals. Late last year geneticists at the University of California, Davis, employed the new technique to breed dairy cows that do not grow horns. The outcome is a boon: cows are routinely dehorned to protect farmers and other cattle from being injured, but the process can be brutally painful and dangerous for the bovines.

More livestock will likely be produced in such a way, says Alison Van Eenennaam, a geneticist who worked on the development of the hornless cows. "This is analogous to breeding," she notes. "It's just precision breeding." —*Monique Brouillette*

Turn to page 56 to learn more about the role of CRISPR technology in agriculture.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Sir Michael Marmot directs the Institute of Health Equity at University College London and is president of the World Medical Association for 2015–2016. His book *The Health Gap* was published by Bloomsbury in 2015.

The Disease of Poverty

Helping parents to help their children can close the rich-poor health gap

By Michael Marmot

In Baltimore, men in one of the most down-at-the-heels, blighted parts of the city live 20 years less, on average, than men in the leafiest, most well-to-do neighborhoods. Numbers such as these are why poverty and lack of access to medical care are often blamed for poor health in the U.S.

But it is not a simple money = health equation. Other numbers make that clear. By global standards, the poor of the U.S. are fantastically rich, yet they die sooner than the poor of other lands. Again, look at the poorest part of Baltimore. In 2010 the median household income here was $17,000, whereas the median in India was $5,150 *after* adjusting for purchasing power. Yet men in this part of Baltimore have a shorter life expectancy—63 years—than the Indian average of just more than 65 years. These Americans have more than triple the median purchasing power of Indians and yet have nearly two years less to live.

The U.S. problem is not limited to the poor. The average 15-year-old American boy has a 13 percent chance of dying before the age of 60. That risk of death—calculated in 2012—is double the probability for such boys in Sweden, about the same as in Turkey and Tunisia, Jordan and the Dominican Republic, and much higher than in Costa Rica, Chile and Cuba. In fact, the U.S. survival figure is lower than that in 51 other countries—although the U.S. spends more on health care than any other land.

To improve health, we have to stop blaming the sufferers and look not only at lack of money but lack of other resources. My research, and that of other scientists, points the finger at social and psychological disempowerment, a personal sense of marginalization in society, as a factor with greater effect than lack of money alone. When people feel deprived relative to those around them, stress rises, and then health suffers. Fortunately, the research also indicates that interventions with parents—improving parenting skills, for example—profoundly empowers their children. This, in turn, appears tied to a lifetime of better health.

A SOCIAL SLOPE

AS A PUBLIC HEALTH SPECIALIST and epidemiologist, I have been investigating reasons for health inequalities for more than 35 years. I first described the connection between a person's social status and his or her health in studies of British civil servants, called the Whitehall Studies. No civil servant is poor or unemployed, and none is as rich as a banker or hedge fund manager. Yet among these white-collar men and women the higher their civil service grade, the longer their life expectancy and the better their health. This has become known as the social gradient, and it is not just about money but about a whole cluster of socioeconomic factors, and the way they give you a sense of control over your life and how you perceive your position in society relative to others. In my book *The Health Gap,* I follow this connection to the U.S. Someone in the middle of the U.S. income distribution curve has worse health than people with higher incomes but better health than poorer people. If we use education as our measure, we find the same thing: more years of education mean longer life expectancy and better health.

Skeptics will counter that the most common causes of death, such as diabetes, cardiovascular disease and cancer, are linked to lifestyle problems such as smoking and obesity, not disempowerment. But look harder. Smoking follows the social gradient: the lower the social position, the greater the smoking. Obe-

Illustration by Thomas Fuchs

sity, too, follows the gradient. When we see social trends such as these, it is inadequate to ask why an individual fails to heed health advice and is thus exposed to causes of ill health. We need to seek the causes of the causes—the social conditions that give rise to these unhealthy lifestyles.

For example, evidence from Britain shows that the more deprived a region or neighborhood is economically, the lower the proportion of children, at age five, who have a good level of cognitive, linguistic, social, emotional and behavioral development. But it is very important to realize that deprivation does not have the same effect in all places. Pick any given level of deprivation, and you will see that some local areas are doing better than others. For instance, one such area will have a higher proportion of children ready for school. These findings suggest that deprivation alone does not determine how children will fare. There is something else going on, and research indicates that variation in parenting skills is a major part of that something.

To test out the contribution of parenting activities to the social gradient in child development, a group of us now at University College London, led by Yvonne Kelly, analyzed data from the U.K. Millennium Cohort Study, a research project in England. We asked mothers of children aged three whether it was important to talk to and to cuddle their children. About 20 percent of mothers denied that these activities were important. Our analyses suggested that about a third of the social gradient in linguistic development and about half of the social gradient in social and emotional development could be attributed to differences in parenting attitudes.

In Latin America, Costa Rica, Cuba and Chile have the highest proportion of children enrolled in preschool, as well as the longest life expectancies.

PARENT POWER

GIVING PARENTS SUPPORT, however, can quickly make a difference in their children's lives. Some good evidence comes from research in the English city of Birmingham. The city scores below the national average on measures of employment, household income and other factors that reflect deprivation. Until recently, that pattern apparently contributed to deficits in child development. In 2007 the percentage of children aged five achieving a good score on measures of social, cognitive and behavioral development was 40 percent in Birmingham, whereas the English average was 46 percent. Then, in that year, Birmingham decided to try to change this situation. It instituted a Brighter Futures program for its 260,000 children. The aim was to adopt programs, which had been shown to be effective elsewhere, that showed parents ways to read, sing, talk, teach and otherwise interact with children to foster development.

In just three years after Brighter Futures started, Birmingham closed the gap between the city and the rest of England. By 2010 the proportion of children, aged five, with a good level of development rose to meet the national average. More detailed studies of program components indicated they were the cause behind the effect. In the U.S., Holly Schindler of the University of Washington, Jack Shonkoff of Harvard University and others showed in a recent paper that focus on early child development in the family, along these same lines, sharply reduced behavior problems in young children.

Do such changes affect adult longevity? In Latin America, Costa Rica, Cuba and Chile have the highest proportion of children enrolled in preschool and the highest percentage of children performing at the top reading level in the sixth grade. These three are also the countries with the longest life expectancy in the region. There is a thread of cause and effect that runs from poor child development through low educational achievement, low incomes, insecure employment, stressful working and living conditions, unhealthy lifestyle, and poor health. We suspect this link exists because there are several biological systems that tie social stresses to physical reactions. For instance, what is called the hypothalamic-pituitary-adrenal (HPA) axis in the nervous system increases the output of the hormone cortisol when the brain responds to stress. In the body, cortisol can suppress immune responses. Children from disadvantaged families are more likely to be stressed, which would activate this HPA axis frequently. (In "Sick of Poverty" in the December 2005 issue of *Scientific American,* Stanford University neurobiologist Robert M. Sapolsky explains this biology.)

There is another strategy to decrease the social gradient in child development: use tax-driven income transfer to reduce socioeconomic inequality. Taxes on wealthier people can pay for government benefit programs for poorer families; essentially this moves assets from one group to another. Compare two wealthy countries, the U.S. and Australia. In the years 2007–2009, 25 percent of children in the U.S. were in poverty, defined as households at less than 50 percent of the median national income. In Australia, 28 percent were in poverty. After adding in the effects of taxes and value of benefit programs, in the U.S. poverty levels were reduced just a little, to 23 percent. But in Australia, poverty levels dropped down to 11 percent. Clearly, income transfers can reduce inequality, and the U.S. has chosen not to use this strategy.

So we return to programs, such as parent training, to enhance child development and education. The fact that childhood may affect adult health inequalities has compelling implications. Politically, it means society should shift more resources to early interventions. Morally, it becomes harder to blame the adult poor for their poverty or poor health. Scientifically, we need more research on the long-term negative effects of childhood experiences because some consequences appear to be reversible. New discoveries may suggest more effective approaches. The science already done gives good cause for optimism. SA

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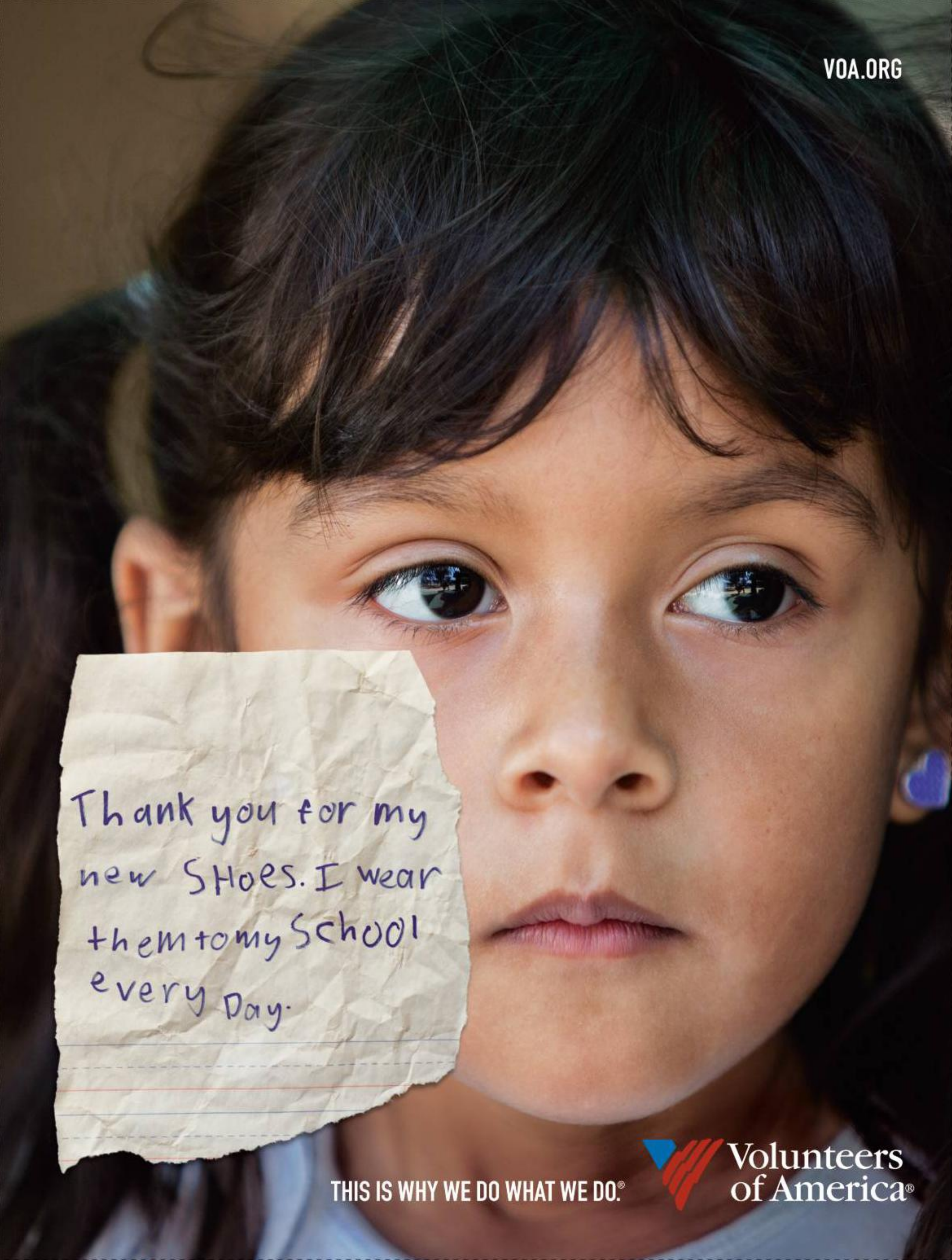
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David Pogue is the anchor columnist for Yahoo Tech and host of several *NOVA* miniseries on PBS.

Untangled

Can a universal cable end the cord war for good?

By David Pogue

The best new technology of the past year wasn't some phone or an app.

Believe it or not, it was a new kind of *USB cable.*

Now, before you suspect that I've inhaled a bit too much of that new-tablet smell, consider:

The new cable, called USB Type-C (or USB-C), is the same on both ends, so you never have to fiddle with it. The connector is also identical on both sides—there's no upside down.

USB-C can replace four different jacks on your gadget: data, video, power and, soon, audio. That's right: A single connector can handle flash drives, hard drives, screens, projectors, charging and headphones (simultaneously, if you have a splitter). Yet the connector is tiny enough for phones and tablets and sturdy enough for laptops and PCs.

Every device from every brand can use the same cable. You can use the charger from my Google phone to charge your Apple laptop or someone else's Microsoft tablet. No more drawers full of mismatched power bricks.

In other words, USB-C represents the dawning of the universal cable.

That USB-C even exists at all is something of a miracle, considering what a big business accessories have become. Apple, for example, makes a staggering amount of money selling cables. Cynical observers accuse it of changing connector types *deliberately,* just to drum up accessory sales. For example, good luck using a 2009 power cord with a 2013 MacBook.

Apple's not alone. A typical charger for a Windows laptop costs $60 to $80.

Several of these big companies worked together to come up with the USB Type-C standard, and even more have adopted it.

The question is: Why? Why would these archrivals work together to create a charger that works interchangeably across devices and brands, wiping out the proprietary-charger industry in one fell swoop?

Brad Saunders, who works for Intel, is chair of the USB 3.0 Promoter Group, a group of six companies that designed USB Type-C (including Intel, Hewlett-Packard and Microsoft). He says that the original reason to design it was speed; the 20-year-old regular USB connector couldn't be made any faster.

"At the same time," he says, "PCs were changing, becoming thinner and lighter. The existing USB connector was just way too big. And it's not as user-friendly as we'd like: you can plug it in the wrong way."

But surely, I asked him, these companies knew that designing One Cable to Rule Them All meant that they'd lose big bucks in sales of their proprietary chargers.

"Well, job one is making money for your company," he admits. "But over time we became motivated by the fact that we could change the world from a green perspective. If we could standardize all these power supplies, we could reduce waste. We started to realize we could have a real impact."

It's weird to imagine all these blood rivals working together, side by side, to create a new standard for everyone's mutual benefit. How often does the world work that way?

"Standards work is kind of odd," says Jeff Ravencraft, president of the USB Implementers Forum. "Companies work together to bake a bigger pie, to expand the market for their products. But once it's over, they have to compete for how big a piece of the pie they'll get. You cooperate at the beginning, and then you compete like hell at the end."

And the cable is already here. Some of the latest phones, tablets and laptops from Google, Apple, Microsoft, Samsung and others come with USB-C jacks built in.

You might think that only the nerdiest nerds could get excited about USB-C. And yet in the coming years this invention could save you hundreds of dollars in duplicate cords, adapters and chargers. It will permit our gadgets to get smaller and faster. It will save space in our drawers, packages, purses and laptop bags. It will keep tons of e-waste out of the landfills.

If that doesn't qualify USB-C as the invention of the year, I don't know what does. SA

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WHAT YOU NEED TO KNOW ABOUT USB-C:
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Illustration by Chris Whetzel

NEW HUMAN SPECIES: *Homo naledi* raises questions about the origin and evolution of our genus. In this replica of the composite skull, white areas indicate missing bone.

EVOLUTION

MYSTERY HUMAN

An astonishing trove of fossils has scientists, and the media, in a tizzy over our origins

By Kate Wong

IN BRIEF

In 2013 cavers discovered a trove of enigmatic fossils deep inside an underground cave system known as Rising Star near Johannesburg, South Africa.

Over the course of two expeditions scientists recovered more than 1,550 specimens belonging to at least 15 individuals from the site.

Last September researchers unveiled the discovery to great fanfare, announcing that the bones represent a new species, *Homo naledi,* that calls into question long-standing ideas about the rise of *Homo.*

Critics have raised concerns about the recovery and analysis of the fossils.

Kate Wong is a senior editor at *Scientific American.*

IN THE BRAND-NEW FOSSIL VAULT at the University of the Witwatersrand, Johannesburg, in South Africa, shelf space is already running out. The glass-doored cabinets lining the room brim with bones of early human relatives found over the past 92 years in the many caves of the famed Cradle of Humankind region, just 40 kilometers northwest of here. The country's store of extinct humans has long ranked among the most extensive collections in the world. But recently its holdings doubled with the discovery of hundreds of specimens in a cave system known as Rising Star. According to paleoanthropologist Lee Berger and his colleagues, who unearthed and analyzed the remains, they represent a new species of human—*Homo naledi,* for "star" in the local Sotho language—that could overturn some deeply entrenched ideas about the origin and evolution of our genus, *Homo.*

HOLE IN THE GROUND: Fossils of *Homo naledi* were found in a cave in South Africa's Cradle of Humankind.

Berger is camera-ready in a brown leather blazer and set to give his spiel to the dozen or so journalists, including me, gathered around him in the vault in late 2015. He directs the visitors' attention to the six black carrying cases—originally made to hold assault rifles—arrayed on tables around the room. Each contains a dizzying assortment of fossils nestled in its foam-lined interior. In the cabinets along the back wall, more *H. naledi* bones fill dozens of clear plastic containers labeled "cranial fragments," "pelvis," "radius." Berger reaches into case number two, which holds the crown jewels of the Rising Star assemblage—the group of bones that defines the species—and lifts out an upper jaw and a lower jaw. He carefully holds them one atop the other and displays the matched pair with a practiced flourish so that everyone gets a good look. The crowd murmurs appreciatively, pens scribble, camera shutters click, flashes pop. And he glides on to the next specimen, fielding questions, posing for photographs and encouraging the visitors to snap selfies with the vault's celebrity charges.

Just a few decades ago the sum total of fossils belonging to our extinct human relatives, also called hominins, could fit in a desk drawer. Those destitute days are long gone. Scientists have since amassed more evidence of the evolutionary history of the human family than of many other animal groups, including our closest living relatives, the great apes. As a result, they now know, for example, that humanity's roots reach back at least seven million years and that for much of that time our ancestors shared the planet with other hominins.

Yet they still have much to learn. Some chapters of the human story are completely unknown from the fossil record; others have been drafted on the basis of evidence so scanty that they are little more than speculation. And so even though the fossil record of humans is vastly bigger than it once was, it is still imperfect enough that new discoveries often alter scientists' understanding of the details of humanity's past—sometimes significantly so.

The Rising Star fossils are the latest to rock the paleoanthropology establishment. Berger and his team argue that *H. naledi* could illuminate the long-sought roots of *Homo* and revamp the human family tree. What is more, the researchers suggest, this creature, which had a brain the size of an orange, engaged in ritual behavior previously attributed exclusively to much brainier hominins—a finding that could upend the prevailing wisdom linking cognitive sophistication to large brain size.

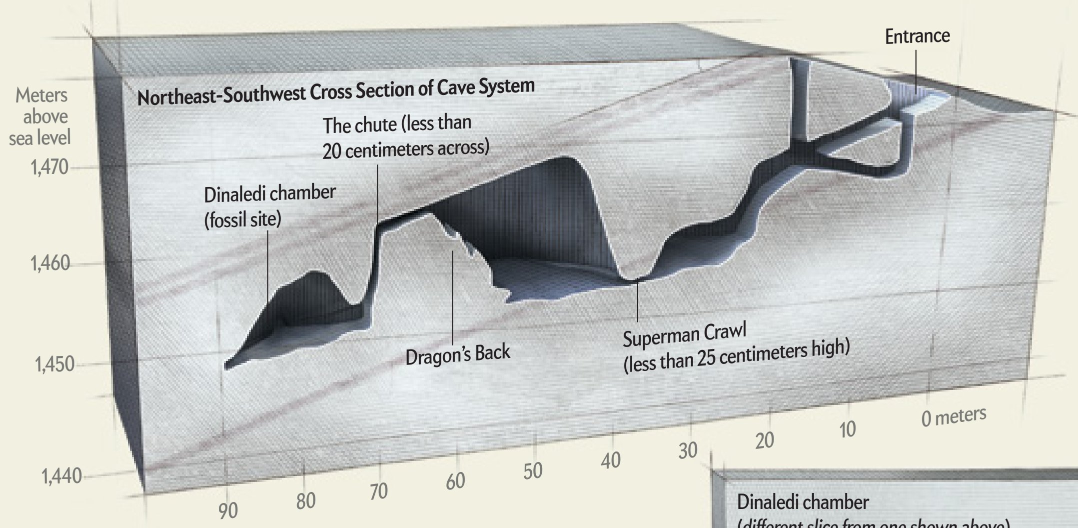
Some critics have dismissed these claims outright. Others have greeted them with uncharacteristic reticence. One major stumbling point for many is that the age of the bones is unknown. They could be more than four million years old or less than 100,000 years old. The lack of a date is not the only concern weighing on outside observers, however. The way the fossils were unearthed, analyzed and revealed to the rest of the world has vexed some of the field's leading scholars, who charge that Berger and his colleagues rushed the job and prioritized publicity over

PRECEDING PAGES: ISTOCKPHOTO (*pushpins*); COURTESY OF JOHN HAWKS *University of Wisconsin–Madison* AND UNIVERSITY OF THE WITWATERSRAND (*all other photographs*)

LOCATION

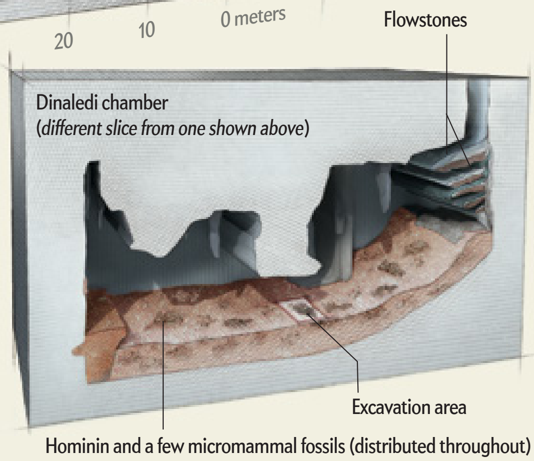
Chamber of Bones

Cavers discovered the fossils of the new human species *Homo naledi* in an underground cave known as Rising Star, just outside Johannesburg, South Africa (*right*). The bones come from the so-called Dinaledi chamber, which sits 30 meters below the surface. To reach it, excavators had to undertake steep climbs and squeeze through tight passages (*below*). *H. naledi* may have taken similar pains to get there: researchers think it may have been intentionally disposing of its dead in the chamber (*inset*), and although geologists are still working to understand how the cave evolved over time, they have yet to identify other plausible routes into the chamber.



Strange Circumstances

An apparent absence of large animal species other than *H. naledi* in the chamber is one of the clues that led the discovery team to hypothesize that the hominins were disposed of there as part of a mortuary custom, as opposed to, say, getting washed in during a flood or dragged in by a hungry carnivore. When the bodies were placed there is unknown, however. Scientists can often estimate the age of hominin remains by looking to associated bones of animal species that are known to have lived during a particular interval or by dating the surrounding rock. Rising Star not only lacks such animal remains, but the nearby flowstone is contaminated with clay, making it difficult to date.



SOURCE: "GEOLOGICAL AND TAPHONOMIC CONTEXT FOR THE NEW HOMININ SPECIES *HOMO NALEDI* FROM THE DINALEDI CHAMBER, SOUTH AFRICA," BY PAUL H.G.M. DIRKS ET AL., IN ELIFE, ARTICLE NO. 09561; PUBLISHED ONLINE SEPTEMBER 10, 2015

science. In a field known for its fierce rivalries, heated debate over new finds is the norm. But there is more on the line in the row over the Rising Star remains than a few egos. How scientists respond to this discovery in the longer term could set a new course in the quest for human origins, changing not only the questions they ask but the ways in which they attempt to answer them.

CHAMBER OF SECRETS

IN A WAY, it was a set of grainy photographs shown to Berger on October 1, 2013, that sparked this spectacle. Berger had hired geologist Pedro Boshoff to search the Cradle for new hominin sites. Over the years miners and fossil hunters had combed the region many times over. But Berger had good reason to think there was more to find. Five years earlier his then nine-year-old son had stumbled across bones of a previously unknown member of the human family, *Australopithecus sediba,* right in the middle of the Cradle.

Now Boshoff and local cavers Rick Hunter and Steven Tucker had found what appeared to be human bones littering the floor of an extremely difficult-to-reach chamber 30 meters down in the Rising Star cave system, just a few kilometers from the spot where Berger and his son had found *A. sediba*. The explorers had not collected any of the material, but they had taken pictures. As soon as Berger saw them, he knew the bones were important. They had features that clearly differed from those of anatomically modern humans—*Homo sapiens*. And there were lots of them, enough to represent a skeleton.

Berger immediately began making plans to recover the remains. There was a problem, though. He was not going to be able to collect them himself. The route from the cave entrance to the chamber that held the bones contained passages far too narrow to accommodate Berger's broad frame or that of most of his scientist colleagues for that matter. Widening these passages would disrupt the integrity of the cave and possibly damage the bones—

Illustration by José Miguel Mayo

a nonstarter, as far as he was concerned. So he put out a call on Facebook for skinny scientists who had experience caving and excavating old remains and who could come to Johannesburg on short notice to mount an expedition in exchange for little more than a plane ticket and the promise of adventure.

Five weeks after Boshoff showed him the tantalizing photographs, Berger had selected his team of excavators—all women, coincidentally—to carry out the difficult, dangerous work of recovering the bones from the chamber, as well as a crew to support the team's efforts; he developed a protocol for collecting the material and documenting exactly where in the chamber each piece of bone came from; and he established a group of senior scientists to oversee the excavation via closed-circuit television and to identify, log and store the specimens as they came out. He also had a plan for how to publicize the endeavor—a full-bore media blitz, carried out in partnership with *National Geographic* and *NOVA,* that would include live tweets and daily blogs, radio interviews and video clips posted from the field, as well as a TV documentary that would air at a later date, after the remains were eventually published. On November 10, cameras rolling, the excavators crawled, climbed and wriggled their way into the pitch-dark chamber and began the recovery effort.

Marina Elliott was the first scientist to enter the chamber. "I didn't know what to expect, but I was excited," she recalls when I accompany her to the Rising Star site. It is high noon on a bright, hot austral summer's day, and outside the cave the wind carries the sound of cars whizzing past on the nearby freeway. But inside the cave it is dim and cool and hushed—the stillness of age. A shaft of light from a natural opening in the ground above bathes the craggy interior, giving it the air of a place of worship.

The serenity of this part of the cave belies the danger farther in, however. Elliott shines her flashlight down one of the corridors, illuminating a perforated curtain of limestone. Behind that wall lies the first of the squeeze points on the route into the fossil chamber, she explains—the Superman Crawl, a tunnel that the women had to negotiate belly to ground and one arm outstretched. The journey did not get easier from there. The jagged Dragon's Back loomed ahead, followed by a 12-meter-long, vertical chute less than 20 centimeters (eight inches) across that opened into the chamber of bones.

But their efforts were richly rewarded. There were bones everywhere—much more than the single skeleton Berger had expected to salvage. Over the next 21 days Elliott and her colleagues hauled out 1,200 specimens. A second, shorter expedition in March 2014 yielded several hundred more. In total, the team recovered more than 1,550 bones and bone fragments of at least 15 individuals—including infants, tweens, young adults and old-timers—from an area the size of a card table. All told it is one of the largest single assemblages of hominin fossils ever found. And the team only scratched the surface. More bones, possibly thousands more, remain in the chamber.

A STAR IS BORN

WITH SAFE AFTER SAFE stuffed with hominin fossils, Berger and his colleagues now faced the daunting prospect of assessing them. Even before the researchers began their formal assessment, while the bones were still coming out of the ground, the find had an air of mystery about it. For one thing, the bones appeared to have a weird combination of primitive and modern traits. For another, no animal remains apart from those of a few small birds and rodents had turned up in the chamber along with the hominin bones. Larger animals such as monkeys, antelopes and hyenas, almost always accompany hominin fossils, particularly those found in underground caves. The absence of such species at Rising Star demanded explanation.

Berger recruited an army of 35 early-career researchers to help describe the fossils over the course of a monthlong workshop in Johannesburg in May 2014. For most of these people—many still working on their Ph.D.s—it was a rare opportunity to work on new fossils, as opposed to studying material that had already been characterized by other, more seasoned scientists. They worked in groups organized by body part: skull, hand, teeth, spine, hip, leg, foot, and so forth.

When they pooled their findings, a startling picture emerged of a tall, slender hominin with upper limbs built for climbing and using tools, lower limbs built for upright striding and a tee-

HEAD TO TOE: Vast Rising Star fossil assemblage includes rare foot bones (*far left*) and multiple leg bones (*near left*). Though fragmentary, the fossils are beautifully preserved and can in some instances be attributed to the same individual, as is the case for the lower jaw and skull fragments above.

ny brain. It is "a really, really strange creature," Berger says.

On a Friday afternoon in December, senior team member John Hawks of the University of Wisconsin–Madison takes me back to the vault to point out some of the salient aspects of the Rising Star remains. The rest of his colleagues are still outside enjoying beer and barbecue at the department holiday party, but Hawks is in his element here among the bones. He bustles around the room, setting the fossil cases out on the tables and selecting replicas of other hominin specimens from the vault's vast collection for comparison.

The skull alone is a mishmash of traits associated with various hominin species. It would have held a brain measuring just 450 to 550 cubic centimeters—as small as that of primitive *Australopithecus afarensis,* best known from the 3.2-million-year-old Lucy skeleton, found in 1974 in Ethiopia. Yet the shape of the skull evokes the more humanlike *Homo erectus*. The teeth resemble those of *Homo habilis,* one of the most primitive members of our genus, in the way they increase in size from the front of the tooth row to the back. But overall the teeth are small, and the molars have simple crowns with fewer, lower cusps—traits associated with later *Homo*.

The bones below the head echo the mix-and-match theme. The upper limb pairs a shoulder and fingers adapted to climbing with a wrist and palm built for manipulating stone tools—an activity that was not thought to become important to hominins until after they had abandoned life in the trees and evolved large, inventive brains. And the lower limb marries a Lucy-like hip joint to a foot that is virtually indistinguishable from our own. Researchers have been operating under the assumption that the signature features of *Homo*—such as a toolmaking hand, big brain and small teeth—evolved in concert. "*Sediba* and *naledi* show that things we thought we evolved together did not," Hawks asserts.

This unprecedented combination of primitive and modern features is not the only distinctive thing about *H. naledi*. The fossils also have traits never before seen in a member of the human family. Hawks plucks one of the finger bones out of its foam cutout. It is the first metacarpal, the bone in the palm that sits below the thumb, and when he displays it next to the same bone from *H. sapiens,* the difference is stark. The shaft of its first metacarpal is smooth, thick and broad for its entire length. *H. naledi*'s, in contrast, is narrow at the base and broad at the top, with a sharp crest running along its shaft and thin wings of bone on the sides. The femur bears unique traits, too, as do other elements.

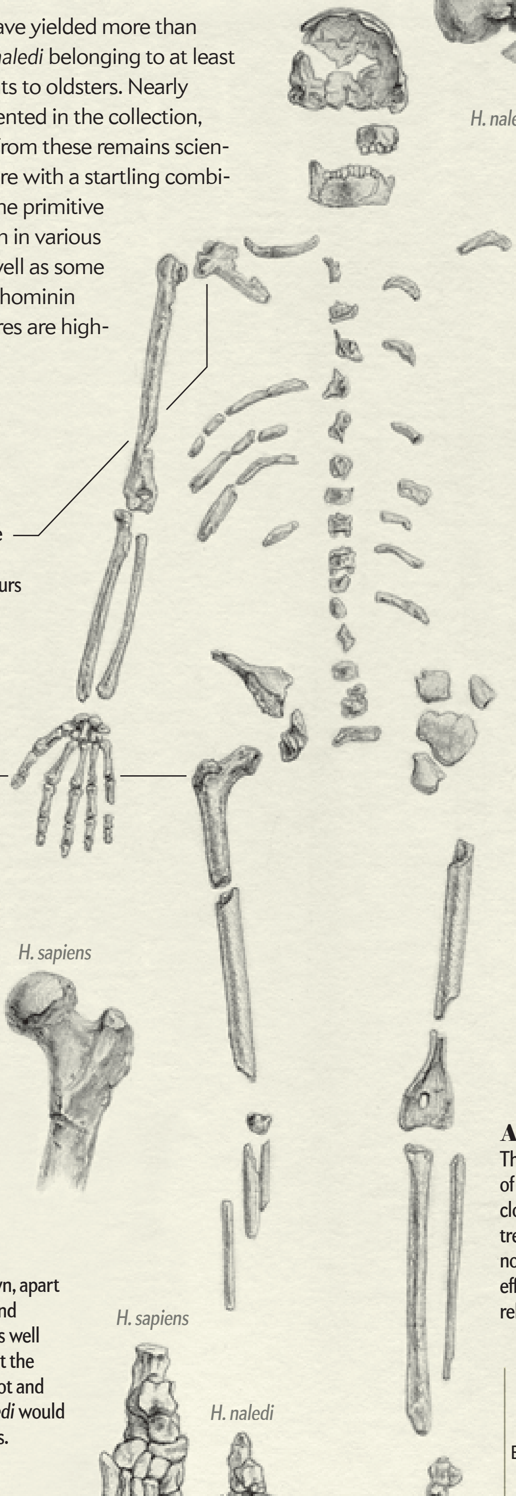
To Berger and his colleagues, the novel combination of australopithecine and *Homo* characteristics, along with the presence of unique traits, easily justified assigning the Rising Star fossils to a new hominin species. Although the researchers have yet to establish the age of the fossils, in their paper announcing the find, published last September in the online open-access journal eLife, they proposed that, given its primitive features compared with early *Homo* species such as *H. habilis* and *H. erectus, H. naledi* might be older than two million years and stem from the base of the genus *Homo*. If so, the discovery would be a major coup: the origin of *Homo* is arguably the biggest unsolved mystery in all of human evolution because fossils transitional between the australopithecines, with their many apelike traits, and later *Homo,* with its modern body plan, are exceedingly rare and mostly scraps. Scientists have been eager to elucidate which hominin species founded the *Homo* branch of the hominin family tree and how the traits in the modern human body plan evolved with new discoveries.

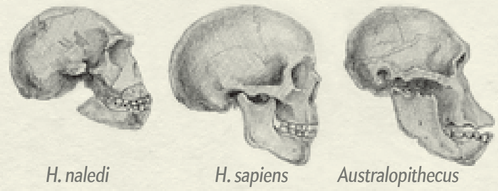
Berger's team did not stop at saying the find could bear on the origin of *Homo,* however. It argued that the unexpected mix of traits evident in *H. naledi* implies that isolated fragments cannot be used to understand the evolutionary relationships of fossil humans, because the part cannot predict the whole—fighting words to those researchers who have interpreted isolated bones as the earliest evidence of the *Homo* lineage.

Perhaps even more provocative than the team's ideas about what *H. naledi* means for understanding hominin relationships

A Novel Mix

The excavations at Rising Star have yielded more than 1,550 fossil specimens of *Homo naledi* belonging to at least 15 individuals ranging from infants to oldsters. Nearly every bone in the body is represented in the collection, many of them more than once. From these remains scientists have reconstructed a creature with a startling combination of traits associated with the primitive australopithecines and traits seen in various species in our genus, *Homo,* as well as some traits not known from any other hominin species. Examples of these features are highlighted in the diagram below.

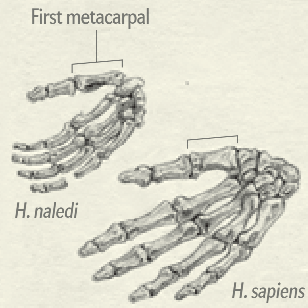




Skull of *H. naledi* housed a brain as small as 450 cubic centimeters—a size that is typical for australopithecines but significantly smaller than the brains of *H. sapiens* and most other members of *Homo.*

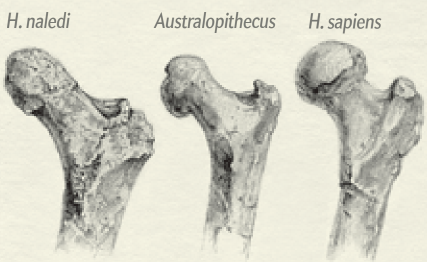
Teeth are primitive in the way they increase in size from front to back. Overall they are small, and the molars have comparatively simple cusps—both traits of later *Homo* species.

Shoulder socket faces up like an ape's or australopithecine's rather than out to the side like ours does. This upward orientation is an adaptation to climbing trees.

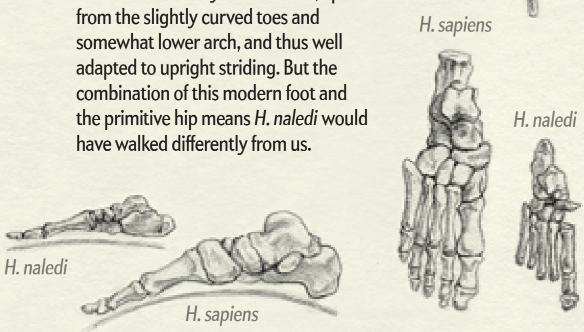


Hand has strongly curved fingers, suggesting that *H. naledi* climbed in trees. Yet the wrist and palm look modern and appear to be adapted to manipulating tools. For its part *H. naledi*'s first metacarpal, the bone in the palm below the lowermost thumb bone, looks neither *Homo*-like nor *Australopithecus*-like and is utterly unique.

Femur has a small head and long neck compared with the large head and small neck seen in the *Homo sapiens* femur. These features suggest that *H. naledi*'s hip worked like an australopithecine's.



Foot is remarkably like our own, apart from the slightly curved toes and somewhat lower arch, and thus well adapted to upright striding. But the combination of this modern foot and the primitive hip means *H. naledi* would have walked differently from us.



A New Twig in Our Tree

The discovery team argues that *H. naledi*'s particular mix of characteristics suggests that the species originated close to the origin of *Homo*—a coveted spot in the family tree. But *H. naledi* preserves parts of the anatomy that are not known for other early *Homo* species, complicating efforts to understand how these extinct hominins are related to one another—and to us.

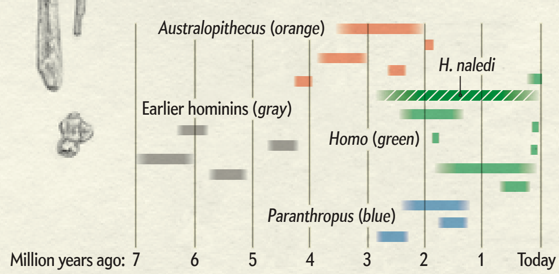


Illustration by Portia Sloan Rollings, Graphic by Jen Christiansen is how it interpreted *H. naledi*'s behavior. In their attempts to figure out how the hominins ended up in the chamber, the researchers considered a number of mechanisms known to account for hominin accumulations at other sites, including the possibility that their bones had washed into the cave system during a flood or that large carnivores had dragged them there to eat. Yet the available evidence did not match any of those explanations. Floodwaters, for instance, would have surely carried the remains of other animals into the chamber, too. And carnivores would have left behind telltale tooth marks on the bones. All things considered, the team concluded, the likeliest explanation was that *H. naledi* had intentionally deposited the bodies in the chamber.

The hominins would have had to go to considerable lengths to do so. Although the team geologists do not yet know exactly how the Rising Star cave system formed and changed over time, they have found only one entrance to the bone chamber—the one the excavators squeezed through to recover the fossils. If that was indeed the only entrance, then whoever disposed of the dead would have had to, at minimum, scale the 20-meter spine of the Dragon's Back to reach the opening of the chute that opens into the chamber. From there they could have either crawled down the chute with the bodies or just dumped them in and let them slide into the chamber below. And if the route into the chamber was always pitch-dark, as the team thinks it was, then the hominins may have required an artificial light source to find their way in. The suggestion was that tiny-brained *H. naledi* not only had a mortuary ritual but mastery of fire.

Ensconced in a leather club chair in the sitting area of his office, coffee mug in hand, Berger launches into a discussion of what the Rising Star find means for human evolution. It's 7:30 in the morning, but the blinds are drawn, and the lights are low. Between the animal hide rugs decorating the floor and the jazz warbling from a vintage-style turntable, the room feels more like a gentleman's hunting lodge than a work space. "There is no age at which [the find] is not disruptive," he exults. If it is old, then critical physical and behavioral traits may have emerged at the root of our genus or earlier, rather than in later *Homo.* Really old *H. naledi* could even oust the australopithecines from the line leading to us, according to Berger. If, on the other hand, the fossils are young, researchers are going to have to reconsider which species left behind the cultural remains at key archaeological sites across Africa.

It may be *H. naledi* originated millions of years ago and managed to persist across the ages unchanged, like a coelacanth, overlapping with other *Homo* species, including *H. sapiens,* for a time. Perhaps it invented some of the cultural traditions archaeologists have traditionally assumed originated with our kind, Berger says. Possibly *H. naledi* interbred with our ancestors and contributed DNA to the modern human gene pool, like Neandertals and Denisovans did.

CASTING ASPERSIONS

WHEN THE TEAM published its papers announcing the discovery in eLife last September, the world went wild for *H. naledi*. Seemingly every media outlet on the planet covered the find. Even the *Onion* joined the bandwagon, running a doctored image of a lachrymal Berger with a story entitled "Tearful Anthropologists Discover Dead Ancestor of Humans 100,000 Years Too Late." Yet underneath that tidal wave of public enthusiasm runs a current of discontent among some of paleoanthropology's elite. No one disputes that the find is important—a cave full of human fossils is extraordinary—but the team's approach to recovering, describing and interpreting the bones has raised eyebrows.

Berger is no stranger to side eye from his academic peers. Telegenic and silver-tongued, he hooked up with *National Geographic* early in his career. The relationship brought research funding, bylines and television appearances. Yet he had found few fossils, and his scientific papers and popular writings met with accusations of sloppy scholarship and grandstanding from some of paleoanthropology's most respected figures, including Tim White of the University of California, Berkeley, and Bernard Wood of George Washington University.

Berger's discovery of *A. sediba* in 2008 raised his scientific profile. Even his harshest critics conceded that the find, which included two largely complete skeletons dated to 1.98 million years ago, was spectacular. But many did not agree with his interpretation of it. Berger had long contended that South Africa was being overlooked in favor of East Africa in the search for *Homo*'s origin. *A. sediba,* with its mosaic of australopithecine and *Homo* traits, seemed to offer a means of potentially rooting *Homo* in South Africa. The problem was that the oldest fossils attributed to *Homo* were East African specimens older than *A. sediba*. Berger argued that fossil fragments like the ones from East Africa that were being held up as the earliest *Homo* could no longer be assigned to one taxon or another because his skeletons, with their surprising combination of traits, showed the whole was not inferable from the part. His peers largely rejected that claim.

With *H. naledi,* Berger doubled down on the public outreach and on those controversial ideas about *Homo*'s origin and fragmentary fossils. It did not take critics long to loose their arrows. White told his university's alumni association magazine, *California,* that the Rising Star fossils looked like primitive *H. erectus,* not a new species. White is best known for his discoveries of hominin fossils in Ethiopia, including those of 2.4-million-year-old *Australopithecus garhi,* which he and Berhane Asfaw of the Rift Valley Research Service and their colleagues said were from the right time and place to be ancestral to *Homo.* He further accused the Rising Star team of damaging fossils during excavation and rushing its findings to publication. Later, in a scathing blog post for the *Guardian,* White warned of the dangers of mixing science and showmanship. "We are witnessing portions of science collapsing into the entertainment industry," he wrote.

White is not the only one with concerns. Carol Ward of the University of Missouri cautions that although the quantity of fossils is stunning, their significance remains unknown. She emphasizes the importance of determining the age of the bones: "When we know how old they are, then we can tell you what they mean for human evolution but not until then."

Ward also has misgivings about the paper describing the fossils, noting that it did not include sufficient data about how they compare with other relevant fossils for outside scientists to be able to evaluate many of the team's claims. Nor did the paper contain a phylogenetic analysis—basically a study in which a computer program compares traits across a group of organisms and thereby reconstructs the members' evolutionary relationships—which could reveal where *H. naledi* fits in the human family tree. "There seems to be a great desire [on the part of the authors] for it to be related to the origins of *Homo,*" she observes, but in the absence of a detailed phylogeny or a date, no one can know if it is.

Many researchers stand by the thinking that, based on present evidence, *Homo* debuted in East Africa. Last March, months before the details of *H. naledi* were released, Brian Villmoare of the University of Nevada, Las Vegas, Kaye Reed of Arizona State University and their colleagues announced their discovery of a 2.8-million-year-old piece of lower jaw from the site of Ledi-Geraru in northeastern Ethiopia that they say is the earliest known representative of our genus. The jaw has clear hallmarks of *Homo,* they observe, as well as traits transitional between *Australopithecus* and *Homo*. Without a date, the *H. naledi* fossils cannot unseat the Ledi-Geraru jaw as the oldest evidence of our lineage, in Reed's view, nor does she accept the argument made by Berger, Hawks and their colleagues, that isolated fragments of anatomy cannot be reliably assigned to one taxonomic group or another. "I have a good date at 2.8, and there are features of *Homo,*" she maintains.

GETTING A GRIP: Hand of *H. naledi* is the most complete one known for an extinct human species.

Part of the reason paleoanthropologists disagree on which fossils herald the dawn of *Homo* is that they are divided over what constitutes *Homo* in the first place. *H. naledi* "highlights an ongoing debate about how to define *Homo,* both for things we have pieces of and things we have more of," comments Susan Antón of New York University, an expert on early members of our genus. Sorting *Homo* from *Australopithecus* is "a very messy thing for everyone right now, and different people have different philosophies about how to make that distinction." She and her collaborators have been defining it on the basis of traits found in the cranium, jaws and teeth. Others have argued that the distinction between the two has to be based on the bones below the head—the postcrania, as they are termed—because they reflect the major adaptive changes hominins underwent as they transitioned from wooded environments to open ones. But those postcranial bones are largely unknown for early *Homo* species. The Rising Star fossils are "an embarrassment of riches," Antón remarks. But the mosaic of traits gives mixed signals, and Berger's team did not explicitly state how it defines *Homo* and why. "We have a lot more talking to do," she says of the field.

Yet even if the Rising Star remains do constitute a new *Homo* species and even if they turn out to be more than two million years old, those facts alone may not be enough to sway the skeptics toward the notion that *H. naledi* was on or near the line leading to us. George Washington University's Wood suspects that the bones represent a relic population that might have evolved its odd traits in relative isolation. "South Africa is a cul-de-sac at the bottom of the African continent," he says. "My guess is gene exchange in this cul-de-sac was probably not as common as it was in East Africa, where you have a lot more potential for homogenization, with genes coming in from southern and central Africa." Wood points to another weird species of *Homo*—the small-brained, small-bodied *Homo floresiensis* that persisted on the island of Flores in Indonesia long after *H. sapiens* originated in Africa—as another example of such a relic population.

The suggestion that small-brained *H. naledi* was ritually disposing of its dead has likewise met with resistance. "It would be quite radical," says archaeologist Alison Brooks of George Washington University. The practice is widely thought to be exclusive to the much larger-brained anatomically modern humans and possibly Neandertals and only became commonplace after 100,000 years ago. "I don't want to rule it out entirely that [the Rising Star researchers] are right," Brooks adds, "but I just think it is so far out there that they really need a higher standard of proof."

In fact, some of the discovery team members themselves struggled with the idea that *H. naledi* was deliberately disposing of its dead in that underground chamber, if only for logistical reasons. "It's hard to get in there with my backpack, never mind dragging a body," Elliott reflects. "But we spent two years trying to find an alternative and couldn't."

If *H. naledi* did in fact transport the dead to the chamber, its behavior need not necessarily reflect cognitive sophistication, however. Travis Pickering of the University of Wisconsin–Madison, who has worked in the Cradle of Humankind for the past 20 years, agrees that intentional disposal of the remains by other hominins is the most sensible explanation for how the bones got into the remote chamber. But "whether that means *Homo naledi* was a rather culturally advanced species with well-developed mortuary practices or simply an atavistic one that had the sense not to cohabit with rotting corpses is currently unanswerable," he comments.

EYE ON THE PRIZE

BERGER DISMISSES THE DETRACTORS, noting that they have made their comments strictly in the popular press and on social media, not in the rigorous forum of a scientific journal. "Their evidence stops at their mouths," he says. Staunchly defending the care with which the team excavated the fossils, he explained in a public post on Facebook that the damage on the bones was already there when Rising Star team members first arrived on the scene. Berger presumes it resulted from unknown amateur cavers who had explored the chamber before them and stepped on the bones. The excavators were able to work quickly, he says, because "we didn't have a lot of problems other teams have." At other sites, fossils are

SCIENTIFIC AMERICAN ONLINE Learn more about *Homo naledi* at ScientificAmerican.com/mar2016/naledi

typically encased in rock. Excavation and cleaning of such fossils are typically extremely laborious and time-consuming. But at Rising Star the fossils were simply lying in damp earth that brushed away easily. And unlike other teams, which are small and conduct their research in distant locales six to eight weeks a year, Berger's is large and based in Johannesburg, so it can work at the site or in the vault any time. If you look at the Rising Star work in terms of person-hours logged in the time between discovery and publication, "it's as much as anyone else has done," he insists.

As for White's suggestion that the fossils belong to primitive *H. erectus,* not a new species, "he disagrees with everything except the ones he basically has named," Berger quips. Assigning the *naledi* remains to *H. erectus* would mean that *erectus* had more variation than is seen in our own species, which is improbable, in his view. More to the point, *H. naledi* has unique traits not seen in any other hominin. "If we're going to be evolutionary biologists, the argument stops there," Berger declares. "Frankly I'm surprised [people] aren't arguing that it's a new genus," rather than merely a new species.

Asked about dating the Rising Star fossils, Berger says the geologists are working on it and will get the timing down eventually. But he maintains that the date will not change their understanding of how *H. naledi* is related to other members of the human family. Although *H. naledi* has some key traits of *Homo,* the overall package is in some ways more primitive than that of *H. habilis* and, for that matter, that of the Ledi-Geraru jaw that currently holds the title of oldest *Homo* fossil. No matter what age the Rising Star fossils turn out to be, they imply that *H. naledi*'s branch of the family tree sprouted before these other branches did. If the fossils are young, then they represent a late population of this species.

Why, then, didn't the team include a phylogeny in the paper announcing the fossils as a new species? To figure out how organisms are related to one another, evolutionary biologists use a method called cladistics that sorts taxa into groups based on novel characteristics they share with their last common ancestor but not earlier ones. The catch is, the method works best when the characteristics are observable in all the organisms in question.

Where fossils are concerned, meeting that requirement is easier said than done because they vary widely in the traits they preserve. In paleoanthropology, researchers have tended to base their cladistic analyses on traits found in skulls and teeth; skulls because they vary widely in form in hominins and thus historically were thought to be particularly useful for defining species and teeth because they are the most common elements in the hominin fossil record. Bones from the rest of the skeleton are not always found in association with skulls or teeth, so it can be difficult to assign them to a species that is defined by cranial or dental remains. Moreover, a skeletal element that is known in one species is often missing in another.

Indeed, some of *H. naledi*'s key elements—including its nearly complete sets of hand and foot bones—are only partly represented in the fossil record of other *Homo* species, such as *H. erectus* and *H. habilis,* if they are even represented at all. Lacking corresponding parts with which to compare them, the researchers could not conduct a cladistic analysis of *H. naledi* that factored in its many postcranial traits of interest. With that course of comparison closed off to them, the researchers ran an analysis based on skull and dental traits. But some of the test results did not make logical sense, suggesting that *H. naledi,* with its many primitive traits, is more closely related to *H. sapiens* than to the much older *H. erectus*. To Berger, that finding underscores that trees based on data from one anatomical region, such as the head or teeth, are unreliable.

Berger remains certain that *H. naledi* will shake up scientists' understanding of human evolution one way or another. But he is not asking his peers to take his word for it. In a departure from the usual way of doing things in paleoanthropology, which has a reputation for secrecy where access to fossils is concerned, he instituted an explicit policy for the Rising Star remains that makes them available to any researcher who applies to see them. And on the day they published the eLife papers, the researchers released free three-dimensional scans of critical bones on MorphoSource, a digital repository for anatomical data, allowing visitors to print their own 3-D replicas of the specimens. The data resolution is not yet high enough for the purposes of carrying out original research, but "it's good enough to check what we're saying," Berger says.

"It's such an overwhelming positive that people are getting access; the complaints are just noise," observes David Strait of Washington University in St. Louis. He notes that in 2000, White wrote a prominent editorial in which he asserted that, given the intense public interest in human origins, paleoanthropologists have a special duty to get things right. "That's completely wrong," Strait asserts. "Of course, we should try to do things well, but science should operate by falsifying possibilities. We narrow down the possible truths to get a better idea of what happened in the past, and there is always the possibility for new data to emerge that change everyone's thinking." By making the fossils available to other researchers, Strait says, Berger has given those scientists who disagree with him an avenue to test their ideas against his: "The field moves forward only if people can study the stuff."

In the meantime, with or without the opposition's approval, work will continue apace at Rising Star. The geologists are busy reconstructing the history of the cave, the excavators are recovering more fossils from the chamber, the molecular biologists will attempt to extract DNA from the bones. And the fossil hunters are seeking new leads. "[*Homo naledi*] should launch the greatest age of exploration there ever was," Berger declares with characteristic zeal. If it doesn't, maybe the team's next find will: he reveals that his explorers have already made additional progress on that front. Pressed for more detail, Berger demurs, other than to say with a sly grin that they have located "more than one" new site that has set his heart to racing like Rising Star did when he first saw those grainy photographs. The show will go on. SA

MORE TO EXPLORE

Homo naledi, a New Species of the Genus _Homo_ from the Dinaledi Chamber, South Africa. Lee R. Berger et al. in eLife, Article No. 09560. Published online September 10, 2015.

Geological and Taphonomic Context for the New Hominin Species _Homo naledi_ from the Dinaledi Chamber, South Africa. Paul H.G.M. Dirks et al. in eLife, Article No. 09561. Published online September 10, 2015.

FROM OUR ARCHIVES

First of Our Kind. Kate Wong; April 2012.

scientificamerican.com/magazine/sa

COSMOLOGY

The Puzzle of Dark Energy

Why is the expansion of the universe accelerating? After two decades of study, the answer is as mysterious as ever, but the questions have become clearer

By Adam G. Riess and Mario Livio

THE UNIVERSE IS GETTING BIGGER EVERY SECOND. GALAXIES ARE FLYING APART FROM one another, clusters of galaxies are zooming away from other clusters, and the empty space between everything is growing wider and wider. This much was known since the 1920s, when observations by Edwin Hubble and others revealed that the cosmos is expanding. But more recently, astronomers found that the process is speeding up—the pace of the expansion of the universe is rising, so that galaxies are receding from one another faster now than they were a moment ago.

This is the startling realization that one of us (Riess), along with collaborators he co-led with Brian Schmidt of Australian National University, came to in 1998 through measurements of distant supernovae explosions. The discovery agreed with findings from another team led by Saul Perlmutter of the University of California, Berkeley, using a similar method published the same year. The conclusion was unavoidable—something was causing the expansion of the universe to pick up speed. But what?

We give the name "dark energy" to whatever is causing the repulsive force that is apparently pulling the universe apart.

Illustration by Kenn Brown, Mondolithic Studios

LIKE A RUBIK'S CUBE, the quandary of dark energy—the mystery of why the expansion of the universe is speeding up—is turning out to be hard to crack.

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.

Mario Livio is an astrophysicist who worked for 24 years with the Hubble Space Telescope and a best-selling author of popular science books, including *Brilliant Blunders: From Darwin to Einstein: Colossal Mistakes by Great Scientists That Changed Our Understanding of Life and the Universe* (Simon & Schuster, 2013).

After studying the situation for nearly two decades, the physical nature of dark energy remains almost as elusive today as it was 18 years ago. In fact, the latest observations only seem to further complicate the picture by showing hints of disagreement with the leading theories.

We are left with several pressing mysteries: What is dark energy? Why does it seem so much weaker than the most straightforward theories predict (and yet strong enough that we detect it)? What does the nature of dark energy mean for the future of the universe? And finally, do the strange characteristics of dark energy imply that our universe got its properties randomly—that in fact, our universe is just one of a vast multiverse containing untold versions of the cosmos, each with different traits and different strengths of dark energy?

An all-out assault to identify the nature of dark energy is under way, and prospects are bright for several new observatory projects to make progress soon. Within the next decade we hope to begin to answer these questions and comprehend the nature of cosmic acceleration—or resign ourselves to leaving some mysteries unsolved indefinitely.

WHAT IS DARK ENERGY?

SCIENTISTS HAVE A NUMBER of hypotheses for what might be driving the acceleration of the universe. The leading candidate arises from the nature of empty space. In quantum physics a vacuum is not "nothing"—rather it is teeming with pairs of "virtual" particles and antiparticles that spontaneously appear and annihilate one another within a tiny fraction of a second. As strange as it may sound, this sea of ephemeral particle pairs carries energy, and energy, just like mass, can produce gravity. Unlike mass, however, energy can create either an attractive or a repulsive gravity, depending on whether its pressure is positive or negative. The vacuum energy in empty space, according to theory, should have a negative pressure and thus may be the source of the repulsive gravity driving the accelerated expansion of the universe.

This idea is equivalent to the "cosmological constant," a term Albert Einstein added to his general relativity equations that represents a constant energy density throughout space. As the name implies, this hypothesis holds that the density of dark energy is constant—that is, unvarying—over space and time. So far the astrophysical evidence we have best fits with the cosmological constant explanation, with some discrepancies.

Alternatively, dark energy may be an energy field dubbed "quintessence" that pervades the universe, imbuing every point in space with a property that counteracts the pull of gravity. Physicists are familiar with fields—the everyday forces of electromagnetism and gravity act via fields (although these usually arise from localized sources and do not pervade all of space).

If dark energy is a field, it would not be a constant and so might change over time. In that case, dark energy might once have been stronger or weaker than it is now and could have affected the universe differently at different times. Likewise, its strength and impact on the evolution of the universe might alter in the future. In the so-called freezing-field version of this idea, dark energy evolves more and more slowly as time progresses; in the thawing variant, the field changes slowly at first and faster later.

A third option may account for cosmic acceleration: there is no dark energy, and the quickening expansion of the universe results from physics not explained by Einstein's theory of gravity (general relativity), which is incomplete. It is possible that in truly extreme regimes, such as the breadth of galaxy clusters or the entire observable universe, the laws of gravity work differently than the theory predicts, and gravity misbehaves. Physicists have put forth a few interesting theoretical suggestions along these lines, but no self-consistent theory that agrees with all the observations currently exists, so dark energy seems to have the upper hand over this option for now. (Previous ideas, such as the notion that cosmic acceleration is a manifestation of an uneven distribution of matter throughout the universe or the result of a network of geometric defects in the structure of space, have by now largely proved to be inconsistent with observational data.)

WHY IS DARK ENERGY SO WEAK?

NONE OF THE PROPOSED explanations for dark energy is very satisfying. The cosmological constant, for example, predicts that dark energy should be vastly stronger than it actually is. When one naively attempts to sum up the energies over all the presumed quantum states associated with the sea of virtual particles and antiparticles in the vacuum of space, one obtains a value that is more than 120 orders of magnitude larger than the observed sum. Factoring in ideas from proposed theories such as supersymmetry—the notion that every known particle has a heavier partner particle that we have not yet discovered—reduces the discrepancy somewhat, but the difference between the predicted and the measured total energy still remains tens of orders of magnitude too high. So if dark energy is explained by the energy of the vacuum, the question is, How did this vacuum energy turn out to be so tiny?

The field explanation for dark energy barely does better on

IN BRIEF

Almost 20 years ago scientists discovered that the expansion of the universe is accelerating and dubbed the source of this acceleration "dark energy."

Intensive investigations since then have not resolved the nature of dark energy but rather exposed a number of further questions: Why is dark energy so much weaker than theory seems to predict, what does it mean for the future of the cosmos, and might dark energy lead to the conclusion that we live in a multiverse?

With the advent of several recent and upcoming experiments, scientists hope that the coming years will finally bring some answers.

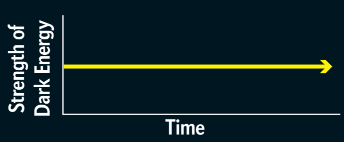
Dark Energy Possibilities and Potential Futures

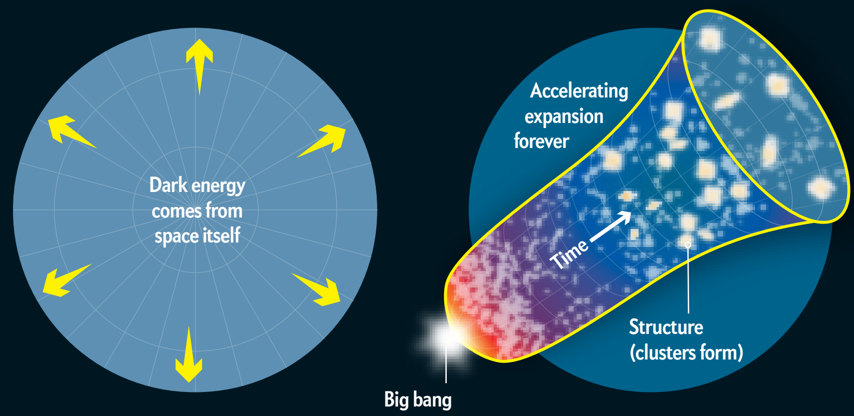
Dark energy is scientists' name for whatever is causing the expansion of the universe to accelerate. Explanations for dark energy fall into three main categories: it may be an unchanging energy arising from empty space (an idea called the cosmological constant) or a varying energy stemming from a field pervading the universe (quintessence). Or dark energy may not exist at all—in that case, gravity would act differently than thought on cosmic scales.

MODEL → **FUTURE**

Cosmological Constant

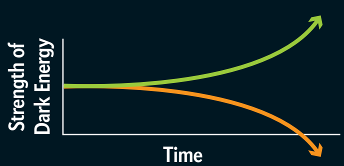
If the vacuum of empty space has an inherent energy, it may push the universe to expand. The strength of such an energy would be constant through time and would act just like the cosmological constant term Albert Einstein added to, and later removed from, his equations of general relativity.

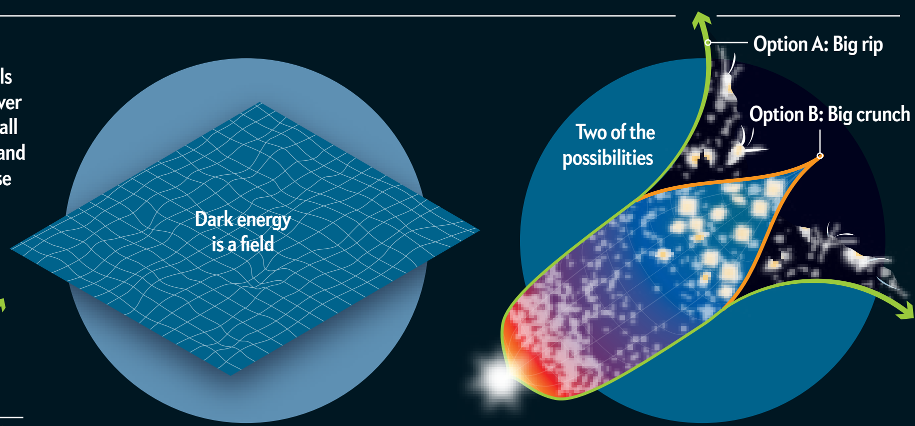




Quintessence

If dark energy comes from a field that fills the cosmos, its strength could change over time, either increasing to eventually rip all structures in space apart or decreasing and changing directions to allow the universe to contract in a big crunch.





There Is No Dark Energy

Dark energy may not exist at all, and the acceleration of the universe's expansion may instead indicate that gravity operates differently than we think on extremely large scales.

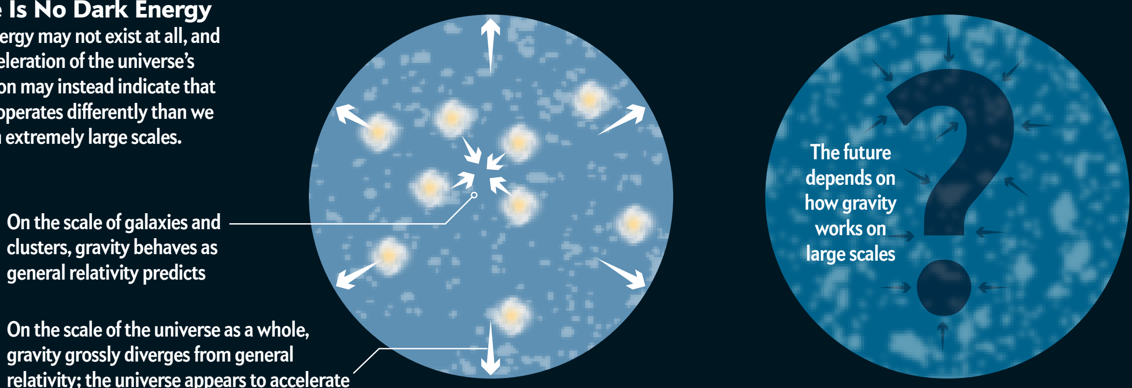


Illustration by Nigel Hawtin

this front. Theorists simply assume (without a good explanation for why it should be so) that the minimum of the potential energy associated with the dark energy field is very low, guaranteeing that only a small amount of dark energy is spread throughout space. Also, these models require the field to have surprisingly minimal interactions with everything else in the universe (apart from its repulsive gravitational push)—a property that is hard to explain. These facts make it difficult to incorporate the dark energy field hypotheses naturally within common particle physics models.

WHAT DOES THIS MEAN FOR THE FUTURE OF THE UNIVERSE?

THE PROPERTIES of dark energy will determine the ultimate fate of our universe. For instance, if dark energy is indeed the energy of empty space (the cosmological constant), the acceleration will continue forever, and about a trillion years from now expansion will cause all the galaxies that are more distant than the Milky Way's closest neighbors (the Local Group, which by then will coalesce to form one large elliptical galaxy) to separate faster than light speed, rendering them undetectable. Even the ancient light from the afterglow of the big bang—the cosmic microwave background (CMB) that fills all of space—will be stretched to wavelengths longer than the size of the visible universe and thus rendered imperceptible. In this scenario, we happen to be living at a very fortunate time when we still have the best possible view of our universe.

If, on the other hand, dark energy is not the energy of the vacuum but rather the energy of some unknown field, then the future is wide open. Depending on the way the field evolves, the universe could eventually stop expanding and start collapsing, falling in on itself to a final "big crunch" that mimics the big bang from whence it came. Or the universe could end up in a "big rip," in which all complex structures, from clusters of galaxies to atoms and atomic nuclei, could become overwhelmed by dark energy and tear apart. And the first scenario, continuous acceleration toward a cold death, is also an option with a dark energy field.

An alternative theory of gravity, if it turns out to be necessary, likewise allows for various outcomes depending on the particularities of the revised theory.

MIGHT WE LIVE IN A MULTIVERSE?

WITH THE COSMOLOGICAL CONSTANT explanation leading the theoretical pack, the problem of its inexplicable weakness comes to the forefront. Realizing this problem with the constant even before the discovery of accelerating expansion, physicist Steven Weinberg of the University of Texas at Austin suggested a new paradigm—one in which the cosmological constant is not uniquely determined from the basic laws of physics but rather is a random variable that assumes different values in different members of a huge ensemble of universes—a multiverse. Some universes may have much larger cosmological constants, but in those the accelerating repulsive force is so large that matter cannot coalesce to form galaxies, planets and life. Because we exist, Weinberg reasons, we clearly have to find ourselves in one of those universes that *can* allow for our existence—one that happened to have a small cosmological constant. This idea, which was further developed by Alexander Vilenkin of Tufts University, Martin Rees of the University of Cambridge, one of us (Livio) and others, is called anthropic reasoning.

There are good reasons, aside from the dark energy consideration, that a multiverse might arise. The widely accepted theory of cosmic inflation suggests the universe ballooned stupendously in its first fraction of a second. Vilenkin and Andrei Linde of Stanford University have shown that once cosmic inflation starts, it is essentially impossible to stop it from occurring again and again, thereby creating an infinite ensemble of bubbles or "pocket universes" that form in isolation from one another and may have very different properties.

A multiverse also seems to be a consequence of string theory, a candidate for a theory that unifies all the forces of nature. Calculations based on versions of string theory called M-theory by Raphael Bousso and Joseph Polchinski suggest that there could be as many as 10^{500} different spacetimes, or universes, each characterized by different values for the constants of nature and even the number of dimensions in space.

Even just mentioning the multiverse idea, however, raises the blood pressure of some physicists. The notion seems hard to swallow and harder to test—perhaps signifying the end of the classical scientific method as we know it. Historically this method has required that hypotheses should be directly testable by new experiments or observations. Yet the concept of the multiverse does make a few predictions that may yield to testing. In particular, some multiverse models predict that the shape of spacetime has a slight curve to it that might be detectable by observations. Another possibility, albeit not a very likely one, is that the cosmic microwave background light may contain ripples that are the signature of a collision of another bubble with our own.

FINDING ANSWERS

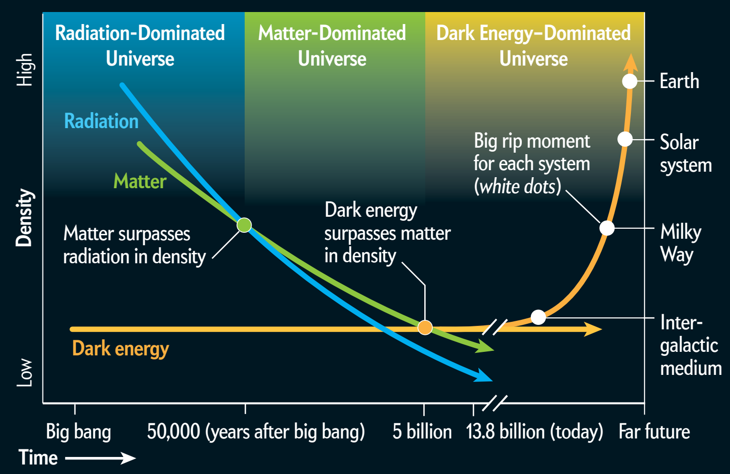
THE BEST WAY WE KNOW of to start to reveal the nature of dark energy is to measure the ratio of its pressure (how much it is in tension with space) to its density (how much of it is in a given amount of space)—a property called its equation of state parameter, w. If dark energy is the energy of the vacuum (the cosmological constant), then w will be constant and equal to -1. If dark energy is associated with a field that changes with time, on the other hand, we would hope to detect its w value differing from -1 and evolving throughout cosmic history. Alternatively, if the observed acceleration necessitates a modification of Einstein's theory of gravity for extreme distances, we would hope to observe an inconsistency between the value of w we find at different scales in the universe.

Astronomers have devised some clever indirect ways to measure dark energy's pressure and density. As a repulsive gravitational pull, dark energy or modified gravity would counteract the pull of regular gravity (which tugs mass in the universe toward other mass), discouraging the formation of large-scale structure—that is, galaxy clusters. Thus, by studying how clusters grew over time, scientists can find out how strong dark energy was at various points in history. We do this by observing how the mass of clusters bends the light of background galaxies behind them through a process known as gravitational lensing. The amount of bending tells us how massive the clusters are, and by observing this effect for clusters at varying distances, we can measure how common massive clusters were at various cosmic epochs. (Because of the time it takes light to reach us, looking far away is akin to looking back in time.)

We can also measure dark energy by studying how the rate of

Cosmic Control

Because dark energy is denser in space than any other constituent of the universe, it exerts the dominant influence on the cosmos and will therefore control its fate. Dark energy was not always on top, though: the other ingredients of the universe—radiation (light) and matter (including atoms and regular matter as well as invisible dark matter)—were dominant when the universe was young and small, and they were packed tightly in space. As the universe expanded over time, matter and radiation spread out, and dark energy overpowered them. If the density of dark energy increases, it may become so powerful that it rips apart all structures in space.



the universe's expansion has changed over time. By observing objects at different distances and measuring their redshift—how much the wavelength of their light has been stretched by the expansion of space—we can learn how much the universe has expanded since that light began its journey. This method, in fact, was how the two teams initially discovered cosmic acceleration; they measured the redshifts of different type 1a supernovae (whose distances are reliably tied to their brightness). A variation on this technique is to observe the apparent size of ripples in the density of galaxies across space called baryon acoustic oscillations (BAOs)—another reliable distance indicator—as a way to trace the expansion history of the universe.

To date, most measurements of w are generally consistent (within the observational uncertainties) with a value of –1 to within 10 percent and thus support the cosmological constant explanation of accelerated expansion. Recently a team led by Riess used the Hubble Space Telescope to probe dark energy back to about 10 billion years ago using the supernova technique and found no evidence for variation over that time.

It is worth noting, however, that some hints of a deviation from cosmological constant predictions have shown up in the past couple of years. For instance, a combination of measurements of the CMB (which tells us about the total mass and energy in the universe) from the Planck satellite with results from gravitational-lensing studies suggests a value for w that is more negative than –1. Observations from the first Panoramic Survey Telescope and Rapid Response System (Pan-STARRS), using more than 300 supernovae to track cosmic expansion, also seemed to indicate a value of w more negative than –1. Very recent observations of baryon acoustic oscillations in data from distant bright galaxies called quasars seem to hint that dark energy density has increased with time. Finally, a small discrepancy between local measurements of the rate of space's expansion today, compared with measurements of the primordial rate of expansion from the CMB, could also be pointing to a deviation from a cosmological constant. As intriguing as these results are, none is yet compelling. More data in the near future may strengthen these discrepancies or reveal them to be systematic flukes.

Work is now under way to achieve a 100-fold improvement in the precision of the measured properties of dark energy in the coming decade. New projects such as the Dark Energy Survey (DES) begun in 2013 and the Large Synoptic Survey Telescope (LSST) due to open around 2021 will gather better information about large-scale structure in the universe and the history of expansion. NASA's Wide-Field Infrared Survey Telescope–Astrophysics Focused Telescope Assets (WFIRST-AFTA) is a 2.4-meter space telescope planned to launch in the mid-2020s that is expected to observe distant supernovae and BAOs, as well as gravitational lensing. The launch of the European Space Agency's Euclid space mission is currently planned for 2020 and will also exploit lensing, BAOs and redshift measurements of galactic distances to determine the three-dimensional distribution of galaxy clusters.

Finally, we can also test theories of modified gravity through measurements within the solar system. One method measures the distance to the moon to such an astonishingly high precision (through reflecting laser light off reflectors placed on the moon by *Apollo* astronauts) that it can detect minute deviations from predictions of general relativity. In addition, ingenious laboratory experiments will search for minuscule discrepancies in the current laws of gravity.

The coming years should be a pivotal time for dark energy research. We have hopes of being able to make real progress in addressing the outstanding questions about the accelerating expansion of the universe. The answers will reveal nothing short of the future of the cosmos. SA

MORE TO EXPLORE

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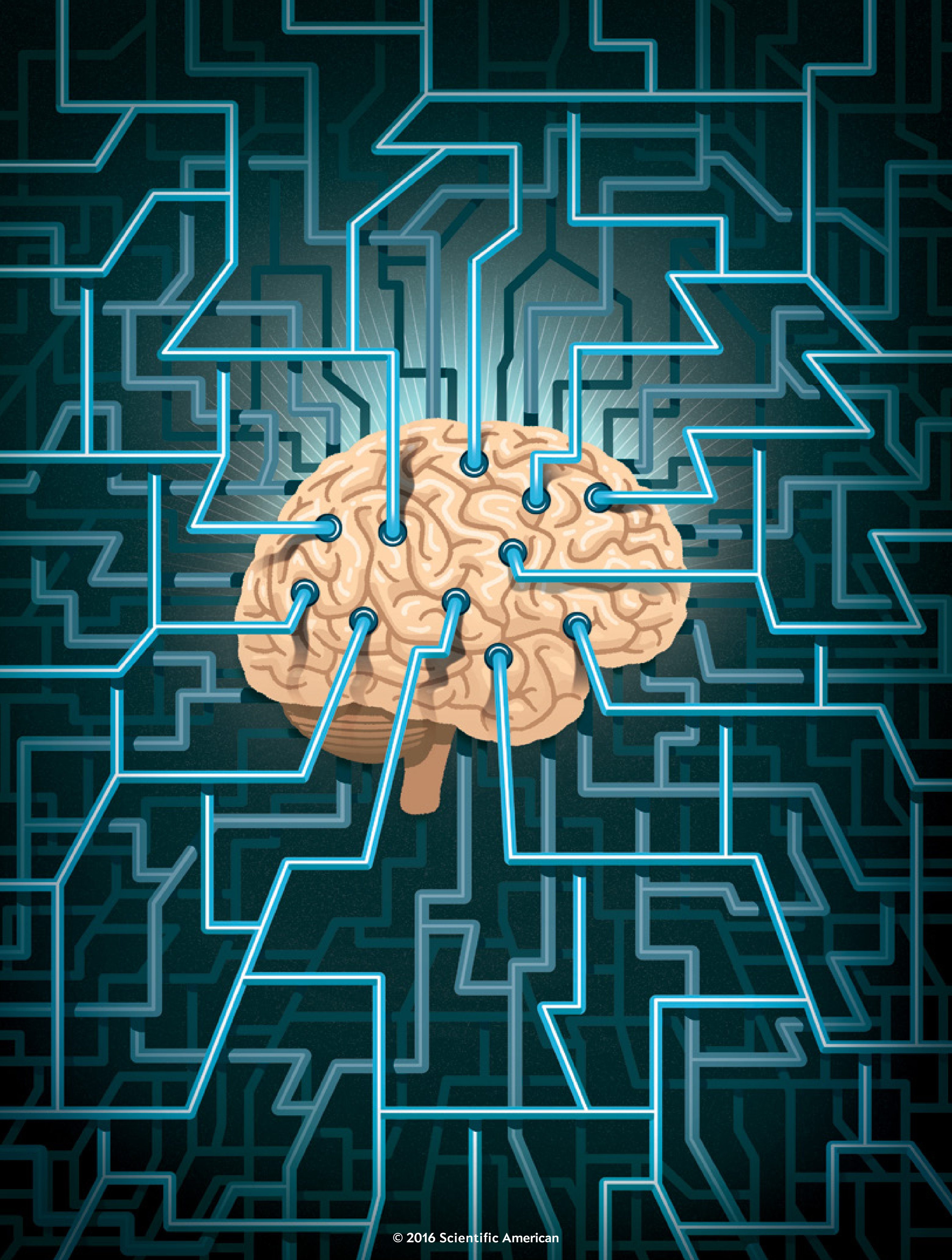
Graphic by Jen Christiansen



NEUROSCIENCE

BRAIN DRAIN

AN INTERNAL PLUMBING SYSTEM RIDS THE BRAIN OF TOXIC WASTES. SLEEP IS WHEN THIS CLEANUP RITUAL OCCURS

By Maiken Nedergaard and Steven A. Goldman

Illustration by Peter Hoey

Maiken Nedergaard studies brain cells called glia at the University of Rochester Medical Center and the University of Copenhagen. In particular, her research focuses on astrocytes, a type of glial cell implicated in a number of neurological disorders.

Steven A. Goldman is a professor of neuroscience and neurology at the University of Rochester School of Medicine and Dentistry and the University of Copenhagen.

THE HUMAN BRAIN WEIGHS ONLY ABOUT THREE POUNDS, OR ROUGHLY 2 PERCENT OF THE average adult body mass. Yet its cells consume 20 to 25 percent of the body's total energy. In the process, inordinate amounts of potentially toxic protein wastes and biological debris are generated. Each day, the adult brain eliminates a quarter of an ounce of worn-out proteins that must be replaced with newly made ones, a figure that translates into the replacement of half a pound of detritus a month and three pounds, the brain's own weight, over the course of a year.

To survive, the brain must have some way of flushing out debris. It is inconceivable that an organ so finely tuned to producing thoughts and actions would lack an efficient waste disposal system. But until quite recently, the brain's plumbing system remained mysterious in several ways. Questions persisted as to what extent brain cells processed their own wastes or whether they might be transported out of the nervous system for disposal. And why is it that evolution did not seem to have made brains adept at delivering wastes to other organs in the body that are more specialized for removing debris? The liver, after all, is a powerhouse for disposing of or recycling waste products.

About five years ago we began trying to clarify how the brain eliminates proteins and other wastes. We also began to explore how interference with that process might cause the cognitive problems encountered in neurodegenerative disease. We thought that disturbances in waste clearance could contribute to such disorders because the disruption would be expected to lead to the accumulation of protein debris in and around cells.

This idea intrigued us because it was already known that such protein clumps, or aggregates, do indeed form in brain cells, most often in association with neurodegenerative disorders. What is more, it was known that the aggregates could impede the transmission of electrical and chemical signals in the brain and cause irreparable harm. In fact, the pathology of Alzheimer's, Parkinson's and other neurodegenerative diseases of aging can be reproduced in animal models by the forced overproduction of these protein aggregates.

In our research, we found an undiscovered system for clearing proteins and other wastes from the brain—and learned that this system is most active during sleep. The need to remove potentially toxic wastes from the brain may, in fact, help explain the mystery of why we sleep and hence retreat from wakefulness for a third of our lives. We fully expect that an understanding of what happens when this system malfunctions will lead us to both new diagnostic techniques and treatments for a host of neurological illnesses.

THE GLYMPHATIC SYSTEM

IN MOST REGIONS of the body, a network of intricate fluid-carrying vessels, known as the lymphatic system, eliminates protein waste from tissues. Waste-carrying fluid moves throughout this network between cells. The fluid collects into small ducts that then lead to larger ones and eventually into blood vessels. This duct structure also provides a path for immune defense, because lymph nodes, a repository of infection-fighting white blood cells, populate ducts at key points throughout the network. Yet for a century neuroscientists had believed that the lymphatic system did not exist in the brain or spinal cord. The prevailing view held that the brain eliminated wastes on its own. Our research suggests that this is not the complete story.

The brain's blood vessels are surrounded by what are called perivascular spaces. They are doughnut-shaped tunnels that surround every vessel. The inner wall of each space is made of the surface of vascular cells, mostly endothelial cells and smooth

IN BRIEF

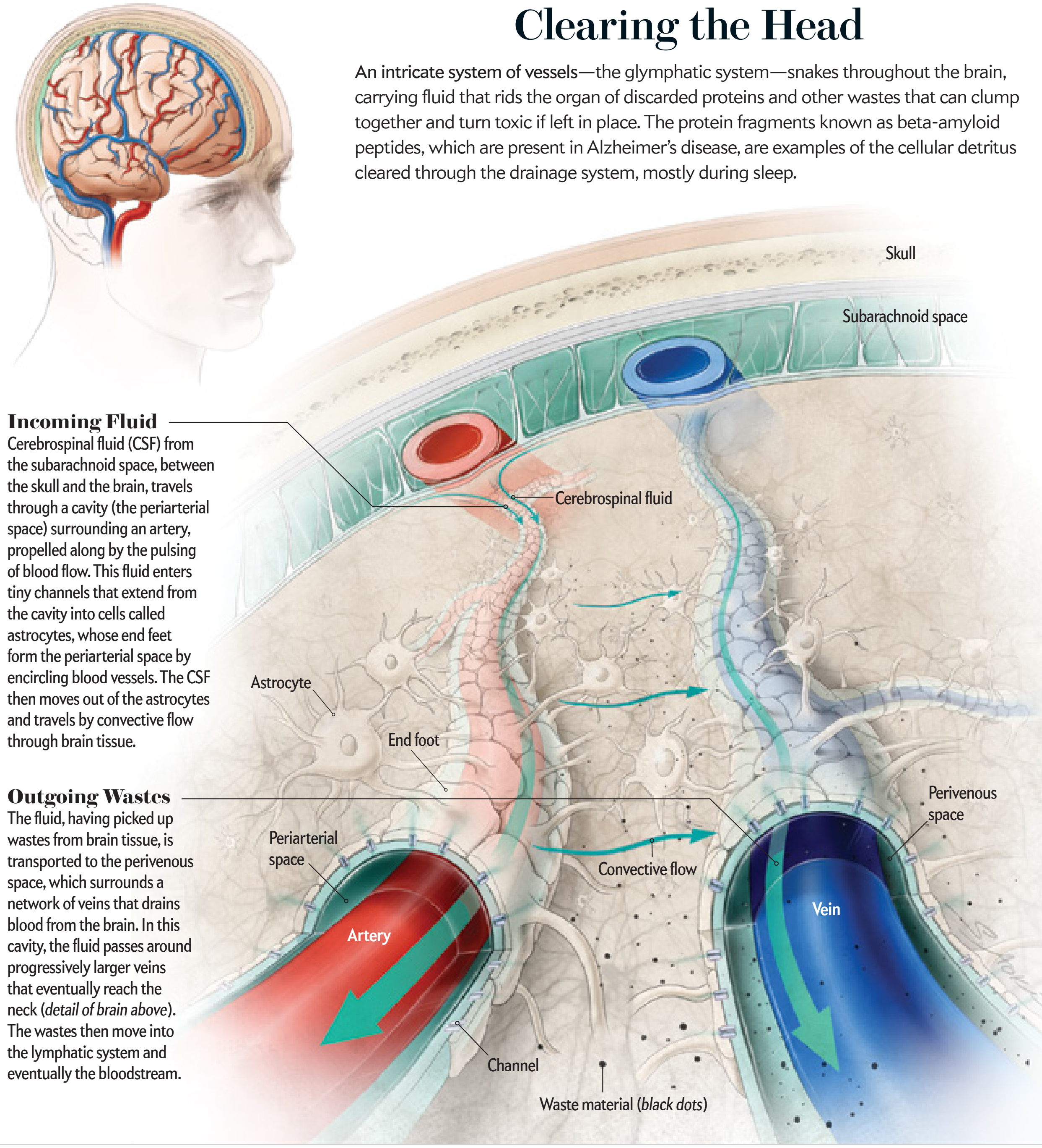
Every day the brain eliminates a quarter of an ounce of used proteins that must be replaced with new ones. The waste-disposal process traffics half a pound of detritus a month and three pounds a year, equivalent to the brain's own weight.

Where do these wastes go if the brain lacks the elaborate network of lymph vessels that transports wastes outside the nervous system? New research has recently found detritus-carrying passages in the brain that are most active during sleep.

The glymphatic system, as these fluid vessels are known, may become a critical target for the treatment of neurological diseases such as Alzheimer's or Parkinson's that result from the buildup of toxic proteins that are not cleared from the brain.

Clearing the Head

An intricate system of vessels—the glymphatic system—snakes throughout the brain, carrying fluid that rids the organ of discarded proteins and other wastes that can clump together and turn toxic if left in place. The protein fragments known as beta-amyloid peptides, which are present in Alzheimer's disease, are examples of the cellular detritus cleared through the drainage system, mostly during sleep.



Incoming Fluid
Cerebrospinal fluid (CSF) from the subarachnoid space, between the skull and the brain, travels through a cavity (the periarterial space) surrounding an artery, propelled along by the pulsing of blood flow. This fluid enters tiny channels that extend from the cavity into cells called astrocytes, whose end feet form the periarterial space by encircling blood vessels. The CSF then moves out of the astrocytes and travels by convective flow through brain tissue.

Outgoing Wastes
The fluid, having picked up wastes from brain tissue, is transported to the perivenous space, which surrounds a network of veins that drains blood from the brain. In this cavity, the fluid passes around progressively larger veins that eventually reach the neck (*detail of brain above*). The wastes then move into the lymphatic system and eventually the bloodstream.

muscle cells. But the outer wall is unique to the brain and spinal cord and consists of extensions branching out from a specialized cell type called the astrocyte.

Astrocytes are support cells that perform a multitude of functions for the interconnected network of neurons that relay signals throughout the brain. The astrocytes' extensions—astrocytic end feet—completely surround the arteries, capillaries and veins in the brain and spinal cord. The hollow, tubelike cavity that forms between the feet and the vessels remains largely free of obstructions, creating a spillway that allows for the rapid transport of fluid through the brain.

Scientists knew about the existence of the perivascular space but until very recently had not identified any specific function for it. Thirty years ago Patricia Grady, then at the University of Maryland, described perivascular fluid flows, but the significance of this finding was not recognized until much later. She reported that large proteins injected into the cerebrospinal fluid (CSF) could later be found in the perivascular spaces of both dogs and cats. At the time, other groups could not replicate her findings, and not knowing the meaning of what such

Illustration by Shizuka N. Aoki

an observation might be, research did not proceed any further.

When we began our investigations into the waste-disposal system of the brain just a few years ago, we focused on prior discoveries that water channels built from a protein called aquaporin-4 were embedded in the astrocytic end feet. In fact, the density of the water channels was comparable to that of those in the kidney, an organ whose primary job is to transport water.

We were immediately interested in the multiplicity of the astrocytic water channels and their positions facing the blood vessel walls. Our interest only grew when we looked more closely because we found that the vascular endothelial cells bordering the perivascular space lacked these channels. Thus, fluid could not be moving directly from the bloodstream into brain tissue. Rather the liquid had to be flowing between the perivascular space and into the astrocytes, thereby gaining access to the brain tissue.

We asked whether the perivascular space might constitute a neural lymphatic system. Could it perhaps provide a conduit for cerebrospinal fluid? Arterial pulsations might drive the CSF through the perivascular space. From there, some of it could enter astrocytes through their end feet. It could then move into the area between cells and finally to the perivascular space around veins to clear waste products from the brain.

Along with our laboratory members Jeff Iliff and Rashid Deane, we went on to confirm this hypothesis. Using chemical dyes that stained the fluid, combined with microscopic techniques that allowed us to image deep inside live brain tissue, we could directly observe that the pumping of blood propelled large quantities of CSF into the perivascular space surrounding arteries. Using astrocytes as conduits, the CSF then moved through the brain tissue, where it left the astrocytes and picked up discarded proteins.

The fluids exited the brain through the perivascular space that surrounded small veins draining the brain, and these veins in turn merged into larger ones that continued into the neck. The waste liquids went on to enter the lymph system, from which they flowed back into the general blood circulation. They combined there with protein waste products from other organs that were ultimately destined for filtering by the kidneys or processing by the liver.

When we began our research, we had no idea that astrocytes played such a critical role in the brain's counterpart of a lymphatic system. Additional proof came when we used genetically engineered mice that lacked the aquaporin-4 protein that makes up the astrocytes' water channels. The rate of CSF flow entering the astrocytes dropped by 60 percent, greatly slowing fluid transport through their brain.

We had now traced a complete pathway within the brain for these cleansing fluids to effectively sweep away waste products. We named our discovery the glymphatic system. The newly coined word combined the words "glia"—a type of brain cell of which the astrocyte is one example—and "lymphatic," thus referencing this newly discovered function of the brain's glial cells.

As we came to recognize the important role of the glymphatic system, we immediately wondered whether proteins that build up in the brain in neurodegenerative diseases might, in the healthy brain, be typically washed out along with other, more mundane cellular waste. In particular, we focused on a protein linked to Alzheimer's called beta-amyloid, which had previously been thought to be cleared under normal circumstances by degradation or recycling processes that take place within all brain cells. In Alzheimer's, aggregates of beta-amyloid form amyloid plaques between cells that may contribute to the disease process. We found that in a healthy brain, beta-amyloid is cleared by the glymphatic system. Other proteins implicated in neurodegenerative diseases, such as the synuclein proteins that turn up in Parkinson's, Lewy body disease and multisystem atrophy, might also be carried away and could build up abnormally if the glymphatic system were to malfunction.

In the healthy brain, the glymphatic system clears proteins associated with Alzheimer's, Parkinson's and other neurological diseases.

A symptom that accompanies Alzheimer's and other neurodegenerative diseases provided a hint of how to proceed. Many patients with Alzheimer's experience sleep disturbances long before their dementia becomes apparent. In older individuals, sleep becomes more fragmented and shallow and lasts a shorter time. Epidemiological studies have shown that patients who reported poor sleep in middle age were at greater risk for cognitive decline than control subjects when tested 25 years later.

Even healthy individuals who are forced to stay awake exhibit symptoms more typical of neurological disease and mental illness—poor concentration, memory lapses, fatigue, irritability, and emotional ups and downs. Profound sleep deprivation may produce confusion and hallucinations, potentially leading to epileptic seizures and even death. Indeed, lab animals may die when deprived of sleep for as little as several days, and humans are no more resilient. In humans, fatal familial insomnia is an inherited disease that causes patients to sleep progressively less until they die, usually within 18 months of diagnosis.

Knowing all this, we speculated that the sleep difficulties of dementia might not just be a side effect of the disorder but might contribute to the disease process itself. Moreover, if the glymphatic system cleared beta-amyloid during sleep at a higher rate than when awake, perhaps the poor sleeping patterns of patients with neurodegenerative disorders might contribute to a worsening of the disease. Because our initial experiments had been performed in anesthetized mice, we further speculated that the fast fluid flows that we noted were not necessarily what we might anticipate in an awake and active brain, which would be subject to other demands in its typical functioning.

To test the idea, Lulu Xie and Hongyi Kang, both in the Ned-

SCIENTIFIC AMERICAN ONLINE Watch Nedergaard discuss the glymphatic system at ScientificAmerican.com/mar2016/nedergaard

ergaard Laboratory, trained mice to sit still underneath a microscope to capture images of a tracer chemical in the CSF using a novel imaging technique called two-photon microscopy. We compared how the tracer moved through the glymphatic system in awake versus sleeping mice. Because imaging is neither invasive nor painful, the mice remain quiet and compliant, so much so that animals often fall asleep while being imaged. We were thus able to image inflows of CSF in a particular area of the same mouse brain during both sleep and wakefulness.

CSF in the glymphatic system, it turned out, fell dramatically while the study mice were awake. Within minutes after the onset of sleep or the effects of anesthesia, however, influxes of the fluid increased significantly. In a collaboration with Charles Nicholson of New York University, we found that the brain's interstitial space—the area between cells through which glymphatic fluid flows on its way to perivascular spaces around veins—rose by more than 60 percent when mice fell asleep. We now believe that the flow of glymphatic fluid increases during sleep because the space between the cells expands, which helps to push fluid through the brain tissue.

Our research also revealed how the rate of fluid flow is controlled. A neurotransmitter, or signaling molecule, called norepinephrine appeared to regulate the volume of the interstitial area and consequently the pace of glymphatic flow. Levels of norepinephrine rose when mice were awake and were scarce during sleep, implying that transient, sleep-related dips in norepinephrine availability led to enhanced glymphatic flow.

THE POWER OF SLEEP

HAVING DEMONSTRATED that the expansion and contraction of the interstitial space during sleep were important to both brain function and protein-waste clearance, we then wanted to test a corollary to this observation: Could sleep deprivation precipitate neurodegenerative disease? Experiments that we conducted in mice showed that during sleep, the glymphatic system did indeed remove beta-amyloid from the brain with remarkable efficiency: its clearance rate more than doubled with sleep. On the other hand, mice genetically engineered so that they lacked aquaporin-4 water channels in astrocytes demonstrated markedly impaired glymphatic function, clearing 40 percent less beta-amyloid than control animals.

The remarkably high percentage of beta-amyloid removed challenged the widely held idea that brain cells break down all their own wastes internally (through degradation processes called ubiquitination and autophagy); now we know that the brain removes a good deal of unwanted proteins whole, sweeping them out for later degradation. These new findings, moreover, seemed to confirm that the sleeping brain exports protein waste, including beta-amyloid, through the glymphatic transport system. Additional support for this thesis came from David M. Holtzman's group at Washington University in St. Louis, which demonstrated that beta-amyloid concentration in the interstitial space is higher during wakefulness than in sleep and that sleep deprivation aggravates amyloid-plaque formation in mice genetically engineered to accumulate it in excess.

So far these investigations have not moved beyond basic research labs. Drug companies have yet to consider antidementia therapies that would physically remove amyloid and other toxic proteins by washing out the brain with glymphatic fluids. But maybe they should. New strategies are desperately needed for a disease that costs the U.S. health care system $226 billion annually. A number of clinical trials for Alzheimer's are under way, although no drug in development has yet demonstrated a clear-cut benefit. Stimulating glymphatic flows offers a new approach that is worth investigating.

A pharmaceutical that regulates the glymphatic system by increasing the rate of CSF flow during sleep could literally flush amyloid out of the brain. A treatment used for a well-known neurological syndrome provides a clue that this approach might work. Normal-pressure hydrocephalus, an illness typically seen in the elderly, is a form of dementia in which excessive CSF accumulates in the hollow central brain cavities, the cerebral ventricles. When a procedure called lumbar puncture removes the fluid by draining it out, patients often exhibit remarkable improvements in their cognitive abilities. The basis for this observation has long been a mystery. Our research suggests that restoring fluid flows through the glymphatic system might mediate the restoration of cognition in these patients.

Even if a new drug is not imminent, knowledge of the glymphatic systems suggests fresh ideas for diagnosing Alzheimer's and other neurological conditions. A recent study by Helene Benveniste of the Stony Brook School of Medicine has shown that standard magnetic resonance imaging can visualize and quantify the activity of the glymphatic system. The technology may allow tests of glymphatic flow designed to predict disease progression in patients suffering from Alzheimer's or related dementias or normal-pressure hydrocephalus. It might even foretell the ability of patients with traumatic brain injuries to recover. Most of our studies of the glymphatic system to date have focused on the removal of protein wastes. Yet the glymphatic system may also prove to be a fertile area for gaining a basic understanding of how the brain works.

Intriguingly, fluids moving through the glymphatic system may do more than remove wastes; they may deliver various nutrients and other cargo to brain tissue. A new study showed that glymphatic channels deliver glucose to neurons to provide energy. Further studies are now investigating whether white matter, the insulationlike sheathing around neurons' wirelike extensions, called axons, may rely on the glymphatic system for delivery of both nutrients and materials needed for maintaining the cells' structural integrity. Such studies promise to elucidate the many unexpected roles of the glymphatic system in the daily life—and nightlife—of the brain. SA

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SYRIAN MAN comforts his wife after a treacherous, 16-kilometer ocean crossing in an overcrowded raft from Turkey to Greece, an escape route for many people leaving war-torn Syria.

Photographs by John Wendle

SUSTAINABILITY

Syria's Climate Refugees

Farmers who have escaped the embattled nation explain how drought and government abuse have driven social violence *By John Wendle*

John Wendle is a freelance writer, photographer and videographer who has covered unrest in the former Soviet Union and Afghanistan since 2005. He is now examining the conflict between humans and the environment. You can see more of his work at http://johnwendle.com and https://instagram.com/johnwendle

KEMAL ALI ran a successful well-digging business for farmers in northern Syria for 30 years. He had everything he needed for the job: a heavy driver to pound pipe into the ground, a battered but reliable truck to carry his machinery, a willing crew of young men to do the grunt work. More than that, he had a sharp sense of where to dig, as well as trusted contacts in local government on whom he could count to look the other way if he bent the rules. Then things changed. In the winter of 2006–2007, the water table began sinking like never before.

Ali had a problem. "Before the drought I would have to dig 60 or 70 meters to find water," he recalls. "Then I had to dig 100 to 200 meters. Then, when the drought hit very strongly, I had to dig 500 meters. The deepest I ever had to dig was 700 meters. The water kept dropping and dropping." From that winter through 2010, Syria suffered its most devastating drought on record. Ali's business disappeared. He tried to find work but could not. Social uprisings in the country began to escalate. He was almost killed by cross fire. Now Ali sits in a wheelchair at a camp for wounded and ill refugees on the Greek island of Lesbos.

Climatologists say Syria is a grim preview of what could be in store for the larger Middle East, the Mediterranean and other parts of the world. The drought, they maintain, was exacerbated by climate change. The Fertile Crescent—the birthplace of agriculture some 12,000 years ago—is drying out. Syria's drought has destroyed crops, killed livestock and displaced as many as 1.5 million Syrian farmers. In the process, it touched off the social turmoil that burst into civil war, according to a study published in March in the *Proceedings of the National Academy of Sciences USA*. A dozen farmers and former business owners like Ali with whom I recently spoke at camps for Syrian refugees say that's exactly what happened.

The camp where I meet Ali in November, called Pikpa, is a gateway to Europe for asylum seekers who survive the perilous sea crossing from Turkey. He and his family, along with thousands of other fugitives from Syria's devastated farmlands, represent what threatens to become a worldwide crush of refugees

IN BRIEF

Drought, which is being exacerbated by climate change and bad government policies, has forced more than a million Syrian farmers to move to overcrowded cities. Water shortages, ruined land and corruption, they say, fomented revolution.

Lack of work, along with ensuing violence, has prompted many Syrians to flee to Turkey and then cross the ocean to Greece. Hundreds of adults and children have drowned along the way.

Climate scientists say Syrian droughts will become more frequent and severe, a trend that could expand across the Middle East and the Mediterranean region.

REFUGEES WHO SURVIVE the seas are often overwhelmed with relief on reaching the Greek island of Lesbos (*far left* and *above*). Kemal Ali, 54, rests at the Pikpa refugee camp there (*left*). He dug wells for farmers until drought caused the water to sink too far underground, then lost use of his legs when a bus he was riding in Syria was hit by cross fire.

from countries where unstable and repressive governments collapse under pressure from a toxic mix of climate change, unsustainable farming practices and water mismanagement.

40 YEARS OF FURY

SYRIA'S WATER CRISIS is largely of its own making. Back in the 1970s, the military regime led by President Hafez al-Assad launched an ill-conceived drive for agricultural self-sufficiency. No one seemed to consider whether Syria had sufficient groundwater and rainfall to raise those crops. Farmers made up for water shortages by drilling wells to tap the country's underground water reserves. When water tables retreated, people dug deeper. In 2005 the regime of Assad's son and successor, President Bashar al-Assad, made it illegal to dig new wells without a license issued personally, for a fee, by an official—but it was mostly ignored, out of necessity. "What's happening globally—and particularly in the Middle East—is that groundwater is going down at an alarming rate," says Colin Kelley of the University of California, Santa Barbara, the *PNAS* study's lead author. "It's almost as if we're driving as fast as we can toward a cliff."

Syria raced straight over that precipice. "The war and the drought, they are the same thing," says Mustafa Abdul Hamid, a 30-year-old farmer from Azaz, near Aleppo. He talks with me on a warm afternoon at Kara Tepe, the main camp for Syrians on Lesbos. Next to an outdoor spigot, an olive tree is draped with drying baby clothes. Two boys run among the rows of tents and temporary shelters as they play a game of war, with sticks for imaginary guns. "The start of the revolution was water and land," Hamid says.

Life was good before the drought, Hamid recalls. Back home in Syria, he and his family farmed three hectares of topsoil so rich it was the color of henna. They grew wheat, fava beans, tomatoes and potatoes. Hamid says he used to harvest three quarters of a metric ton of wheat per hectare in the years before the drought. Then the rains failed, and his yields plunged to barely half that amount. “All I needed was water,” he says. “And I didn’t have water. So things got very bad. The government wouldn’t allow us to drill for water. You’d go to prison.”

For a while, Ali was luckier than Hamid: he had connections. As long as he had a sack full of cash, he could go on digging with no interference. “If you bring the money, you get the permissions you need fast,” he explains. “If you don’t have the money, you can wait three to five months. You have to have friends.” He manages a smile, weakened by his condition. His story raises another long-standing grievance that contributed to Syria’s downfall: pervasive official corruption.

MANY ESCAPEES from Syria cross into Turkey and travel to the western coast, where they crowd onto rafts destined for Lesbos (*map*). While at the Kara Tepe transit camp, refugees pray, bide their time and try to stay warm as they wait to go to Mytilene, the main port and capital of Lesbos (*photographs*). Once there they can buy ferry tickets to Athens and continue their journey through mainland Europe.

Syrians generally viewed thieving civil servants as an inevitable part of life. After more than four decades under the two Assad family totalitarian regimes, people were resigned to all kinds of hardship. But a critical mass was developing. In recent years Iraqi war refugees and displaced Syrian farmers have inundated Syria’s cities, where the urban population ballooned from 8.9 million in 2002, just before the U.S. invasion of Iraq, to 13.8 million in 2010, toward the end of the drought. What it meant for the country as a whole was summarized in the *PNAS* study: “The rapidly growing urban peripheries of Syria, marked by illegal settlements, overcrowding, poor infrastructure, unemployment and crime, were neglected by the Assad government and became the heart of the developing unrest.”

By 2011 the water crisis had pushed those frustrations to the limit. “Farmers could survive one year, maybe two years, but after three years their resources were exhausted,” says Richard Seager, one of the *PNAS* study’s co-authors and a professor at Columbia University’s Lamont-Doherty Earth Observatory. “They had no ability to do anything other than leave their lands.”

Hamid agrees: “The drought lasted for years, and no one said anything against the government. Then, in 2011, we had had enough. There was a revolution.” That February the Arab Spring uprisings swept the Middle East. In Syria, protests grew, crackdowns escalated and the country erupted with 40 years of pent-up fury.

NO FARMING, NO FUTURE

THIS YEAR Hamid had to abandon his family’s farm. The violence had become too much for him. “I left Syria because of the war and because there was no work,” he says.

Ali likewise tried to stick it out, but few of his former customers could afford to drill as deep as the water had sunk. And the war made ordinary activities practically impossible. His home village was only a short distance from the wreckage of Kobane on the Turkish border. That town was in ruins by the time the Kurds succeeded in recapturing it from ISIS, the militant group that has been terrorizing the region. Last July he headed for Syria’s capital, Damascus, hoping to find work and a place where his family could be safe. He was on his way there by bus when a rocket struck the vehicle. He awoke in a Damascus hospital, paralyzed from the waist down. The blast had peppered his spine with shrapnel. Somehow his family managed to get him back north, and together they made their way across Turkey to the shores of the Aegean.

Desperate strangers of all ages gather along the Turkish coast every day, not only from Syria but from all over the Middle East. They crowd onboard big rafts and set out for the roughly 16-kilometer crossing to Lesbos. The boats are routinely overloaded, and in rough seas they are easily swamped. Most cannot swim, and 20 percent are children. Drownings happen all the time.

Many do reach Lesbos alive, and they move on as quickly as possible. On the island’s northern beaches the first rays of sunrise illuminate discarded orange life vests and broken boats as far as the eye can see. Last November alone more than 100,000 foreign migrants passed through Greece, according to the International Organization for Migration. (A stunning 776,376 migrants had arrived in Greece since January 2015.) A bobbing orange dot on the horizon foretells the imminent arrival of yet another boat from Turkey. Nearing shore, one man stands up among the huddled passengers and raises his arms in triumph, flashing V-for-victory peace signs with both hands.

Louy al-Sharani, a 25-year-old from Damascus, splashes ashore with his older brother. They set off at a fast pace, carrying their bags up the steep coastal road. They both want to reach Norway as soon as possible. The brother is in a hurry to find work so he can bring his wife over before summer, when the couple’s first child is due. Al-Sharani says he is eager to start earning his second master’s degree. “I was born to use my mind,” he says. “I wasn’t born to hold a machine gun and shoot people.”

SCIENTIFIC AMERICAN ONLINE For a slide show and video of Syrian refugees, see ScientificAmerican.com/mar2016/wendle

Their mother sold all her jewelry, including her wedding ring, to give them $6,000 for the trip. They've already spent $2,400 to get this far, al-Sharani says. Still, what choice do they have? Before the war, Sharani earned a master's in agricultural economics, but now he sees no future in Syria for himself or for the country's farmers. As if the long-term drought wasn't bad enough, ISIS has made the country's prospects even more hopeless. He claims that warring factions are now stealing wheat reserves, in effect using food as a weapon to control populations. "A farmer today can't find water to irrigate, can't find government support, and always the rebels or the Syrian army is putting pressure on him. There are a million ways to die in Syria, and you can't imagine how ugly they are," he says. "After 10 years, what I see, unfortunately, is a new Afghanistan."

(IN)FERTILE CRESCENT

COLUMBIA'S SEAGER isn't quite so pessimistic. The refugee crisis will eventually subside, he assumes, and the war in Syria will run its course. Nevertheless, he says, the region's droughts will be more frequent and more severe for the foreseeable future. After closely studying dozens of climate models, he and Kelley and their colleagues are convinced that continued greenhouse gas emissions will widen the Hadley cell, the band of air that envelops the earth's tropics in a way that could further desiccate the lands of the eastern Mediterranean.

In fact, Seager says, the Fertile Crescent could lose its current shape and might cease to exist entirely by the end of this century because of severely curtailed water flow in the Euphrates and Jordan rivers. "There's not a lot of precipitation there, and when it does shift, it makes a difference," he warns. "There's something specific about the Mediterranean that is making it hydrologically very sensitive to rising greenhouse gases."

Having gotten out, Ali and his family are trying to somehow get him to Germany, where they hope surgeons will be able to restore his ability to walk. Outdoors in his chair to get a few minutes of sun, Ali is thinking of the friends he left behind in Syria. "The life of a farmer has always been hard," he says. "Their biggest problem was water—period. Because water is life."

His son wheels him indoors for a rest. Weak winter sunlight partially illuminates a big room lined with a couple of dozen beds. Plastic sacks and cheap duffle bags are heaped everywhere, holding their owners' few remaining possessions. As Ali's children lift him into bed, his face crumples in pain and exhaustion. Fardous, his 19-year-old daughter, tucks his colostomy bag against his body and arranges the donated blankets to cover him. "It is written in the Quran," Ali repeats. "Water is life." SA

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Map by Mapping Specialists

BIOLOGY

editing the mushroom

A powerful new gene-editing tool is sweeping agriculture. It could transform the debate over genetic modification

By Stephen S. Hall

THE HUNDRED OR SO FARMERS crowding the ballroom of the Mendenhall Inn in Chester County, Pennsylvania, might not have had a background in gene editing, but they knew mushrooms. These local growers produce a staggering 1.1 million pounds of mushrooms on average every day, which is one reason Pennsylvania dominates the annual $1.2-billion U.S. market. Some of the mushrooms they produce, however, turn brown and decay on store shelves; if you've ever held a slimy, decomposing, formerly white mushroom in your hand, you know why no ones buys them. Mushrooms are so sensitive to physical insult that even careful "one-touch" picking and packing can activate an enzyme that hastens their decay.

IN BRIEF

The gene-editing tool called CRISPR allows scientists to alter an organism's genome with unprecedented precision.

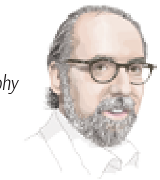
CRISPR has the potential to put powerful genetic-modification capabilities into the hands of small agricultural firms, rather than big agribusinesses, because it is easy and inexpensive to use.

Proponents say it is less biologically disruptive than traditional plant-breeding techniques practiced for thousands of years. Regulators tend to agree.

CRISPR could transform the debate over genetically modified foods—or be seen as the latest Frankenfood.

PHOTOGRAPH BY EMMA TODD

Illustration by Owen Gildersleeve



Stephen S. Hall is an award-winning science writer. He is author, most recently, of *Wisdom: From Philosophy to Neuroscience* (Knopf, 2010).

On a foggy morning last fall, at a continuing education seminar on mushrooms, a biologist named Yinong Yang took the podium to deliver news of a possible solution for the browning problem. Yang, a cheerfully polite professor of plant pathology at Pennsylvania State University, is not an expert in the field. ("The only thing I know about mushrooms is how to eat them," he says.) But he edited the genome of *Agaricus bisporus,* the most popular dinner-table mushroom in the Western world, using a new tool called CRISPR.

The mushroom farmers in the audience had probably never heard of CRISPR, but they understood it was a big deal when Yang showed a picture of actress Cameron Diaz awarding inventors Jennifer Doudna and Emmanuelle Charpentier the Breakthrough Prize in November 2014, which came with a check for $3 million each. And they understood the enormous commercial implications when Yang showed them photographs comparing brown, decayed mushrooms with pristine white CRISPR-engineered *A. bisporus,* the all-purpose strain that annually accounts for more than 900 million pounds of white button, cremini and portobello mushrooms. (Penn State understood the commercial implications, too; the day before Yang's talk, the university filed for a patent on the mushroom work.)

In its brief three years as a science story, CRISPR has already generated more fascinating subplots than a Dickens novel. It is a revolutionary research tool with dramatic medical implications, thorny bioethical conundrums, an awkward patent spat and, floating over it all, billion-dollar commercial implications for medicine and agriculture. The technique has blown through the basic research community like an F5 tornado. Academic laboratories and biotech companies are chasing novel treatments for diseases such as sickle-cell anemia and beta-thalassemia. And there has even been speculation about DIY artists and bioentrepreneurs creating everything from purple-furred bunnies to living, breathing gene-edited tchotchkes, like the miniaturized pigs recently made in China as pets. The prospect of using CRISPR to repair embryos or permanently edit our DNA (a process known as human germ-line modification) has sparked fevered talk of "improving" the human species and calls for international moratoriums.

The CRISPR revolution may be having its most profound—and least publicized—effect in agriculture. By the fall of 2015 about 50 scientific papers had been published reporting uses of CRISPR in gene-edited plants, and there are preliminary signs that the U.S. Department of Agriculture, one of the agencies that assesses genetically modified agricultural products, does not think all gene-edited crops require the same regulatory attention as "traditional" genetically modified organisms, or GMOs. With that regulatory door even slightly ajar, companies are racing to get gene-edited crops into the fields and, ultimately, into the food supply.

The transformative aspect of CRISPR lies in its unprecedented precision. CRISPR allows you to knock out any gene or, with a little more effort, to add a desirable trait by inserting a gene in a specific place in a genome. This makes it, according to its practitioners, the least biologically disruptive form of plant breeding that humans have ever devised—including the "natural" breeding techniques that have been practiced for thousands of years. It also enables scientists to sidestep, in many cases, the controversial techniques of inserting DNA from other species into plants; these "transgenic" crops, such as the Monsanto-made corn and soybeans that are resistant to the herbicide Roundup, have aroused particular ire in GMO critics and led to public distrust of the technology. Yet some scientists are optimistic that CRISPR crops are so fundamentally different that they will change the tenor of the debate over GMO foods. "The new technology," says Daniel F. Voytas, an academic and company-affiliated scientist, "is necessitating a rethinking of what a GMO is."

Will consumers agree? Or will they see CRISPR crops as the latest iteration of Frankenfood—a genetic distortion of nature in which foreign (and agribusiness-friendly) DNA is muscled into a species, with unpredictable health or environmental consequences? Because CRISPR is only now being applied to food crops, the question has not yet surfaced for the public, but it will soon. Farmers such as Yang's mushroom growers will be the first to weigh in—probably in the next year or two.

Moments after Yang's talk, an industry scientist confronted him with the central challenge of CRISPR food. The researcher conceded Yang's point that the improved mushrooms required minimal tinkering with DNA compared with conventional GMOs. "But," the scientist said, "it *is* genetic modification, and some people will see it as we are playing God. How do we get around that?"

How well Yang and other scientists applying these gene-editing techniques to food can answer that question will determine whether CRISPR is a potentially transformational tool or one that will be stymied by public opposition.

"WOW, THAT'S THE ONE!"

THE TELLTALE SIGN of any transformational technology is how quickly researchers apply it to their own scientific problems. By that standard, CRISPR ranks among the most powerful additions to biology's tool kit in the past half a century. The gene-edited mushroom is a case in point.

Yinong Yang—his first name means "also practices agriculture" in Chinese—never worked with mushrooms until 2013, but you might say he was to the task bred. Born in Huangyan, a city south of Shanghai known as the citrus capital of China, he dabbled with some primitive gene-editing enzymes in the mid-1990s as a graduate student at the University of Florida and later at the University of Arkansas. He vividly remembers opening the August 17, 2012, issue of *Science,* which contained a paper from Doudna's lab at the University of California, Berkeley, and Charpentier's lab describing CRISPR's gene-editing potential. "Wow," he thought. "That's the one!" Within days he was hatching plans to improve traits in rice and potato plants through gene editing. His lab published its first CRISPR paper in the summer of 2013.

He was not alone. Plant scientists jumped on CRISPR as soon as the technique was published. Chinese scientists, who quickly embraced the technology, shocked the agricultural community in 2014 when they showed how CRISPR could be used to make bread wheat resistant to a long-standing scourge, powdery mildew.

The gene-editing revolution had begun before the arrival of CRISPR, however. For people like Voytas, CRISPR is merely the latest chapter in a much longer scientific saga that is just now bearing fruit. He first attempted gene editing in plants 15 years ago, while at Iowa State University, with a technology known as zinc fingers; his first gene-editing company foundered on patent issues. In 2008 he moved to the University of Minnesota and in 2010 patented, with former Iowa State colleague Adam Bogdanove, now at Cornell University, a gene-editing system in plants based on TALENs, a subsequent gene-editing tool. That same year Voytas and his colleagues started a company now known as Calyxt. Without the hoopla of CRISPR, agricultural scientists have used TALENs to produce gene-edited plants that have already been grown in fields in North and South America. Calyxt, for example, has created two strains of soybean modified to produce a healthier oil, with levels of monosaturated fats comparable to olive and canola oils. And the company has gene-edited a potato strain to prevent the accumulation of certain sugars during cold storage, reducing the bitter taste associated with storage, as well as the amount of acrylamide, a suspected carcinogen, produced when potatoes are fried.

Because these genetic modifications did not involve the introduction of any foreign genes, the USDA's Animal and Plant Health Inspection Service (APHIS) decided last year that the crops do not need to be regulated as GMOs. "The USDA has given regulatory clearance to plant a potato variety and two soybean varieties, so the potato and one of the soybean varieties are in the field this year," Voytas told me last October. "They basically considered these as just standard plants, as if they were generated by chemical mutagens or gamma rays or some nonregulated technology. The fact that we got regulatory clearance and can go almost immediately from the greenhouse to the field is a big plus. It allows us to really accelerate product development."

Animal scientists have also jumped on the gene-editing bandwagon. Researchers at the small Minnesota-based biotech firm Recombinetics have genetically blocked the biological signal that governs the growth of horns in Holstein cows, the workhorse of the dairy industry. They accomplished this by using gene editing to replicate a mutation that naturally occurs in Angus beef cattle, which do not grow horns. Ag scientists tout this application of gene editing as a more humane form of farming because it spares male Holstein cows from a gruesome procedure during which dairy farmers physically gouge out and then cauterize developing horns (the procedure is done to protect both dairy cattle and dairy farmers from injury). Scott Fahrenkrug, the company's CEO, says the process does not involve transgenes, just the introduction of a few letters of DNA "to match the food we already eat." Korean and Chinese scientists, meanwhile, have teamed up to produce a pig with much more muscle mass, by using gene editing to knock out a gene called myostatin.

The speed, ease and thrift of CRISPR make it an even more attractive technique than TALENs. "Without a doubt," Voytas says, in the future CRISPR "is going to be the plant-editing tool of choice." But the murky patent situation—both the University of California and the Broad Institute (run jointly by the Massachusetts Institute of Technology and Harvard University) claim to have invented CRISPR—may slow commercial agricultural development. DuPont recently reached a "strategic alliance" with Caribou Biosciences, a biotech associated with U.C. Berkeley, to use CRISPR applications in agriculture, but executives at two small biotechs told *Scientific American* that they were wary of developing CRISPR-related products while the patent dispute remains unresolved.

That's not a big issue for academic labs. The mushroom story took a decisive turn in October 2013, when a Penn State alum named David Carroll popped into Yang's lab. Carroll, who happened to be president of Giorgi Mushroom, wondered if new gene-editing techniques could be used to improve mushrooms. Emboldened by the power of CRISPR to create highly precise mutations, Yang replied, "What kind of trait do you want?" Carroll suggested antibrowning, and Yang immediately agreed to try it.

Yang knew exactly which gene he wanted to target. Biologists had previously identified a family of six genes, each of which encode an enzyme that causes browning (the same class of genes also triggers browning in apples and potatoes, both of which have been targeted by gene editors). Four of the so-called browning genes churn out that enzyme in the fruiting body of mushrooms, and Yang thought that if he could shut down one of them through a gene-editing mutation, he might slow the rate of browning.

The brilliant ease of CRISPR derives from the fact that it is straightforward for biologists to customize a molecular tool—a "construct"—that creates such mutations. Like a utility knife that combines a compass, scissors and vise, these tools excel at two tasks: homing in on a very specific stretch of DNA and then cutting it (the vise, or scaffolding, holds everything in place during the cutting). The homing is accomplished by a small piece of nucleic acid called the guide RNA, which is designed to mirror the DNA sequence in the target area and attach to it using the unique and specific attraction of DNA base pairs made famous by James Watson and Francis Crick (where As grab onto Ts and Cs grab onto Gs). If you make a piece of guide RNA that is 20 letters long, it will find its mirror sequence of DNA—with GPS-like precision—amid the string of 30 million letters that spell out the *Agaricus* mushroom genome. The cutting is then accomplished by the Cas9 enzyme, originally isolated from bacterial cultures in yogurt, which rides in on the back of the guide RNA. (The term "CRISPR/Cas9" is a bit of a misnomer now because CRISPR refers to *c*lustered *r*egularly *i*nterspersed *s*hort *p*alindromic *r*epeats, patches of DNA that occur only in bacteria. It is the Cas9 protein, loaded with an RNA targeting sequence, that edits plant, fungal and human DNA, even though no CRISPRs are involved.)

Once gene editors cut DNA at the desired spot, they let nature perform the dirty work of mutation. Any time the double helix of DNA is cut, the cell notices the wound and sets out to repair the break. These repairs are not perfect, however, which is exactly what makes CRISPR so powerful at creating mutations. During the repair process, a few letters of DNA usually get deleted; because a cell's protein-making machinery reads DNA in three-letter "words," deleting a couple of letters subverts the entire text and essentially inactivates the gene by creating what is known as a reading frame shift. That is precisely what happened with the gene-edited mushroom. In Yang's work, a tiny deletion of DNA inactivated one of the enzymes that promote browning—a mutation that Yang and his colleagues confirmed with DNA analysis. Editing complete. According to Yang, a skillful molecular biologist could in about three days build a custom-designed mutation tool to edit virtually any gene in virtually any organism.

That sentiment echoes the mantra scientists constantly in-

PLANT BREEDING

Genetic Modification by Any Other Name

People have been cultivating crops for thousands of years, and for all that time they have aimed to identify and incorporate beneficial traits (higher yields, for example, or disease resistance) into existing plant varieties. First they used conventional crossbreeding. In the early 20th century scientists learned to deliberately mutate the DNA of existing plants and hope for desirable traits to appear at random. Today new "precision breeding" techniques such as CRISPR enable scientists to mutate specific genes or insert new genetic traits with unprecedented precision. Yet *all* these techniques alter the DNA of the plants, so what counts as a genetically modified organism (GMO), anyway?

Key Concepts

Mutagenesis Since the 1920s agricultural scientists have deliberately mutated the DNA of plant seeds with x-rays, gamma rays or chemicals and then grown the plants to see if they have acquired beneficial traits. If so, the mutated plants can be crossbred with existing varieties. Plants created this way are not considered GMOs by the U.S. Department of Agriculture.

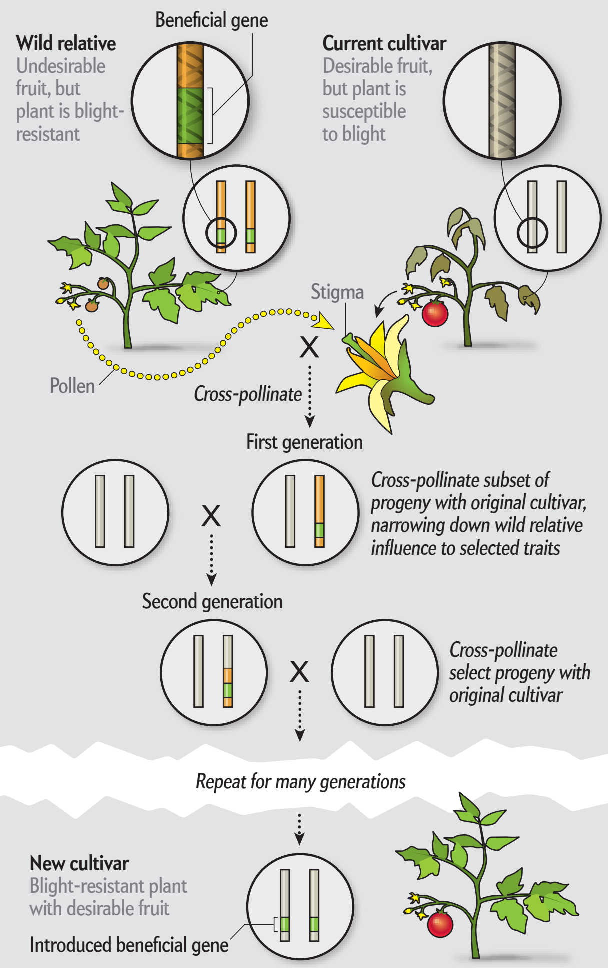
Gene Silencing For the past decade scientists have been able to turn off genes that confer unwanted traits by introducing a disruptive form of RNA into plant cells. This "interfering" RNA (or iRNA) is engineered to disrupt a specific sequence of DNA underlying an undesirable trait. Several food crops, including nonbrowning potatoes and apples, have been created in this way. The USDA does not call them GMOs.

Cisgenesis This process involves introducing a specific gene from a related plant species. The transfer is typically accomplished by a plant-infecting microbe called *Agrobacterium tumefaciens*, which can insert the gene into a semirandom spot in the plant's DNA. The USDA reviews cisgenic plants on a case-by-case basis to determine their regulatory status.

Transgenesis The technique involves the transfer of foreign DNA encoding a desired trait into an unrelated plant species. As in cisgenesis, *A. tumefaciens* is used to smuggle in the foreign DNA when the bacterium infects a plant cell. Examples of transgenic crops include corn into which a herbicide-resistant gene has been inserted. Ninety percent of all soybeans grown in the U.S. are transgenic; the USDA considers transgenic plants to be GMOs.

Conventional Crossbreeding

Includes selective breeding and crossbreeding following mutagenesis. During natural breeding, large segments of chromosomes—up to millions of base pairs—are introduced along with the desired trait into a domesticated cultivar. Subsequent crosses typically reduce the amount of transferred DNA, but the insert often remains hundreds of thousands of base pairs long and can drag along undesirable genes ("linkage drag") in the process. A 2010 genomic analysis of *Arabidopsis* (considered the "mouse model" of plants) showed that conventional breeding introduced approximately seven spontaneous new mutations per billion base pairs of DNA in each generation.

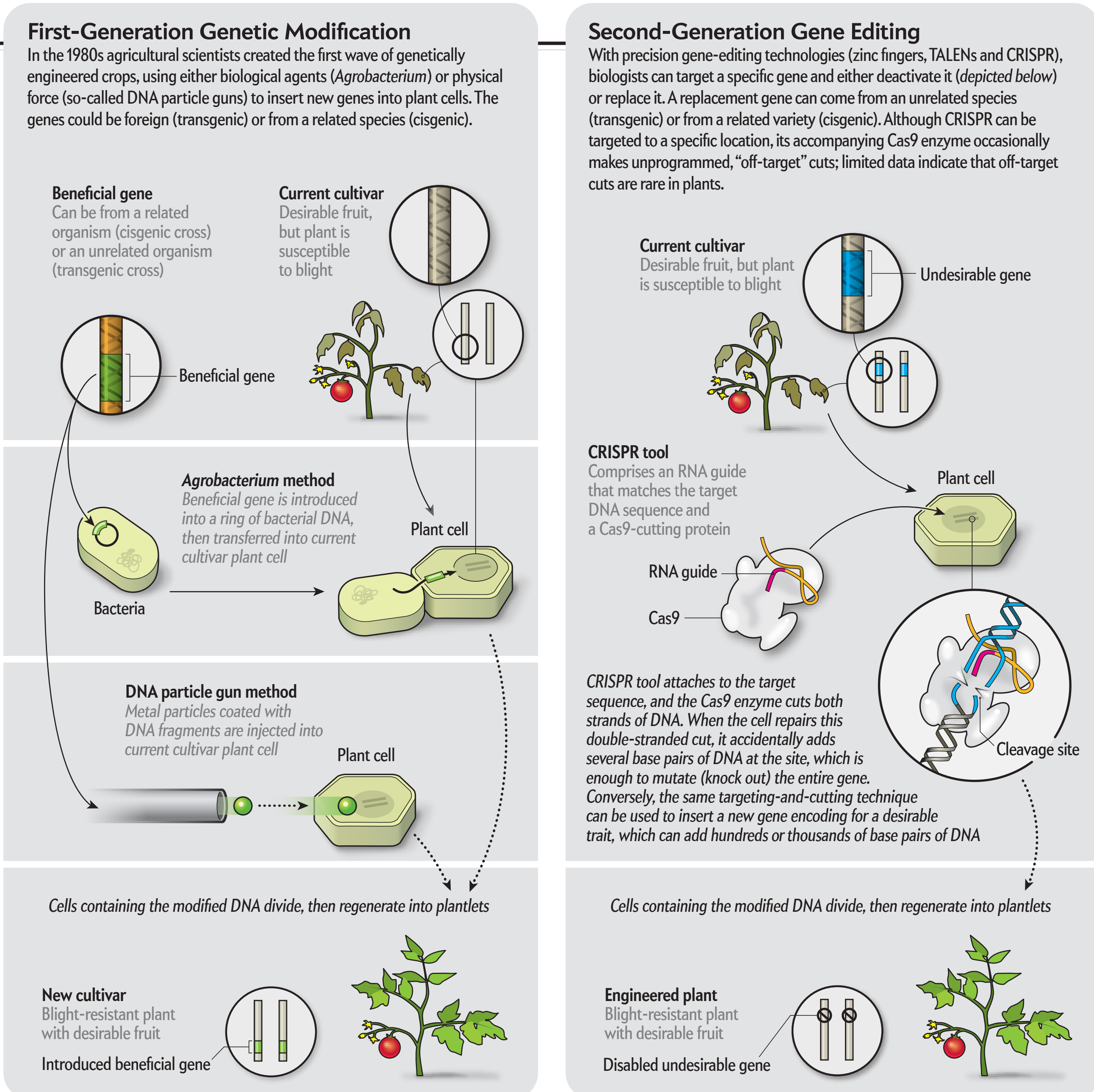


voke about CRISPR: it is fast, cheap and easy. It took about two months of lab work to create the antibrowning mushroom; Yang's demeanor suggested that the work was routine, if not ridiculously easy. And it was remarkably inexpensive. The trickiest step, making the guide RNA and its scaffolding, cost a couple of hundred dollars; a number of small biotech firms now make custom-order CRISPR constructs to edit any gene desired. The biggest cost is manpower: Xiangling Shen, a postdoctoral fellow in Yang's lab, worked on the project part-time. "If you don't consider manpower, it probably cost less than $10,000," Yang says. In the world of agricultural biotech, that is chump change.

And that doesn't begin to hint at the potentially game-changing thrift of CRISPR in the regulatory arena. Last October, Yang gave an informal presentation of the mushroom work to federal regulators at the USDA's APHIS, which decides if genetically modified food crops fall under government regulatory control (in short, whether they are considered a GMO); he came away from the meeting convinced that USDA regulators did not believe the CRISPR mushroom would require special or extended regulatory review. If true, that may be the most important way CRISPR is cheaper: Voytas has estimated that the regulatory review process can cost up to $35 million and take up to five and a half years.

Another advantage of the mushroom as a proof of principle for CRISPR in agriculture is the speed at which fungi grow: from spawn to maturity, mushrooms take about five weeks, and they can be grown year-round in windowless, climate-controlled facilities known as mushroom houses. The gene-edited soybeans and

Illustrations by Jen Christiansen



potatoes created by Calyxt, in contrast, take months to field-test, which is why the company sought, and received, regulatory clearance to grow its soybeans in Argentina last winter (2014–2015). "You bop back and forth over the equator," Voytas says, "so you can get multiple plantings in a year." Calyxt harvested its first North American gene-edited crops from the field last October.

One of the long-standing fears about genetic modification is the specter of unintended consequences. In the world of biotech foods, this usually means unexpected toxins or allergens making modified foods unhealthy (a fear that has never been documented in a GMO food) or a genetically modified crop running amok and devastating the local ecology. CRISPR is even making people such as John Pecchia think about unintended economic consequences. One of two mushroom professors at Penn State, Pecchia spends a lot of time in a low-slung cinder-block building situated on the outskirts of the campus, which houses the only center of academic mushroom research in the U.S. In the spring of 2015 Pecchia took some of Yang's starter culture and grew up the first batch of gene-edited mushrooms. Standing outside a room where a steamy, fetid mix of mushroom compost was brewing at 80 degrees Celsius, he notes that a mushroom with a longer shelf life might result in smaller demand from stores and also enable unexpected competition. "You could open up the borders to foreign mushroom imports," he adds, "so it's a double-edged sword."

In the tortuous path of genetically modified foods to market, here is one more paradox to chew on. No one knows what the gene-edited mushroom tastes like. They've been steamed and boiled, but not for eating purposes. Every mushroom created so far has been destroyed after Yang conducted browning tests. Once proof of principle has been established, Pecchia says, "we just steam them away."

TRANSGENE-FREE MODIFICATION

WILL THE PUBLIC STEAM, sauté or otherwise welcome gene-edited food into their kitchens and onto their plates? That may be the central question in the most intriguing chapter in the CRISPR food story, which coincides with a crucial juncture in the tumultuous, 30-year debate over genetically modified crops.

When Yang described his mushroom project to the Pennsylvania farmers—and to officials at the USDA last October—he used a telltale phrase to describe his procedure: "transgene-free genetic modification." The phrase is a carefully crafted attempt to distinguish the new, high-precision gene-editing techniques like CRISPR from earlier agricultural biotech, where foreign DNA (transgenes) were added to a plant species. For Yang and many others, that delicate wording is important in recasting the GMO debate. Indeed, the acronym "GEO" (for gene-edited organism) has begun to crop up as an alternative to "GMO" or "GM."

New technologies like CRISPR are forcing some governments to reconsider the definition of a genetically modified organism.

The reframing is as much philosophical as semantic, and it is unfolding as the Obama administration is overhauling the system by which the government reviews genetically modified crops and foods. Known as the Coordinated Framework for Regulation of Biotechnology, this regulatory process, which has not been updated since 1992, defines roles for the USDA, the Food and Drug Administration, and the Environmental Protection Agency. The power of CRISPR has added urgency to the regulatory rethink, and scientists are using the opportunity to revisit a very old question: What exactly does "genetically modified" mean? Voytas, whose track record of publications and patents in gene-edited food crops makes him a sort of editor in chief of small agricultural biotechs in the U.S., answered with a grim little laugh when asked that question: "The GM term is a tricky one."

What's so tricky about it? Most critics of biotech food argue that any form of genetic modification is just that, genetic modification, bringing with it the possibility of unintended mutations or alterations that could pose risks to human health or the environment. Scientists such as Voytas and Yang reply that *all* forms of plant breeding, dating all the way back to the creation of bread wheat by Neolithic farmers 3,000 years ago, involve genetic modification and that the use of traditional breeding techniques is not a biologically benign process. It creates, as Yang put it, "huge" genetic disruptions. (Nina Fedoroff, a plant biologist and former president of the American Association for the Advancement of Science, has referred to domesticated versions of bread wheat, created by traditional breeding, as "genetic monstrosities.")

Before the era of recombinant DNA in the 1970s, which allowed first-generation agricultural biotech, plant breeders typically resorted to brute-force methods (x-rays, gamma rays or powerful chemicals) to alter the DNA of plants. Despite this blunderbuss approach, some of these random, man-made mutations modified genes in a way that produced desirable agricultural traits: higher yields, or more shapely fruit, or an ability to grow in adverse conditions such as drought. These beneficial mutations could then be combined with beneficial traits in other strains but only by crossing—or mating—the plants. That type of crossbreeding takes a lot of time (often five to 10 years), but at least it is "natural."

But it is also very disruptive. Any time DNA from two different individuals comes together during reproduction, whether in humans or plants, the DNA gets scrambled in a process known as chromosomal reassortment. Spontaneous mutations can occur in each generation, and millions of base pairs of DNA can be transferred when breeders select for a desired trait. It is natural, yes, but also "a big mash-up," according to Voytas. "In that process, you don't just move one gene," he says. "You often move a pretty big chunk of DNA from the wild species." Moreover, the desirable trait often drags along with it an undesirable trait on the same piece of DNA during the process of breeding; this "linkage drag" can actually harm the naturally bred plant. On the basis of several recent findings on the genetics of rice plants, some biologists hypothesize that domestication has inadvertently introduced "silent" detrimental mutations as well as obvious beneficial traits.

Although CRISPR is more precise than traditional breeding, the technique is not infallible. The precision cutting tool sometimes cuts an unintended region, and the frequency of these "off-target" cuts has raised safety concerns (it is also the main reason that gene editing of human sperm and egg cells is still considered unsafe and unethical). Jennifer Kuzma, a policy analyst at North Carolina State University, who has followed the science—and politics—of GMO agriculture since its inception, says, "That precision has merit, but it doesn't necessarily correlate with risk reduction," adding that off-target cuts "may introduce a different pathway to hazard." Feng Zhang of the Broad Institute (which holds the patent that is now being disputed) has published several refinements in the CRISPR system that improve specificity and reduce off-target hits.

The ease and relative thrift of CRISPR have also allowed academic labs and small biotechs back into a game that has historically been monopolized by big agribusinesses. Only deep-pocketed companies could afford to run the costly regulatory gauntlet in the beginning, and to date, almost every crop modification created by genetic engineering was done to enhance the economics of food production for farmers or companies, be it the increased yields of Monsanto's herbicide-resistant field crops or the shipping hardiness of Calgene's ill-fated Flavr-Savr tomato. Those genetic crop modifications were more appealing to agribusiness than consumers, and they were not very food-centric.

SCIENTIFIC AMERICAN ONLINE For more coverage of CRISPR, go to ScientificAmerican.com/mar2016/crispr

As a group of agricultural policy experts at the University of California, Davis, recently observed, "the multinational corporations that have dominated the field for the past decade and a half do not have a glowing record in terms of innovation beyond traits for pesticide and herbicide resistance."

The new players have brought a different kind of innovation to agriculture. Voytas, for example, argues that the precision of gene editing is allowing biotech scientists to target consumers by creating healthier, safer foods. Voytas and his colleague Caixia Gao of the Chinese Academy of Sciences have pointed out that plants have many "antinutritionals": noxious self-defense substances or outright toxins that could be gene-edited away to improve nutritional and taste traits. Calyxt's gene-edited potato, for example, reduces a bitter taste trait associated with cold storage of the tubers.

But Voytas goes even further. He believes the Calyxt soybean could be sold to farmers as a non-GMO product because, unlike 90 percent of soybeans grown in the U.S., the gene-edited strains do not have any transgenes. "A lot of people don't want GM products," he says. "We could maybe make non-GM soybean oil and non-GM soybean meal with our product."

Like any powerful new technology, CRISPR has inspired some agricultural dreamers to envision almost science-fiction scenarios for the future of farming—scenarios that are already making their way into the scientific literature. Michael Palmgren, a plant biologist at the University of Copenhagen, has proposed that scientists can use the new gene-editing techniques to "rewild" food plants, that is, to resurrect traits that have been lost during generations of agricultural breeding. A number of economically significant food crops—notably rice, wheat, oranges and bananas—are highly susceptible to plant pathogens; the restoration of lost genes could increase disease resistance. The idea, Palmgren and his Danish colleagues recently noted, aspires to "the reversal of the unintended results of breeding."

Attempts at rewilding are already under way but with a twist. Rather than restoring lost wild traits to domestic breeds, Voytas says his University of Minnesota lab is attempting what he calls "molecular domestication": transferring agriculturally desirable genes from existing hybrids back into wild species that are hardier and more adaptable, such as the ancestral form of corn, and potatoes. "It's usually only a handful of critical changes that occurred—five, six or seven genes—that allowed a weedy species to become desirable, such as changes in fruit size or corn ear number, those sorts of things," Voytas says. Rather than crossing the wild varieties with the domesticated strains, which would require a 10-year breeding regime, he says, "maybe we can just go in and treat those genes and domesticate the wild variety."

There are early signs that gene editing, including CRISPR, may also enjoy a speedier regulatory path. So far U.S. regulators appear to view at least some gene-edited crops as different from transgenic GMO crops. When Calyxt first asked the USDA if its gene-edited potatoes required regulatory review, federal officials took about a year before concluding, in August 2014, that gene editing did not require special consideration; when the company went back to the USDA last summer with its gene-edited soybeans, government reviewers took only two months to reach a similar conclusion. To companies, this suggests that U.S. authorities view the new techniques as fundamentally distinct from transgenic methods; to critics, it suggests a regulatory loophole that companies are exploiting. Yang's mushrooms may be the first CRISPR food considered by the USDA.

And new technologies like CRISPR are forcing some governments to reconsider the definition of a GMO. Last November the Swedish Board of Agriculture decreed that some plant mutations induced by CRISPR do not meet the European Union's definition of a GMO, and Argentina has similarly concluded that certain gene-edited plants fall outside its GMO regulations. The E.U., which has historically restricted genetically modified plants, is currently reviewing policy in light of the new gene-editing techniques, but its oft-delayed legal analysis will not be made public until the end of March at the earliest. While there is not much middle ground, Voytas and others have suggested one potential compromise: gene editing that causes a mutation, or "knock out," should be viewed as analogous to traditional forms of plant breeding (where x-rays, for example, are used to create mutations), whereas gene editing that introduces new DNA (a "knock in") deserves regulatory scrutiny on a case-by-case basis.

The day of food-market reckoning for gene-edited crops may not be too far off; Voytas estimates that Calyxt will have a "small commercial launch" of its soybeans by 2017 or 2018. "It's going to take some time to get enough seed for, say, half a million acres," he says. "But we're pushing as hard and fast as we can."

How will the public respond? Kuzma predicts that people who have historically opposed genetic modification will not be drinking CRISPR Kool-Aid anytime soon. "The public that opposed first-generation GMOs is not likely to embrace this second generation of genetic engineering, just because you're tweaking a little bit of DNA," she says. "They're just going to lump it together with GMOs." Kuzma is more concerned about the need to revamp the overall regulatory structure and bring more voices into the review process, at an "inflection point" at which more and more gene-edited foods are wending their way to the marketplace.

And what about the mushroom? Beyond polite applause at the end of Yinong Yang's talk, the reaction of mushroom farmers remains unclear. Yang acknowledged as much when he told the farmers, "Whether this can be commercialized, that's up to you guys." For now, the antibrowning mushroom is just a lab project, a proof of principle. If growers are unconvinced of the value of the antibrowning mushroom or fear consumers will shun it, the well-edited mushroom may never see the light of day. That's usually a good thing for a mushroom, which grows in the dark, but is perhaps more ominous for a new and potentially transformative technology. SA

MORE TO EXPLORE

Precision Genome Engineering and Agriculture: Opportunities and Regulatory Challenges. Daniel F. Voytas and Caixia Gao in *PLOS Biology,* Vol. 12, No. 6, Article No. e1001877; June 10, 2014.

Conflicting Futures: Environmental Regulation of Plant Targeted Genetic Modification. Adam Kokotovich and Jennifer Kuzma in *Bulletin of Science, Technology & Society,* Vol. 34, Nos. 3–4, pages 108–120; June–August 2014.

Feasibility of New Breeding Techniques for Organic Farming. Martin Marchman Andersen et al. in *Trends in Plant Science,* Vol. 20, No. 7, pages 426–434; July 2015.

A Face-Lift for Biotech Rules Begins. Emily Waltz in *Nature Biotechnology,* Vol. 33, No. 12, pages 1221–1222; December 2015.

FROM OUR ARCHIVES

The Gene Genie. Margaret Knox; December 2014.

scientificamerican.com/magazine/sa

GEOLOGY

anatomy OF A MASS MURDERER

Huge regions with epic volcanic explosions are now blamed for four of Earth's "big 5" mass extinctions *By Howard Lee*

THE BIGGEST EXTINCTIONS IN OUR PLANET'S HISTORY HAVE BEEN BLAMED, AT various times, on asteroids, gas-emitting microbes or volcanic eruptions. The five mass die-offs destroyed most animals and plants on Earth, including the dinosaurs 66 million years ago. New evidence points strongly to cataclysmic eruptions as the real culprits. Highly accurate rock dates pin such eruptions to the same times as four of the major extinctions and tie the explosions to lethal changes in the atmosphere, as the illustrations here show.

Howard Lee is a science writer based in New Jersey.

For example, 251.9 million years ago life collapsed in the Permian extinction. More than 95 percent of marine species and 70 percent of land species vanished. At around this period, there was a tremendous amount of volcanic activity in a region called the Siberian Traps. To see if the geologic activity began before the extinction and could have been at fault, geochronologists Seth Burgess and Samuel Bowring of the Massachusetts Institute of Technology and their colleagues went to Siberia to nail down the timing.

The scientists collected tiny crystals of zircon and perovskite from erupted rocks. When the crystals are formed, they contain uranium, which converts to lead at a steady rate after the crystals cool on Earth's surface; the ratio of uranium to lead reveals how long ago the eruption occurred. Most of the erupted rock made it to the planet's surface starting just 300,000 years before the extinction peaked, the team reported in August 2015 in the journal *Science Advances*. Geochemists have also found signs of a huge burst of carbon dioxide—another lethal eruption consequence—into the atmosphere at this time, a pattern repeated for the extinctions at the end of the Devonian, Triassic and Cretaceous periods.

These are not everyday eruptions. The blowups come from giant fields, sometimes thousands of miles across, strewn with volcanic vents. Geologists call these areas "large igneous provinces" (LIPs). Their remnants today form vast swaths of hardened lava in remote areas of Asia and elsewhere. Large igneous province eruptions are spectacular: magma bursts into the air in mile-high incandescent fountains, yellow-hot lava forms long rivers, and a scorching, sulfurous haze drifts for miles. But it is not the lava or ash that makes extinctions truly "mass"; the sulfur dioxide and carbon dioxide gases drive the lethal death spirals.

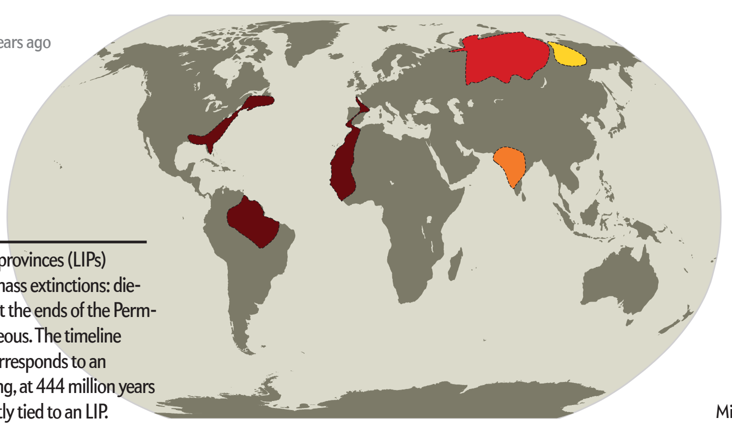
Some of the new dates have prompted geophysicist Mark Richards of the University of California, Berkeley, and geologist Walter Alvarez, who helped originate the asteroid impact theory of dinosaur demise, to refine that idea. In an April 2015 paper published in *GSA Bulletin,* their team suggests that energy from the asteroid slamming into the planet accelerated the most violent eruptions in the Cretaceous era. Thus combined with volcanoes, the impact theory, unlike the dinosaurs, lives on. SA

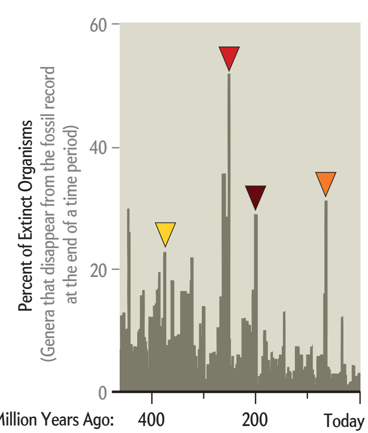
Viluy Traps LIP
Late Devonian, 373 million years ago

Siberian Traps LIP
End of Permian, 252 Mya

Central Atlantic LIP
End of Triassic, 201 Mya

Deccan Traps LIP
End of Cretaceous, 66 Mya





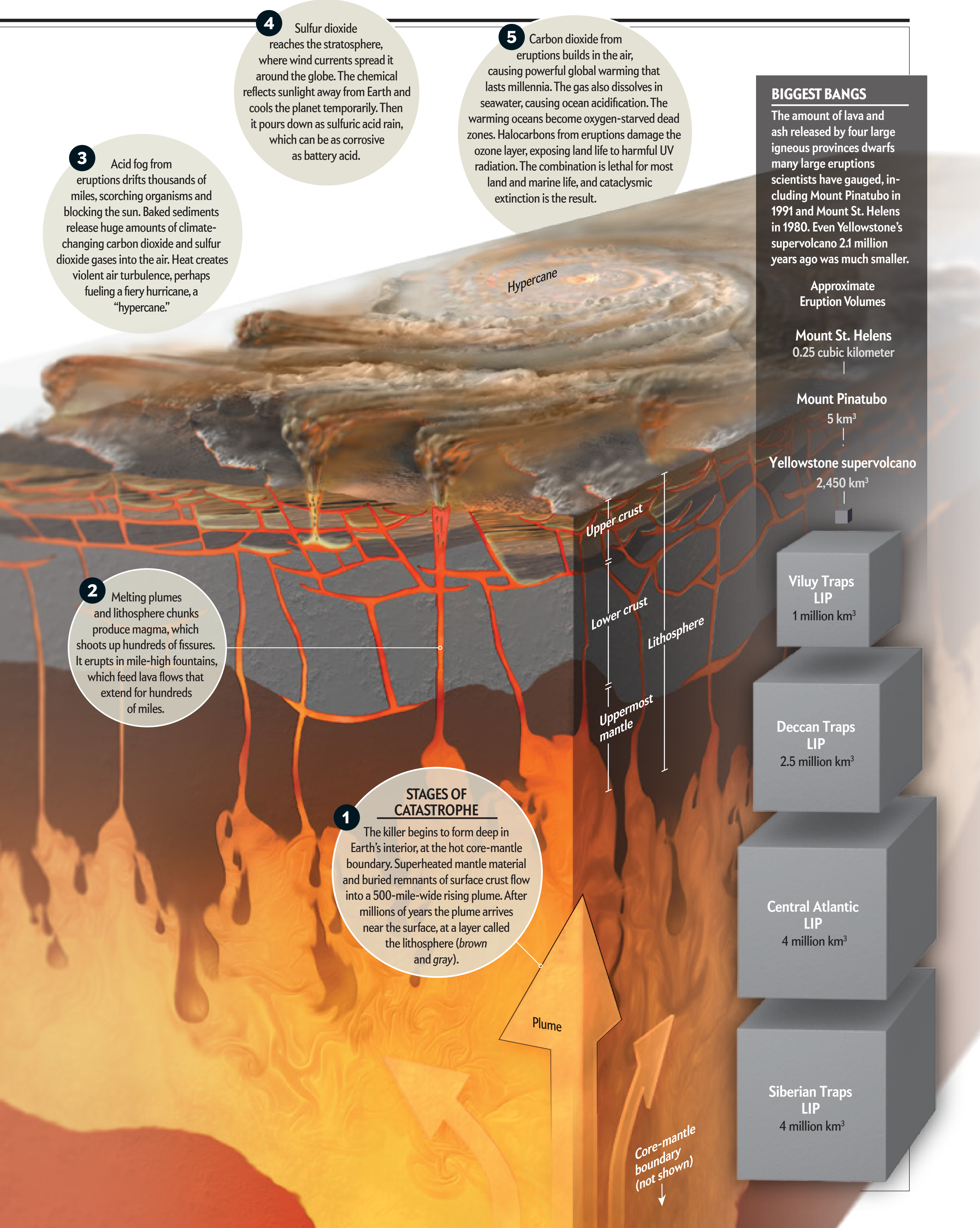
WHERE AND WHEN

The map shows large igneous provinces (LIPs) blamed for four of the "big 5" mass extinctions: die-offs in the Late Devonian and at the ends of the Permian, the Triassic and the Cretaceous. The timeline shows how closely each LIP corresponds to an extinction. The Ordovician dying, at 444 million years ago, is the only one not currently tied to an LIP.

SOURCES: "CYCLES IN FOSSIL DIVERSITY," BY ROBERT A. ROHDE AND RICHARD A. MULLER, IN *NATURE*, VOL. 434; MARCH 10, 2005 (SUPPLEMENTARY INFORMATION) (*extinction chart*); "LARGE IGNEOUS PROVINCES AND SILICIC LARGE IGNEOUS PROVINCES: PROGRESS IN OUR UNDERSTANDING OVER THE LAST 25 YEARS," BY SCOTT E. BRYAN AND LUCA FERRARI, IN *GEOLOGICAL SOCIETY OF AMERICA BULLETIN*, VOL. 125, NOS. 7–8; JULY 2013 (*map*); USGS *volcanoes.usgs.gov* AND "LARGE IGNEOUS PROVINCES AND MASS EXTINCTIONS: AN UPDATE," BY DAVID P. G. BOND AND PAUL B. WIGNALL, IN *GSA SPECIAL PAPERS*, VOL. 505; 2014 (*eruption volumes*)

SCIENTIFIC AMERICAN ONLINE Learn about the eruptions that were behind world's largest extinction at ScientificAmerican.com/mar2016/extinctions

Illustration by Emily Cooper


4 Sulfur dioxide reaches the stratosphere, where wind currents spread it around the globe. The chemical reflects sunlight away from Earth and cools the planet temporarily. Then it pours down as sulfuric acid rain, which can be as corrosive as battery acid.
5 Carbon dioxide from eruptions builds in the air, causing powerful global warming that lasts millennia. The gas also dissolves in seawater, causing ocean acidification. The warming oceans become oxygen-starved dead zones. Halocarbons from eruptions damage the ozone layer, exposing land life to harmful UV radiation. The combination is lethal for most land and marine life, and cataclysmic extinction is the result.
3 Acid fog from eruptions drifts thousands of miles, scorching organisms and blocking the sun. Baked sediments release huge amounts of climate-changing carbon dioxide and sulfur dioxide gases into the air. Heat creates violent air turbulence, perhaps fueling a fiery hurricane, a "hypercane."
Hypercane
2 Melting plumes and lithosphere chunks produce magma, which shoots up hundreds of fissures. It erupts in mile-high fountains, which feed lava flows that extend for hundreds of miles.
Upper crust
Lower crust
Lithosphere
Uppermost mantle
STAGES OF CATASTROPHE
1 The killer begins to form deep in Earth's interior, at the hot core-mantle boundary. Superheated mantle material and buried remnants of surface crust flow into a 500-mile-wide rising plume. After millions of years the plume arrives near the surface, at a layer called the lithosphere (*brown* and *gray*).
Plume
Core-mantle boundary (not shown)
BIGGEST BANGS
The amount of lava and ash released by four large igneous provinces dwarfs many large eruptions scientists have gauged, including Mount Pinatubo in 1991 and Mount St. Helens in 1980. Even Yellowstone's supervolcano 2.1 million years ago was much smaller.
Approximate Eruption Volumes
Mount St. Helens
0.25 cubic kilometer
Mount Pinatubo
5 km³
Yellowstone supervolcano
2,450 km³
Viluy Traps LIP
1 million km³
Deccan Traps LIP
2.5 million km³
Central Atlantic LIP
4 million km³
Siberian Traps LIP
4 million km³

EARLY HUMAN DEVELOPMENT is controlled in part by the polarity of newly formed cells. Electron micrographs show a cross section of a sperm still in the testis (*1*) and as it nears the much larger egg (*2*). At 22 days after fertilization, the cells of the neural crest (*yellow, 3*) have not yet joined to form the tube that gives rise to the brain and spine, which are distinctly visible at six weeks (*4*).

TO AVOID MISSHAPEN CREATURES, ONE SMALL SET OF GENES AND PROTEINS ENSURES THAT CELLS LINE UP TOGETHER PROPERLY

BIOLOGY

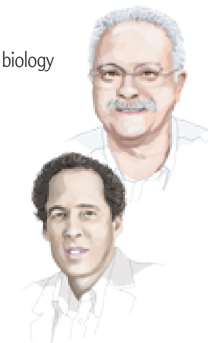
THE CELLULAR COMPASS

By Paul N. Adler and Jeremy Nathans

Building a body is not simple. Fish, frogs and people all start from a single cell that becomes, seemingly against many odds, a highly organized, very complicated creature. Fertilized eggs split into two cells that become four, then eight, 16 and—within a matter of weeks—tens of thousands of cells. By this point the original spherical ball has rearranged itself into an elongated shape, bulging rounder and thicker at one end, with a shallow furrow running along its length. Soon another astonishing cellular ballet begins. The furrow deepens, and the cells that make up its walls begin to lean toward one another until they touch and stick together, forming a long, hollow tube that will eventually give rise to the brain at the bulging end and the spinal cord at the other.

LENNART NILSSON TT

To assemble so precisely, these and other cells in the embryo must sense where they are in relation to the rest of the organism. Each cell needs to know where an animal's front, back, top and bottom are located. Each cell also must figure out which direction is closer to or farther from the rest of the body. We and other developmental biologists have spent the past few decades trying to understand how this cellular orientation system works. As part of this larger quest, we have discovered a key component that contains several proteins that function together as a miniature compass within each cell. Without this compass, the heart, lungs, skin and other organs could not develop properly. In humans, when one of these proteins is altered by mutation, serious birth defects are the result.



Paul N. Adler is a professor of biology at the University of Virginia.

Jeremy Nathans is a professor of molecular biology and genetics, neuroscience and ophthalmology at the Johns Hopkins University School of Medicine and an investigator at the Howard Hughes Medical Institute.

Although there is much that we still do not understand about how this orientation system functions, what we have discovered so far sheds new light on fundamental processes of development across the animal kingdom. So far we have learned the most about how the compass works in epithelial cells, which typically cover a tissue surface like flagstones on a sidewalk, forming layers that are just one cell in thickness. If the cotton sheet on a bed were made up of epithelial cells, the proteins that we and others have found would allow any given cell in the sheet to sense which of its sides is closer to the head or the foot of the bed.

Organisms with cells that know where they are within the body benefit from a distinct evolutionary advantage: their complex tissues no longer need to be symmetrical in all directions; different parts can specialize. The hairlike cilia at one end of the cochlear duct of the ear, for example, distinguish high-frequency sounds; those at the other end detect low-frequency sounds. Scientists refer to the ensuing asymmetry of the tissue layer as planar polarity because opposing poles can be seen through the plane of the tissues.

Once animals invented a tool that worked, they stuck with it. Like the genes that code for many regulatory proteins, the genes that code for planar polarity proteins are very similar among evolutionarily distant species. For example, the versions present in mammals are quite similar to those in insects. Not surprisingly, these genes are also ancient—having evolved more than 500 million years ago with the rise of the animal kingdom.

INSECTS LEAD THE WAY

MUCH OF WHAT WE KNOW about planar polarity stems from studies with insects that began in the mid-20th century. For convenience, these experiments focused on the easily accessible hard outer shell, or cuticle, found on most adult insects and not on internal organs. This hard outer layer is secreted by a layer of softer epidermal (skin) cells, which lies just underneath the cuticle.

When viewed through a microscope, the outer surface of the cuticle reveals a well-ordered landscape of ridges and scales dotted at regular intervals with hairs and bristles. Some of these protrusions are sensitive to changes in pressure or in the concentration of chemicals and thus help the creatures respond to their environment. Moreover, nearly every hair or bristle lines up in parallel with its nearest neighbors, so that all their tips tend to point in the same direction. On the wings, the hairs point away from the body. On the body itself, hairs and bristles point away from the head. Like the walls of a newly forming neural tube, these cells seem to know which way is back and front. They also appear to know which direction is closer to or farther from other tissues (proximal or distal, respectively).

Cells appear to share this directional information with one another, as demonstrated by Peter Lawrence of the University of Cambridge, the late Michael Locke of the University of Western Ontario and others in a series of pioneering experiments conducted more than 40 years ago. These scientists carefully cut out tiny squares of skin from the epidermal layer that gives rise to the exoskeleton in kissing bugs (the genus *Rhodnius*) and milkweed bugs (*Oncopeletus*). They then turned the squares 180 degrees and reimplanted them in the epidermis on the host insects' abdomen.

One might simply expect that the ridges or bristles on the cuticle that eventually formed from the turned-around graft to point in the opposite direction from the ridges or bristles surrounding it. But after the next molt, when the insects had shed their old exoskeleton and synthesized a new one, the researchers observed a striking change. Instead of lining up in opposite directions, the structures formed beautiful swirls across the borders of the transplanted square. The pattern of swirls suggested that neighboring cells had adjusted their orientations to minimize the differences between them. Clearly, the cells were able to communicate with one another about which direction their ridges and bristles should point. But how?

To reveal the underlying cellular and molecular machinery required a change in tactics—from surgical manipulations to a genetic approach. And when it comes to genetics, the best understood insect is the common fruit fly (*Drosophila melanogaster*), which has been studied in detail since 1910.

Starting in the 1980s, researchers, including one of us (Adler), began investigating tissue polarity in fruit flies. Our general approach was to identify and study mutant fruit flies with defects in the polarity system to deduce how it worked

IN BRIEF

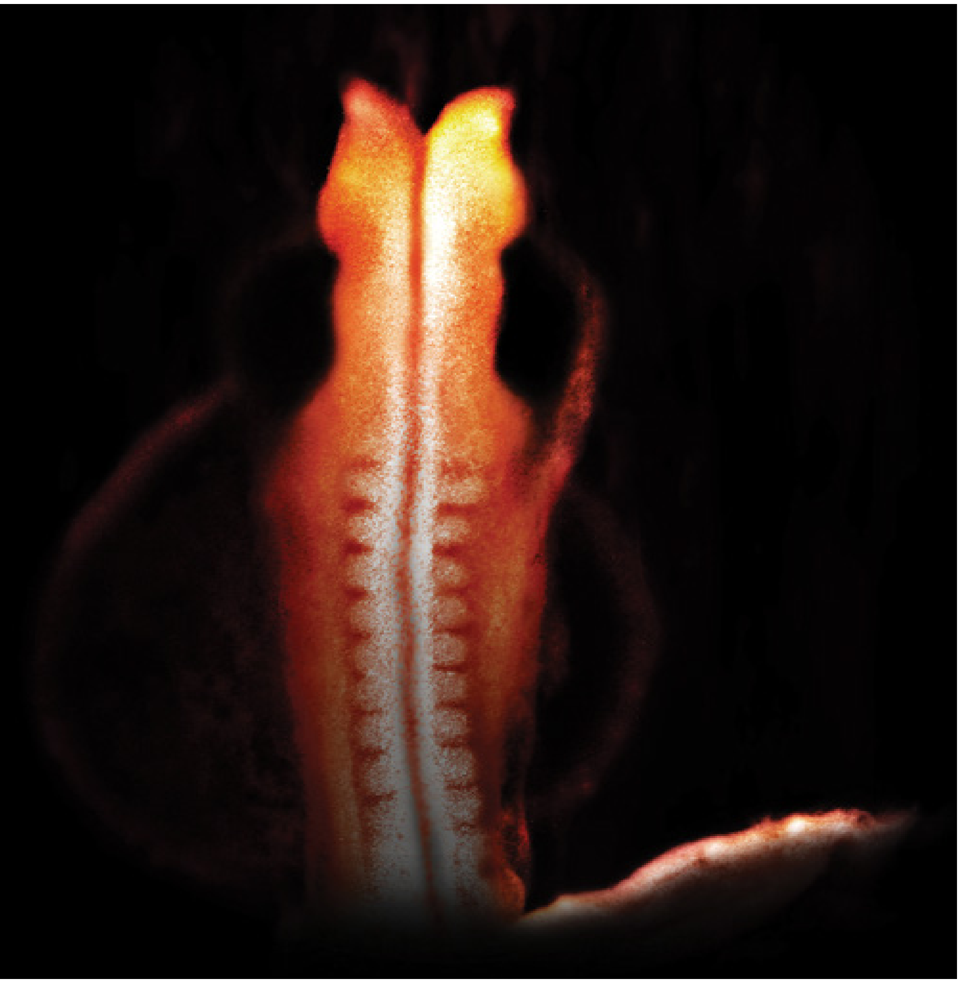
All animal cells need to know where they are located with regard to the rest of the body.

Over the past few decades researchers have identified a few key proteins that permit cells to sense in which direction an animal's front, back or head, among other things, lies.

These proteins are so important that the genes that code for them have not changed much in the more than half a billion years since they first evolved.

then a graduate student in Adler's laboratory, examined developing wings to see how the array of hairs were formed and how mutations in tissue polarity genes altered that process. Wong found that each epithelial cell formed a hair at its most distal edge and that mutations that altered polarity were associated with a shift in the site of hair formation. This result led Wong and Adler to hypothesize that polarity proteins are part of a pathway that regulates the architecture of the cytoskeleton, the meshwork of polymerized proteins that controls cell shape and movement.

Charles R. Vinson, also then a graduate student in the Adler lab, demonstrated local cell-to-cell signaling by creating small patches of *frizzled* mutant cells during the development of an otherwise normal wing. The mutant cells caused neighboring nonmutant cells farther away from the body to reorient their hairs approximately 180 degrees so that the hairs pointed back toward the mutant patch. The orientations of nonmutant cells that were at a greater distance from the mutant patch remained unaffected. Vinson and Adler interpreted this result to mean that the polarity system controls cell orientation with short-range signals and that there may be no need for a precise signal distributed over long distances—as might occur with a chemical gradient—to determine proper orientation.



CLOSE-UP: A computer-generated image highlights the neural folds of a 22-day-old human embryo. The knobs on both sides of the structure give rise to skeletal muscles and bones.

SCIENCE SOURCE

typically. We knew, for example, that the hairs on a *Drosophila* wing, like those on the abdomens of kissing and milkweed bugs, point in a uniform direction, in this case toward its farthest edge. Mutations in a gene called *frizzled,* however, made it look as though the fruit fly was having a bad hair day, with many hairs pointing in the wrong direction; changes in another gene, called *dishevelled,* caused a similar pattern, as its name suggests. This similarity was a clue that these different genes were part of a single system that controlled cell orientation.

Two groups—one led by David Gubb and Antonio García-Bellido, both then at the Autonomous University in Madrid, and the other by Adler—systematically studied how *frizzled* and *dishevelled* and other mutations affected the orientation of various parts of the fruit fly cuticle. Eventually we and others determined that in *Drosophila* six different genes code for proteins that serve as the key components of the polarity system. Two of these six, which Adler isolated in 1998, acted a lot like *frizzled.* Mutations in either of these genes resulted in a series of swirls that reminded him of the brushstrokes in Vincent van Gogh's paintings. So he named one gene *van Gogh* and the other *starry night.*

Another step in understanding the cellular basis for planar polarity in *Drosophila* came a few years earlier, when Lily Wong,

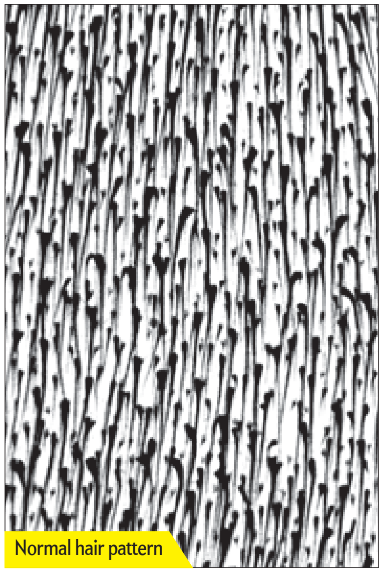
AN ATTRACTIVE MODEL

THE IDEA that polarity proteins might regulate the formation of the cytoskeleton led various researchers to try to figure out exactly where in the cell these proteins are distributed. It turns out that the polarity proteins are not evenly distributed, and thus they can affect different sides of the cell in different ways. By 2005 Tadashi Uemura of Kyoto University in Japan, Jeffrey Axelrod of Stanford University, Marek Mlodzik of the Icahn School of Medicine at Mount Sinai, and David Strutt and Helen Strutt of the University of Sheffield in England had revealed a series of striking patterns. For example, in the single layer of cells that forms the surface of a fruit fly wing, van Gogh proteins accumulate predominantly on the side of each cell closest to the body. In contrast, frizzled proteins accumulate predominantly on the side closer to the end of the wing. Starry night proteins are found on both sides of each cell.

The asymmetrical patterns suggested to us and others a working model for how the directional system works. The model postulates two types of interactions between the van Gogh and frizzled proteins—one that attracts them toward one another, and a second one that repels them away from one another. Van Gogh proteins found on the side of a wing cell closest to the

Tissue Organizers

Fish, birds and mammals all share a special feature when it comes to their skin. Whether covered by scales, feathers or hairs, the outermost layer of their body is organized into regular patterns that, among other things, allow the animals greater protection against the elements. These organizational features do not happen by accident. Researchers have isolated half a dozen genes that help cells sense directions so that they can follow specific patterns. Hair cells in a mouse, for example, grow in parallel to one another, as show in the photograph at the right. But when one of these directional genes (*Frizzled6*) is altered, the hairs grow in swirls, as in the photograph at the far right.



Normal hair pattern

Mutant hair pattern

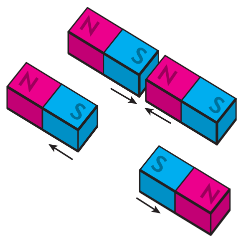
From Magnets to Cells: Defining Polar Opposites

Inspired by the way that magnets work, the authors suggest a possible explanation for how cells sense direction in complex tissues. Magnets align themselves in such a way that opposite poles (*visualized here as red* and *blue*) attract each other and like poles (*blue* and *blue*) repel each other.

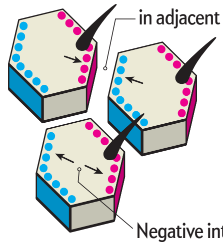
Perhaps something similar is happening in epithelial cells, which typically align themselves across a single layer. Certain direction-sensing proteins push each other apart (interact negatively) when found within the same cell but attract each other (interact positively) when found in adjacent cells (*far right*). These interactions create the blue and red regions depicted below.

As the proteins alternately push and pull each other from one row to the next, the pattern of asymmetry spreads until the entire layer is polarized.

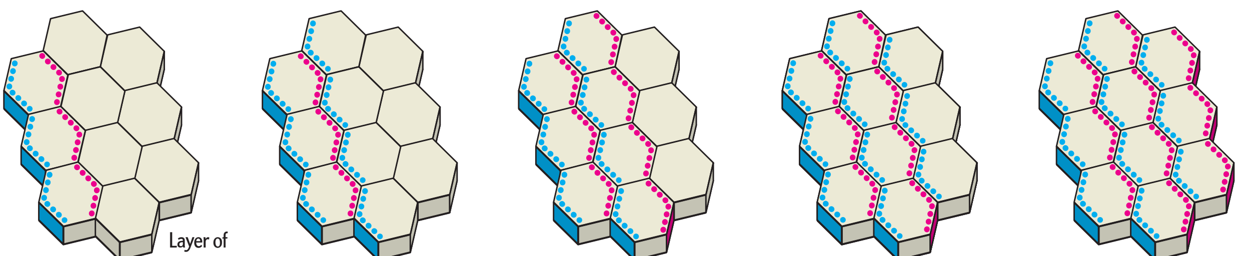
Polarity in Magnets



Polarity in Epithelial Cells



Propagation of the Polarity Pattern over Time →



body, for example, appear to attract frizzled proteins on the adjacent surface of a neighboring cell. Meanwhile, within each cell, frizzled and van Gogh proteins repel one another, so that they end up on opposite sides of the cell. At present, we do not know the mechanisms of the hypothesized attractive and repulsive forces, and this remains an area of intense investigation.

To see how this model works to spread directional signals among a group of cells, imagine looking down at a sheet made up of many rows of cells with planar polarity proteins that are more or less randomly distributed within each cell. Now place, on the proximal side of the sheet, a new row of cells in which the proteins are not randomly distributed; instead the frizzled proteins are lined up on the distal side, and the van Gogh proteins are lined up on the proximal side of the cells. The model predicts that the attractive forces between the frizzled proteins in the new first row of cells and the otherwise randomly distributed van Gogh proteins in their now second-row neighbors would pull more of the van Gogh proteins over to the proximal surface of the second row of cells [*see box above*].

Any frizzled proteins in the second row, however, would

COURTESY OF JEREMY NATHANS (*hair photographs*)

Illustration by Jen Christiansen

then begin to gather on the distal side of the cells, away from the van Gogh proteins accumulating on the proximal side. As the frizzled proteins would gather on the distal side of the second row of cells, they would attract van Gogh proteins on the adjoining proximal surface of the third row. Thus, the asymmetrical pattern of tissue polarity proteins would spread from one row of cells to the next throughout the sheet.

This model is consistent with a large body of experimental data. In particular, the model predicts that the patterns of protein asymmetry should be extremely stable because any wayward cell—that is, a cell with an incorrect pattern of polarity protein accumulation—will be nudged back into the right orientation by signals from its proximal and distal neighbors. In this way, each cell creates its own compass, which defines its orientation and also influences the orientations of its neighbors.

Organisms with cells that know where they are within the body have an evolutionary advantage: their complex tissues no longer need to be symmetrical in all directions; they can specialize.

VARIATIONS ON A THEME

INSECTS, OF COURSE, are not the only animals that exhibit planar polarity. Inspired by the *Drosophila* experiments of Gubb and Adler, researchers (including Nathans) began looking for planar polarity genes in vertebrates. These experiments, and subsequent large-scale sequencing studies of various genomes, uncovered remarkably similar polarity genes throughout the animal kingdom. Interestingly, there appear to be no similar genes in plants, implying that the beautiful patterns of flowers and other plant organs are programmed by entirely different polarity systems.

For reasons that remain unclear, mammals have multiple versions of each *Drosophila* polarity gene. For example, humans and other mammals have three different *starry night* genes, whereas fruit flies have only one. *Frizzled* and *dishevelled* genes come in multiple copies as well.

Nathans has been particularly interested in teasing out the details of the planar polarity system in mammals. As with the earlier insect experiments, different structures within the skin—in this case, hairs—proved to be the best and most accessible place to start.

In contrast to the fly wing, where each cell produces one hair, each mammalian hair emerges from a follicle that is composed of dozens to hundreds of cells. Moreover, unlike the neighboring cells on an insect's wings, mammalian hair follicles do not touch one another directly; neighboring hair follicles are usually separated by many dozens of skin cells. Despite these differences in surface structures between insects and mammals, the results of eliminating polarity genes are quite similar. In 2004 Nino Guo, then a graduate student in Nathans's laboratory, used genetic engineering methods to eliminate the *Frizzled6* gene in mice. Guo and Nathans were surprised to see that the hair follicles on the mutant mice were no longer parallel to one another but had reoriented to create a series of whorls reminiscent of the patterns seen on the mutant *Drosophila* wings [*see box on opposite page*].

Perhaps the biggest surprise occurred, however, when Nathans's lab started looking at how neurons in the mammalian brain are connected to one another. The major pathways in this complex network are laid down during embryonic development—as individual neurons send out axons (the "wires" that mediate long-range communication in the brain) that grow along predefined routes toward their targets. Nathans and his colleague, Yanshu Wang of Johns Hopkins University School of Medicine, found that *Frizzled3* plays an essential role in guiding axons through the maze of embryonic neural tissue. When the researchers produced mice that lacked a *Frizzled3* gene, the axons could no longer find their way and began following aberrant trajectories. Nathans's group then decided to test whether the *Frizzled6* gene, which was so important to hair patterns, could take the place of *Frizzled3,* and vice versa. Using genetically engineered mice, the team found that *Frizzled3* was fully capable of replacing *Frizzled6,* resulting in normal hair patterns. Yet *Frizzled6* could partially but not fully replace *Frizzled3* in directing the growth of axons. Thus, the polarity systems found in the skins and brains of mice are similar but not identical.

The resulting polarity systems play an important role in the existence of all vertebrates (including humans), from the earliest days of embryonic life to our every breathing moment, when the cilia in our airways propel any accumulating mucus in just one direction—up and out of the chest. As researchers obtain ever greater insights into the ways that individual cells sense their place in the body plan, we are continually amazed by the beauty of embryonic development. Among the many genetic changes that gave rise to the incredible diversity within the animal kingdom was a group of polarity-signaling genes. This set of genes—and their associated proteins—proved so successful over the past half a billion years that complex animals have used them ever since to solve a wide variety of evolutionary challenges. SA

MORE TO EXPLORE

When Whorls Collide: The Development of Hair Patterns in Frizzled 6 Mutant Mice. Yanshu Wang, Hao Chang and Jeremy Nathans in *Development,* Vol. 137, No. 23, pages 4091–4099; December 1, 2010.

Planar Signaling and Morphogenesis in Drosophila. Paul N. Adler in *Developmental Cell,* Vol. 2, No. 5, pages 525–535; May 2002.

FROM OUR ARCHIVES

The Molecular Architects of Body Design. William McGinnis and Michael Kuziora; February 1994.

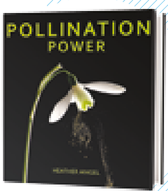
scientificamerican.com/magazine/sa

By Clara Moskowitz

MORE TO EXPLORE
FOR MORE BOOK RECOMMENDATIONS, VISIT
SCIENTIFICAMERICAN.COM/MAR2016/RECOMMENDED

Pollination Power

by Heather Angel. University of Chicago Press, 2016 ($40)



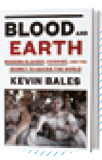
Photographer Angel has traveled the world to document how plants attract pollinators. Her mesmerizing images showcase magenta hibiscus trumpets in Hawaii, stubbly Arabian starflower stamens and pollen-covered bees in Tajikistan, as well as beetles, butterflies and birds swooping in to feed. Angel's words highlight the various ways flowers communicate with such creatures. For instance, some plants change color to signal that their pollen is ready, and others open and close petals with precise timing to allow and deny entry. The photographs and text are all tied together in a gorgeous large-format book.

HUMMINGBIRD HAWK MOTH sips nectar from a loofah flower in Xinjiang, China.

HEATHER ANGEL

Blood and Earth: Modern Slavery, Ecocide, and the Secret to Saving the World

by Kevin Bales. Spiegel & Grau, 2016 ($27)

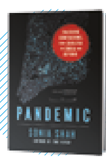


The terrible evil of slavery still haunts the world. A seven-year exploration of modern slavery—from forced labor to pay off debts to outright bondage—finds it inextricably interwoven with some of the worst environmental destruction on the planet. Activist and writer Bales's powerful book shows how slavery is involved in harvesting shrimp and gathering the wood in the tables it is served on and even in the mining that enables manufacture of the world's favorite gadget: the cell phone. This ubiquity, Bales shows, means that all of us have a role to play in ending slavery and that doing so will also help remedy some of the biggest environmental challenges on earth, such as climate change. "There's always been a moral case for stopping slavery," he writes. "Now there's an environmental reason too."

—David Biello

Pandemic: Tracking Contagions, From Cholera to Ebola and Beyond

by Sonia Shah. Sarah Crichton Books, 2016 ($26)



A pandemic is the worst kind of disease eruption—one not just isolated to a single community (an outbreak) or even a region (an epidemic) but a sickness that spreads the world over. To clarify how these plagues take such wide hold, journalist Shah tracks the history and science of past pandemics. By weaving historical evidence, expert analysis and personal anecdote (including her travels in cholera-stricken Haiti), Shah shows how political and practical factors, such as city crowding and lack of infrastructure, have paved the way for global sicknesses. She uses cholera, responsible for seven pandemics in the past two centuries, as a case study. Rather than waging war against a pandemic after it is already full-blown, Shah argues, we must focus on proactive defenses against disease to prevent the next blow.

—Jennifer Hackett

Seven Brief Lessons on Physics

by Carlo Rovelli. Riverhead Books, 2016 ($18)

This small book—fewer than 100 pages—contains some large ideas. In a series of translated essays first published in an Italian newspaper, theoretical physicist Rovelli, one of the founders of a popular theory called loop quantum gravity, explains the major concepts of modern physics. His concise and comprehensible writing makes sense of intricate notions such as general relativity, quantum mechanics, cosmology and thermodynamics. Rovelli's enthusiastic and poetic descriptions communicate the essence of these topics without getting bogged down in details.

He also comments on the scientific merit of humility, noting that Albert Einstein began an early passage in a seminal paper on the quantization of light with the phrase "It seems to me" and that Charles Darwin introduced some of his great ideas on evolution with the words "I think"—sentiments that Rovelli sums up by observing, "Genius hesitates."

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

Left Behind

Political bias troubles the academy

By Michael Shermer

In the past couple of years imbroglios erupted on college campuses across the U.S. over trigger warnings (for example, alerting students to scenes of abuse and violence in *The Great Gatsby* before assigning it), microaggressions (saying "I believe the most qualified person should get the job"), cultural appropriation (a white woman wearing her hair in cornrows), speaker disinvitations (Brandeis University canceling plans to award Ayaan Hirsi Ali an honorary degree because of her criticism of Islam's treatment of women), safe spaces (such as rooms where students can go after a talk that has upset them), and social justice advocates competing to signal their moral outrage over such issues as Halloween costumes (last year at Yale University). Why such unrest in the most liberal institutions in the country?

Although there are many proximate causes, there is but one ultimate cause—lack of political diversity to provide checks on protests going too far. A 2014 study conducted by the University of California, Los Angeles, Higher Education Research Institute found that 59.8 percent of all undergraduate faculty nationwide identify as far left or liberal, compared with only 12.8 percent as far right or conservative. The asymmetry is much worse in the social sciences. A 2015 study by psychologist José Duarte, then at Arizona State University, and his colleagues in *Behavioral and Brain Sciences,* entitled "Political Diversity Will Improve Social Psychological Science," found that 58 to 66 percent of social scientists are liberal and only 5 to 8 percent conservative and that there are eight Democrats for every Republican. The problem is most relevant to the study of areas "related to the political concerns of the Left—areas such as race, gender, stereotyping, environmentalism, power, and inequality." The very things these students are protesting.

How does this political asymmetry corrupt social science? It begins with what subjects are studied and the descriptive language employed. Consider a 2003 paper by social psychologist John Jost, now at New York University, and his colleagues, entitled "Political Conservatism as Motivated Social Cognition." Conservatives are described as having "uncertainty avoidance," "needs for order, structure, and closure," as well as "dogmatism and intolerance of ambiguity," as if these constitute a mental disease that leads to "resistance to change" and "endorsement of inequality." Yet one could just as easily characterize liberals as suffering from a host of equally malfunctioning cognitive states: a lack of moral compass that leads to an inability to make clear ethical choices, a pathological fear of clarity that leads to indecisiveness, a naive belief that all people are equally talented, and a blind adherence in the teeth of contradictory evidence from behavior genetics that culture and environment exclusively determine one's lot in life.

Duarte et al. find similar distortive language across the social sciences, where, for instance, certain words are used to suggest pernicious motives when confronting contradictory evidence—"deny," "legitimize," "rationalize," "justify," "defend," "trivialize"—with conservatives as examples, as if liberals are always objective and rational. In one test item, for example, the "endorsement of the efficacy of hard work" was interpreted as an example of "rationalization of inequality." Imagine a study in which conservative values were assumed to be scientific facts and disagreement with them was treated as irrational, the authors conjecture counterfactually. "In this field, scholars might regularly publish studies on … 'the denial of the benefits of a strong military' or 'the denial of the benefits of church attendance.'" The authors present evidence that "embedding any type of ideological values into measures is dangerous to science" and is "much more likely to happen—and to go unchallenged by dissenters—in a politically homogeneous field."

Political bias also twists how data are interpreted. For instance, Duarte's study discusses a paper in which subjects scoring high in "right-wing authoritarianism" were found to be "more likely to go along with the unethical decisions of leaders." Example: "not formally taking a female colleague's side in her sexual harassment complaint against her subordinate (given little information about the case)." Maybe what this finding really means is that conservatives believe in examining evidence first, instead of prejudging by gender. Call it "left-wing authoritarianism."

The authors' solution to the political bias problem is right out of the liberal playbook: diversity. Not just ethnic, race and gender but viewpoint diversity. All of us are biased, and few of us can see it in ourselves, so we depend on others to challenge us. As John Stuart Mill noted in that greatest defense of free speech, *On Liberty,* "He who knows only his own side of the case, knows little of that." SA

SCIENTIFIC AMERICAN ONLINE
COMMENT ON THIS ARTICLE AT
SCIENTIFICAMERICAN.COM/MAR2016

Illustration by Izhar Cohen

ANTI GRAVITY
THE ONGOING SEARCH FOR FUNDAMENTAL FARCES

Steve Mirsky has been writing the Anti Gravity column since a typical tectonic plate was about 35 inches from its current location. He also hosts the *Scientific American* podcast Science Talk.

Fuzzy Math

Facial hair illustrates an inequality in American medicine

By Steve Mirsky

Back in the early 2000s, evolution deniers were fond of publishing lists of scientists who doubted Charles Darwin's discovery. Hey, you can always find a few dozen Ph.D.s who, like the Scarecrow at the end of *The Wizard of Oz,* have a diploma instead of an education. So in 2003 the National Center for Science Education, which champions evolution instruction in public schools, published a statement with its own list of 220 Ph.D.s who accept evolution—all named Steve.

You see, with only about 1 percent of Americans named Steve, the 220 signatories thus represented more than 20,000 scientists. And the number who have signed on to what's called

Project Steve, partly to honor evolutionary biologist Stephen Jay Gould, continues to grow. As of late 2015, the Steves had reached 1,382, including Nobel laureates Steven Chu and Steve Weinberg. (I would gladly be a signatory were I allowed, but I'm ineligible. Because I don't have a doctorate. Not because of some false fealty to journalistic objectivity that would require me to claim no position regarding reality. That stance would make me this Stevie skeevy.)

Now comes a new effort to illustrate a point by pitting apples against a tiny subset of oranges: researchers compared the number of women in leadership positions in American medical academia with the number of men with mustaches in those roles. The study was in the infamous Christmas issue, which always features lippy research, of the *BMJ* (known in a less hurried age as the *British Medical Journal*). (And hence, both American mustaches and British moustaches to come.)

You can see where we're going here, but I'll tweeze out some details. The researchers looked at the heads of more than 1,000 departments of 50 top U.S. medical schools. "For each department leader we determined the URL of their institutional website and identified medical specialty, institution, name, and sex," the investigators wrote. Then they looked at the heads of the heads: "To be included, leaders had to have a photo available on the webpage so we could check the presence and type of facial hair."

To properly count mustaches, they established classification parameters: "We defined a moustache as the visible presence of hair on the upper cutaneous lip and included both stand alone moustaches (for example, Copstash Standard, Pencil, Handlebar, Dali, Supermario) as well as moustaches in combination with other facial hair (for example, Van Dyke, Balbo, the Zappa). Department leaders with facial hairstyles that did not include hair on the upper lip (for example, Mutton Chops, Chin Curtain) were considered not to have a moustache." The journal article included a helpful chart with 33 different furry faces that could also be posted at barbershops for patrons to point at and say, "I wanna look like that guy." And because assumptions can poison the well of scientific investigation, the researchers declared: "We evaluated each leader for the presence of facial hair regardless of sex."

The authors noted that for the past 15 years women have made up almost half of all U.S. medical students, and their best estimate was that fewer than 15 percent of all men, whatever their job, wear mustaches. Nevertheless, they found that medical school departments were significantly more likely to be run by a mustachioed individual, who was almost certainly a man, than by a woman.

The research team also established an "overall moustache index," which has nothing to do with med school bigwigs who wear both mustaches and overalls. By the way, that combo is not as nutty as it might sound—I knew a big, bearded biophysicist at one of the institutions included in this study who almost always wore a pair of overalls to the lab. Denim, if memory serves.

No, the overall mustache index is in fact a ratio of women to mustaches. And the study found its value to be 0.72. "We believe," the researchers said, "that every department and institution should strive for a moustache index [of at least] 1. There are two ways to achieve this goal: by increasing the number of women or by asking leaders to shave their moustaches." After weighing those choices, they said that the only real option for deans was "to hire, retain, and promote more women." In fact, anything less should make us all bristle. SA

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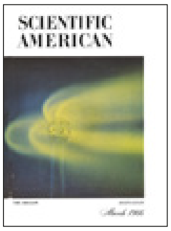
INNOVATION AND DISCOVERY AS CHRONICLED IN *SCIENTIFIC AMERICAN*

Compiled by Daniel C. Schlenoff



March 1966

The Race to the Moon

"The surface of the moon appears to be quite solid and unexpectedly low in radioactivity. These are the two chief scientific findings to come out of the successful Soviet 'soft landing' of an unmanned spacecraft on the moon on February 3. According to Academician Nikolai Barabashov, a leading Soviet selenologist, the Luna 9 photographs 'proved beyond doubt that the upper layer of the lunar soil is a spongelike, rough-textured mass scattered with individual sharp-edged fragments of various sizes.' The long-standing question of whether or not this layer is strong enough to support heavy objects appears to have been settled. Soviet workers charged with analyzing the photographs point out that the 220-pound Luna 9 instrument package 'did not sink into the soil to any substantial degree.'"

North Sea Oil

"The most active area of oil and gas exploration in the world is now the North Sea and its environs. The special inducement is the prospect of finding large fuel deposits in immediate proximity to major markets and in a region of relative political stability. Writing in the *Geographical Review,* Trevor M. Thomas points out that there are in the North Sea salt domes of the type that provide the structural basis of much of the oil entrapment in the Gulf of Mexico region. Extensive magnetic and seismic surveys have been carried out at sea by a large number of companies. According to Thomas, the work is extremely speculative, but it seems likely that valuable deposits will be found."

March 1916

Naval Aviation Takes Off

"The seaplane as a naval scout should be able to operate from a moving ship as a base, and to do this with much the same indifference to the state of the weather as its fellow aeroplane in the military service. Thanks to the initial work of Captain Washington I. Chambers, U.S.N., a short-run catapulting railway is placed permanently aboard the U.S.S. 'North Carolina.' It is from this ship that seaplanes have repeatedly been launched [*see illustration*] in the past few weeks in the open sea and with the armored cruiser under way."

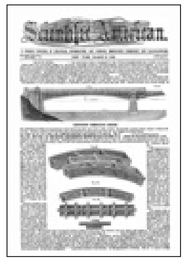
More images of naval technology in 1916 are at www.ScientificAmerican.com/mar2016/naval-technology

Seaplane launched from an American cruiser at sea, **1916**

SCIENTIFIC AMERICAN, VOL. CXIV, NO. 12; MARCH 18, 1916

Taming Nature's Fury

"The period of stormy weather in the Netherlands which set in around Christmas was marked by a terrific gale on the night of the 13th and 14th of January. On that night of terror, the calamity that befell the southern portion of the Province of North Holland is the worst of all—far worse than can be remembered to have ever happened since the fearful St. Elizabeth flood in 1421, when 10,000 people were drowned, and it must be entirely placed to the credit of better organization of help, better roads, better telegraphic and telephonic communication and railway service, that on this occasion the victims are numbered only by tens instead."



March 1866

Unregulated Food

"*Trichina spiralis* is a small microscopic worm or animalcule, which is found in the muscles and intestines of various animals, especially pigs and rabbits, in enormous quantities. We learn by the London *Lancet* that at Hedersleben, in Prussian Saxony, upward of ninety deaths have occurred from this disease. All this havoc has been caused by one trichinous pig! The butcher, having recognized the abnormal appearance of the meat of this pig, had carefully disguised it by mixing it with the meat of two healthy pigs. He made this confession shortly before his death, which was caused by trichiniasis contracted from his own meat. His wife also died of the disease."

Geologic Periods

"All the facts of geology tend to indicate an antiquity of which we are beginning to form but a dim idea. Take, for instance, our well-known chalk. This consists entirely of shells and fragments of shells deposited at the bottom of an ancient sea. Such a process as this must be very slow; probably we should not be much above the mark if we were to assume a rate of deposition of ten inches a century. Now the chalk is more than 1,000 feet in thickness, and would have required, therefore, more than 120,000 years for its formation."

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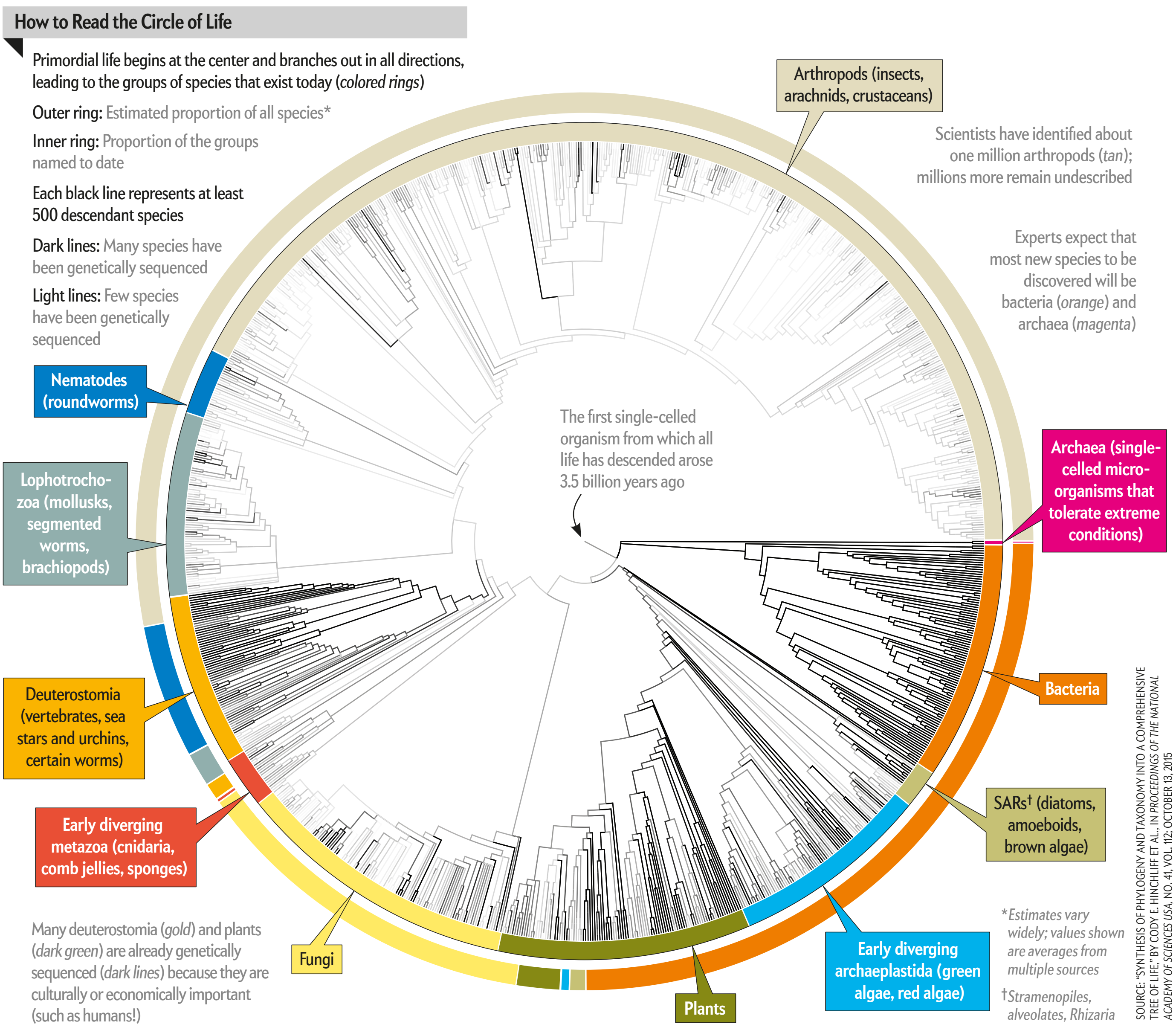
FOR MORE ON RAPIDLY EXPANDING TREES OF BACTERIAL LIFE, GO TO SCIENTIFICAMERICAN.COM/MAR2016/GRAPHIC-SCIENCE

The Circle of Life

Lineages of all known species on earth are finally pieced together

Since Charles Darwin's day, biologists have depicted how new organisms evolve from old ones by adding branches to numerous trees that represent portions of the animal, plant and microbial kingdoms. Researchers from a dozen institutions recently completed a three-year effort to combine tens of thousands of trees into one diagram, most readable as a circle (*below*). The lines inside the circle represent all 2.3 million species that have been named. Biologists have genetic sequences for only about 5 percent of them, however; as more are finished, the relationships within and across groups of species may change. Experts estimate that up to 8.7 million species may inhabit the planet (about 15,000 are discovered every year). "We expect the circle to broaden," says Karen Cranston, a computational evolutionary biologist at Duke University.

Anyone can propose updates to the database (OpenTreeOfLife.org). Greater detail could improve understanding of evolution and help scientists invent drugs, make crops more productive and better control infectious diseases. —*Mark Fischetti*



SOURCE: "SYNTHESIS OF PHYLOGENY AND TAXONOMY INTO A COMPREHENSIVE TREE OF LIFE," BY CODY E. HINCHLIFF ET AL., IN *PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES USA*, NO. 41, VOL. 112; OCTOBER 13, 2015

Graphic by Stephen Smith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Preproduction model shown. Available spring 2016.