ORGAN REPAIRS
The forgotten compound that can repair damaged tissue PAGE 56

DENGUE DEBACLE
A vaccination program gone wrong PAGE 38

HOW EELS GET ELECTRIC
Insights into their shocking attack mechanisms PAGE 62

SCIENTIFIC AMERICAN

MIND READER

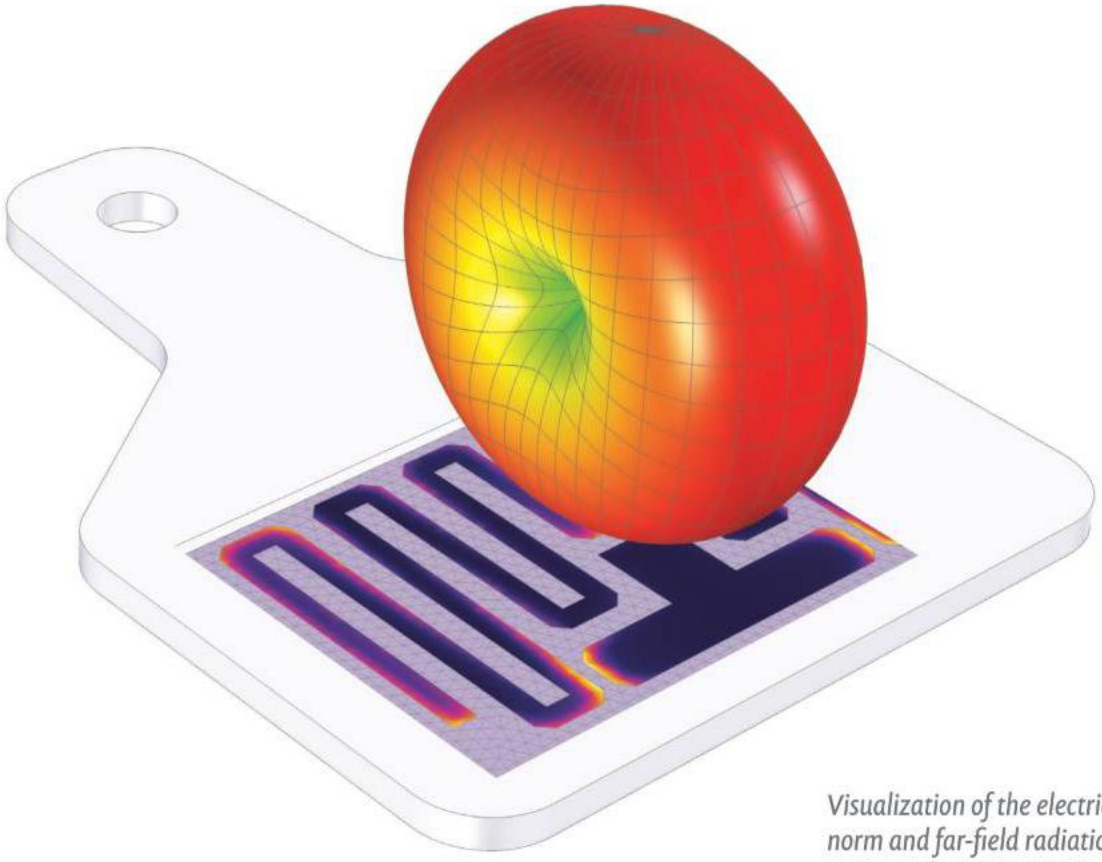
A new brain-machine interface detects what the user wants

PLUS

QUANTUM GRAVITY IN A LAB
Could new experiments pull it off? PAGE 48

APRIL 2019
ScientificAmerican.com

Smartphones, smart homes, smart...healthcare?



Visualization of the electric field norm and far-field radiation pattern of a UHF RFID tag.

RFID tags are used across many industries, but when it comes to healthcare, there is a major design challenge: size. If wearable RFID tags are too big and bulky, they could cause patient discomfort. Or, if the tag is for a biomedical implant, it has to be smaller than a grain of rice! Design engineers can optimize the size of an RFID tag for its intended purpose using RF simulation.

The COMSOL Multiphysics® software is used for simulating designs, devices, and processes in all fields of engineering, manufacturing, and scientific research. See how you can apply it to designing RFID tags.

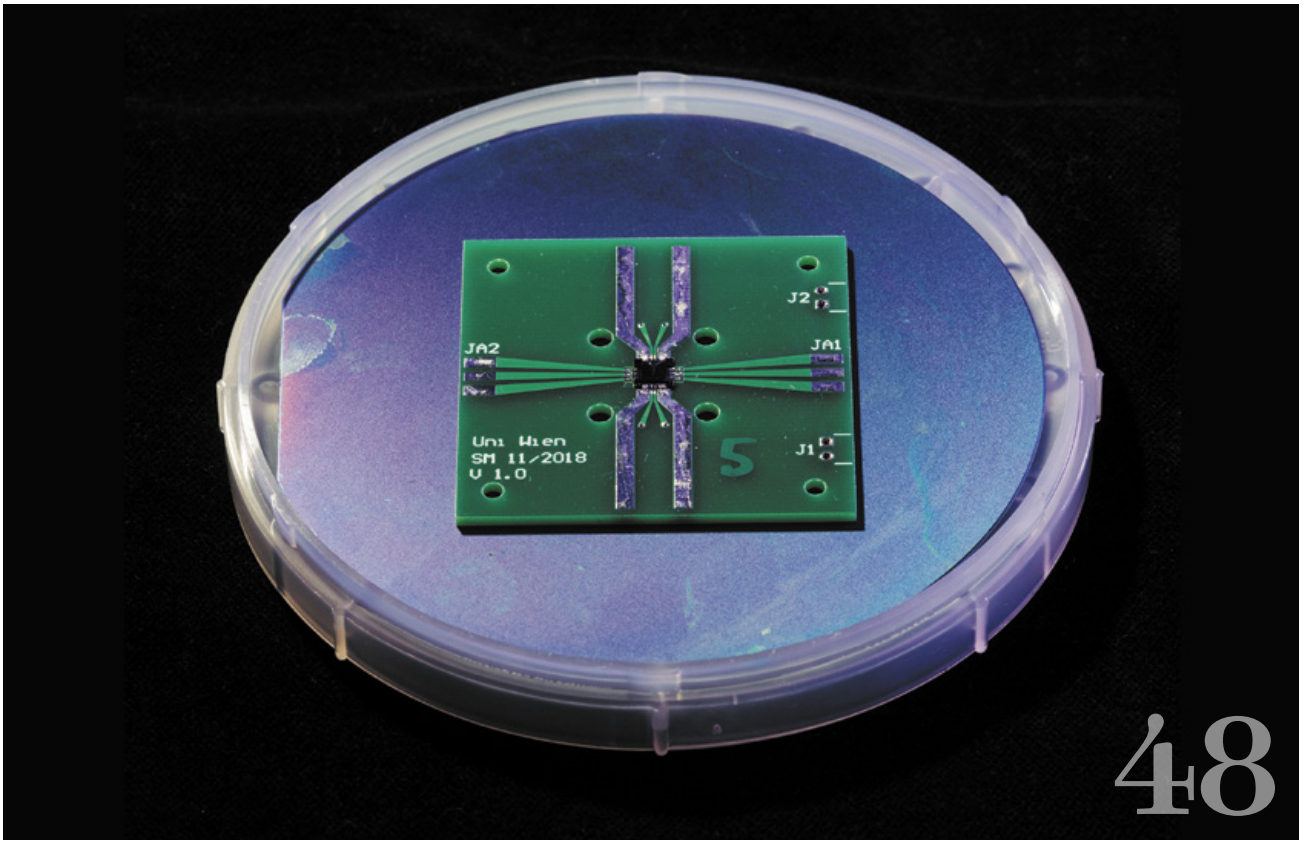
comsol.blog/biomed-RFID-tags

COMSOL

APRIL 2019

VOLUME 320, NUMBER 4

SCIENTIFIC AMERICAN



48

ON THE COVER
Tapping into the brain's neural circuits lets people with spinal cord injuries manipulate computer cursors and robotic limbs. Early studies underline the need for technical advances that make brain-machine interfaces faster and more versatile. The latest versions may begin to realize the promise of direct neural communication. **Illustration by Mark Ross.**

Photograph by Mattia Balsamini

SCIENTIFIC AMERICAN

10

20

76

ON THE WEB

A New Era of Human Spaceflight
Rockets and spacecraft built by SpaceX and Boeing are set to transport U.S. astronauts to the International Space Station. *Scientific American* details the rise of "New Space."
Go to www.ScientificAmerican.com/apr2019/new-space

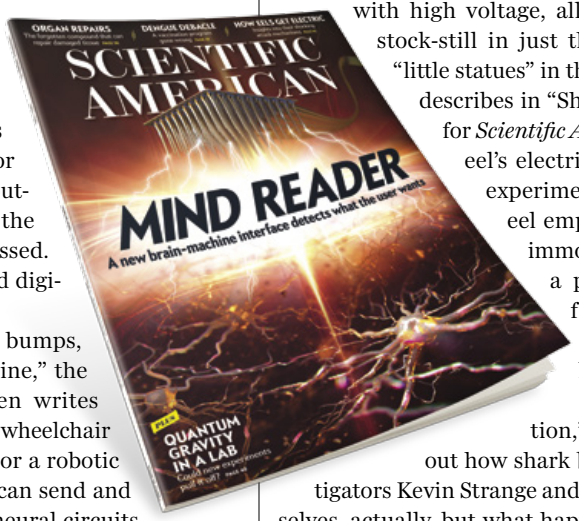
Scientific American (ISSN 0036-8733), Volume 320, Number 4, April 2019, published monthly by Scientific American, a division of Springer Nature America, Inc., 1 New York Plaza, Suite 4600, New York, N.Y. 10004-1562. Periodicals postage paid at New York, N.Y., and at additional mailing offices. Canada Post International Publications Mail (Canadian Distribution) Sales Agreement No. 40012504. Canadian BN No. 127387652RT; TVQ1218059275 TQ0001. Publication Mail Agreement #40012504. Return undeliverable mail to Scientific American, P.O. Box 819, Stn Main, Markham, ON L3P 8A2. **Individual Subscription rates:** 1 year $49.99 (USD), Canada $59.99 (USD), International $69.99 (USD). **Institutional Subscription rates:** Schools and Public Libraries: 1 year $84 (USD), Canada $89 (USD), International $96 (USD). Businesses and Colleges/Universities: 1 year $399 (USD), Canada $405 (USD), International $411 (USD). Postmaster: Send address changes to Scientific American, Box 3187, Harlan, Iowa 51537. **Reprints inquiries: (212) 451-8415. To request single copies or back issues, call (800) 333-1199. Subscription inquiries: U.S. and Canada (800) 333-1199; other (515) 248-7684. Send e-mail to scacustserv@cdsfulfillment.com.**

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

The Joy of Science

"I get goose bumps every time I see it." "I saw something so strange that I had to drop everything else to investigate." "A tale of shark bites at a Scottish pub has led us to some new ideas about rebuilding broken bodies."

Those sentences appear in three of the feature articles in this issue written by the researchers who are doing the work. As a culture, we often focus on the achievements of science. But for me, the stories of how we got to those outcomes—including the side tracks and the bumps in the road—are not to be missed. And you can find them in our print and digital editions.



What gives a neuroscientist goose bumps, for instance? In "The Intention Machine," the issue's cover story, Richard Andersen writes about watching a paralyzed person in a wheelchair using thoughts to control a computer or a robotic limb. These brain-machine interfaces can send and receive communications to and from neural circuits in the body. Whereas existing interfaces are imprecise or sluggish, newer versions could be placed in brain areas that would allow them to deduce a person's intentions to move. That would make them more versatile for individuals with certain injuries. Andersen's feature starts on page 24.

What was so strange a biologist had to drop other things to check it out? Kenneth C. Catania explains the allure of the electric eel's shocking attacks. As an eel hit a prey fish in a tank with high voltage, all the other nearby fish became stock-still in just three milliseconds, floating like "little statues" in the water. "I was hooked," Catania describes in "Shock and Awe," his fourth article for *Scientific American*. "I had to know how the eel's electric attack worked." In a series of experiments, he has discovered how the eel employs electric fields to track and immobilize prey. When threatened by a potential predator, it can leap from the water to intensify the current delivered. You can learn how by turning to page 62.

Dive into "A Shot at Regeneration," beginning on page 56, to find out how shark bites drew the attention of investigators Kevin Strange and Viravuth Yin: not the bites themselves, actually, but what happened to the wounded dolphins afterward. Strange and Yin heard a story about how dolphins were beset by sharks, receiving bite wounds "45 centimeters long and 12 centimeters deep. But remarkably the dolphins healed up in weeks, with no signs of infection." What could heal tissue so quickly? I won't spoil the surprise. SA

COVER IMAGE BY MARK ROSS

Illustration by Nick Higgins

December 2018

"All technologies must be evaluated in the current reality that anything that can be exploited for a profit probably will, regardless of the dangers."

GEOFF DAVIES
AUSTRALIAN NATIONAL UNIVERSITY

TALES OF ENTANGLEMENT

"Spooky Action," by Ronald Hanson and Krister Shalm, discusses quantum entanglement, in which two particles exhibit a "spooky" connection regardless of distance.

The authors do not explain why something as nonspooky as the following can't be going on: Suppose I hide a pair of gloves in two different envelopes and send one (without knowing which) to my friend on Mars, with a note to open it on receipt. The envelopes are now "entangled" because if my friend finds a left glove, then I will find a right glove, and vice versa—before a light signal has had time to travel to Earth.

GORDON B. HAZEN *Professor emeritus of industrial engineering and management sciences, Northwestern University*

The article made this old sci-fi fan's imagination run wild. Do we know that entangled particles are "monogamous"? If an electron can be entangled with one partner, why not multiple partners simultaneously? Could entanglement be a relationship among a large number of particles independent of location? And if so, could manipulating allow for truly instant messaging across interstellar distances?

BOB MORRISON *Asheboro, N.C.*

THE AUTHORS REPLY: Regarding Hazen's suggestion: Just as "correlation does not imply causation," it does not always imply entanglement. The nonspooky correlation of the two gloves is determined the moment they are placed in their envelopes and is an example of a "hidden variable theory." John Bell showed that any such theory will not have correlations that are as rich as those allowed by quantum entanglement. In our experiments, once our particles are sent to their distant locations, they are randomly measured in one of two ways. Because the particles do not know in advance how we are measuring them, they cannot agree ahead of time how to correlate their outcomes. It appears as if measuring one particle randomly and instantaneously influences its distant partner, which is the spookiness that Albert Einstein referred to.

In answer to Morrison: It is possible to entangle many different particles with one another, and this is an active area of research—for instance, for building quantum computers. But if two particles are maximally entangled, there can be no entanglement with any other particles at the same time. In that sense, entanglement is indeed monogamous, which ensures a level of privacy that is unmatched in classical physics and is at the heart of quantum applications in secure communication.

Alas, faster-than-light communication must remain science fiction. With entanglement, the outcome is random but correlated. Let's say you and a distant friend share entangled electrons and have agreed that if they are measured to be "up," that means "yes," whereas "down" means "no." Your partner will get the same result as you, so the electrons appear to have somehow influenced one another faster than the speed of light. But there is no way to force your electron to be "up" to send a "yes" response. When it is measured, the electron, not you, will "choose" with a 50 percent probability of whether it will be up or down. It is no better than flipping a coin.

WISE TECHNOLOGIES

In "Sacred Groves," Madhav Gadgil discusses the ecological benefits of areas of primeval forest in India protected as the homes of deities. Gadgil illustrates how the sacred in traditional cultures can transmit practical wisdom distilled from bitter experience, which we need to help save our planet. Such perspectives make me less sanguine about the technologies *Scientific American* often features. I appreciate the lure of discovery, having had a 40-year career in the physics of the earth, but not everything we might create ought to be created. All technologies must be evaluated in the current reality that anything that can be exploited for a profit probably will, regardless of the dangers.

The greatest service to humanity at the moment would be rendered not by implementing technical innovations of uncertain benefit but by gaining the emotional maturity to appreciate and act on the kind of wisdom portrayed in "Sacred Groves."

GEOFF DAVIES *Retired senior fellow, Australian National University*

OCEAN CONSERVATION

In "The Last of the Ocean Wilderness" [Forum], Kendall Jones and James Watson raise the point that we have depleted about "90 percent of formerly important coastal species" and that any conservation agreements should set wilderness-retention targets. But their recommendation does not go far enough. I think to be successful over the short and the long term, we must also spearhead public campaigns that identify overexploited ocean species, explain what classifies as pollution and how it can affect ocean life, and make a list of recommended actions geared toward the average consumer. And we should monitor overfishing or illegal fishing by enforcing existing legislation; using nontransferable unique numbers to tag fishing vessels; encouraging seafood traceability through documentation; and monitoring vessels via inspection stations, drones and satellites.

VASILIOS VASILOUNIS *Brooklyn, N.Y.*

ATTRIBUTION LEERY

Please refrain from misattributing popular sayings to celebrities. "Rethinking the 'Anthropocene,'" by the Editors [Science Agenda], quotes Albert Einstein as asserting, "We cannot solve our problems with the same thinking we used when we created them." There is no evidence that Einstein said or wrote those words. The nearest we come seems to be a passage in a 1948 essay in which he argued that a "supranational organization" should be given sole authority over atomic weapons: "Our situation is not comparable to anything in the past. It is impossible, therefore, to apply methods and measures which at an earlier age might have been sufficient. We must revolutionize our thinking, revolutionize our actions, and must have the courage to revolutionize relations among nations of the world. Clichés of yesterday will no longer do today, and will, no doubt, be hopelessly out of date tomorrow."

STEVEN WENNER *Cohasset, Mass.*

THE EDITORS REPLY: We would like to thank Wenner for pointing out that this quote is most likely apocryphal, as is indicated by the seeming elusiveness of a primary source and the existence of several variations. In the future, we will not allow for the inclusion of any quotes commonly attributed to famous figures unless they can be fully substantiated.

CLARIFICATION

"A Meditation on Keyboard Shortcuts," by David Pogue [TechnoFiles], should not have implied that Apple was the first to use keyboard shortcuts by referring to them as "Apple's brilliant innovation." The company was an early adopter of shortcuts.

ERRATA

"Hidden Inferno," by Shannon Hall, should have described winds blowing potential volcanic ash from the Laguna del Maule region in Chile to Argentina as westerly, not easterly. Further, it should not have described 1,200 degrees Celsius as 50 percent hotter than 800 degrees C, because such comparisons break down at different scales of temperature: in kelvins, the former temperature would be 37 percent hotter than the latter.

SCIENTIFIC AMERICAN®
ESTABLISHED 1845

EDITOR IN CHIEF AND SENIOR VICE PRESIDENT
Mariette DiChristina

MANAGING EDITOR **Curtis Brainard** COPY DIRECTOR **Maria-Christina Keller** CREATIVE DIRECTOR **Michael Mrak**

EDITORIAL

CHIEF FEATURES EDITOR **Seth Fletcher** CHIEF NEWS EDITOR **Dean Visser** CHIEF OPINION EDITOR **Michael D. Lemonick**

FEATURES

SENIOR EDITOR, SUSTAINABILITY **Mark Fischetti** SENIOR EDITOR, SCIENCE AND SOCIETY **Madhusree Mukerjee**
SENIOR EDITOR, CHEMISTRY / POLICY / BIOLOGY **Josh Fischman** SENIOR EDITOR, TECHNOLOGY / MIND **Jen Schwartz**
SENIOR EDITOR, SPACE / PHYSICS **Clara Moskowitz** SENIOR EDITOR, EVOLUTION / ECOLOGY **Kate Wong**

NEWS

SENIOR EDITOR, MIND / BRAIN **Gary Stix** ASSOCIATE EDITOR, TECHNOLOGY **Sophie Bushwick**
ASSOCIATE EDITOR, SPACE / PHYSICS **Lee Billings** ASSOCIATE EDITOR, SUSTAINABILITY **Andrea Thompson**
ASSISTANT EDITOR, NEWS **Tanya Lewis**

DIGITAL CONTENT

MANAGING MULTIMEDIA EDITOR **Eliene Augenbraun** ENGAGEMENT EDITOR **Sunya Bhutta**
SENIOR EDITOR, MULTIMEDIA **Steve Mirsky** COLLECTIONS EDITOR **Andrea Gawrylewski**

ART

ART DIRECTOR **Jason Mischka** SENIOR GRAPHICS EDITOR **Jen Christiansen**
PHOTOGRAPHY EDITOR **Monica Bradley** ART DIRECTOR, ONLINE **Ryan Reid**
ASSOCIATE GRAPHICS EDITOR **Amanda Montañez** ASSISTANT PHOTO EDITOR **Liz Tormes**

COPY AND PRODUCTION

SENIOR COPY EDITORS **Michael Battaglia, Daniel C. Schlenoff** COPY EDITOR **Aaron Shattuck**
MANAGING PRODUCTION EDITOR **Richard Hunt** PREPRESS AND QUALITY MANAGER **Silvia De Santis**

DIGITAL

PRODUCT MANAGER **Ian Kelly** WEB PRODUCER **Jessica Ramirez**

CONTRIBUTORS

EDITORIAL **David Biello, Deboki Chakravarti, Lydia Denworth, W. Wayt Gibbs, Ferris Jabr, Anna Kuchment, Robin Lloyd, Melinda Wenner Moyer, George Musser, Christie Nicholson, John Rennie, Ricki L. Rusting**
ART **Edward Bell, Bryan Christie, Lawrence R. Gendron, Nick Higgins**

EDITORIAL ADMINISTRATOR **Ericka Skirpan** SENIOR SECRETARY **Maya Harty**

PRESIDENT
Dean Sanderson

EXECUTIVE VICE PRESIDENT **Michael Florek**

CLIENT MARKETING SOLUTIONS

VICE PRESIDENT, COMMERCIAL **Andrew Douglas**
PUBLISHER AND VICE PRESIDENT **Jeremy A. Abbate**
MARKETING DIRECTOR, INSTITUTIONAL PARTNERSHIPS AND CUSTOMER DEVELOPMENT **Jessica Cole**
PROGRAMMATIC PRODUCT MANAGER **Zoya Lysak**
DIRECTOR, INTEGRATED MEDIA **Jay Berfas**
DIRECTOR, INTEGRATED MEDIA **Matt Bondlow**
SENIOR ADMINISTRATOR, EXECUTIVE SERVICES **May Jung**

CONSUMER MARKETING

HEAD, MARKETING AND PRODUCT MANAGEMENT **Richard Zinken**
E-MAIL MARKETING MANAGER **Chris Monello**
MARKETING AND CUSTOMER SERVICE COORDINATOR **Christine Kaelin**

ANCILLARY PRODUCTS

ASSOCIATE VICE PRESIDENT, BUSINESS DEVELOPMENT **Diane McGarvey**
CUSTOM PUBLISHING EDITOR **Lisa Pallatroni**
RIGHTS AND PERMISSIONS MANAGER **Felicia Ruocco**

CORPORATE

HEAD, COMMUNICATIONS, USA **Rachel Scheer**

PRINT PRODUCTION

PRODUCTION CONTROLLER **Madelyn Keyes-Milch** ADVERTISING PRODUCTION CONTROLLER **Dan Chen**

LETTERS TO THE EDITOR

Scientific American, 1 New York Plaza, Suite 4600, New York, NY 10004-1562 or editors@sciam.com
Letters may be edited for length and clarity. We regret that we cannot answer each one.
Join the conversation online—visit *Scientific American* on Facebook and Twitter.

HOW TO CONTACT US

Subscriptions
For new subscriptions, renewals, gifts, payments, and changes of address: U.S. and Canada, 800-333-1199; outside North America, 515-248-7684 or www.ScientificAmerican.com

Submissions
To submit article proposals, follow the guidelines at www.ScientificAmerican.com. Click on "Contact Us." We cannot return and are not responsible for materials delivered to our office.

Reprints
To order bulk reprints of articles (minimum of 1,000 copies): Reprint Department, Scientific American, 1 New York Plaza, Suite 4600, New York, NY 10004-1562; 212-451-8415. For single copies of back issues: 800-333-1199.

Permissions
For permission to copy or reuse material: Permissions Department, Scientific American, 1 New York Plaza, Suite 4600, New York, NY 10004-1562; randp@SciAm.com; www.ScientificAmerican.com/permissions. Please allow three to six weeks for processing.

Advertising
www.ScientificAmerican.com has electronic contact information for sales representatives of Scientific American in all regions of the U.S. and in other countries.

The WHO Takes a Reckless Step

The World Health Organization is now promoting unproved traditional Chinese medicine

By the Editors

For more than 2,000 years Chinese healers have used herbal powders and tinctures, dust made from various animal parts and strategically placed needles to treat a host of human ailments. These are used in hundreds of nations globally, but the practice in China is perhaps the most extensive, documented and catalogued. Traditional Chinese medicine (TCM) is based on the concept of qi, a system of energy that flows along meridians in the body to maintain health.

Over the past decade proponents of TCM have worked hard to move it into the mainstream of global health care—and it appears those efforts are coming to fruition. The latest (11th) version of the World Health Organization's list known as the *International Statistical Classification of Diseases and Related Health Problems* (*ICD*) will include these remedies for the first time.

According to its own mandate, the WHO sets the norms and standards for medical treatment around the globe and articulates "ethical and evidence-based policy options." It categorizes thousands of diseases and influences how doctors treat them; how insurers cover those treatments; and what kind of research is done on which ailments. More than 100 countries rely on the document to determine their medical agendas.

To include TCM in the *ICD* is an egregious lapse in evidence-based thinking and practice. Data supporting the effectiveness of most traditional remedies are scant, at best. An extensive assessment was done in 2009 by researchers at the University of Maryland: they looked at 70 review papers evaluating TCM, including acupuncture. None of the studies proved conclusive because the data were either too paltry or did not meet testing standards.

To be sure, many widely used and experimentally validated pharmaceuticals, including aspirin, decongestants and some anticancer chemotherapies, were originally derived from plants or other natural sources. Those drugs have all gone through extensive clinical testing of safety and efficacy, however. Giving credence to treatments that have not met those standards will advance their use but will also diminish the WHO's credibility.

China has been pushing for wider global acceptance of traditional medicines, which brings in some $50 billion in annual revenue for the nation's economy. And in 2016 Margaret Chan, then the WHO director, praised China's plans to do so. But while it's a good idea to catalogue TCM and make health workers aware of treatments used by millions, their inclusion in the *ICD* recklessly equates them with medicines that have undergone clinical trials.

In China, traditional medicines are unregulated, and they frequently make people sick rather than curing them. One particularly troublesome ingredient, aristolochic acid, is commonly used in traditional remedies and has been linked to fatal kidney damage and cancers of the urinary tract.

A 2018 study in the *British Journal of Clinical Pharmacology* tested 487 Chinese products taken by sick patients and discovered 1,234 hidden ingredients, including approved and banned Western drugs, drug analogues and animal thyroid tissue. And in 2012 a team led by Megan Coghlan, then at Murdoch University of Australia, identified the DNA sequences in 15 samples of traditional medicines in the form of powders, tablets, capsules, bile flakes and herbal teas. The samples also contained plants that produce toxic chemicals and animal DNA from vulnerable or endangered species (the Asiatic black bear and saiga antelope, for example) and other creatures protected by international laws.

Thus, the proliferation of traditional medicines would have significant environmental impacts on top of the negative health effects. It would contribute to the destruction of ecosystems and increase the illegal trade of wildlife. China announced last October that it was legalizing the controlled trade of rhinoceros horn and tiger bone. (The move was postponed in November, following a global outcry.) Both are believed by practitioners to have the power to cure a range of ailments, from fever to impotence—although no study has found any beneficial outcome of ingesting either. Allowing even the controlled harvest of otherwise endangered creatures will boost illegal poaching, critics say.

Until they undergo rigorous testing for purity, efficacy, dosage and safety, the WHO should remove traditional medicines from its list. These remedies should be given the same scrutiny as other treatments before being included in standard care practices. SA

JOIN THE CONVERSATION ONLINE
Visit *Scientific American* on Facebook and Twitter
or send a letter to the editor: editors@sciam.com

Illustration by Christina Ung

Han de Groot is CEO of the Rainforest Alliance.

A Low-Tech Climate Fix

Keeping forests intact can go a long way toward saving the planet

By Han de Groot

Climate change disproportionately affects the world's most vulnerable people, particularly poor rural communities that depend on the land for their livelihoods and coastal populations throughout the tropics. We have already seen the stark asymmetry of suffering that results from extreme weather events, such as hurricanes, floods, droughts, wildfires, and more.

For remedies, advocates and politicians have tended to look toward cuts in fossil-fuel use or technologies to capture carbon before it enters the atmosphere—both of which are crucial. But this focus has overshadowed the most powerful and cost-efficient carbon capture technology in the world. Recent research confirms that forests are absolutely essential in mitigating climate change, thanks to their ability to absorb and sequester carbon. In fact, natural climate solutions such as conservation and restoration of forests, along with improvements in land management, can help us achieve 37 percent of our climate target of limiting warming to a maximum of two degrees Celsius above preindustrial levels, even though they currently receive only 2.5 percent of public climate financing.

Forests' power to store carbon dioxide is staggering: one tree can store an average of about 48 pounds in one year. Intact forests could take in the CO_2 emissions of some entire countries.

For this reason, policy makers and business leaders must create and enforce policies to prevent deforestation; foster reforestation of degraded land; and promote the sustainable management of standing forests in the fight against climate change. Protecting the world's forests ensures they can keep performing essential functions such as producing oxygen, filtering water and supporting biodiversity. Not only does all the world's population depend on forests to provide clean air, clean water, oxygen and medicines, but 1.6 billion people rely on them directly for their livelihoods.

Unfortunately, a huge amount of forest continues to be converted into agricultural lands to produce a handful of resource-intensive commodities—despite zero-deforestation commitments from companies and governments. So now is the time to increase forest protection and restoration. This action will also address a number of other pressing global issues. For example, increasing tree cover can help tackle the problem of food security in many areas: trees can enhance farm productivity and give farmers another source of revenue through the sale of fruits, nuts or timber—all the while storing carbon dioxide—in a practice known as agroforestry. It is estimated that increased investment in this area could help sequester up to 9.28 gigatons of carbon dioxide while saving a net $709.8 billion by 2050. In productive landscapes where it would be difficult to increase tree cover dramatically, agroforestry serves as an attractive compromise.

In less developed, rural areas—especially in the tropics—community-based forest-management programs can forge pathways out of poverty. In the Petén region of Guatemala, for instance, community-managed forests boasted a near-zero deforestation rate from 2000 through 2013, as compared with 12 percent in nearby protected areas and buffer zones. These communities have built low-impact, sustainable forest-based businesses that have bolstered the economy of the region enough to fund the creation of local schools and health services. Their success is especially poignant in a location where, outside these community-managed zones, deforestation rates have increased 20-fold.

Landscape restoration promises an unparalleled return on investment, in terms of ecosystem services and carbon sequestered and stored. It could potentially sequester up to 1.7 gigatons of carbon dioxide every year, according to the International Union for Conservation of Nature. Reforestation projects can also intersect neatly and positively with human systems—restored forests supply a renewed resource base and new economic opportunities for communities.

The Bonn Challenge, issued by world leaders with the goal of bringing 150 million hectares of degraded lands into restoration by 2020, has been adopted by 57 governments and other organizations. Many groups have pledged to halve global deforestation by 2020 through the New York Declaration on Forests. And in an exemplary display of public-private-sector cooperation, the Cocoa and Forests Initiative in Côte d'Ivoire, Ghana and Colombia aims to end deforestation from cocoa cultivation.

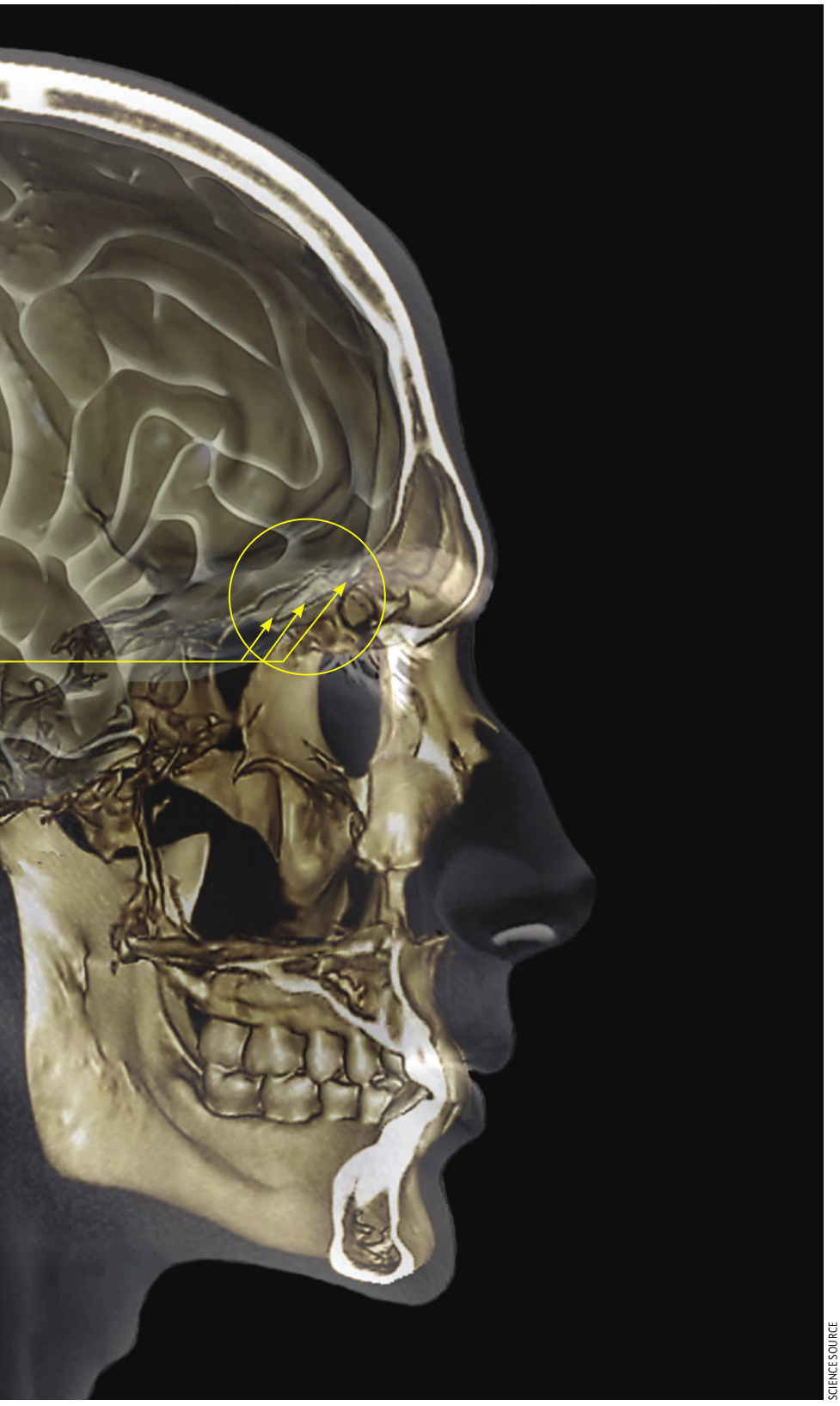
More trees mean better lives on a more sustainable planet. SA

JOIN THE CONVERSATION ONLINE
Visit *Scientific American* on Facebook and Twitter or send a letter to the editor: editors@sciam.com

Illustration by Nicole Xu

ADVANCES

An implant that could restore a sense of smell would involve electrodes placed on the brain's olfactory bulb (*arrows*).



SCIENCE SOURCE

INSIDE

NEUROTECH

Aroma Therapy

A cochlear implant–like device could one day restore smell

When Scott Moorehead tells people he cannot smell, they usually make a joke about how lucky he is—he must not be troubled by dirty diapers or people passing gas. "All the jokes are hilarious," Moorehead says, with a hint of sarcasm. But his lack of smell also means he is vulnerable to natural gas leaks and burning food. He is self-conscious about his own scent, so he takes extra showers. And he has had to give up one of his favorite hobbies: matching wines with exotic flavors.

After a concussion left Moorehead without a sense of smell six years ago, these losses were all he could think about. "Just knowing that I was never going to be able to smell my wife again or my kids" was hard to cope with, he says.

Although the nerves that control smell can often regrow after an injury—they are some of the only neurons known to rapidly replace themselves—Moorehead's lesion was too severe. He now has anosmia, which means his sense of smell is gone. But he is participating in a nascent effort at the Virginia Commonwealth University (VCU) School of Medicine and Harvard Medical School to develop a partially

implantable device that could help people with brain injuries decode and interpret everyday scents.

Research on smell lags decades behind that on vision and hearing, says Joel Mainland, an olfactory neuroscientist and associate member of the Monell Chemical Senses Center in Philadelphia, who is not involved in the new work. Smell studies receive less funding than research on other senses does, he says. And smell involves many sensory components. Whereas vision requires interpreting input from three types of receptors, taste involves 40 and olfaction 400.

A surprisingly large number of people have an impaired sense of smell—23 percent of U.S. adults age 40 and older, according to one national survey, and 62.5 percent of those age 80 and older, according to another. Such a decline can result from injury, chronic sinus problems, genetics or aging, says VCU professor Richard Costanzo, who has studied smell for four decades and is co-leading the initiative to develop the new device. Often dismissed as inconsequential, smell contributes to taste, so people who cannot smell are at risk for malnutrition, as well as social isolation, Costanzo says.

Some smell-restoration treatments exist, Mainland says, including smell training, in which people repeatedly expose themselves to certain odors and practice identifying them. Other treatments may uncover specific causes of smell loss, such as chronic sinusitis. But for someone with the damage Moorehead suffered, none of these is effective.

Smell, like all senses, is a multistep process. Scents, technically called odorant molecules, enter through the nose or mouth and pass through a layer of mucus before binding to olfactory receptor neurons. This binding triggers electrical signals that reach certain spots in the brain's olfactory bulb. "One nerve cell may respond to a brownie but not to pound cake, and its neighbor might do the opposite," says Eric Holbrook, chief of rhinology at Massachusetts Eye and Ear Hospital and an associate professor at Harvard Medical School. "One nerve cell probably responds to multiple chemicals, but they have some specificity."

Holbrook, who is collaborating with the VCU team, is now trying to find a shortcut to stimulate the brain's olfactory bulb and then trigger a sensation of smell. Ultimately the researchers plan to create a device that will operate somewhat like a cochlear implant, an electronic device that partially restores hearing. Cochlear implants turn sounds into electrical signals that the brain interprets; in a similar way, the VCU-Harvard team hopes to convert chemical scents into useful electrical signals. Holbrook published a study in February in the *International Forum of Allergy & Rhinology* suggesting that electrical stimulation in the nasal cavity and sinuses can make a healthy person perceive an odor, even if it is not present. That is a long way from restoring a sense of smell in someone who has lost it, but it is an important step along the way, Holbrook says.

A cochlear implant has an external sound processor worn behind the ear that includes a microphone and microcomputer. That component transmits signals to an internal piece under the skin that stimulates nerves in the cochlea, the organ that converts sound vibrations into nerve impulses. Similarly, the VCU-Harvard team envisions a device that would potentially fit under the nose—or on a pair of glasses—and include an odor sensor and a small external microprocessor, as well as an internal part to stimulate different areas of the olfactory bulb, Costanzo says.

Daniel Coelho, a cochlear implant surgeon at VCU who is collaborating with Costanzo, says the researchers must still refine sensors so they can discriminate among enough odors to be useful. The plan is to miniaturize and expedite smell processing such as that carried out by so-called electronic noses, which are used for bomb detection and identification of spoiled food. In addition, researchers must determine the optimal surgical approaches to safely implant a device that can stimulate the brain to perceive smells.

Developing such an olfactory implant will take years, Coelho says, but it is not impossible. "It's a pretty straightforward idea. We're not inventing anything radically new," he notes. Rather the team is putting existing technology together in a new way.

Moorehead, who injured himself falling off a skateboard while trying to teach his then six-year-old how to ride, is not optimistic about regaining his sense of smell. But he could not pass up the opportunity to help others, including the researchers. "It just kept seeming painfully obvious," Moorehead says, "that this is what I'm supposed to do." —*Karen Weintraub*

ETHAN DANIELS *Getty Images*

MARINE BIOLOGY

Coral Reefugees

Ancient corals migrated to escape warming waters

As the planet and oceans continue to heat up, sites where coral has recently thrived are becoming less and less habitable. For instance, thanks to extreme ocean temperatures, much of Australia's Great Barrier Reef suffered mass bleaching in 2016 and 2017 that turned parades of colorful coral into dull, white masses.

But paleontologists have now discovered a haven to which one region's reefs might relocate—via oceanic currents when corals are still in their free-floating larval stage—to escape overheating. By studying fossils in Daya Bay, just northeast of Hong Kong in the

Bleached leather corals in Buyat Bay, Indonesia

South China Sea, a team of researchers found that during periods of warming in the distant past, coral reefs migrated away from equatorial warm waters to the bay's more hospitable subtropical latitudes.

"We showed that the higher-latitude reefs up around China did grow during earlier warm periods," says Tara Clark, a paleoecologist at the University of Wollongong in Australia. In 2015 Clark led a group of scientists on an expedition to Daya Bay. There the researchers randomly collected dead corals and calculated their ages using radioisotopic dating techniques. The ancient reefs grew between 6,850 and 5,510 years ago, the scientists reported in January in *Geology,* which coincides with a time when ocean temperatures around South China and nearby seas were one to two degrees Celsius warmer on average than they are today. This trend suggests that some of today's reefs may be able to set up shop in places such as Daya Bay in the decades to come, as temperatures climb.

The idea of refuges for imperiled reefs on the move is not new, but using the fossil record to help pinpoint such places is a relatively novel approach, says John Pandolfi, a marine paleoecologist at the University of Queensland in Australia, who was not involved in the new work. "It's absolutely fundamental to understanding the dynamics of ecological communities and their responses to ecological change," he says. Such change often occurs on broader timescales than those of humans, and the fossil record can reveal that long-term change, Pandolfi notes.

Although the fossil evidence suggests that Daya Bay could one day provide a haven for corals, there are some hurdles in the way of making the refuge an inviting place, Clark says. Not all corals, for instance, are equally fit to trek across the ocean to a new home. And Daya Bay is now heavily polluted, which could jeopardize its ability to sustain reefs. But in light of the new discovery, Clark says, "we might as well do the best we can to protect these areas, just in case." —*Lucas Joel*

PSYCHOLOGY

Biases Aren't Forever

Implicit prejudice against certain groups is declining

Psychologists have lots of evidence that implicit social biases—our unconscious, knee-jerk attitudes associated with specific races, sexes and other categories—are widespread, and many assumed they do not evolve. The feelings are just too deep. But a new study finds that over roughly the past decade, both implicit and explicit, or conscious, attitudes toward several social groups have grown warmer.

The study used data from a standard test of implicit attitudes collected via a Web site called Project Implicit. Participants were asked to quickly press a certain computer key in response to positive words, such as "happy," and a different key in response to negative words, such as "tragic," that appeared on a screen. These words were interspersed with images or words that represented two categories of people, such as blacks and whites, and participants were asked to flag these using the same keys. Faster reactions when, for example, black rather than white faces shared a key with negative words suggested a racial bias.

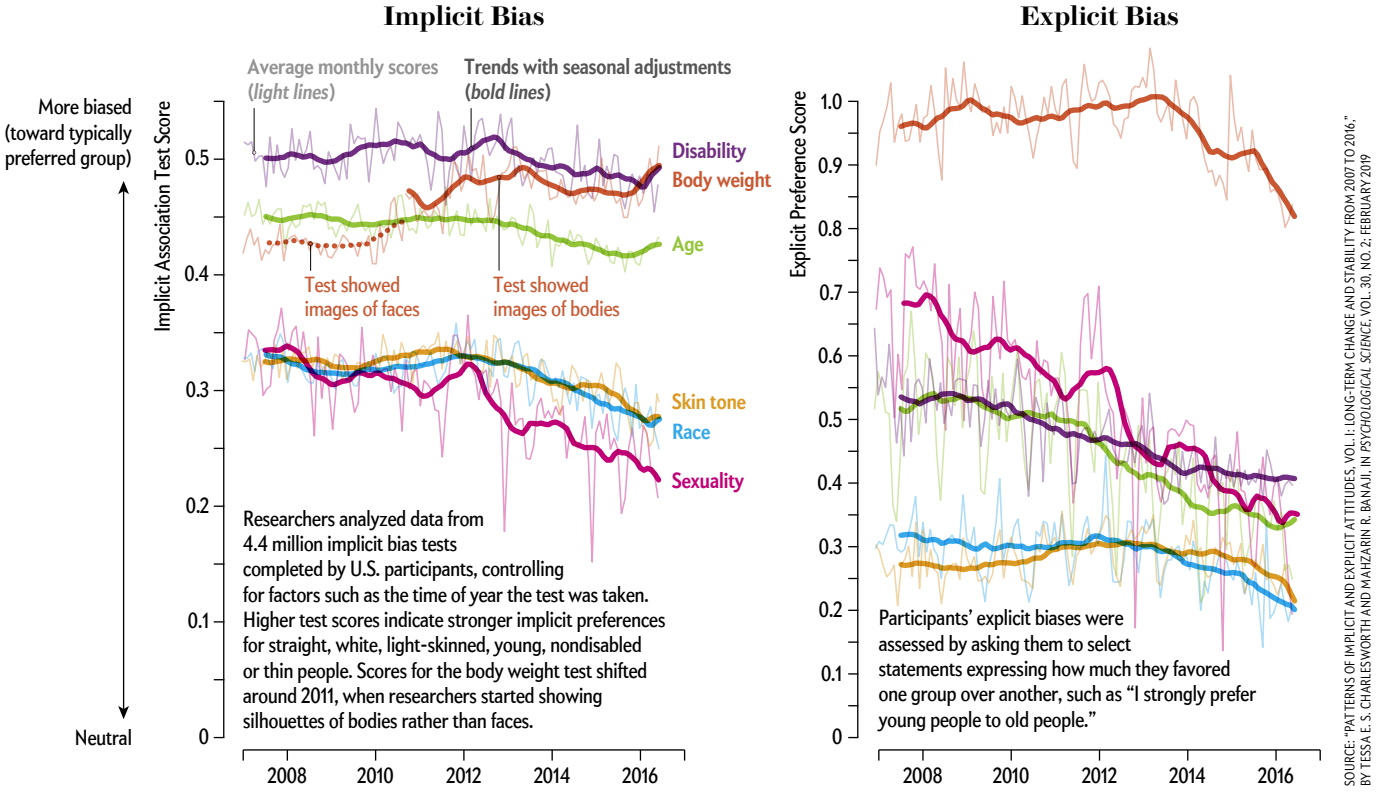
Tessa Charlesworth and Mahzarin Banaji, psychologists at Harvard University, analyzed more than four million results collected over a 10-year period from U.S. adults who had taken implicit association tests for sexuality, race, skin tone (in which faces differ in color but not shape), age, disability and body weight. Respondents also answered questions on the screen asking them to explicitly rate how much they liked people in each of the categories.

In line with previous findings, explicit bias decreased in all six categories from 2007 through 2016; the drop ranged from 49 percent (for sexuality) to 15 percent (for body weight). But more surprisingly, implicit bias also decreased—by 33 percent for sexuality, 17 percent for race and 15 percent for skin tone (*graphic*). Most of the reductions occurred in all generations, the researchers reported in a study published online in January in *Psychological Science*. "It's a really cool paper," says Keith Payne, a psychologist at the University of North Carolina at Chapel Hill, who has found similar bias reductions in his own work. "I think it's going to start a lot of conversations."

Charlesworth and Banaji also found, however, that implicit biases about age and disability did not change over time, and those against overweight people nudged up by 5 percent.

Several factors might explain the discrepancies among categories, the researchers say. In their data set, implicit biases for race, skin tone and sexuality were lower to begin with than those for age, disability and body weight. And the types of implicit biases that decreased the most are also the biases that have received more societal attention. Meanwhile the stigma associated with obesity may have increased in recent years.

Next, the team plans to explore implicit and explicit attitude change across demographics and geographical regions, as well as whether trends have changed since the 2016 U.S. presidential election. —*Matthew Hutson*



SOURCE: "PATTERNS OF IMPLICIT AND EXPLICIT ATTITUDES. VOL. I: LONG-TERM CHANGE AND STABILITY FROM 2007 TO 2016," BY TESSA E. S. CHARLESWORTH AND MAHZARIN R. BANAJI, IN *PSYCHOLOGICAL SCIENCE*. VOL. 30, NO. 2; FEBRUARY 2019

Graphic by Amanda Montañez

PALEONTOLOGY

Tiny Dino

A carnivore left the smallest known dinosaur footprints

A series of one-centimeter-long, 110-million-year-old footprints found in South Korea were left by what may be the tiniest nonbird dinosaur ever discovered. "These were made by several incredibly small raptor dinosaurs," says Anthony Romilio, a co-author of a study detailing the discovery and a postdoctoral researcher in paleontology at the University of Queensland in Australia. "Prior to our find, there would have been few who would have imagined that some raptors were so small that two or three could have easily fitted in your cupped hand."

Each footprint resembles the number 11, suggesting that these creatures walked on two toes per foot. The only dinosaurs known to match this style of prints are dromaeosaurs—a family of speedy predators that included *Velociraptor mongoliensis,* of *Jurassic Park* fame. These raptors had four toes on each foot; one was diminutive like a cat's dewclaw, and another had a sickle-shaped claw and was held above the ground while a raptor walked. The sparrow-sized dromaeosaurs that left these footprints would have had hips that were only four to five centimeters high. Their tracks, found in the South Korean city of Jinju, were described last November in *Scientific Reports* by a team led by Kyung Soo Kim of the country's Chinju National University of Education.

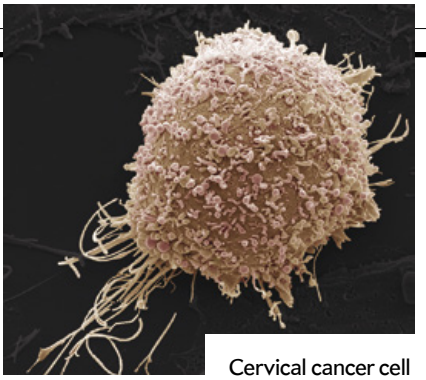
The prints look like they were left by an adult dinosaur smaller than any known type other than birds, Romilio says. Still, the possibility remains that a clutch of dinosaur chicks could have made them; similar footprints 10 times bigger—possibly from an adult—have been found at a site 30 kilometers away. Skeletal fossil evidence from the region is needed to pin down which hypothesis is correct, Romilio notes.

"Most people expect dinosaur tracks to be huge, bathtublike depressions, and some dinosaurs did leave some pretty big holes in the ground," says Anthony Martin, a paleontologist at Emory University who studies trace fossils (such as footprints and burrows) and was not involved in the study. But the new finding "shows us that we also sometimes need to think small." Even if the footprints were left by hatchlings, he adds, they hint that these juvenile dinosaurs were precocious and able to leave their nest soon after hatching, similar to some modern birds. —*John Pickrell*

HEALTH TECH

Cervical Cancer App

An AI algorithm diagnoses the disease from images



Cervical cancer cell

STEVE GSCHMEISSNER *Science Source*

One of the most common and cost-effective ways to detect cervical cancer is the pap smear, in which cells are scraped from a woman's cervix and sent to a laboratory for analysis. But this method requires equipment and medical expertise that are not always available in some low-income countries. Now scientists are making an app they hope could use artificial intelligence to identify precancerous or cancerous cells with just a photograph.

The app is being developed by researchers at the National Institutes of Health and Global Good; the latter is a joint effort by Bill Gates and invention firm Intellectual Ventures. Their preliminary results, published online in January in the *Journal of the National Cancer Institute,* suggest that such an approach could significantly improve cervical cancer diagnosis in low-resource settings.

Cervical cancer rates are higher in countries or regions that lack the resources to conduct pap smears. Health care providers in these areas often use a less accurate diagnostic technique, in which they swab the cervix with dilute acetic acid and visually inspect it for any white spots that might signal abnormal cells.

Over a seven-year period NIH researchers routinely photographed the cervixes of more than 9,400 women in Costa Rica. They used these images to train an AI algorithm to recognize characteristics of abnormal tissue—and to predict later cancer development. When the algorithm analyzed new images, it performed better than a clinical expert did by visual inspection.

"We were surprised to see that computers could see much more sensitively and clearly which cervixes are or are not precancerous," says Mark Schiffman, a molecular epidemiologist at the National Cancer Institute and senior author of the paper. "I really thought [the AI was] cheating." The scientists ultimately plan to implement their algorithm on mobile phones and aim to train future iterations of the program with digital camera photos. —*Wudan Yan*

ANIMAL FORENSICS

Catching Paleo Killers

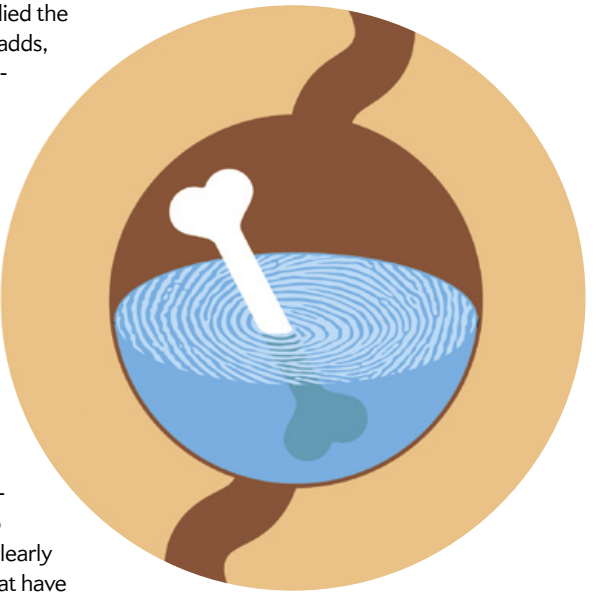
New technique identifies predators of ancient animals

Nowadays detectives can use DNA analysis to help catch a killer. But what happens when a crime scene has been exposed to the elements for thousands of years? DNA does not always stay intact that long—so for a paleontologist trying to figure out what kind of predator killed a long-dead fossil animal, the case often goes cold.

But a new method promises to help researchers identify these ancient killers. It relies on the fact that when a predator gulps down the bones of its prey—say, when a swooping owl snatches and eats a small rodent in the night—the diner's stomach juices leave behind microscopic etchings on the surface of the victim's bones.

These etchings occur in patterns that are unique to the type of predator that did the deed, making them a bit like fingerprints that scientists can use to crack unsolved cases, explains Rebecca Terry, a paleontologist at Oregon State University, who led the team that studied the etchings. This technique, she adds, will help researchers paint pictures of what kinds of predators were active in long-vanished ecosystems, particularly in areas where fossils are scarce. "It's really powerful," she says.

Terry and her team used a scanning electron microscope to examine the leftover bones that modern predatory birds regurgitate as pellets after a meal. They also looked at the feces of carnivorous mammals. "A bone that passes into and out of a nocturnal owl is clearly distinguishable from bones that have been eaten by diurnal raptors" or mammals, Terry says. Patterns etched on bones inside an owl's stomach tend to be relatively short and close together; those from the stomach of a hawk or mammal tend to be longer and more widely spaced, according to the study, which was published last November in *PALAIOS.* And the patterns left by the modern-day owls and mammals, Terry adds, were "indistinguishable" from those found on fossil bones digested by similar predators long ago.



These findings will help answer one of paleontologists' most basic questions about the fossils of animals they suspect were killed and eaten: "Whodunit?" As Joshua Miller, a paleobiologist at the University of Cincinnati, who was not involved in the new research, says, "You can actually look at an individual bone and get some perspective on why that bone is where you found it. And that's really neat." —*Lucas Joel*

Illustration by Thomas Fuchs


BECAUSE SOMEDAY
I'll stay overnight for observation.
Plan for your someday without sacrificing the things you want to do today.
Together, we'll help you achieve what matters most.
• Live the life you want today, and into the future.
• Develop a long-term financial game plan.
• Get, and stay, on track toward your goals.
Talk with Fidelity today about your finances.
Because you don't have to know all the answers—
that's why we're here to help.
Fidelity INVESTMENTS
Fidelity.com/yoursomeday
866.715.2058
Investing involves risk, including the risk of loss.
The trademarks and/or service marks appearing above are the property of FMR LLC and may be registered.
Fidelity Brokerage Services LLC, Member NYSE, SIPC. 900 Salem Street, Smithfield, RI 02917
© 2017 FMR LLC. All rights reserved. 815617.2.0

COGNITIVE SCIENCE

Failing Successfully

Research reveals how to turn defeat to one's advantage

GETTY IMAGES

People often say that "failure is the mother of success." This cliché might have some truth to it, but it does not tell us how to actually turn a loss into a win, says Emmanuel Manalo, a professor of educational psychology at Kyoto University in Japan. As a result, he says, "we know we shouldn't give up when we fail—but in reality, we do."

Manalo and Manu Kapur, a professor of learning sciences at the Swiss Federal Institute of Technology Zurich, put together a special issue of the journal *Thinking Skills and Creativity* last December on benefiting from failure. The issue's 15 studies provide teachers and educational researchers with a guide for achieving success. One study reported, for example, that the sooner and more often students fail at a task, such as building a robot, the sooner they can move forward and improve. Another confirmed that feedback on failures is most constructive when the giver comes across as caring, and the receiver is prepared to weather negative emotions.

Manalo and his co-authors also contributed their own study focused on overcoming one fundamental, everyday form of failure: not completing a task. They asked 131 undergraduates to write an essay about their school experiences. Half of the students received instructions for structuring their writing, and half were left to their own devices; all, however, were stopped prior to finishing. Afterward the researchers found that those in the structured group were more motivated to complete their essays, compared with those who lacked guidance—even if the latter were closer to being done. Knowing *how* to finish, in other words, was more important than being close to finishing.

The researchers dubbed this finding "the Hemingway effect," for the author's self-reported tendency to stop writing only when he knew what would happen next in the story—so as to avoid writer's block when he returned to the page. Manalo believes that learning how to fail temporarily can help people avoid becoming permanent failures at many tasks, such as completing a dissertation, learning a language or inventing a new technology.

Demystifying failure and teaching students not to fear it make goals more attainable, says Stephanie Couch, executive director of the Lemelson-MIT Program, a nonprofit organization dedicated to developing and supporting inventors. Couch, whose work was also featured in the special issue, adds that we "should really be thinking of failure as part of a process of iterating toward success." —*Rachel Nuwer*

APPLIED PHYSICS

Entropy in Art

Computer program uses physics to find patterns in paintings

For the romantics among us, physicist Haroldo Ribeiro's recent work might seem prosaic. He has developed a computer program that deconstructs works of art into sets of numbers. Now Ribeiro has applied his physics-inspired metrics to nearly 140,000 digitized paintings indexed on the visual art encyclopedia WikiArt to look for trends in the evolution of painting styles.

The process, described by Ribeiro and his colleagues last September in the *Proceedings of the National Academy of Sciences USA*, involves assessing the complexity and entropy, or disorder, of these digitized artworks. Complexity is based on the variability of patterns within each image, ranging from highly variable (more complex) to uniform (less complex). Entropy is determined by the degree of chaos in the image; the more "regular" the painting, the lower the entropy.

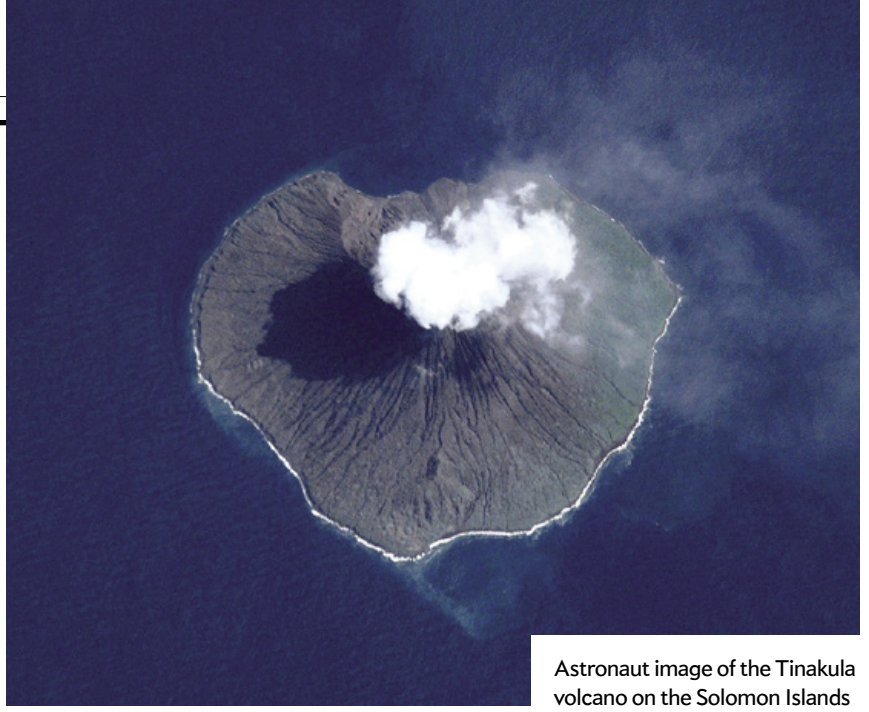
The new algorithm analyzes two-by-two grids of pixels within each painting and scores them using the two metrics. Ribeiro and his colleagues observed that shifts in the magnitude of complexity and entropy among various paintings mirror stylistic shifts throughout art history. Modern art—with blended edges and loose brushstrokes—generally possesses low complexity and high entropy. Postmodern art, a simpler style with recognizable objects and stark, well-defined edges (for example, Andy Warhol's soup cans), has high complexity and low entropy. In the late 1960s there was a rapid shift from modern to postmodern art; the algorithm is able to quantify the extremity of this shift.

These simple metrics could be used to better understand how art has evolved, capture information about various artistic periods and determine how these periods interacted, the researchers say. By learning from these patterns, the program could even be used to sort lesser-known works of art into specific artistic styles.

Maximilian Schich, a professor of arts and technology at University of Texas at Dallas, is in favor of the cross-disciplinary research. "One thing I think is very elegant in this paper is that they look at the complexity at the local level, the pixels and the surrounding pixels," Schich says. "You could say, 'Yeah, that's too simple—it doesn't explain all of the painting.' But it's research that is valuable." —*Jess Romeo*

ROB KIM *Getty Images*

Jackson Pollock's paintings have a high degree of entropy.



Astronaut image of the Tinakula volcano on the Solomon Islands

EARTH SCIENCE

Spying Volcanoes from Space

An orbiting observatory monitors signs of eruptions every one to two hours

Scientists are zooming out to get a more complete global view of volcanic eruptions—1.6 million kilometers out, to be precise. That is the distance to the Deep Space Climate Observatory (DSCOVR), a satellite originally conceived by former vice president Al Gore. Using an instrument onboard DSCOVR that can detect gases belched by volcanoes, researchers can now take snapshots of eruptions every one to two hours. Monitoring these events, which often spew ash that can trigger engine failure in airplanes, can help scientists quickly pinpoint potentially dangerous airspace.

Many of Earth's roughly 1,500 potentially active volcanoes are in remote areas, so it can be difficult to regularly study ongoing eruptions or identify new ones, says Simon Carn, a volcanologist at Michigan Technological University. "U.S. volcanoes are pretty well monitored, but elsewhere it's a different story," Carn adds. "There's definitely a need for satellite monitoring."

Carn and his colleagues used DSCOVR's Earth Polychromatic Imaging Camera (EPIC) to observe 16 eruptions. They collected ultraviolet measurements of sulfur dioxide (SO_2), a gas frequently emitted by volcanoes. Sulfur dioxide is the easiest volcanic gas to measure because it is relatively rare in the atmosphere, Carn says. The EPIC observations provided a new view of Earth's surface every 68 to 110 minutes—much more frequently than most other ultraviolet satellite instruments. "Eruptions can evolve rapidly, so the higher the frequency of observations, the better our ability to track them," Carn says.

EPIC captured SO_2 measurements just a few hours after the start of several eruptions; it also revealed changes other satellites did not detect, the researchers reported last October in *Geophysical Research Letters*. For instance, EPIC showed that the eruption of Tinakula on the South Pacific's Solomon Islands on October 20, 2017, actually consisted of two separate explosive events that released different amounts of sulfur dioxide.

This work represents a "significant step forward" in tracking volcanic clouds, says Andrew Hooper, a volcanologist at the University of Leeds in England, who was not involved in the research. The observations, he states, "could ultimately help mitigate the impacts of volcanic eruptions."

Currently DSCOVR transmits data to Earth only when the satellite is in view of receiver antennas in Virginia and Alaska. Installing more receivers around the globe would allow scientists to collect and analyze measurements nearly instantaneously, Carn says, noting that "we're a day or two behind real time." —*Katherine Kornei*

EARTH SCIENCES AND IMAGE ANALYSIS LABORATORY AND NASA'S JOHNSON SPACE CENTER

IN THE NEWS

Quick Hits

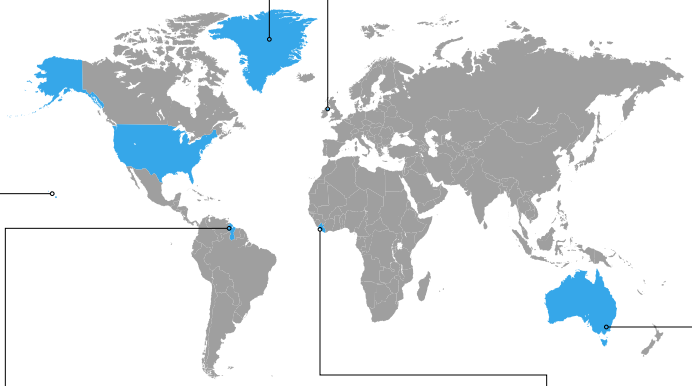
By Jim Daley

GREENLAND

The massive ice sheet covering Greenland is melting almost four times faster than it was in 2003, scientists have found. The gigantic hunk of ice could become a major contributor to sea-level rise in coming decades.

NORTHERN IRELAND

Bacteria in a soil sample from Northern Ireland effectively halt the growth of four types of antibiotic-resistant "superbugs," including methicillin-resistant *Staphylococcus aureus* (MRSA). Researchers say the discovery is an important step in the battle against such resistant bacteria.



U.S.

A 14-year-old Hawaiian snail named George, believed to be the last of its species, has died. The archipelago's population of land snails—which was once incredibly diverse—has substantially declined.

AUSTRALIA

Overuse of water from the Murray-Darling River system sparked a massive die-off of fish in the Down Under state of New South Wales. An estimated 100,000 to one million fish suffocated because the river levels were too low to flush out farm runoff; this led to algal blooms that resulted in bacterial proliferation, which caused a drop in oxygen.

GUYANA

The Guyanese government signed an agreement with the European Union to curb illegal logging, improve forest management and expand the South American nation's legal timber industry, which exports to the E.U.

LIBERIA

Health officials announced that they found the Ebola virus in a bat in West Africa for the first time. Previously it had been found only in bats in Central Africa. The discovery could help reveal how the virus jumps to humans.

For more details, visit www.ScientificAmerican.com/apr2019/advances

Psychotherapy in a Flash

Brief, intensive treatments can work for phobias, OCD, and more

By Claudia Wallis

Psychotherapy is not what most people think of as a quick fix. From its early Freudian roots, it has taken the form of 50- to 60-minute sessions repeated weekly (or more often) over a period of months or even years. For modern cognitive-behavioral therapy (CBT), 10 to 20 weekly sessions is typical. But must it be so? "Whoever told us that one 50-minute session a week is the best way to help people get over their problems?" asks Thomas Ollendick, director of the Child Study Center at Virginia Tech.

For nearly 20 years Ollendick has been testing briefer, more intensive forms of CBT for childhood anxiety disorders and getting results that closely match those of slower versions. His center often has a waiting list for treatments that include a four-day therapy for obsessive-compulsive disorder (OCD) and a three-hour intervention for specific phobias (such as fear of flying, heights or dogs). Around the U.S. and Europe, short-course therapies for anxiety disorders have begun to catch on, creating a nascent movement in both adult and child psychology.

The idea originated with Swedish psychologist Lars-Göran Öst, now professor emeritus at Stockholm University. Some 40 years ago Öst got the impression that not all his phobia patients needed multiple weeks of therapy and decided to ask if they would like to try a single, three-hour session. His first taker was a 35-year-old spider-phobic woman. "She lived five hours away, so she was happy," he recalls, to be treated in one go. He later showed the efficacy of the approach in a clinical trial, although it took four years to recruit 20 participants. "People with a specific phobia rarely apply for treatment," he explains. "They adjust their lives [say, avoiding spiders] or think they can't be helped." Öst went on to work with a team in Bergen, Norway, to test an intensive therapy for OCD known as the Bergen four-day treatment. By the early 2000s Ollendick was adapting brief therapies for adolescents and kids.

The details vary, but the quick treatments have some common features. They generally begin with "psychoeducation," in which patients learn about their condition and the catastrophic thoughts that keep it locked in place. In Bergen, this is done in a small group. With children, the lessons may be more hands-on and concrete. For instance, Ollendick might help a snake-phobic kid grasp why the creature moves in a creepy, slithering way by having the child lie on the floor and try to go forward without using any limbs.

A second part usually involves "exposure and response prevention," in which patients confront in incremental steps whatever triggers their anxiety: perhaps shopping, for agoraphobics, or having dirty hands, for people with OCD. With support from the therapist, they learn to tolerate it and see it as less threatening. Patients leave with homework to reinforce the lessons. Parents may be taught how to support a child's progress.

How well do these approaches work? A 2017 meta-analysis by Öst and Ollendick looked at 23 randomized controlled studies and found that "brief, intensive, or concentrated" therapies for childhood anxiety disorders were comparable to standard CBT. With the quicker therapies, 54 percent of patients were better immediately post-treatment, and that rose to 64 percent on follow-up—presumably because they continued to practice and apply what they had learned. With standard therapy, 57 percent were better after the final session and 63 percent on follow-up. The severity of symptoms and whether the patient was also taking antianxiety medication did not seem to impact outcomes.

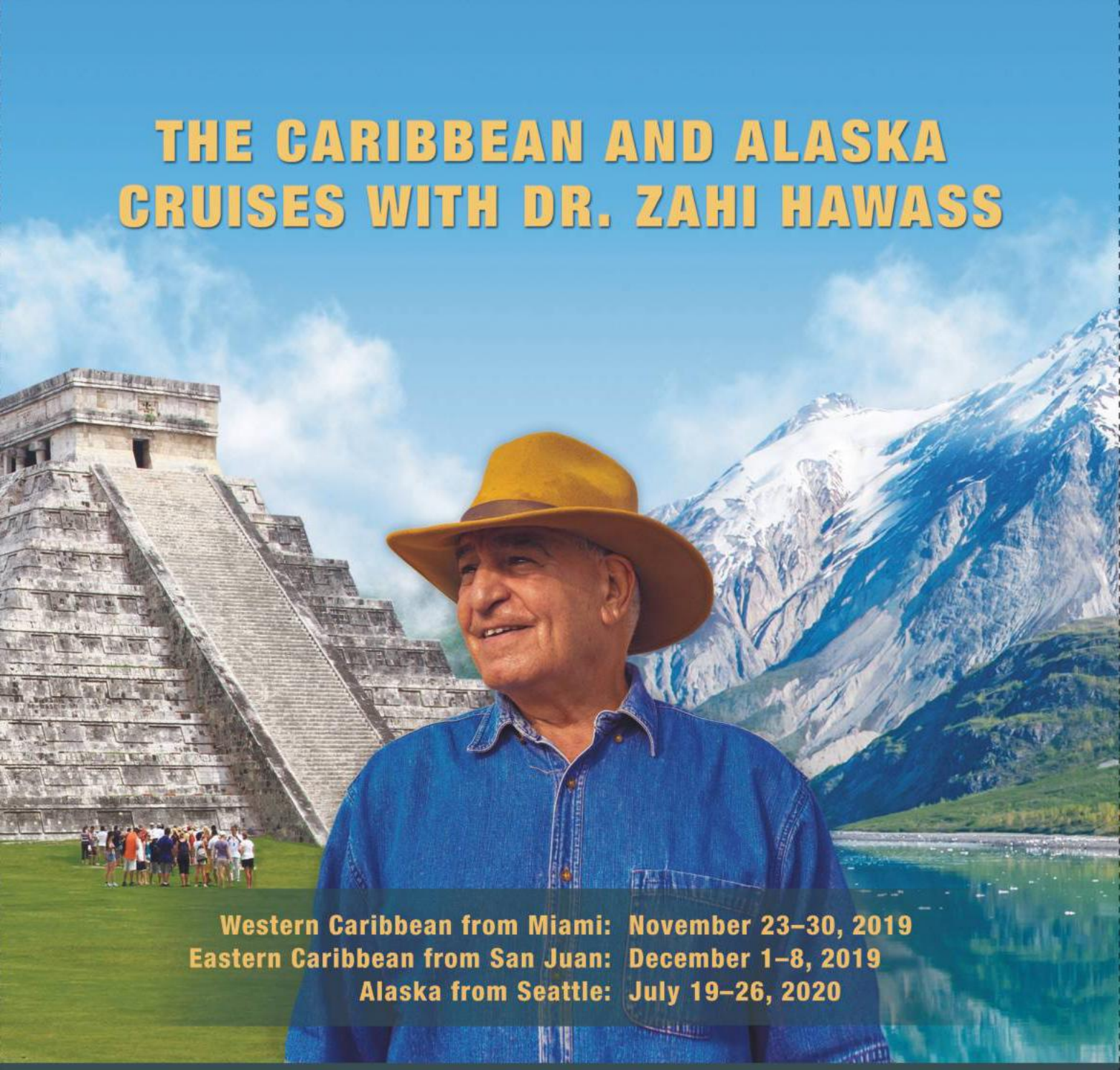
An obvious advantage to quick therapy is that it accelerates relief. Children with panic disorder, for instance, may refuse to leave home for fear of triggering an episode of shortness of breath, a racing heart and nausea. "They start to avoid places like the mall, the movies, the school dance," says child psychologist Donna Pincus of Boston University. Pincus developed an eight-day treatment for the disorder as an alternative to three months of CBT, which, she observes, "is a long time if you are not going to school or are avoiding doing things that are fun or healthy."

Making these briefer therapies more widely available could help address the sad fact that only about a third of patients with anxiety disorders get any kind of treatment. A weeklong therapy could be completed over a school or work vacation. Rural patients who cannot find CBT nearby could be treated during a short out-of-town stay. The intensive approach requires special training and a big shift for therapists—and health insurers—accustomed to the tradition of 50-minute blocks. But is there really anything sacred about that? SA

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

Illustration by Celia Krampien

THE CARIBBEAN AND ALASKA CRUISES WITH DR. ZAHI HAWASS



Western Caribbean from Miami: November 23–30, 2019
Eastern Caribbean from San Juan: December 1–8, 2019
Alaska from Seattle: July 19–26, 2020

For the first time ever, the living legend of archaeology joins our guests at sea! Take a cruise with Dr. Zahi Hawass, the most famous Egyptologist in the world, one of Time's 100 Most Influential People and Egypt's former Minister of Antiquities.

Dr. Zahi Hawass: *What is special about these cruises? We bring the pharaohs to Alaska and the Caribbean! You will enjoy the cruise during the day and in the evening I will bring you the magic of Ancient Egypt. I will tell you about the most important discoveries I have made in the last 20 years. Find out more about King Tut's secrets and how he died, the mysteries of the Sphinx and pyramids. Join me and you will never forget it!*

For more information visit:
WWW.ARCHAEOCRUISES.COM

ARCHAEOLOGICAL PATHS

contact@archaeologicalpaths.com
US phone: 917-719-1974

Machines That Mine Your Mind

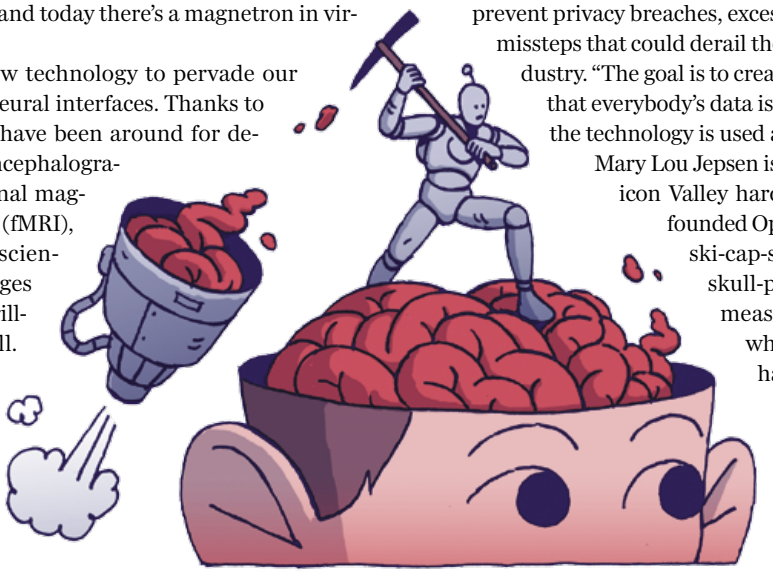
How to make sure noninvasive neural interfaces stay that way

By Wade Roush

Sometimes a technology that's been simmering in the laboratory or the clinic for decades makes the leap to mainstream consumption almost overnight.

Take the cavity magnetron. The precursor to this curious form of vacuum tube was invented at General Electric around 1920. It wasn't until 1940 that British scientists found a magnetron design that could pump out microwave energy at unprecedented power. That discovery fueled a crash program at the Massachusetts Institute of Technology to build airborne radar units, an advance that helped the Allies turn back Nazi Germany in Europe. The conflict had barely ended when a Raytheon engineer noticed that microwaves could also melt chocolate. The "Radarange" debuted in 1947, and today there's a magnetron in virtually every kitchen.

The next old-but-new technology to pervade our lives may be so-called neural interfaces. Thanks to noninvasive tools that have been around for decades, such as electroencephalography (EEG) and functional magnetic resonance imaging (fMRI), physicians and neuroscientists can measure changes in your brain without drilling a hole in your skull. And now some of the problems that made these tools finicky, expensive and hard to interpret are being ironed out, meaning that neural interfaces are suddenly showing up at Amazon and Target. Which presents a challenge because measuring brain activity isn't like making microwave popcorn. There are enormous privacy and ethical issues at stake.



The story of Toronto-based InteraXon, a brain-machine interface start-up founded in 2007, shows how fast things are changing. Getting reliable brain-wave measurements via EEG used to mean pasting dozens of electrodes to a subject's scalp. But InteraXon built a wearable EEG device with just a few electrodes that rest against the forehead and behind the ears, along with software to classify the brain waves they measure. Low-frequency "alpha" waves indicate a relaxed state; higher-frequency "beta" or "gamma" waves indicate a busy or concentrating mind.

Wade Roush is the host and producer of Soonish, a podcast about technology, culture, curiosity and the future. He is a co-founder of the podcast collective Hub & Spoke and a freelance reporter for print, online and radio outlets, such as *MIT Technology Review*, Xconomy, WBUR and WHYY.

The company's first applications were on the whimsical side. Visitors to the Ontario pavilion at the 2010 Winter Olympics in Vancouver could don a headband and use their thoughts to control the lights shining on Niagara Falls and other distant Ontario landmarks. Later the company built thought-controlled slot cars and *Star Wars* games. "After all this thought controlling, we hit upon this very important recognition," InteraXon co-founder Ariel Garten told me. "Although you *could* control technology with your brain, the way that you did it was not very effective. Frankly, you could just turn the thing with your hand much more readily."

But in 2014 the company released its Muse headband, now in its second iteration: it pairs with a smartphone app to help users practice mindfulness meditation. When the software detects brain waves indicating a wandering mind, wearers hear feedback in the form of crashing waves or thunder. These sounds cue them to return their attention to their breath. "It's like doing a rep at the gym," Garten says. "That's you saying, 'Okay, I have this muscle called my attention, and I'm going to strengthen it.'"

But it's one thing to use EEG data to diagnose sleep disorders or epilepsy; it's quite another to start monitoring the brain states of millions of healthy consumers. So Garten also founded the Center for Responsible Brainwave Technologies, which aims to prevent privacy breaches, excessive scientific claims or other missteps that could derail the nascent neural-interfaces industry. "The goal is to create a set of standards to ensure that everybody's data is kept safe at all times and that the technology is used appropriately," Garten says.

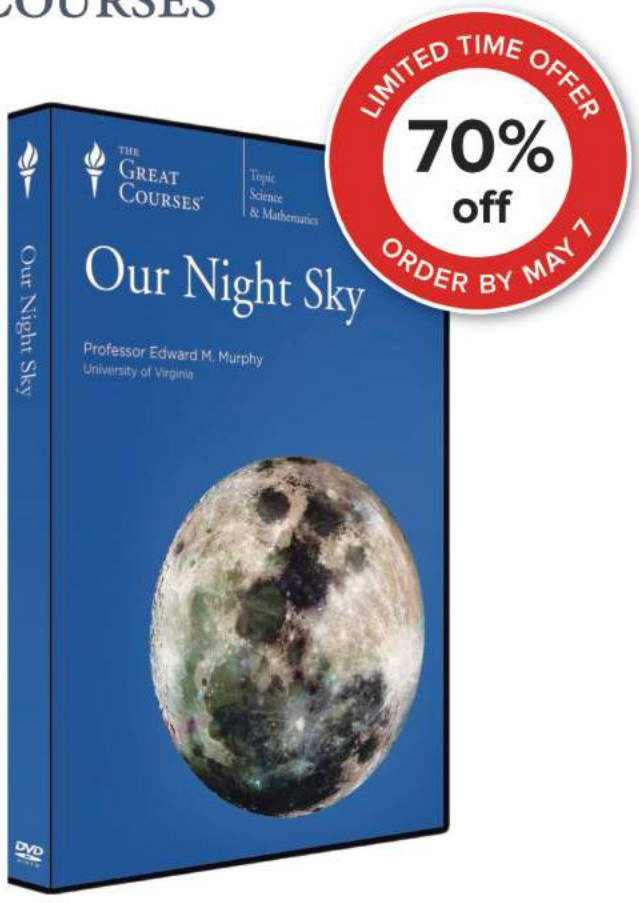
Mary Lou Jepsen is onboard with that. She's a Silicon Valley hardware engineer who recently founded Openwater, a start-up building a ski-cap-shaped device that will use skull-penetrating infrared light to measure blood flow—a sign of which brain areas are working hardest. Jepsen conceived the technology as a low-cost substitute for fMRI for diagnosing brain injuries or neurodegenerative diseases. But one day, she says, it might also be used to read thoughts. That could be a boon for people with disabilities, but it is also a privacy nightmare in the making. "I think the mind-reading scenarios are farther out, but the reason I'm talking about them early is because they do have profound ethical and legal implications," Jepsen says. "The only way we're going to release something is if we have ways to define what it means to be responsible."

As with so many other technologies, consumer neural interfaces seem destined to reach consumers before they're fully cooked. For now they'll be best served with a healthy side of caution. SA

JOIN THE CONVERSATION ONLINE
Visit *Scientific American* on Facebook and Twitter or send a letter to the editor: editors@sciam.com

Illustration by Wren McDonald

THE GREAT COURSES®



Learn How to Become an Expert Stargazer

For thousands of years, the star-filled sky has been a source of wonder, discovery, entertainment, and instruction. All you need to feel at home in its limitless expanse is **Our Night Sky**, a richly illustrated 12-lecture course that gives you an unrivaled tour around the sky—all while teaching you about the science, technology, and pure pleasure of stargazing. With award-winning astronomer and professor Edward M. Murphy, you'll learn how to use a star map to orient yourself at any date and time; how to read coordinates to locate planets, constellations, and other objects; how to select the best equipment; and more.

From asteroids to the zodiac, from the Big Dipper to variable stars, **Our Night Sky** provides a comprehensive overview of what there is to see and the best way to see it, whether you are a novice observer or an old hand at astronomy.

Offer expires 05/07/19

THEGREATCOURSES.COM/9SA

1-800-832-2412

Our Night Sky

Taught by Professor Edward M. Murphy
UNIVERSITY OF VIRGINIA

LECTURE TITLES

1. The Constellations and Their Stars
2. Seeing and Navigating the Sky
3. Using Binoculars and Backyard Telescopes
4. Observing the Moon and the Sun
5. Observing the Planets with a Telescope
6. Meteor Showers, Comets, Eclipses, and More
7. The Northern Sky and the North Celestial Pole
8. The Fall Sky
9. The Winter Sky
10. The Spring Sky
11. The Summer Sky
12. The Southern Sky and the Milky Way

The Night Sky Planisphere included FREE!

Along with this course, you will receive the same Night Sky Planisphere Star Chart used by Professor Murphy throughout his lectures. This sturdy, easy-to-use star finder is an invaluable aid for locating major constellations and stars visible in the Northern Hemisphere.

Our Night Sky
Course no. 1846 | 12 lectures (30 minutes/lecture)

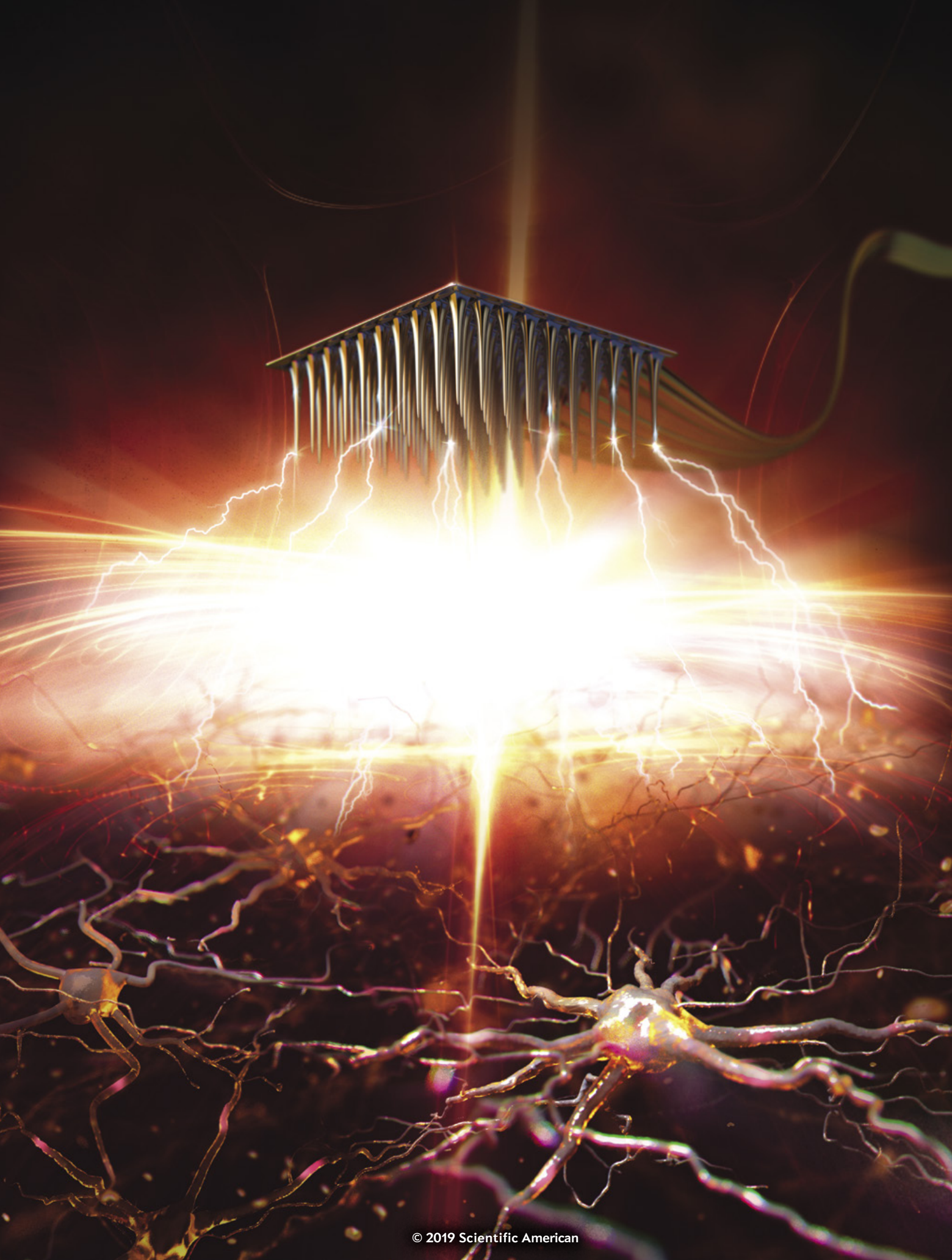
SAVE UP TO $160

DVD	~~$199.95~~	NOW $39.95
Video Download	~~$169.95~~	NOW $24.95

+$10 Shipping & Processing (DVD only)
and Lifetime Satisfaction Guarantee

Priority Code: 172885

For over 25 years, The Great Courses has brought the world's foremost educators to millions who want to go deeper into the subjects that matter most. No exams. No homework. Just a world of knowledge available anytime, anywhere. Download or stream to your laptop or PC, or use our free apps for iPad, iPhone, Android, Kindle Fire, or Roku. Over 700 courses available at www.TheGreatCourses.com.



NEUROTECH

THE INTENTION MACHINE

A new generation of brain-machine interface can deduce what a person wants

By Richard Andersen

Illustration by Mark Ross

Richard Andersen is James G. Boswell Professor of Neuroscience and the Tianqiao and Chrissy Chen Brain-Machine Interface Center Leadership chair and center director at the California Institute of Technology. He studies the neural mechanisms of sight, hearing, balance, touch and action, and the development of neural prostheses. Andersen is a member of the National Academy of Sciences and the National Academy of Medicine.

I GET GOOSE BUMPS EVERY TIME I SEE IT. A PARALYZED VOLUNTEER SITS IN A WHEELCHAIR WHILE controlling a computer or robotic limb just with his or her thoughts—a demonstration of a brain-machine interface (BMI) in action.

That happened in my laboratory in 2013, when Erik Sorto, a victim of a gunshot wound when he was 21 years old, used his thoughts alone to drink a beer without help for the first time in more than 10 years. The BMI sent a neural message from a high-level cortical area. An electromechanical appendage was then able to reach out and grasp the bottle, raising it to Sorto's lips before a sip was taken. His drink came a year after surgery to implant electrodes in his brain to control signals that govern the thoughts that trigger motor movement. My lab colleagues and I watched in wonderment as he completed this deceptively simple task that is, in reality, intricately complex.

Witnessing such a feat immediately raises the question of how mere thoughts can control a mechanical prosthesis. We move our limbs unthinkingly every day—and completing these motions with ease is the goal of any sophisticated BMI. Neuroscientists, though, have tried for decades to decode neural signals that initiate movements to reach out and grab objects. Limited success in reading these signals has spurred a search for new ways to tap into the cacophony of electrical activity resonating as the brain's 86 billion neurons communicate. A new generation of BMI now holds the promise of creating a seamless tie between brain and prosthesis by tapping with great precision into the neural regions that formulate actions—whether the desired goal is grasping a cup or taking a step.

IN BRIEF

Brain-machine interfaces, or BMIs, can send and receive messages to and from neural circuits. **Existing BMIs** tend to provide imprecise or sluggish performance. **New research** puts the interfaces in brain areas that formulate a person's intentions to move, making the technology more versatile for those with spinal cord injuries.

FROM BRAIN TO ROBOT

A BMI OPERATES by sending and receiving—"writing" and "reading"—messages to and from the brain. There are two major classes of the interface technology. A "write-in" BMI generally uses electrical stimulation to transmit a signal to neural tissue. Successful clinical applications of this technology are already in use. The cochlear prosthesis stimulates the auditory nerve to enable deaf subjects to hear. Deep-brain stimulation of an area that controls motor activity, the basal ganglia, treats motor disorders such as Parkinson's disease and essential tremor. Devices that stimulate the retina are currently in clinical trials to alleviate certain forms of blindness.

"Read-out" BMIs, in contrast, record neural activity and are still at a developmental stage. The unique challenges of reading neural signals need to be addressed before this next-generation technology reaches patients. Coarse read-out techniques already exist. The electroencephalogram (EEG) records the average activity over centimeters of brain tissue, capturing the activity of many millions of neurons rather than that from individual neurons in a single circuit. Functional magnetic resonance imaging (fMRI) is an indirect measurement that records an increase in blood flow to an active region. It can image smaller areas than EEG, but its resolution is still rather low. Changes in blood flow are slow, so fMRI cannot distinguish rapid changes in brain activity.

To overcome these limitations, ideally one would like to record the activity of individual neurons. Observing changes in the firing rate of large numbers of single neurons can provide the most complete picture of what is happening in a specific brain region. In recent years arrays of tiny electrodes implanted in the brain have begun to make this type of recording possible. The arrays now in use are four-by-four-millimeter flat surfaces with 100 electrodes. Each electrode, measuring one to 1.5 millimeters long, sticks out of the flat surface. The entire array, which resembles a bed of nails, can record activity from 100 to 200 neurons.

The signals recorded by these electrodes move to "decoders" that use mathematical algorithms to translate varied patterns of single-neuron firing into a signal that initiates a particular movement, such as control of a robotic limb or a computer. These read-out BMIs will assist patients who have sustained brain in-

jury because of spinal cord lesions, stroke, multiple sclerosis, amyotrophic lateral sclerosis and Duchenne muscular dystrophy.

Our lab has concentrated on tetraplegic subjects, who are unable to move either their upper or lower limbs because of upper spinal cord injuries. We make recordings from the cerebral cortex, the approximately three-millimeter-thick surface of the brain's two large hemispheres. If spread flat, the cortex of each hemisphere would measure about 80,000 square millimeters. The number of cortical regions that specialize in controlling specific brain functions has grown as more data have been collected and is now estimated to encompass more than 180 areas. These locations process sensory information, communicate to other brain regions involved with cognition, make decisions or send commands to trigger an action.

In short, a brain-machine interface can interact with many areas of the cortex. Among them are the primary cortical areas, which detect sensory inputs, such as the angle and intensity of light impinging on the retina or the sensation triggered in a peripheral nerve ending. Also targeted are the densely connected association cortices between the primary areas that are specialized for language, object recognition, emotion and executive control of decision-making.

A handful of groups have begun to record populations of single neurons in paralyzed patients, allowing them to operate a prosthesis in the controlled setting of a lab. Major hurdles still persist before a patient can be outfitted with a neural prosthetic device as easily as a heart pacemaker. My group is pursuing recordings from the association areas instead of the motor cortex targeted by other labs. Doing so, we hope, may provide greater speed and versatility in sensing the firing of neural signals that convey a patient's intentions.

The specific association area my lab has studied is the posterior parietal cortex (PPC), where plans to initiate movements begin. In our work with nonhuman primates, we found one subarea of the PPC, called the lateral intraparietal cortex, that discerns intentions to begin eye movements. Limb-movement processing occurs elsewhere in the PPC. The parietal reach region prepares arm movements. Also, Hideo Sakata, then at the Nihon University School of Medicine in Japan, and his colleagues found that the anterior intraparietal area formulates grasping movements.

The PPC provides several possible advantages for brain control of robotics or a computer cursor. It controls both arms, whereas the motor cortex in each hemisphere, the area targeted by other labs, activates the limb on the opposite side of the body. The PPC also indicates the goal of a movement. When a nonhuman primate, for instance, is visually cued to reach for an object, this brain area switches on immediately, flagging the location of a desired object. In contrast, the motor cortex sends a signal for the path the reaching movement should take. Knowing the goal of an intended motor action lets the BMI decode it quickly, within a couple of hundred milliseconds, whereas figuring out the trajectory signal from the motor cortex can take more than a second.

INTERFACE TECHNOLOGY, developed by Richard Andersen of Caltech (*left*) and his team, enabled Erik Sorto (*right*) to move a robotic arm.

LANCE HAYASHIDA AND CALIFORNIA INSTITUTE OF TECHNOLOGY

FROM LAB TO PATIENT

IT WAS NOT EASY to go from experiments in lab animals to studies of the PPC in humans. Fifteen years elapsed before we made the first human implant. First, we inserted the same electrode arrays we planned to use in humans into healthy nonhuman primates. The monkeys then learned to control computer cursors or robotic limbs.

We built a team of scientists, clinicians and rehabilitation professionals from the California Institute of Technology, the University of Southern California, the University of California, Los Angeles, the Rancho Los Amigos National Rehabilitation Center, and Casa Colina Hospital and Centers for Healthcare. The team received a go-ahead from the Food and Drug Administration and institutional review boards charged with judging the safety and ethics of the procedure in the labs, hospitals and rehabilitation clinics involved.

A volunteer in this type of project is a true pioneer because he or she may or may not benefit. Participants ultimately join to help users of the technology who will seek it out once it is perfected for everyday use. The implant surgery for Sorto, our first volunteer, took place in April 2013 and was performed by neurosurgeons

Charles Liu and Brian Lee. The procedure went flawlessly, but then came the wait for healing before we could test the device.

My colleagues at NASA's Jet Propulsion Laboratory, which built and launched the Mars rovers, talk about the seven minutes of terror when a rover enters the planet's atmosphere before it lands. For me it was two weeks of trepidation, wondering whether the implant would work. We knew in nonhuman primates how similar areas of the brain functioned, but a human implant was testing uncharted waters. No one had ever tried to record from a population of PPC neurons before.

During the first day of testing we detected neural activity, and by the end of the week there were signals from enough neurons to begin to determine if Sorto could control a robot limb. Some of the neurons varied their activity when Sorto imagined rotating his hand. His first task consisted of turning the robot hand to different orientations to shake hands with a graduate student. He was thrilled, as were we, because this accomplishment marked the first time since his injury he could interact with the world using the bodily movement of a robotic arm.

People often ask how long it takes to learn to use a BMI. In fact, the technology worked right out of the box. It was intuitive and easy to use the brain's intention signals to control the robotic arm. By imagining different actions, Sorto could watch recordings of individual neurons from his cortex and turn them on and off at will.

We ask participants at the beginning of a study what they would like to achieve by controlling a robot. For Sorto, he wanted to be able to drink a beer on his own rather than asking someone else for help. He was able to master this feat about one year into the study. With the team co-led by research scientist Spencer Kellis of Caltech, which included roboticists from the Applied Physics Laboratory at Johns Hopkins University, we melded Sorto's intention signals with the processing power furnished by machine vision and smart robotic technology.

The vision algorithm analyzes inputs from video cameras, and the smart robot combines the intent signal with computer algorithms to initiate the movement of the robot arm. Sorto achieved this goal after a year's time with cheers and shouts of joy from everyone present. In 2015 we published in *Science* our first results on using intention signals from the PPC to control neural prostheses.

Sorto is not the only user of our technology. Nancy Smith, now in her fourth year in the study, became tetraplegic from an automobile accident about 10 years ago. She had been a high school teacher of computer graphics and played piano as a pastime. In our studies with lead team members Tyson Aflalo of Caltech and Nader Pouratian of U.C.L.A., we found a detailed representation of the individual digits of both hands in Smith's PPC. Using virtual reality, she could imagine and move 10 fingers individually on left and right

By Thought Alone

For 15 years neuroscientists have built brain-machine interfaces (BMIs) that allow neural signals to move computer cursors or operate prostheses. The technology has moved forward slowly because translating the electrical firing of neurons into commands to play a video game or move a robot arm are highly intricate processes.

A group at the California Institute of Technology has tried to advance the neuroprosthetic field by tapping into high-level neural processing—the intent to initiate an action—and then conveying the relevant electrical signals to a robotic arm. Instead of sending out signals from the motor cortex to move an arm, as attempted by other laboratories, the Caltech researchers place electrodes in the posterior parietal cortex (PPC), which transmits to a prosthesis the brain's intent to act.

Decoding neural signals remains a challenge for neuroscientists. But using BMI signals from the posterior parietal cortex, the top of the cognitive command chain, appears to result in faster, more versatile control of prosthetic technology.

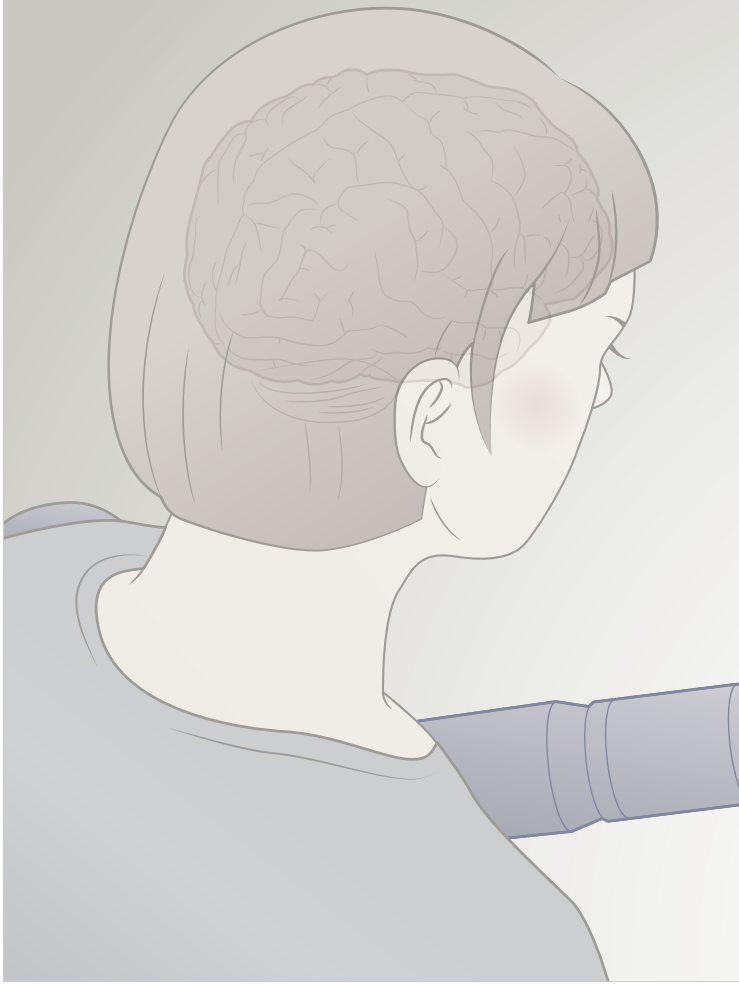
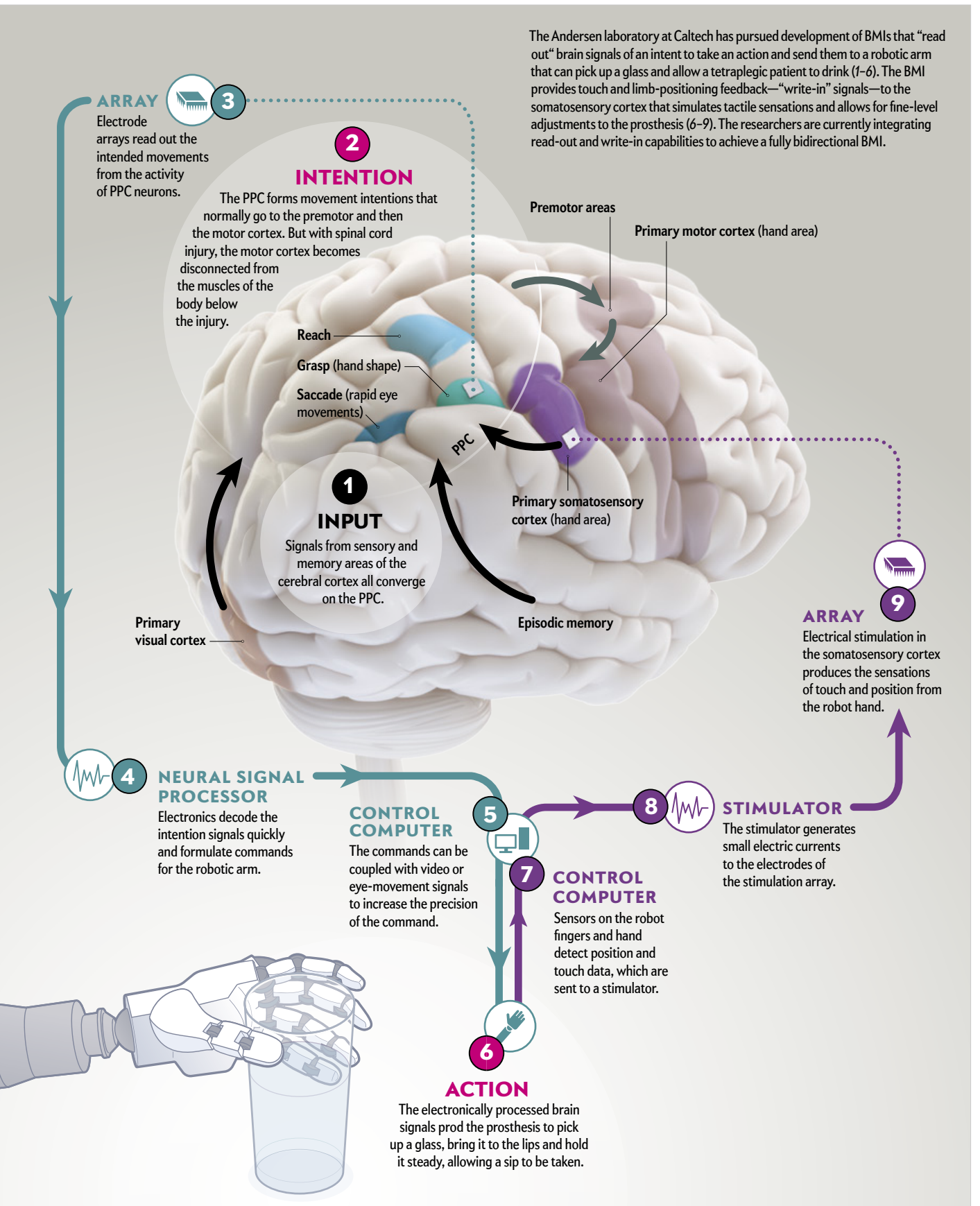


Illustration by AXS Biomedical Animation Studio

The Andersen laboratory at Caltech has pursued development of BMIs that "read out" brain signals of an intent to take an action and send them to a robotic arm that can pick up a glass and allow a tetraplegic patient to drink (*1–6*). The BMI provides touch and limb-positioning feedback—"write-in" signals—to the somatosensory cortex that simulates tactile sensations and allows for fine-level adjustments to the prosthesis (*6–9*). The researchers are currently integrating read-out and write-in capabilities to achieve a fully bidirectional BMI.



"avatar" hands displayed on a computer screen. Using the imagined movement of five fingers from one hand, Smith could play simple melodies on a computer-generated piano keyboard.

HOW THE BRAIN REPRESENTS GOALS

WE WERE THRILLED in working with these patients to find neurons tuned to processing signals related to one's intentions. The amount of information to be gleaned from just a few hundred neurons turned out to be overwhelming. We could decode a range of cognitive activity, including mental strategizing (imagined versus attempted motion), finger movements, decisions about recalling visual stimuli, hand postures for grasping, observed actions, action verbs such as "grasp" or "push," and mathematical calculations. To our surprise, inserting a few tiny electrode arrays enabled us to decode much of what a person intends to do.

Inserting a few tiny electrode arrays into the brain enabled us to decode much of what a person intends to do.

The question of how much information can be recorded from a small patch of brain tissue reminded me of a similar scientific problem that I had encountered early in my career. During my postdoctoral training with the late Vernon Mountcastle at the Johns Hopkins School of Medicine, we examined how visual space is represented in the PPC of monkeys. Our eyes are like cameras, with the photosensitive retinas signaling the location of visual stimuli imaged on them—the entire image is referred to as a retinotopic map. Neurons respond to limited regions of the retina, referred to as their receptive fields. In other ways, processing visual perception is different than a video camera recording. When a video camera moves around, the recorded image also shifts, but when we move our eyes the world seems stable. The retinotopic image coming from the eyes must be converted into a visual representation of space that takes into account where the eyes are looking so that as they move, the world does not appear as if it were sliding around.

The PPC is a key processing center for high-order visual space representation. To reach and grab an object, the brain needs to take into account where the eyes are looking to pick it up. PPC lesions in humans produce inaccurate reaching. In Mountcastle's lab, we found individual PPC neurons had receptive fields that registered parts of a scene. The same cells also carried eye-position information. The two signals interacted by multiplying the visual response by the position of the eyes in the head—the product of which is called a gain field.

I continued to pursue this problem of understanding the brain's representation of space when I took my first faculty position at the Salk Institute for Biological Studies, right across the street from the University of California, San Diego. Working with David Zipser, a U.C.S.D. theoretical neuroscientist developing neural networks, we reported in *Nature* on a computational model of a neural network that combined retinotopic locations with gaze direction to make maps of space that are invariant to eye movements. During training of the neural networks, their middle layers developed gain fields, just as was the case in the PPC experiments. By mixing signals for visual inputs and eye positions within the same neurons, as few as nine neurons could represent the entire visual field.

Recently this idea of mixed representations—populations of neurons responding to multiple variables (as with the gain fields)—has attracted renewed attention. For instance, recordings from the prefrontal cortex show a mixing of two types of memory task and different visual objects.

This work, moreover, may have a direct bearing in explaining what is happening in the PPC. We discovered this when we asked Smith, using a set of written instructions, to perform eight different combinations of a task. One of her undertakings required strategizing to imagine or attempt an action. Another necessitated using the right and left side of the body; a third entailed squeezing a hand or shrugging a shoulder. We found that PPC neurons mixed all these variables—and the intermingling exhibited a specific pattern, unlike the random interactions we and others had reported in lab animal experiments.

Activity of populations of neurons for strategizing and for controlling each body side tends to overlap. If a neuron fires to initiate the movement of the left hand, it will most likely also respond for an attempted righthand movement, whereas neuron groups that control the shoulder and hand are more separated. We refer to this type of representation as partially mixed selectivity. We have since found similarities in partially mixed representations that seem to make up a semantics of movement. The activity of cells tuned for the same action type tends to overlap. A neuron that responds to videos of a person grasping an object will also likely become active when a person reads the word "grasp." But cells responding to an action such as pushing tend to get separated into their own group. In general, partially mixed coding appears to underlie computations that are similar (movements of the left hand are similar to those of the right). It also separates those that exhibit varying forms of neural processing (movement of the shoulder differs from movement of the hand).

Mixed and partially mixed coding have been found in certain parts of the association cortex—and new studies must explore whether they appear in other locations that govern language, object recognition and executive control. Additionally, we would like to know whether the primary sensory or motor cortical regions use a similar partially mixed structure.

Another near-future goal is to find out how much learning new tasks can affect the performance of the volunteers using the prosthesis. If learning readily takes place, any area of the brain might then be implanted and trained for any conceivable BMI task. An implant in the primary visual cortex could learn to control nonvisual tasks. But if learning is more restricted, an implant in, say, a motor area would be trained only for motor tasks. Early results suggest that an implant may have to be placed in the area that has been previously identified as controlling particular cognitive activities.

WRITING IN SENSATIONS

A BMI MUST DO MORE than just receive and process brain signals—it must also send feedback from a prosthesis to the brain. When we reach to pick up an object, visual feedback helps to direct the hand to the target. The positioning of the hand depends on the shape of the object to be grasped. If the hand does not receive touch and limb-positioning signals once it begins to manipulate the object, performance degrades quickly.

Finding a way to correct this deficit is critical for our volunteers with spinal cord lesions, who cannot move their body below the injury. They also do not perceive the tactile sensations or positioning of their body that are essential to fluid movement. An ideal neural prosthesis, then, must compensate through bidirectional signaling: it must transmit the intentions of the volunteer but also detect the touch and positioning information arriving from sensors on a robotic limb.

Robert Gaunt and his colleagues at the University of Pittsburgh have addressed this issue by implanting microelectrode arrays in the somatosensory cortex of a tetraplegic person—where inputs from the limbs process feelings of touch. Gaunt's lab sent small electric currents through the microelectrodes, and the subject reported sensations from parts of the surface of the hand.

We have also used similar implants in the arm region of the somatosensory cortex. To our pleasant surprise, our subject, FG, reported natural sensations such as squeezing, tapping and vibrations on the skin, known as cutaneous sensations. He also perceived the feeling that the limb was moving—a sensation referred to as proprioception. These experiments show that subjects who have lost limb sensation can regain it through BMIs that write-in perceptions. The next step is to use sensor-laden robotic hands to check if somatosensory feedback improves robotic dexterity under brain control. Also, we would like to know if subjects detect a sense of "embodiment," in which the robot limb appears to become part of their body.

Another major challenge is to develop better electrodes for sending and receiving neural signals. We have found that implants continue to function for a relatively lengthy five years. But better electrodes would ideally push the longevity of these systems even further and increase the number of neurons that can be recorded from. Another priority—an increase in the lengths of the electrodes' tiny spikes—would help access areas located within folds of the cortex.

Flexible electrodes, which move with the slight jostling of the brain—from changes in blood pressure or the routine breathing cycle—will also allow for more stable recordings. Existing electrodes require recalibrating the decoder because the stiff electrodes change position with respect to neurons from day to day—researchers would ultimately like to follow the activity of identical neurons over weeks and months.

The implants need to be miniaturized, operate on low power (to avoid heating the brain), and function wirelessly so no cables are needed to connect the device to brain tissue. All current BMI technology needs to be implanted with a surgical procedure. But one day, we hope, recording and stimulation interfaces will be developed that can receive and send signals through the skull and provide performance equal to existing surgically implanted arrays.

BMIs, of course, are aimed at assisting people with paralysis. Yet science-fiction books, movies and the media have focused on the use of the technology for enhancement, conferring "superhuman" abilities that might allow a person to run faster and jump higher. But enhancement will be achieved only when noninvasive technologies able to detect the activities of single neurons precisely are developed.

Finally, I would like to convey the satisfaction of doing basic research and making it available to patients. Fundamental science is necessary to both advance knowledge and develop medical therapies. To be able to then transfer these discoveries into a clinical setting brings the research endeavor to its ultimate realization. A scientist is left with an undeniable feeling of personal fulfillment in sharing with patients their delight at being able to move a robotic limb to interact again with the physical world. SA

MORE TO EXPLORE

Reach and Grasp by People with Tetraplegia Using a Neurally Controlled Robotic Arm. Leigh R. Hochberg et al. in *Nature,* Vol. 485, pages 372–375; May 17, 2012.

High-Performance Neuroprosthetic Control by an Individual with Tetraplegia. Jennifer L. Collinger et al. in *Lancet,* Vol. 381, pages 557–564; February 16, 2013.

Decoding Motor Imagery from the Posterior Parietal Cortex of a Tetraplegic Human. Tyson Aflalo et al. in *Science,* Vol. 348, pages 906–910; May 22, 2015.

Intracortical Microstimulation of Human Somatosensory Cortex. Sharlene N. Flesher et al. in *Science Translational Medicine,* Vol. 8, No. 361, Article No. 361ra141; October 19, 2016.

Proprioceptive and Cutaneous Sensations in Humans Elicited by Intracortical Microstimulation. Michelle Armenta Salas et al. in *eLife,* Vol. 7, Article No. e32904; April 10, 2018.

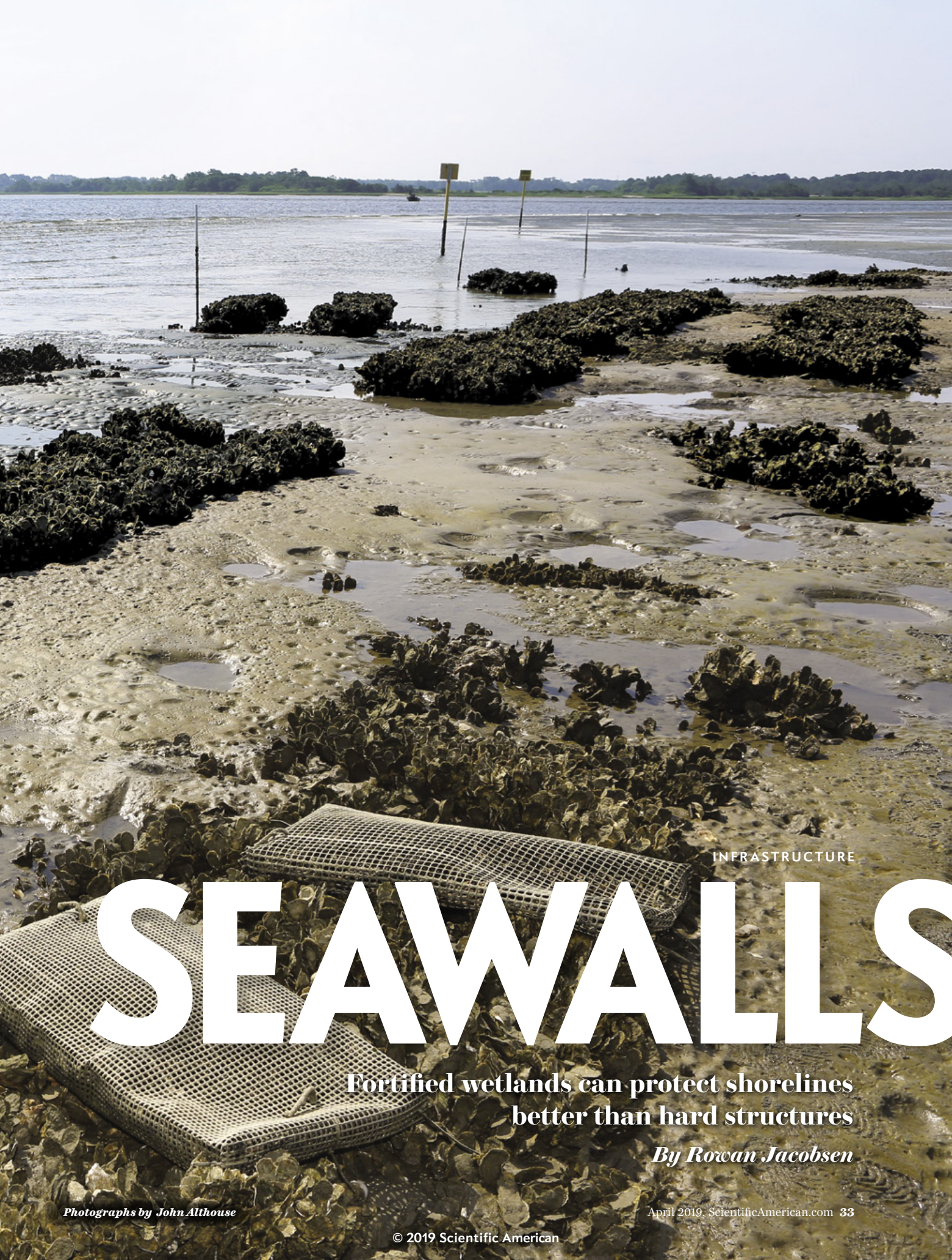
FROM OUR ARCHIVES

Is Anybody in There? Adrian M. Owen; May 2014.

scientificamerican.com/magazine/sa

OYSTERS are tested in experimental configurations for shoring up a coastline near Beaufort, N.C.

BEYOND



INFRASTRUCTURE

SEAWALLS

Fortified wetlands can protect shorelines better than hard structures

By Rowan Jacobsen

Photographs by John Althouse

Rowan Jacobsen is author of *A Geography of Oysters, The Living Shore* and other books. He wrote about the genes of extinct flowers in our February issue.

ON AUGUST 27, 2011, HURRICANE IRENE CRASHED INTO NORTH CAROLINA, eviscerating the Outer Banks. The storm dumped rain shin-high and hurled three-meter storm surges against the barrier island shores that faced the mainland, destroying roads and 1,100 homes.

After the storm, a young ecologist then at the University of North Carolina at Chapel Hill named Rachel K. Gittman decided to survey the affected areas. Gittman had worked as an environmental consultant for the U.S. Navy on a shoreline-stabilization project and had been shocked to discover how little information existed on coastal resilience. "The more I researched, the more I realized that we just don't know very much," she explains. "So much policy and management is being made without the underlying science." She decided to make shorelines her specialty.

What Gittman found was eye-opening. Along the hard-hit shorelines, three quarters of the bulkheads were damaged. The walls, typically concrete and about two meters high, are the standard homeowner defense against the sea in many parts of the country. Yet none of the natural marsh shorelines were impaired. The marshes, which extended 10 to 40 meters from the shore, had lost no sediment or elevation from Irene. Although the storm initially reduced the density of their vegetation by more than a third, a year later the greenery had bounced back and was as thick as ever in many cases.

Gittman's study confirmed what many experts had begun to suspect. "Armored" shorelines such as bulkheads offer less protection against big storms than people think. By reflecting wave energy instead of dispersing it, they tend to wear away at the base, which causes them to gradually tilt seaward. Although they still function well in typical storms, they often backfire when high storm surges overtop them, causing them to breach or collapse, releasing an entire backyard into the sea.

In a later study, Gittman and other researchers surveyed 689 waterfront owners and found that the 37 percent of properties protected by bulkheads had suffered 93 percent of the damage. And bulkhead owners routinely had four times the annual maintenance costs of residents who relied on nature instead. Salt marshes bent but did not break.

In recent years more scientists and policy makers have come to believe that "living shorelines"—natural communities of salt marsh, mangrove, oyster reef, beach and coral reef—can be surprisingly effective in a battle coastal residents have been losing for years. U.S. shores are disintegrating as higher seas, stronger storms and runaway development trigger an epidemic of erosion and flood damage. Every day waves bite off another 89 hectares of the country. Every year another $500 million of property disappears. Overall, some 40 percent of the U.S. coastline is suffering ongoing erosion. In some places, the rate of loss is breathtaking. Go to Google Earth Engine's Timelapse feature and watch Shackleford Banks melt away like ice cream on a summer sidewalk.

Historically, almost all money spent on coastal defense has gone toward "gray" infrastructure: seawalls, bulkheads, levees and rock revetments. That is beginning to c-hange as researchers become more sophisticated in measuring the long-term impact of "green" coastal defenses. Insurance companies and governments are finally taking notice and might actually turn the tide toward living defenses.

WETLANDS OUTPERFORM WALLS

AROUND THE TIME that Hurricane Irene was barreling up the East Coast, Michael W. Beck, a research professor at the University of California, Santa Cruz, and then lead marine scientist for the Nature Conservancy, was initiating a collaboration with the insurance industry that today may begin to change coastal conservation. "A lot of people were saying that ecosystems worked for flood protection, but the evidence was thin," Beck tells me at his Santa Cruz office. The physical mechanisms were clear: oyster and coral reefs limited erosion and flood damage by acting as natural breakwaters (offshore seawalls), dispersing wave energy with their corrugated surfaces. Salt marshes and mangroves, with their earthen berms and friction-generating forests of stalks, could rake more than 50 percent of the energy out of storm surges in less than 15 meters of territory.

IN BRIEF

Surprising data show that in many places marshes protect shorelines better than walls and are cheaper to construct.

Scientists are perfecting techniques for rebuilding tattered wetlands, creating custom configurations for individual shorelines.

Governments and disaster planners are starting to give more consideration to living shorelines, and money to restore them is rising.

DEVELOPERS survey oysters that have settled onto Oyster Catcher, a jute-and-cement material designed to help babies and adults thrive, protecting marshes between them and solid land.

But although scientists understood the physics, no one had put it into a form that could be used easily by policy makers. Beck set out to rectify that. "If I want to change practices, I can't bring my ecosystem model to FEMA or the U.S. Army Corps of Engineers," he explains. "I have to look at *their* risk model and put ecosystems into *that*."

Beck and his colleagues began collaborating with Lloyd's of London, Swiss Re and others in the insurance industry, which have some of the best data and models in the world on assets and risk. When he plugged data on coastal ecosystems into their risk models, it became clear that living shorelines were excellent defenses. And, he notes, "when I tell the Corps, FEMA and the development banks that these are the numbers from the insurance industry, I automatically have a different level of credibility."

The first study focused on damages from Superstorm Sandy, which clobbered New York and New Jersey in 2012. Working with Risk Management Solutions, a leading risk-modeling firm, the scientists showed that wetlands prevented $625 million of flood damage from the storm, which was surprising given that the coasts in the region had already lost 60 to 90 percent of their protective wetlands over time. In areas that flooded, the few remaining wetlands lowered flood damage by 11 percent on average. As important was the ability to buffer garden-variety floods: in one local study, properties behind marshes suffered 16 percent less annual flood damage than properties that had lost their marshes. "That's well within the range for which you could expect [insurance] premium reductions," Beck points out.

He and his partners then turned their economic and risk-management models on the Gulf Coast from Texas to Florida, which is regularly battered by big storms. They did an exhaustive analysis of the annual expected benefits and costs of all types of infrastructure. The team estimated that the coast would suffer $134 billion of losses over 20 years if no preventive measures were taken. Elevating homes could prevent $39.4 billion of those losses, but it is incredibly expensive. At an average of $83,300 per house, it would cost $54 billion to prevent that $39 billion in damages. The six-meter-high dikes being built in Louisiana were a worse option; at $33,000 per meter, they were an absurdly expensive way to protect a relatively limited amount of property, returning just $1 in savings for every $4 of expense. Smaller levees built on land in front of many low-lying coastal communities prevented much more damage for almost the same cost.

In terms of bang for the buck, sandbags were the best investment, saving $8.4 billion of damages for a mere $0.84 billion in expense. Natural defenses ranked high as well. Wetlands restoration, which could prevent $18.2 billion of losses, would cost just $2 billion. Oyster-reef restoration could prevent $9.7 billion in losses for $1.3 billion. Barrier island restoration offered $5.9 billion of prevention for $1.2 billion. And "beach nourishment" (replenishing depleted beaches with sand dredged from the seafloor) in the eastern Gulf could save $9.3 billion for $5.5 billion.

That last one surprised many people because replacing beach sand year after year is often seen as a fool's errand. "If the only choices you gave me were beach nourishment versus fully gray infrastructure," Beck says, "I'd choose the former as the lesser of two evils."

Overall, the research found that $57.4 of the $134 billion could be prevented cost-effectively, almost all of it through green infrastructure.

One type of restoration that was not part of the study is large-scale diversion of the Mississippi River. Diverting sediment-laden water through a gap in the river's levees and letting that sediment filter into struggling marshes can restore their health and elevation, but the region is subsiding so quickly that not even the famously muddy Mississippi can save it from the encroaching sea. "It is going to be expensive to re-create an entire ecosystem," Beck says, "and it is better and cheaper to start earlier."

Cost-effective restoration may be tricky on long, sandy coasts, too. Beaches and barrier islands are by nature transient. Planting grasses to rebuild dunes can help keep beaches in place but only temporarily in many cases. At some point, residents will have to move back from the receding shoreline.

Beck is quick to point out that built infrastructure is still incredibly important and that cost-effectiveness is not the only consideration. "Anywhere you've got significant people and property," he says, natural solutions will "be used together with some form of built infrastructure." Metropolitan areas, ports and other places where the risk tolerance for a major flood would be extremely

low need seawalls, even if such structures are not cost-effective. Still, Beck says, certain populated areas can benefit from a hybrid approach: "Even if you're building levees, they can be shorter if they have marshes in front."

ECOLOGISTS, including Rachel Gittman (*in white*), measure water levels and grasses at Carrot Island, N.C.

SHORELINE TRIALS AND ERRORS

ONE REASON living shorelines are becoming an economically viable approach for coastal defense is that researchers and municipalities are getting better at rebuilding them. Early marsh-restoration designs, which followed forestry science and gave each plant plenty of space to avoid competition, were actually counterproductive. It turns out that in bare mudflats, "when marsh plants are together, they share oxygen, so their growth rate is twice as high," says Brian Silliman, an ecologist at Duke University. Root them in large clumps, and the growth rate of each individual plant can triple. Add blue crabs, which eat the snails that eat the salt-marsh grasses, and the plants do even better.

Scientists are also finding that marshes do best when they have a protective sill—a linear berm that fronts the seaside edge of the grass and stands. Made of hard material such as shell, stone or concrete, its height and position are typically chosen so that water covers it at high tide, but it is exposed during low tide. The sill takes the brunt of wave energy but also traps sediment behind it, allowing the grass to thrive and marsh floor to retain its elevation or even rise.

Almost any hard material can make a successful sill. Large shoreline-stabilization projects use big boulders or stackable concrete blocks, a practice that has been criticized by some experts who say that these structures are living shorelines in name only. But many lower-profile restorations integrate sills more seamlessly into the natural habitat. In the Southeast and Gulf Coast regions, marshes historically possessed a natural sill in the form of an intertidal oyster reef. Many of those reefs were overharvested long ago, ruining the sill and exposing the marshes to erosion.

In these warm, oyster-friendly waters, new sills can be formed by placing a hard substrate along the low-tide line at the front edge of the marsh for baby oysters to set on. Some sites with lots of wave action have used small, hollow concrete structures or plastic mesh "onion bags" stuffed with shell and lashed together. When successful, these artificial materials are quickly covered by oysters and disappear into the interstices of the growing reef. But the concrete often remains visible for years, and the bags have been criticized for breaking and scattering plastic through the environment.

Gittman, now at East Carolina University, is testing an alternative material called Oyster Catcher that is made of jute cloth dipped in Portland cement and rolled into various hollow configurations. It hardens with extensive surface area to recruit larval oysters. In addition to being light and flexible, it holds together just long enough to get a reef established, then disintegrates. The product received its first big test when Hurricanes Florence and Michael struck North Carolina last fall. Michael tossed shell bags up into the marshes, but the Oyster Catcher reefs did not budge. The showing was encouraging, but Gittman worries that conservation groups may oversell the potential. "A living shoreline can't save your house from a Category 5 storm. Although neither can a bulkhead."

Gittman and Beck both stress the need to tailor living shorelines to local conditions. One reason oyster restoration is so cost-effective in the Gulf and the Southeast is because there have been plentiful wild oysters to seed new reefs with babies. That is not the case in most of the country. Chesapeake Bay, for example, was long the poster child for futile oyster restoration. Oyster populations in the bay had fallen to less than 1 percent of historical norms, and decades of effort and tens of millions of dollars barely budged the needle.

"Conceptually, Chesapeake Bay was not our best model," Beck says. "It put oyster-reef restoration back because it made it look so difficult and expensive. Well, when you're working in a system where you've only got 1 percent left, guess what? It ain't easy. When you're in the Gulf of Mexico and you've still got 50 percent of your reefs left, it's a different story. If you build it, the oysters will come."

Beck extends that lesson to coral reefs, the most underappreciated of natural defenses. "Coral reefs are the single most effective ecosystem for flood-risk reduction," he says. Corals, which have evolved to take a daily pounding that would destroy most other living things, form natural seawalls exactly where you want them—just offshore, in front of resorts, beach towns, coastal roads and other pricey assets. When healthy, they make remarkably effective breakwaters, reducing wave energy up to 97 percent. They are also affordable: reef restoration averages about $1,300 per meter versus $20,000 for artificial breakwater construction. The insurance industry's assessment for mitigating risk from climate change in the Caribbean found that reviving reefs and mangroves was an order of magnitude more cost-effective than seawalls or breakwaters.

Even though reefs do not line a lot of shorefronts, the annual expected benefits they generate are significant—more than $100

million a year in the U.S. alone and more than $400 million a year each in Mexico, Malaysia, Indonesia, the Philippines and Cuba.

Of course, many coral reefs are not healthy, and losing just a single meter of reef height doubles the direct damages from flooding. For that reason alone, Beck believes reef-restoration projects will multiply. Although the science of coral restoration is young, the potential is enormous—so long as a reef has not already collapsed. "Some of these corals actually grow pretty fast," Beck says. "For example, in places in Indonesia where there's still good reef habitat and lots of healthy corals around small sites that have been destroyed by blast fishing, reefs can turn around pretty quickly."

RISING TIDE OF SUPPORT

COASTAL RESTORATION may finally be getting the attention it deserves. "Things are really beginning to change," Beck says. The Army Corps, which for decades has favored hardscape solutions, has launched an Engineering With Nature initiative—something many planners thought they would never see. The National Oceanic and Atmospheric Administration has made living shorelines a centerpiece of its coastal-resilience blueprint. Hundreds of projects have been completed or are underway around the country, ranging from shoreline stabilizations in Maryland to bulkhead removal in Puget Sound. Most are small, community-based efforts, but larger ventures are becoming more common.

Stimulus funding that flowed after the American Recovery and Reinvestment Act of 2009 increased the size of some projects significantly. Kilometers of oyster-reef projects now line Alabama, Texas and Louisiana. The flagship is Coffee Island, off the Alabama coast. The shoreline had receded up to 100 meters. The Nature Conservancy placed a three-kilometer-long line of shell bags and concrete balls about 30 meters offshore, paralleling the island. The reef immediately blocked wave energy, allowing the marsh to rebuild. Within two years approximately 200 baby oysters per square meter had colonized the structure, covering it and attracting fish, crabs and birds.

Outside the Gulf Coast and the Southeast, restoration projects may be more challenging. California, for example, is a tough undertaking. "In San Francisco Bay," Beck says, "we've lost more than 90 percent of the natural marshes, so you have to go in and re-create an environment wholesale in and around a hell of a lot of people."

Yet where there is a will—and local money—there is a way. The San Francisco Bay Clean Water, Pollution Prevention, and Habitat Restoration Measure, passed by Bay Area voters in 2016, raises $25 million a year for 20 years through a parcel tax. That $500 million will be used to build 40,000 hectares of wetlands—the largest shoreline restoration undertaken in the U.S.—using various techniques. The most novel is horizontal levees. Instead of a high, narrow mound that lines the shore, horizontal levees are broad mudflats, marshes and grasslands that gradually rise from the water's edge, sometimes for hundreds of meters back onto the land. They are graded with vast amounts of earth (often repurposed from building projects) and planted with starter plugs. They can be lower and 40 percent less costly than a traditional levee because the breadth absorbs floodwater. The configuration also gives marsh communities space to retreat as seas rise.

Another encouraging sign is the Living Shorelines Act, introduced in the U.S. House of Representatives by Frank Pallone, whose New Jersey district was devastated by Superstorm Sandy. The bill would designate $20 million in grants a year to living-shoreline work. A Senate version was introduced by Chris Murphy of Connecticut and Kamala Harris of California. Their prospects in the current Congress were uncertain at press time, but their existence shows that living shorelines are gaining ground.

North Carolina's Coastal Resources Commission recently approved a new process that will make it as easy to obtain a living-shoreline permit as that for a bulkhead. Maryland has an even stronger law in place, requiring a homeowner to prove why a bulkhead is needed instead of a natural shoreline. Other states may follow these leads.

The most promising indication of all may be the 2018 agreement made by the Nature Conservancy, the reinsurance industry and the Mexican state of Quintana Roo to create a trust fund to protect the Mesoamerican Reef, off the coast of Cancún and Puerto Morelos. The deal will include the first insurance policy ever taken out on a natural ecosystem. If the reef is damaged by a storm, insurance funds are released to rebuild its natural capital.

For living shorelines to become an important part of any long-term coastal defense plan, policy makers in government, insurance and development will have to start improving and installing them before bad storms hit—and funding the next round of projects through postdisaster spending afterward. That requires good science and good economic numbers—which now exist—as well as good proof in the form of demonstration projects, which are increasingly common.

The first significant examples of postdisaster spending on natural infrastructure could occur as FEMA and other agencies look to spend more than $100 billion in recovery funds from recent hurricanes. Although FEMA's traditional hazard-mitigation investments have focused on tactics such as buying out damaged coastal homes or elevating them, the agency has adjusted its new "benefit-cost analysis" policy to favor investment in natural infrastructure. Beck expects this change in emphasis to result in federally funded projects of unprecedented scope in Florida, Puerto Rico and the Gulf Coast. Other large-scale development may soon follow worldwide as governments, disaster-risk managers, businesses, banks and insurers look to mitigate their risk exposure as cost-effectively as possible. When that happens, it will mark a moment when society realizes nature is not a luxury. It is the future. SA

This article was produced in collaboration with the Food & Environment Reporting Network, a nonprofit investigative news organization.

MORE TO EXPLORE

Marshes with and without Sills Protect Estuarine Shorelines from Erosion Better Than Bulkheads during a Category 1 Hurricane. Rachel K. Gittman et al. in *Ocean & Coastal Management,* Vol. 102, Part A, pages 94–102; December 2014.

Managing Coasts with Natural Solutions: Guidelines for Measuring and Valuing the Coastal Protection Services of Mangroves and Coral Reefs. Edited by M. W. Beck and G.-M. Lange. World Bank, January 2016.

Living Shorelines Academy: www.livingshorelinesacademy.org

FROM OUR ARCHIVES

Architects of the Swamp. John Carey; December 2013.

scientificamerican.com/magazine/sa

PUBLIC HEALTH

THE DENGUE DEBACLE

Is a runaway immune reaction making a dengue vaccine dangerous?

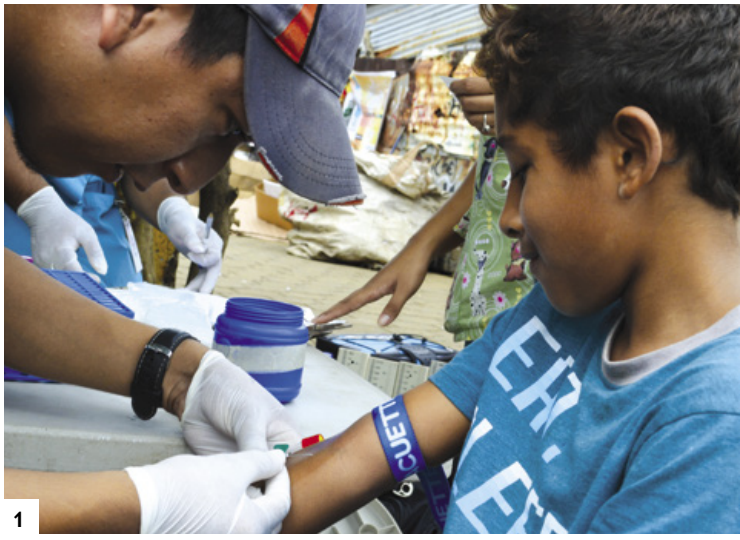
By Seema Yasmin and Madhusree Mukerjee

AEDES AEGYPTI **mosquito spreads several dangerous viruses, including four that cause dengue disease. Whereas a first bout of dengue is usually mild, the second one can be lethal—a peculiarity that may be creating problems for the first ever licensed dengue vaccine.**

IN DECEMBER 2015 then president Benigno Aquino III of the Philippines and others negotiated a deal with pharmaceutical company Sanofi to purchase three million doses of Dengvaxia, the first vaccine ever licensed for dengue. The plan was to give a million schoolchildren, nine years of age, three doses of the vaccine each, sparing them from the worst outcomes of dengue: shock, organ failure and death.

Seema Yasmin is director of the Stanford Health Communication Initiative at Stanford University, where she also teaches science journalism and global health storytelling. She is an Emmy Award–winning reporter and author, medical doctor and frequent contributor to *Scientific American*.

Madhusree Mukerjee is *Scientific American*'s senior editor for science and society.



1

The virus comes in four varieties. All are spread by female *Aedes* mosquitoes, primarily *Aedes aegypti,* with a penchant for sucking blood during the day, when individuals are unprotected by bed nets. In the past five decades these viruses, which are related to those that cause West Nile fever, yellow fever and Zika, have spread in waves across the tropical and subtropical world, increasing dengue incidence 30-fold and affecting upward of 390 million people each year.

Not everyone infected with a dengue virus gets sick: three out of four who get bitten will have no symptoms. The rest may suffer one of three sets of symptoms: a fever that mimics many other viral illnesses; "dengue fever," which is accompanied by headache, pain behind the eyes, aching joints and bones, and, in rare cases, internal bleeding; and severe disease encompassing dengue hemorrhagic fever and dengue shock syndrome. In severe cases, plasma seeps out of capillaries, liquid pools around organs, massive internal bleeding ensues, and the brain, kidneys and liver begin to fail. Although swift hospitalization and careful case management can and do save lives, more than 20,000 people die of dengue every year. Many are children.

Dengue is scary enough that health practitioners in developing countries have been eagerly awaiting a vaccine for decades. Yet when internist Antonio Dans and pediatrician Leonila Dans, both clinical epidemiologists at the University of the Philippines Manila College of Medicine, read about Aquino's vaccination campaign in the *Philippine Star*, the first thing that struck them was the price tag. At three billion pisos ($57.5 million) for procurement alone, the Dengvaxia campaign would cost more than the entire national vaccination program for 2015, which covered pneumonia, tuberculosis, polio, diphtheria, tetanus, pertussis, measles, mumps and rubella. It would reach less than 1 percent of the country's approximately 105 million residents. And although dengue was reported to kill an average of 750 people annually in the Philippines, it was not even among the top 10 causes of mortality. Among infectious diseases, pneumonia and tuberculosis took a far heavier toll.

Perusing an interim report from researchers at Sanofi Pasteur—the vaccine division of Sanofi—on Dengvaxia's clinical trials, Dans and Dans found further cause for concern. Among Asian children two to five years old, those who had received the

IN BRIEF

A mosquito-borne disease, dengue affects almost 400 million people worldwide every year. Whereas most of those affected barely notice a first dengue infection, a second one can kill.

A controversial old theory, called antibody-enhanced development (ADE), explains why a second dengue infection can be much deadlier than the first. New studies strongly support this theory.

The first ever vaccine licensed for dengue appears to mimic an initial dengue infection, possibly exacerbating a second one. The role of ADE in driving this phenomenon remains contested.

PRECEDING PAGES: GETTY IMAGES

2

CHILD IN MANAGUA, Nicaragua, yields a blood sample (*1*) for an extensive study of dengue disease. Another child (*2*) looks down his neighborhood street.

PAOLO HARRIS PAZ (*1* and *2*)

vaccine were seven times *more* likely than unvaccinated children to have been hospitalized for serious dengue in the third year after vaccination. Close examination of the data revealed that although the vaccine was on average safer for older children, it was statistically impossible to rule out the possibility that for some kids, Dengvaxia made things worse.

In March 2016 Dans and Dans and other medical professionals wrote to then secretary of health Janette Garin, warning that the vaccine could be risky for some children and that the Philippines may not possess enough trained health care workers to monitor so many of them for possible adverse effects. A potentially safer vaccine was in the pipeline and probably worth waiting for, they reasoned.

The same month, however, the highly respected advisory group on vaccines at the World Health Organization—which provides guidance to countries on immunization policy—stated in a briefing paper on Dengvaxia that the hospitalizations of young vaccinated children, when observed over several years, were not statistically significant. "No other safety signals have been identified in any age group" older than five, it stated. A "theoretical possibility" existed that the vaccine could be risky for some children, and further research was necessary lest the issue "compromise public confidence" in the vaccine. It nonetheless "should be introduced as part of a routine immunization program in appropriate settings." These included regions where 70 percent or more of a population had already had dengue, where immunization of early adolescents could reduce hospitalizations by up to 30 percent over a period of 30 years. A subsequent position paper from the same group stated that the vaccine was safe for children age nine and older, for whom it was recommended.

In retrospect, it did not surprise Dans and Dans that the authorities chose to ignore their concerns. "It was either believe us or believe the WHO," says Antonio Dans. "If I were them, I'd believe the WHO. I mean, who were we? We were just teachers in a small medical school." Filipino authorities were apparently so confident about Dengvaxia's safety that they did not oblige Sanofi Pasteur to submit results from so-called pharmacovigilance trials that would usually test the safety of a new drug or vaccine in local conditions. The induction of a new pharmaceutical product into the national program typically took three to five years, says Anthony Leachon, a former president of the Philippine College of Physicians, but the dengue vaccination program began right away, in April 2016.

Days later came the first report of a postvaccination fatality, of a boy with congenital heart disease. Garin explained in a press briefing that the boy's death was unrelated to Dengvaxia. Dans and Dans persisted for months, however, speaking to the press and posting a brief video on Facebook that warned—on the basis of a decades-old, highly contested theory called antibody-dependent enhancement (ADE)—that if a child had never had dengue before, the vaccine might actually make a dengue infection dead-

How Antibodies May Aggravate Dengue

Four related viruses transmitted by *Aedes* mosquitoes cause dengue disease. A theory called antibody-dependent enhancement, postulated in the 1970s by Scott B. Halstead, seeks to explain why a second bout of dengue, with a different virus, is deadlier than the first. A first infection, with, say, dengue virus 1, prompts B cells to make antibodies that coat the viruses and deliver them to white blood cells such as macrophages, which trap and kill them. The B cells subsequently become quiescent, awakening after a second infection to make the same antibodies. But antibodies to dengue virus 1 cannot bind well with, for example, dengue virus 2. The antibodies still deliver the invaders to the macrophages but in a way that enables them to escape destruction and instead commandeer the macrophages. They use the subjugated cells' machinery to replicate themselves, flooding the body with viruses. These release a protein that damages blood vessels, causing serious dengue disease.

Illustration by Tami Tolpa

lier than it normally would have been. Garin responded with her own warning: medical practitioners who engaged in "misinformation" on Dengvaxia would be responsible for every death from dengue that could have been prevented by the vaccine.

There the matter rested until November 2017, when Sanofi Pasteur issued its own advisory: those who had never experienced a dengue infection should not get Dengvaxia. A month later the WHO issued fresh guidelines, recommending the vaccine only for those with a "documented past dengue infection." The Philippines halted the vaccination program that December even as parents and the press responded with fury, recriminations and further reports of children's deaths. More than 830,000 schoolchildren had been vaccinated. According to the Department of Health (DOH), as of September 2018, 154 of the vaccinated children had died of various illnesses. The vast majority of these fatalities were unrelated to the vaccine, but clinical observations or blood tests confirmed that 19 of them had been caused by dengue.

Sanofi Pasteur contends that the deaths in the Philippines could have arisen from a failure of the vaccine to protect a small fraction of those vaccinated. In contrast, some experts argue, as Dans and Dans did, that Dengvaxia mimics a prior encounter with dengue—which can prime a patient's body to respond in a dangerous way to a second dengue infection.

The controversy has not slowed down the rollout of Dengvaxia, which is currently licensed in more than 20 countries. In October 2018 the U.S. Food and Drug Administration announced that it would prioritize review of Sanofi Pasteur's application to approve Dengvaxia. That means it could be approved in the U.S., for use in dengue-endemic areas such as Puerto Rico, before the Philippines completes its investigation into the deaths of vaccinated children—and before Sanofi Pasteur publishes its final report from the six-year-long clinical trials.

A BAFFLING DISEASE

FOR MOST VIRUSES, such as measles, the second bout, if it occurs at all, is much milder than the first. For dengue, a second bout is far more likely to kill. Scientists and doctors have struggled for years to understand why this is so. In the 1950s and 1960s, when epidemics of severe dengue began to rise in Asia, they wondered if they were dealing with an altogether new infection. The dengue they were familiar with kept patients bedridden and fatigued, but this new manifestation sent them to the hospital or the morgue. Had the virus mutated? Or was the immune system to blame?

A young scientist fresh out of medical school was seeking an answer. Scott B. Halstead began to study mosquito-borne viruses in 1957, while working for the U.S. Army in Japan. He confronted his first major dengue outbreak four years later, when stationed at a military laboratory next door to the Bangkok Children's Hospital. Doctors thought the youngsters who were carried into the hospital had been poisoned; almost a quarter of them died. Halstead led the team that identified dengue as the cause of the outbreak. He went on to make a second, more baffling, discovery. Children who were infected with dengue for a second time—each time with a different dengue virus—and babies born to mothers who were immune to dengue were most at risk for severe dengue and death. No one could explain why.

In 1964 R. A. Hawkes, then a researcher at Australian National University in Canberra, found that cell cultures infected with Murray Valley encephalitis, West Nile, Japanese encephalitis or Getah viruses infected more cells when the virus was mixed with antibodies compared with the virus alone. Hawkes proposed that the antibodies were stabilizing the virus and increasing their ability to attach to cells. Independently, Halstead was wondering if much the same was happening with dengue.

To understand why two different dengue infections were needed to make the second one lethal, Halstead infected 118 monkeys with different combinations of the four dengue viruses and measured the amount of virus in their blood. In 1973 he published his results: some monkeys, which were infected a second time and with a different dengue virus, had much higher viral loads. Four years later he provided a possible explanation, calling it antibody-dependent enhancement.

Say your first infection is with the dengue virus called DENV-1. Antibodies against that virus can linger in your blood for decades, even your entire life. When you are infected a second time with a different dengue virus, say DENV-2, 3 or 4, the antibodies against DENV-1 could paradoxically accelerate the replication of the new virus inside infected cells, precipitating a potentially fatal dengue infection.

Since refined by Halstead and other researchers, the ADE mechanism goes as follows: A dengue virus is a string of ribonucleic acid enclosed in a protein capsule, which features an array of characteristic protuberances on its surface. During a first infection with dengue, the immune system's B cells make an antibody called immunoglobulin G, or IgG, which latches onto one or more of these irregularities. On attachment, the antibodies can deliver the virus to immune system cells such as macrophages. The word "phage" derives from the Greek word meaning "to eat": macrophages are literally "big eaters." They engulf the virus and digest it with enzymes. Thus, once it is bound to antibodies, the dengue virus is normally trapped and destroyed inside macrophages.

When an infection is over, some antibody-making B cells become dormant. In the event of a second infection with a different dengue virus, these cells wake up to churn out the exact same antibodies as before. Halstead postulated that some of these antibodies can still stick to the surface of the unfamiliar virus but often fail to block its most lethal protrusions—its guns, so to speak. The antibodies still deliver the intruder to macrophages but without having disarmed it. That enables the virus to immobilize the macrophage's own defense system and take over the cell, whose resources it then uses to churn out more copies of itself. The antibody's unwitting assistance helps the new dengue variety produce 1,000 times more copies of itself than if it were acting alone.

Halstead's reward for coming up with the ADE hypothesis was a mix of indifference or disbelief from his peers, he recalls. Today, at 89 years old, he is an adjunct professor at the Uniformed Services University of the Health Sciences in Bethesda, Md., where he continues to argue his case. Many dengue experts describe him as the Godfather of ADE. "Back then, I was thinking I've made a discovery that's very important," he says. "Except nobody wanted to believe ADE was real."

More than four decades later Eva Harris, a dengue expert at the University of California, Berkeley, found strong evidence that ADE was not only real but that it contributed to severe dengue disease in children. Harris had not set out to prove or disprove ADE: she was initially skeptical of the phenomenon and not all that keen on engaging in the decades-long debate. Instead

her team, including statistical modeler Leah Katzelnick, was studying the ways in which dengue sickens children. That goal then led the researchers to help establish a lab in Nicaragua and to begin one of the more challenging types of scientific projects: a long-term pediatric cohort study. Harris and her associates in Managua, Nicaragua's capital city, had the not so easy task of following thousands of children.

For more than 15 years the scientists working on the Nicaraguan Pediatric Dengue Cohort Study cared for the children if they got sick and went to their homes to collect data and blood samples. Out of 6,684 subjects, the researchers found 618 who had been sick with dengue and nearly four dozen who developed severe disease. Scouring more than 41,000 blood samples, taken over more than a dozen years, they made a striking discovery. Children with a specific concentration of antibodies—not low enough to be useless, not high enough to offer protection, but a concentration of antibodies in a middling range—were at a nearly eight times higher risk of acquiring dengue hemorrhagic fever and dengue shock syndrome.

ADE handily explains this finding. If the antibodies are not there to begin with or are present at very low densities, they cannot enhance a subsequent dengue infection to cause serious disease. If antibodies are present at high densities (as happens shortly after an initial infection), they somehow manage to cover any new dengue virus sufficiently to disable it, enabling macrophages to kill it. If, however, the antibody concentrations are in what Harris describes as a "danger zone"—not low and not high—they may facilitate the virus's entry into the macrophages without disarming it, thereby accelerating virus production.

Harris's *Science* paper describing these results was, in the words of Jean Lim, a virologist at the Icahn School of Medicine at Mount Sinai, a "rock star study" that swayed some of the staunchest naysayers of ADE. Her unexpected findings may also have hit on the solution to the dengue vaccine mystery.

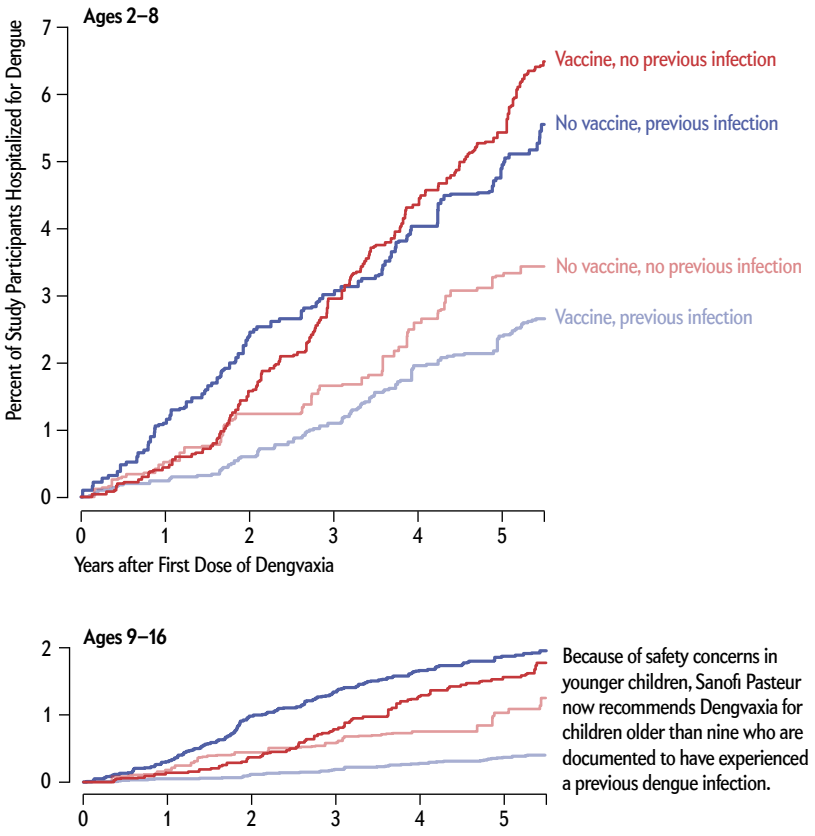
A RED FLAG

COINCIDENTALLY, DAYS AFTER Harris's paper was published in November 2017, Sanofi Pasteur made the announcement that enraged Filipino parents: do not get Dengvaxia if you have not had dengue. A month later the WHO followed suit, stating that only individuals who were proved to already have had dengue should be given the vaccine.

That was exactly what Halstead had been saying since March 2016, when he published an analysis in *Vaccine* arguing that Dengvaxia might cause harm. Perhaps in people who had never had dengue, the vaccine was acting like a first dengue infection, priming the body with just the right quantity of Trojan-horse antibodies to help a real infection turn severe. Young children were less likely to have already encountered dengue, and for them, the vaccine was more likely to act as a first infection. They were also more likely than adults to develop severe dengue after a second

How Safe Is Dengvaxia?

Using a newly developed test, Sanofi Pasteur researchers evaluated which of the children in its clinical trials for Dengvaxia, the first ever licensed vaccine for dengue, had experienced a dengue infection prior to vaccination. They found that if a child had a previous infection (*blue lines*), the vaccine was very effective in protecting him or her against hospitalization for dengue. If, however, the child had no sign of a previous dengue infection (*red lines*), he or she was far more likely than unvaccinated children of the same age group to be hospitalized with serious dengue fever, years after vaccination. The effect was far more pronounced in younger children (*top graph*), who are more likely than older children (*bottom graph*) to develop severe dengue in the first place.



Because of safety concerns in younger children, Sanofi Pasteur now recommends Dengvaxia for children older than nine who are documented to have experienced a previous dengue infection.

SOURCE: "EFFECT OF DENGUE SEROSTATUS ON DENGUE VACCINE SAFETY AND EFFICACY," BY SARANYA SRIDHAR ET AL., IN *NEW ENGLAND JOURNAL OF MEDICINE*, VOL. 379, NO. 4; JULY 26, 2018

Graphic by Amanda Montañez

infection (as Halstead and others observed when a second dengue virus invaded Cuba in 1981). The problem was, there was no simple way to tell which children were dengue-negative before they received Dengvaxia—because Sanofi Pasteur had not collected those data for all of them before vaccinating them.

"I hate to say I told you so," Harris says. "But we saw this coming." At meetings and over long conference calls, she had informed Sanofi Pasteur researchers that they were not collecting the kind of data that could gauge the vaccine's potential to put lives at risk. Instead of testing all children for prior dengue infection before they received Dengvaxia, Sanofi Pasteur tested only 10 to 20 percent of them. The company argues that it was forging through unchartered territory using the best protocols known to vaccine science. "It's routine in many vaccine trials to bleed only 10 to 20 percent of participants," says Su-Peing Ng, global medical head at Sanofi Pasteur.

After the disturbing hospitalization rate came to light, the researchers could not go back and bleed the thousands of children in the clinical trials to check their dengue status prior to vaccination. It was too late—they had already been vaccinated. Sanofi Pasteur worked with scientists at the University of Pittsburgh to develop a novel assay that could test the vaccinated children for evidence of prior dengue infection. That reassessment was the basis for the company's November 2017 warning that only those who had had dengue before should receive Dengvaxia.

The earlier recommendations had been based on the preliminary findings from the clinical trials, which showed that Dengvaxia was safer for older children. As the new tests revealed, however, age served in part as a proxy for prior dengue infection. Nine-year-olds are more likely than toddlers to have already had a dengue infection, especially in places where dengue is endemic, so giving the vaccine to them should be, on average, safe. But neither age nor endemicity is a surefire way of knowing whether a child has had dengue: the only way to know for certain is through a blood test. "Mixed in with a group of nine-year-olds will always be some kids who have never had dengue," Halstead says.

Halstead had very publicly let the WHO know about his concerns. In a December 2016 paper in the *Journal of Infectious Diseases,* he stated that a claim made by the WHO's principal advisory group on vaccines was wrong. The group had said that the risk of hospitalization for kids aged two to five peaks in the third year after vaccination and then "dissipates." Halstead argued that longer-term results from Sanofi Pasteur's clinical trials refuted this assertion. Independently analyzing the clinical trial data, Dans, Dans and others argued in a paper in the *Journal of Clinical Epidemiology* that there was "no biological basis for a threshold age of 9 years" beyond which Dengvaxia could be assumed to be safe.

The WHO stands by its decision to recommend the vaccine for older children who live in countries hardest hit by dengue, however. "The review done was extremely thorough, transparent and according to our published procedures," says Joachim Hombach, senior health adviser in the WHO's department of immunization, vaccines and biologicals. "Different options of possible recommendations were discussed, and the one published in 2016 was the consensus position of the advisory committee."

ONGOING CONTROVERSY

IN JULY 2018 Sanofi Pasteur published its reanalysis of clinical trial data using the Pittsburgh test in the *New England Journal of Medicine*. The review confirmed a higher risk of severe disease and hospitalization in "seronegative" children (those who had no evidence of prior dengue infection in their blood) who had received the vaccine, compared with those who had not. The "vaccine partially mimics primary infection and increases the risk of severe dengue during subsequent infection," the researchers wrote. Although ADE advocates had predicted this finding, the paper said that the "immunopathogenic mechanisms underlying these findings remain unknown."

Halstead contends that Sanofi Pasteur researchers are in "denial" about the evidence from their own trials. Ng counters that exactly how ADE boosts infection has yet to be demonstrated in humans. "ADE is more of a lab observation, an in vitro observation. We've not seen it clinically proven in humans," she says. "We don't know if the underlying mechanism is ADE or not." The overall impact of Dengvaxia on public health remains beneficial, Ng asserts. In children who are age nine and older and who already had dengue, Dengvaxia reduces the rate of severe disease and hospitalization by around 80 percent, according to Sanofi Pasteur. (For reasons that remain unclear, two bouts of dengue appear to confer lifelong immunity to the disease. Strictly speaking, the vaccine is useful only for those who have had one bout but not two.)

According to Sanofi Pasteur, the vaccine "partially mimics primary infection and increases the risk of severe dengue during subsequent infection."

Ng is not the only one who disputes that ADE is the main mechanism behind life-threatening dengue disease. Duane Gubler, founding chief of the dengue branch at the Centers for Disease Control and Prevention and an emeritus professor in the Emerging Infectious Diseases Program at Duke-NUS Medical School in Singapore, argues that DENV-2 and DENV-3 have historically been associated with outbreaks of severe disease. As such, the type of virus could be at least as important as ADE in determining the course of an infection. Alan Rothman, a professor of cell and molecular biology at the University of Rhode Island, says T cells, which recruit and activate macrophages and secrete inflammatory chemicals, are more directly involved in causing severe dengue than are antibodies. Halstead, on the other hand, regards T cells primarily as

VACCINATED CHILDREN and their parents protest the Philippines' 2016–2017 dengue immunization program.

BULLIT MARQUEZ AP Photo

saviors. They kill dengue-infested macrophages, he says, at which time the viruses may release a protein that damages blood vessels. Doctors nonetheless can save a patient by maintaining his or her fluid levels, buying the T cells time to clean out the virus.

TOWARD A SAFER VACCINE

WITH DENGUE INFECTING around a million people every day and popping up in places it has never been seen before, the need for a safe vaccine is becoming ever more urgent. Armed with the new information from Sanofi Pasteur, novel dengue vaccine makers are quick to say they are doing things differently. "We've designed our trial in such a way to ask the most important question—how does it perform in dengue naives?" says Rajeev Venkayya, president of the Global Vaccine Business Unit at Takeda Pharmaceutical Company. Takeda is currently testing its dengue vaccine in children ages four to 16 years in Latin America and Asia. "When we started this trial in 2016, we were well aware of the concern about this issue in naives," Venkayya says. "So we made sure to have naives in our trial and collect baseline blood samples from 100 percent of participants." In January 2019 Takeda announced preliminary results from its clinical trials: the vaccine was effective. Fully assessing safety will likely take more time, however.

At least two other dengue vaccines are being developed, one by the National Institutes of Health and one by GlaxoSmithKline. They are years from being licensed—if they are found to be safe and effective. Gubler says that any vaccine will likely protect well against a couple of dengue viruses but not so well against the others. "And that being the case, there's always a risk of ADE," he continues. "So do we use those vaccines, or do we shelve them and wait another 50 years for a perfect vaccine?" Halstead is far more optimistic. "There's a really good vaccine out there," he says—the NIH vaccine, which, he wrote in a paper, "has met virtually all of the goals needed to demonstrate preclinical efficacy and safety for humans," even if it has yet to undergo extensive clinical trials.

The FDA's October 2018 announcement that it would expedite review of Dengvaxia has added fresh urgency to this debate. The burden of dengue disease in the U.S. is in territories such as Guam, the U.S. Virgin Islands, Samoa and Puerto Rico, where Gubler was based as chief of the CDC's dengue branch. He supports the use of the vaccine in places such as Puerto Rico, where, he says, the dengue surveillance system is far more robust than in the Philippines. That is, medical practitioners there should be able to keep tabs on vaccinees and ensure prompt hospitalization if they develop signs of serious disease. "I'm in favor of using it in highly endemic areas without pretesting because I think with good disease surveillance and case management, the risk of ADE is minimal," Gubler says.

Halstead disagrees: "This is a harmful product unless administered only to proven seropositive individuals." But proving previous dengue infection requires lab testing, which is not always available in many parts of the world with dengue epidemics. Controversially, the WHO advised in September 2018 that although prior screening for dengue infection was preferable, when such testing was not feasible, countries could nonetheless consider administering Dengvaxia in populations with 80 percent or higher dengue endemicity for those age nine and older. Asked to explain the ethical rationale for this recommendation, Hombach stated that the WHO had carefully weighed the pros and cons; it had also noted that such a campaign should be accompanied by "full disclosure of the risks of vaccination of persons with unknown serostatus." Effectively explaining such complex issues in ethnically di-

verse countries, where many people may not comprehend the languages that health officials speak or be able to read information sheets could, however, be a challenge. Sanofi Pasteur takes a more cautious view. Spokesperson Karen Batoosingh says that "the vaccine should be available for people with a prior infection to prevent against subsequent infections" and that the company is striving to develop "a new rapid dengue test to ensure broader access to the vaccine for all those who could benefit from its protective value."

LOSS OF TRUST

THE REPERCUSSIONS from the vaccination program are still reverberating across the Philippines. Speaking before a senate inquiry panel, Aquino explained that dengue incidence in the country had been increasing at an alarming rate, and he had hoped that Dengvaxia could prevent the virus from invading densely populated urban areas. By this past February, however, both the senate and the house of representatives had recommended that Aquino, Garin and other senior officials be charged under an antigraft law for irregularities in the procurement and administration of the vaccine. The families of nearly three dozen dead children have brought criminal cases against Garin and other Filipino officials, accusing them of reckless imprudence amounting to homicide and torture. (Asked to comment on the circumstances in which the vaccination campaign was rolled out, Undersecretary of Health Enrique Domingo stated that he had stepped into the position in December 2017, after the uproar began, and had no personal knowledge of what had taken place.)

Amid the fear and suspicion, several outbreaks of measles have crept across the Philippines. In February, the country reported that more than 8,400 have become sick and more than 130 have died. Parents were too frightened to vaccinate their kids. According to a study by the London-based Vaccine Confidence Project, in 2018 fewer than a third of Filipinos strongly agreed that vaccines are important, down from 93 percent in 2015. In that study, published in *Human Vaccines & Immunotherapeutics,* Heidi Larson, the project's director, and her co-authors argued that "biased media hype"—in particular, "false narratives aiming to vilify authorities, scientists and regulators" and "senate and congress inquiries that resembled the inquisition"—had prompted public panic and loss of trust in vaccines. Dans, Dans, Halstead and others teamed up to respond that several factors had contributed to the decline in public confidence, not least Sanofi's "exaggerated" claims of the safety of Dengvaxia: "The outrage was a result of the loss of trust rather than its cause."

Asked by *Scientific American* if he was giving ammunition to antivaxxers, Halstead responded that he had co-founded the Children's Vaccine Initiative in the 1990s, which later morphed into Gavi, a global public-private partnership that strives to improve vaccine access for children in poor countries. "I have very strong bona fides as a supporter of vaccines and vaccination," he says.

Even as the scientists battle it out, the parents of the vaccinated children are suffering sleepless nights, according to Antonio Dans. "The mothers are really distressed about, Was my child seronegative when he was vaccinated? Why weren't we told it could be harmful? They call us and say, My child has a cough, should we rush him to the hospital? He seems to me slightly febrile, should he go to school?" he relates. "And how do you monitor a cold and a fever in [roughly] a million kids and find out if it's dengue or not? That's a logistical nightmare, and that's what we were warning DOH about." Virtually every death in the vaccinated group was being blamed on Dengvaxia, even if it was clearly unrelated, he adds—and much of this rage and turmoil could have been avoided by accurate and timely scientific advice from trusted authorities. "So that's the sad thing here—that the WHO added to the confusion," Dans concludes.

Halstead worries that as antibody levels in the vaccinated seronegative wane with time, to an intermediate level where ADE becomes more likely, they will become increasingly predisposed to developing severe dengue when they do experience an actual infection. Using Sanofi Pasteur's figures from the clinical trials—that five out of every 1,000 seronegative vaccinated children were hospitalized for dengue, of whom two had severe dengue—he calculated that more than 4,000 children could be hospitalized for vaccine-enhanced dengue disease in the Philippines. "I rub my eyes at what's happening," he says. "Why isn't Sanofi spending a lot of time thinking, 'Okay, now that we've sensitized so many people [to ADE], how are we going to protect them?'" Asked this question, Ng responded that it was unclear whether the cases of severe dengue in the vaccinated group arose from vaccine failure or ADE. All patients, regardless of whether they had dengue before or had been vaccinated or not, should guard against mosquito bites, be monitored for early signs of dengue disease, and seek prompt treatment on indications of more severe disease. Asked when the final report from the clinical trials would be published, Sanofi Pasteur responded that the outcomes had been displayed on a poster at a meeting of the American Society of Tropical Medicine and Hygiene in late 2018.

Vaccines have saved uncountable lives. Naturally occurring smallpox has been wiped off the face of the planet, and polio has almost been vanquished; tetanus and rabies no longer inspire terror. Despite these achievements, public fear of vaccines has been growing, placing millions of children at risk of avoidable disease. The increasing skepticism about vaccines is almost entirely the result of misinformation. Even so, the twists and turns of the Dengvaxia story complicate the usual narrative of valiant scientists battling public ignorance and prejudice in the quest to keep everyone safe.

The dengue saga also raises difficult questions about how pharmaceutical companies and regulators should proceed in the context of evolving scientific knowledge and imperfect vaccines. Is it ethical to endanger a minority in the interest of protecting a majority, as the WHO's September 2018 advisory on Dengvaxia implies? Who should be making these difficult decisions: global bodies of experts, national health authorities, fully informed parents and doctors, or some combination of these? And who should be held accountable when things go wrong? SA

MORE TO EXPLORE

Dengue. Edited by Scott B. Halstead. *Tropical Medicine: Science and Practice,* Vol. 5. Imperial College Press, 2008.

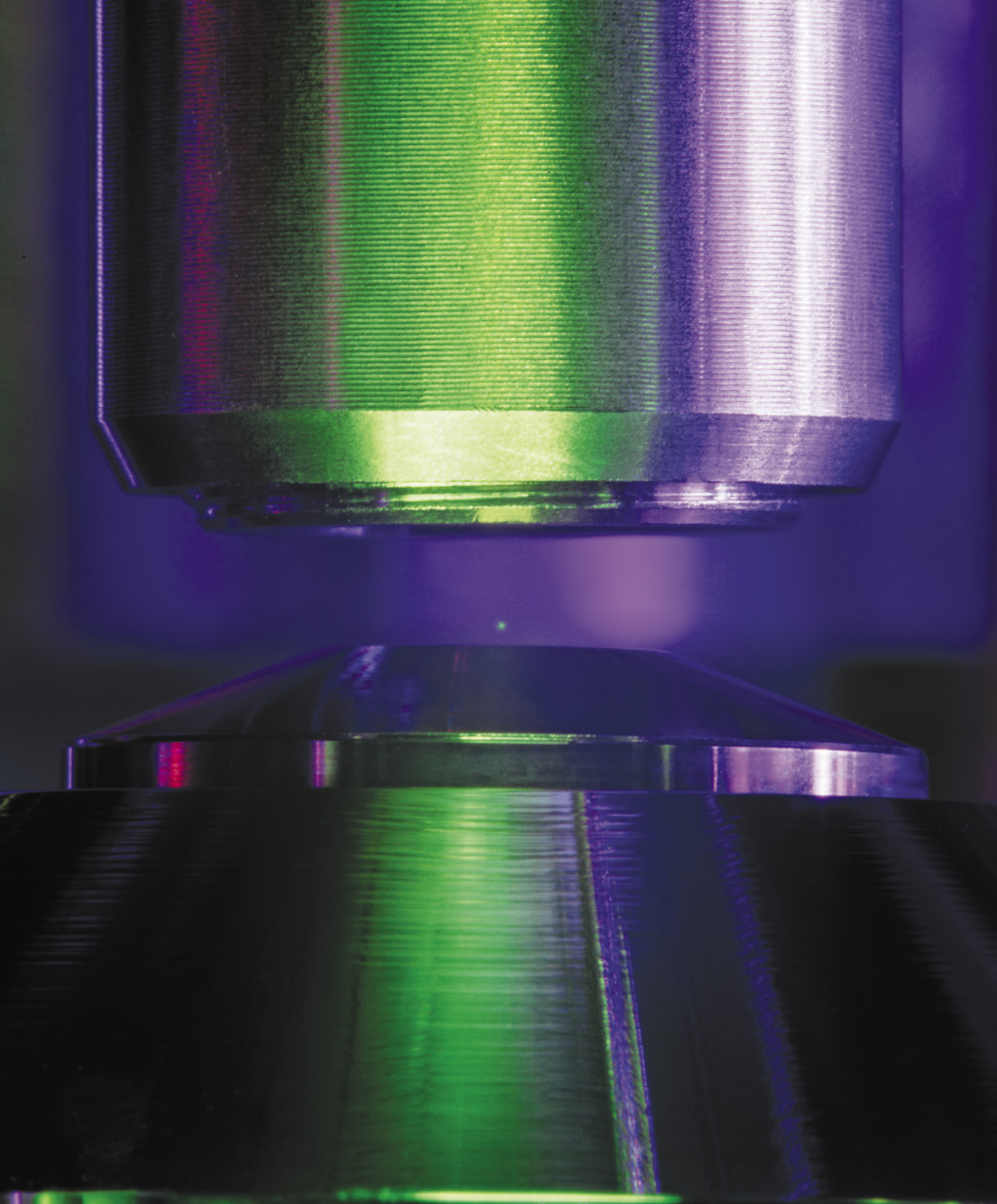
Dengue Antibody-Dependent Enhancement: Knowns and Unknowns. Scott B. Halstead in *Microbiology Spectrum,* Vol. 2, No. 6, Article No. 0022-2014; December 2014.

Effect of Dengue Serostatus on Dengue Vaccine Safety and Efficacy. Saranya Sridhar et al. in *New England Journal of Medicine,* Vol. 379, No. 4, pages 327–340; July 26, 2018.

FROM OUR ARCHIVES

Buzz Kill. Dan Strickman; July 2018.

scientificamerican.com/magazine/sa



LEVITATING A PARTICLE of silica, via laser beam, is a first step toward experiments to test gravity on minuscule scales. The project is running at Markus Aspelmeyer's laboratory at the University of Vienna.

PHYSICS

QUANTUM GRAVITY IN THE LAB

Physicists attempting to unify the theories of gravity and quantum mechanics have long thought practical experiments were out of reach, but new proposals offer a chance to test the quantum nature of gravity on a tabletop

By Tim Folger

IN BRIEF

To unify the famously uncooperative theories of quantum mechanics and general relativity, scientists will likely have to reach down to the unimaginably small realm of the "Planck scale." Practical experiments probing this scale have long been thought impossible, but several new proposals stand to change that.

Physicists are hoping that by making extremely precise measurements of gravity in small-scale setups—experiments that will fit onto a tabletop in a laboratory—they can detect effects from the intersection of gravity and quantum theory.

The experiments aim to show whether gravity becomes quantized—that is, divisible into discrete bits—on extremely tiny scales.

Photographs by Mattia Balsamini

IN 1797 HENRY CAVENDISH, ONE OF GREAT BRITAIN'S LEADING scientists, built a contraption to weigh the world.

At the time, Earth's mass was unknown, as was its composition. Was it mostly solid rock? Did it vary with depth? Astronomer Edmond Halley even suggested that Earth might be hollow. Isaac Newton had compared Earth's mass with that of other bodies in the solar system and knew, for example, that Earth was more massive than the moon. He had even suggested a way to determine Earth's *absolute* mass: measure the gravitational attraction between two small spherical masses with great accuracy, then extrapolate Earth's own mass from the result. But Newton summarily dismissed his own idea—he thought the attraction between the spheres would be too small to detect, even with impractically large masses. "Nay, whole mountains will not be sufficient to produce any sensible effect," he wrote in his masterpiece, the *Principia,* which laid out his laws of motion and gravitation.

On an August day more than a century later Cavendish proved Newton wrong. The device he had built in a shed on his estate in southwest London consisted of two 1.6-pound lead balls attached to opposite ends of a six-foot-long wood rod, which hung from a wire fastened to an overhead beam. Two much heavier lead spheres, each weighing nearly 350 pounds, were suspended separately about nine inches away from the lighter balls. Cavendish expected that the gravitational pull of the heavy spheres on the smaller ones would make the wood rod rotate ever so slightly, and he was right—it moved just over a tenth of an inch.

This allowed him to directly measure the gravitational force exerted by each of the larger spheres on the smaller ones. Because he already knew that Earth exerted a gravitational force of 1.6 pounds on each of the small spheres (in the English system of units, a pound is by definition a measure of force), Cavendish could set up a simple ratio: the gravitational force between the small sphere and the large sphere compared with the gravitational force between the small sphere and Earth. Because the gravitational force is directly proportional to the masses being measured, he could use that ratio to solve for Earth's unknown mass. Over the course of nine months he repeated the experiment 17 times and found that Earth weighed 13 million billion billion pounds, a result essentially identical to the best modern estimates.

"It's an incredible story," says Markus Aspelmeyer, who has been recounting the Cavendish experiment during a Skype call. "It was the first precision tabletop experiment [with gravity]." Cavendish's 220-year-old tour de force, though not actually conducted on a tabletop, is a source of inspiration for Aspelmeyer, a physicist at the University of Vienna in Austria. Like Cavendish, he has plans for an ambitious, seemingly impossible experiment, one that might transform our understanding of gravity: he wants to use a small-scale setup—literally on a tabletop in his lab—to find evidence that gravity might be a quantum phenomenon.

Of the four fundamental forces in the universe, gravity is the only one that cannot be described by the laws of quantum mechanics, the theory that applies to all other forces and particles known to physics. Electromagnetism; the "strong" nuclear force that binds atomic nuclei; and the "weak" nuclear force that causes radioactive decay—they are all quantum to the core, leaving gravity as a sole, mysterious outlier.

This exception has vexed physicists since Albert Einstein's heyday. Einstein never managed to unify his own theory of gravity—the general theory of relativity—with quantum mechanics. Most physicists who now work on the problem believe that the unification occurs when we zoom in on the cosmos to what is called the Planck scale, after Max Planck, one of the founders of quantum theory. Distances on the Planck scale are so tiny—100 trillion trillion times as small as a hydrogen atom—that spacetime itself is thought to assume quantum characteristics. A quantum spacetime would no longer be the smooth continuum described by general relativity; it would be coarse-grained, like a digital photograph that becomes pixelated when magnified. That graininess is a hallmark of quantum theory, which confines the energy, momentum and other properties of particles to discrete bits, or quanta. But what exactly is a quantum of spacetime? How could time or distance be measured if space and time themselves are fractured like broken rulers?

"All our theories of physics either explicitly or implicitly require the existence of rods and clocks: something occurred [here] at this time and then did

Tim Folger is a freelance journalist who writes for *National Geographic, Discover* and other national publications. He is also the series editor for *The Best American Science and Nature Writing,* an annual anthology published by Houghton Mifflin Harcourt.

1

2

SUPERCONDUCTING CIRCUITS (*1*) aid the levitation experiment. Researchers are also trying to measure the gravitational fields of millimeter-wide gold spheres (*2*) to observe gravity closer to the quantum realm.

this [there] at a later time," says Miles Blencowe, a theoretical physicist at Dartmouth College. "Where do you start if you don't even have a time parameter or a distance parameter?" Lajos Diósi, a theoretical physicist at the Wigner Research Center for Physics in Budapest, sums up the conundrum this way: "We don't know what will be there, but we know for sure that there will be a total scrambling of the spacetime continuity if you go down to the Planck scale."

Unfortunately for physicists, there is no way to observe phenomena on the Planck scale and thus no way to check the predictions of various theories of quantum gravity to see which of them might be right. "The situation is not that we do not have theories of quantum gravity," says Carlo Rovelli, a theoretical physicist at Aix-Marseille University in France. "We do. The problem is that we have more than one."

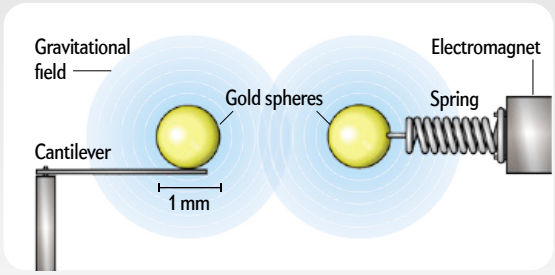
In physics, the higher the energy scale of your experiment, the smaller the distance you can probe. And probing the Planck scale directly would require a machine more than 15 orders of magnitude more powerful than CERN's Large Hadron Collider (LHC) near Geneva, the largest particle accelerator ever built, with a circumference of 27 kilometers. As one physicist says, such an accelerator would need to be roughly the size of our galaxy. Machines such as the LHC bash particles together at nearly the speed of light, and physicists hope something new will emerge from the debris. The basic approach is not much different from blowing up a safe to find out what is inside. The practitioners of tabletop physics aim to replace brute force with finesse, like safecrackers listening to the tumblers of a lock clicking into place. "You're trading high energy for high precision is the way I look at it," says Eric Adelberger, a physicist at the University of Washington. "There's the energy frontier, and there's the precision frontier. If you can measure something really, *really* well, you can test physics that's going on at some really high-energy scale." Now at least three groups, including Aspelmeyer's, are designing experiments to do just that. The scientists are optimistic that these projects will finally reach the levels of precision needed to probe into the realm where gravity goes quantum.

A THOUGHT EXPERIMENT

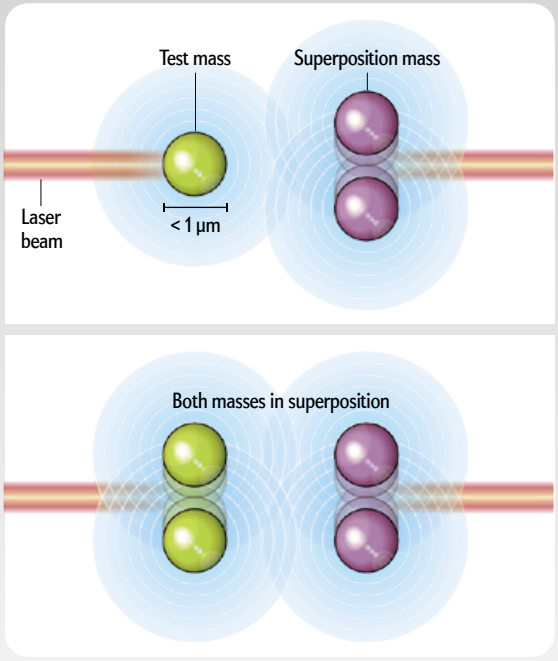
TO UNDERSTAND WHY PRECISION allows physicists to indirectly access higher energies, and thus smaller scales, consider a historical analogue: Brownian motion. In a paper published in 1905, Einstein showed that the puzzling random movements of pollen grains in a jar of water could be explained by collisions with water molecules, even though the molecules themselves were many orders of magnitude too small to be observed directly. Aspelmeyer and other physicists are betting that the unobservably

Quantum Gravity Experiments

To understand whether gravity fits into quantum theory, physicists are designing experiments to measure gravitational fields with extreme precision to search for signs of quantum behavior. Such behavior might include "superposition"—the ability of quantum particles to occupy two places simultaneously—and "entanglement"—a kind of connection between quantum objects where their fates become intertwined. If researchers can find evidence of gravitational fields displaying superposition or entanglement, they will know that gravity has quantum properties.



PRELIMINARY EXPERIMENT #1
One experiment, proposed by physicist Markus Aspelmeyer, will ultimately attempt to put a mass into a superposition state of being in two locations simultaneously and then try to see if the gravitational field of the mass splits into two as well. A preliminary version of this trial will develop the technology to detect gravitational fields of smaller objects than ever before—in this case, two tiny gold spheres. An electromagnet attached to a spring will cause one ball to vibrate, and the other, at the end of a cantilever, should oscillate in response to the changing gravitational pull.



ULTIMATE EXPERIMENT #1
Eventually the team will aim to put one of these spheres into a state of superposition. If this ball's gravitational field goes into superposition, too, and exists in two places, then the other mass should feel the pull of both fields and become entangled, entering superposition as well.

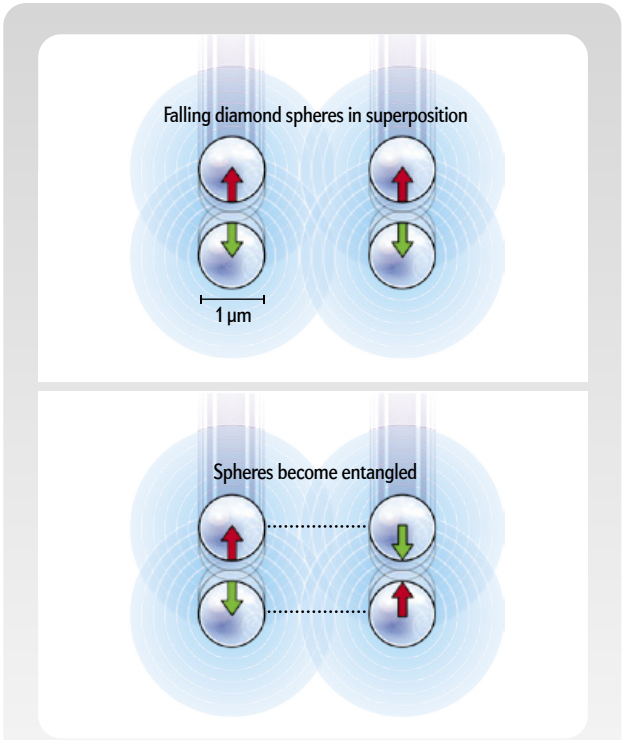
small things happening in the Planckian realm might similarly influence phenomena accessible to tabletop experiments. And although particle accelerators cannot be upgraded by orders of magnitude—we are unlikely to see accelerators with 1,000-kilometer circumferences—the precision of tabletop experiments may well improve by a few orders of magnitude in the decades ahead.

Such gains might allow Aspelmeyer to test a key assumption shared by all theories of quantum gravity: that gravity itself should display some profoundly strange quantum properties. "If that is really true, there should be some consequences for phenomena at an energy scale that is much much smaller [than the high energies that correspond with the Planck scale]"—that is, at roughly the scale we inhabit, Aspelmeyer says. "The question is: Can we come up with experiments that possibly test those consequence?"

What Aspelmeyer has in mind is an experiment that would measure the gravitational attraction between two spherical masses. Unlike Cavendish, though, Aspelmeyer will not be weighing Earth, and his milligram masses are orders of magnitude smaller than Cavendish's lead balls. He wants to test whether gravity interacts at all with the quantum properties of small masses. Specifically, he intends to look at what kind of gravitational effects might be generated by an object placed in a "Schrödinger's cat"-like state of being both here and there at once.

In the quantum world, particles have the uncanny ability to be in two places simultaneously—a superposition, as physicists call it. Scientists have observed quantum superpositions many times in laboratories, but they are delicate states. Interactions with any nearby particles quickly cause objects in superposition to "collapse" into a single position. But while the superpositions last, Aspelmeyer wonders what properties these particles have. Do they create their own minuscule gravitational fields, for instance? "Imagine you place an object in a superposition," he says, "and now you ask a question: How does it gravitate? That is the question we want to answer."

Illustration by Ben Gilliland



EXPERIMENT #2

A second experimental concept, proposed by two groups (by Sougato Bose and his colleagues and, independently, by Chiara Marletto and Vlatko Vedral), would drop two diamond spheres side by side for a couple of seconds. If the spheres are just 100 microns apart, the proximity of their gravitational fields should cause the spheres to become entangled, the physicists reason. If that happens, the experimenters will detect a correlation between the direction of their spins after the drop. If the particles do not become entangled—presumably because gravity does not experience this quantum phenomenon—then the spins should be random.

The experiment Aspelmeyer hopes to carry out was first proposed as a *Gedankenexperiment*—a thought experiment—by the legendary physicist Richard Feynman at a conference in 1957. Feynman argued that if gravity is indeed a quantum phenomenon, a superposition of a particle in two places at once would create two separate gravitational fields. According to the general theory of relativity, gravitational fields are distortions of space and time. Thus, in the case of a small mass in a quantum superposition, two different spacetimes would coexist side by side, almost like two separate mini universes, a state of affairs that should not exist in Einstein's theory.

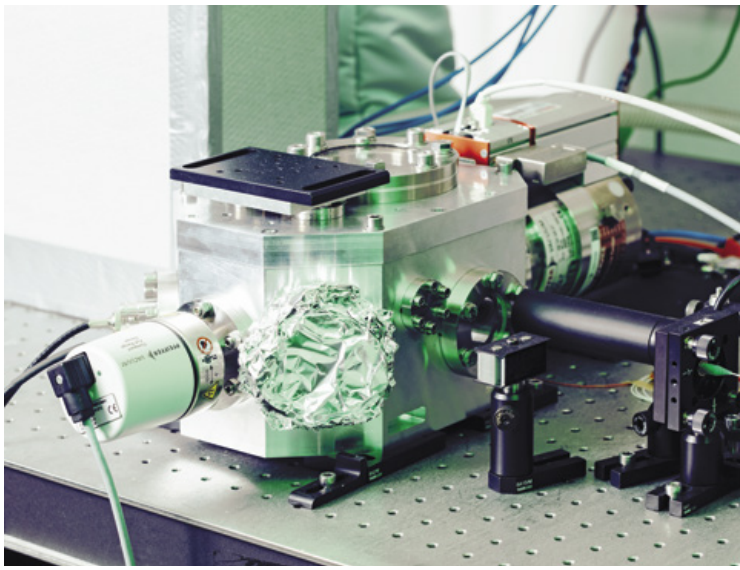
If that spacetime superposition arose, how would another object—a test mass—interact with it? Would the motion of the test mass indicate that it had felt the pull of two different gravitational fields? Or would the interaction cause the superposition to collapse, as some physicists believe, resulting in normal gravitational dynamics? If the superposition persisted and if the test mass *did* interact with the superposition's gravitational fields, it would be strong evidence that the test mass and the superposition had become "entangled"—a telltale feature of quantum mechanics where the properties of two separate particles become inextricably linked. Feynman argued that because only quantum phenomena can become entangled, the experiment would show that gravity, like all other known forces in the universe, is fundamentally quantum.

Such an outcome would not in itself validate any particular theory of quantum gravity, but it would be indirect evidence that gravity is quantized on the Planck scale. Even more broadly, the experiment would provide compelling evidence that the laws of quantum mechanics hold at *all* scales, not just in the realm of photons, atoms and other fundamental particles. Some physicists have clung to the idea that quantum mechanics might break down when it comes to describing the macroscopic world. Roger Penrose, for example, a physicist at the University of Oxford, and Diósi have suggested that gravity causes superpositions above a certain size to collapse, effectively dividing the quantum world from the so-called classical one.

"One of the areas where quantum theory is supposed to fail is when it comes to describing gravity," says Chiara Marletto, a theoretical physicist at Oxford. "There have been a number of eminent scientists who maintain that gravity will be exactly the place where quantum theory breaks down. So, instead of having a quantized [theory of] gravity, we should actually make quantum theory classical for it to describe gravity." In this way of thinking, quantum theory might need to be modified to make it consistent with general relativity, rather than trying to fit gravity into quantum theory as it is.

TURNING THOUGHT INTO REALITY

THE TECHNOLOGY AND EXPERTISE needed to decide the issue did not exist when Feynman came up with his idea, and even now the project remains daunting. For several years now Aspelmeyer's lab has been pushing to measure the gravitational fields of ever smaller masses. It is a tricky undertaking: Earth's enormous gravity swamps the fields of even relatively large objects. The smallest mass for which a gravitational field has been measured so far is a 700-milligram tungsten sphere. That is about the mass of a paper clip or a raisin—a gargantuan object compared to quantum particles.



To realize Feynman's thought experiment, Aspelmeyer and his colleagues will need to work with objects considerably smaller than paper clips. They are now developing a prototype experiment to detect the gravitational fields of millimeter-wide gold spheres (gold was chosen for its density and purity) weighing just a few tens of milligrams. "That's a factor of tens or hundreds less heavy than anything else that has been measured so far," Aspelmeyer says. In the experiment, the researchers will place two gold spheres a few millimeters apart, with one attached to a small, spring-mounted magnet and the other fixed to the end of a micromechanical cantilever. When the electromagnet is turned on, the sphere on the spring will start vibrating, creating a changing gravitational field that in turn makes the mass on the cantilever bounce up and down like a diver on a board. The cantilever's motion—tracked by lasers—essentially amplifies the gravitational force of the sphere attached to the spring, making it easier to detect against the background of Earth's field.

After honing their gravitational-measuring skills with ordinary, nonquantum masses, Aspelmeyer's team would then tackle superpositions. If he could put two small spheres into superpositions, Aspelmeyer could test how their gravitational fields interacted. The results could suggest that the particles were entangled, supporting Feynman's intuition about gravity's quantum nature.

A quantum spacetime would no longer be the smooth continuum described by general relativity; it would be coarse-grained.

What will it take to pull all this off? To have a realistic shot at creating a quantum superposition, Aspelmeyer will need to shrink his millimeter-size gravitational test masses down to fractions of a micron—a 1,000-fold reduction. At the same time, he will need superpositions of objects that are massive enough to have detectable gravitational fields. For that he will likely draw on the talents of a colleague at Vienna, Markus Arndt, who holds the record for the largest object ever placed in a superposition: a behemoth of a molecule containing more than 800 atoms. And instead of being stuck to springs and cantilevers, the masses would be suspended in space with "optical tweezers"—tightly focused laser beams.

"If I can detect the gravitational field of an object over which I can obtain quantum control, then I am in business," Aspelmeyer says. "This would be the long-term dream—not tomorrow, not in five years. Both from the top down and bottom up—from making [the gravitational] masses smaller and making the [superposition] masses larger—we think we know how to get there and bring those two domains together. Now we just need to work hard."

Arndt, Aspelmeyer's likely collaborator, says the experiment presents a host of challenges: the small, spherical masses will be difficult to isolate gravitationally and prone to interacting with any nearby surface. "There are so many effects that are hard to suppress," he says. "Still, it has to be tried, by all means. If we don't start now, it won't be done in 10 years." Arndt compares the effort that will be required with the search for gravitational waves, a phenomenon predicted by Einstein's general theory of relativity. More than three years ago the giant Laser Interferometer Gravitational-wave Observatory (LIGO) finally detected the first gravitational wave, but the discovery was a long time coming. "It was a 40-year effort to get the gravitational-wave detector going," Arndt says.

THE LAST REFUGE OF QUANTUM HOLDOUTS

ASPELMEYER IS NOT THE ONLY PHYSICIST working on the problem. In December 2017 two independent groups simultaneously published their own very similar takes on Feynman's thought experiment. Sougato Bose, a physicist at University College London, and his colleagues and Marletto and her Oxford colleague Vlatko Vedral described a way to test for the gravitational entanglement between superpositions

VACUUM CHAMBERS isolate small masses from the outside world to measure their gravitational fields with minute precision.

of microscopic particles without having to measure their gravitational fields.

In the proposed experiment, pairs of micron-wide diamond spheres would be put into superpositions and allowed to fall in a vacuum for a couple of seconds in Earth's gravitational field. If the spheres were close enough together—about 100 microns apart, according to Bose's estimates—their gravitational fields should cause the particles to become entangled. When that happens, the properties of the entangled particles will instantaneously correlate in ways that are not possible in classical physics. One particle's spin, for example—whether it points up or down in a magnetic field—will flip in the opposite direction as soon as the spin of its entangled partner is measured.

By tracking how often such correlations occur—Bose says that 10,000 trials should yield an answer—he, Marletto and Vedral could determine whether the falling diamonds had indeed become entangled. Once again, entanglement would suggest that gravity itself must have quantum properties. "Our work will prove that gravity is quantum in the sense that it obeys the superposition principle," Bose says. The experiment faces many of the same challenges that Aspelmeyer's does: the need for large superpositions that last for seconds at a time and stay close enough together so that gravity can entangle them. "That makes the thing very difficult," Bose says. "But I'm sure I'll see it in my lifetime."

Both experiments, if they pan out, would give physicists their first indirect evidence that gravity—and therefore spacetime itself—must be quantized on the Planck scale. And that is an exciting prospect for Rovelli and other quantum-gravity theorists, who have spent years working on theories without any experimental feedback. "I think it's a game changer, this idea, the attempt to see quantum gravity in the lab," Rovelli says. "As far as we know [gravity's quantum nature] should definitely be real, otherwise we haven't learned a thing about the world."

A century after its birth quantum mechanics remains the most baffling of scientific theories. Some physicists, most famously Einstein, doubted that it could be the final word on the nature of reality. Yet countless experiments have confirmed the theory's predictions, typically with multidecimal-point accuracy. In some sense, the question of whether gravity is quantum or classical represents a last refuge for those who feel that there must be *something* wrong with quantum mechanics. If these tabletop experiments succeed, that refuge will crumble.

"Quantum theory teaches us a completely different way of describing what we can say about nature," Aspelmeyer says. "The rule book that we have found through quantum theory is a fundamental one and has to apply in general to all the theories we have." SA

MORE TO EXPLORE

A Micromechanical Proof-of-Principle Experiment for Measuring the Gravitational Force of Milligram Masses. Jonas Schmöle et al. in *Classical and Quantum Gravity,* Vol. 33, No. 12, Article No. 125031; June 23, 2016. https://iopscience.iop.org/article/10.1088/0264-9381/33/12/125031

Gravitationally Induced Entanglement between Two Massive Particles Is Sufficient Evidence of Quantum Effects in Gravity. C. Marletto and V. Vedral in *Physical Review Letters,* Vol. 119, No. 24, Article No. 240402; December 15, 2017. Preprint available at https://arxiv.org/abs/1707.06036

Spin Entanglement Witness for Quantum Gravity. Sougato Bose et al. in *Physical Review Letters,* Vol. 119, No. 24, Article No. 240401; December 15, 2017. Preprint available at https://arxiv.org/abs/1707.06050

FROM OUR ARCHIVES

Tangled Up in Spacetime. Clara Moskowitz; January 2017.
Crossing the Quantum Divide. Tim Folger; July 2018.

scientificamerican.com/magazine/sa

MEDICINE

A Shot at Regeneration

A once abandoned drug compound shows an ability to rebuild organs damaged by illness and injury

By Kevin Strange and Viravuth Yin

Illustration by Sam Falconer

Biologist **Kevin Strange,** CEO of Novo Biosciences, is a former president of the MDI Biological Laboratory (MDIBL) in Bar Harbor, Me.

Viravuth Yin is the chief scientific officer at Novo and an associate professor at MDIBL.

A TALE OF SHARK BITES AT A SCOTTISH PUB HAS LED US TO SOME NEW IDEAS about rebuilding broken bodies. In the early 2000s American geneticist Michael Zasloff of Georgetown University had traveled to the University of St. Andrews to give a talk about several natural antibiotics found in animal skin. After the lecture, he and some of the university scientists went for a drink, and one of them, a marine biologist, began to talk about how dolphins were frequently savaged by sharks, sustaining some bite wounds 45 centimeters long and 12 centimeters deep. But remarkably the dolphins healed up in weeks, with no signs of infection.

Zasloff was struck by this swift recovery from terrible injuries, and he could not get the conversation out of his mind. He spent the next several years reading reports about bitten dolphins and talking to marine biologists who studied these animals. In 2011 he published a letter to the *Journal of Investigative Dermatology* entitled "Observations on the Remarkable (and Mysterious) Wound-Healing Process of the Bottlenose Dolphin." He noted that the dolphins did not seem like they were simply patching torn flesh with a scar, which produces different kinds of cells, but instead might be actually regenerating the damaged tissue. And soon after that, he called one of us. Strange, at the time president of the MDI Biological Laboratory, was pushing the institution to investigate natural and synthetic compounds that stimulated regeneration, and Zasloff thought some of the antibiotics he had found in animal skin might also foster this kind of regrowth. Anything that helped the body replace or restore cells destroyed by disease or injury would be a major medical boon.

Six years after that phone call, the three of us (Yin, Strange and Zasloff) have shown that a natural antibiotic called MSI-1436, originally identified by Zasloff in a small shark, dramatically stimulates several types of damaged organs to regrow in zebra fish and prompts heart muscle to regenerate in mice. The compound appears to release some molecular "brakes" holding back a tissue's natural ability to regenerate after sustaining damage. In mice that have a condition that mimics muscular dystrophy in people, it appears to slow down muscle degeneration. We are still experimenting in animals and have not shown these effects in humans, but MSI-1436 has an important advantage over the legion of drug candidates that look good in test tubes but fail in people: it has already been shown to be safe.

In 2007 this compound was tested in humans as a potential treatment for obesity and type 2 diabetes because it improves cell sensitivity to insulin. The studies, regulated by the U.S. Food and Drug Administration, demonstrated that MSI-1436 was well tolerated at high doses and did not harm patients. But because the drug comes as a liquid that needs to be injected every day, it was unlikely to be popular with patients who already had alter-

IN BRIEF

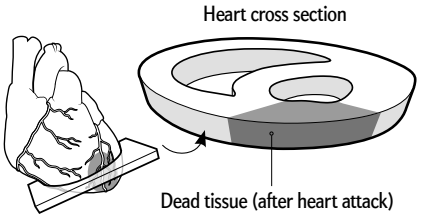
Stem cell treatments grab many headlines about healing and regrowing body parts but have had minimal success.

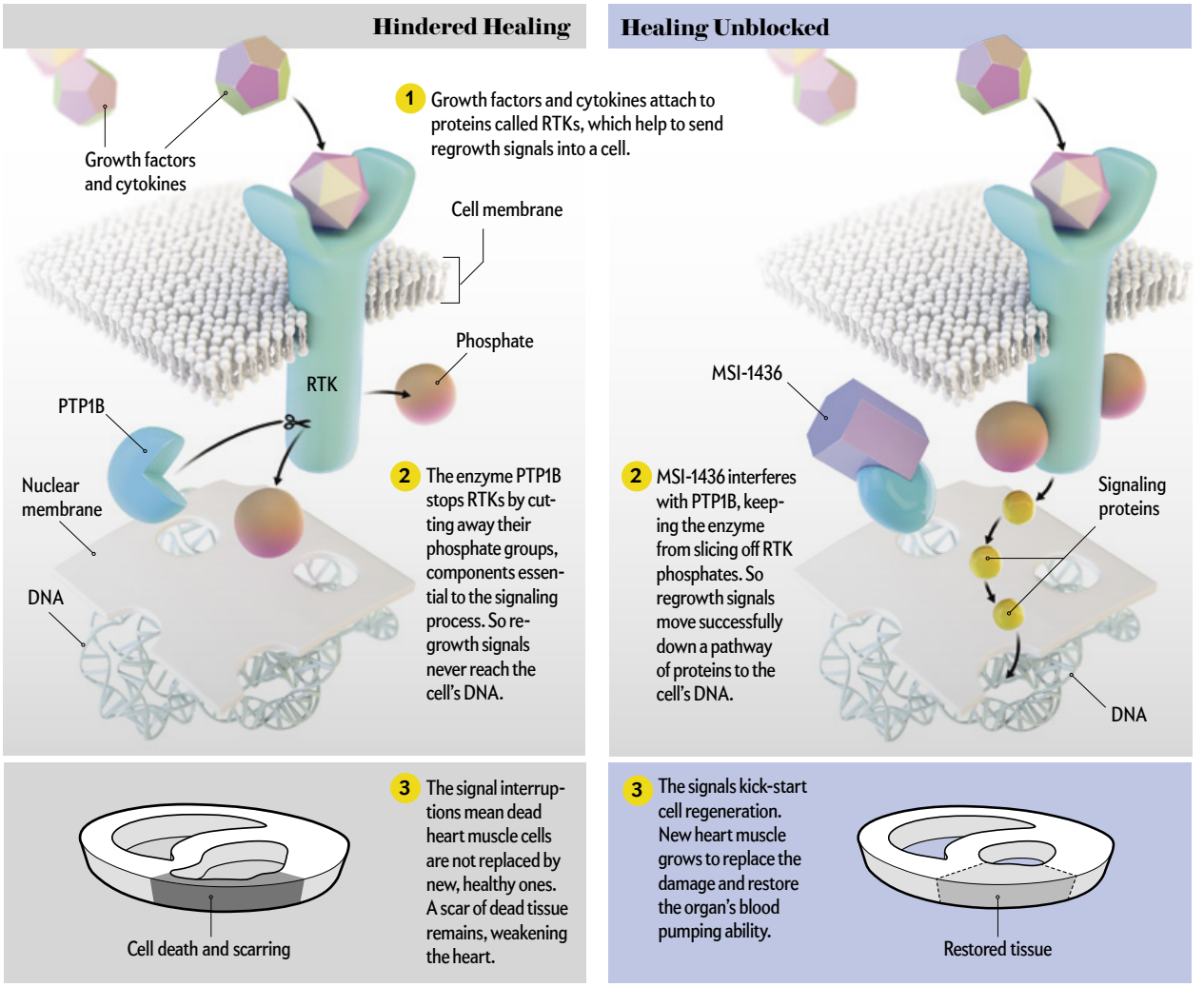
A compound called MSI-1436 may be more promising, animal experiments show. It takes the brakes off the body's natural ability to regenerate cells.

The molecule, originally intended as a diabetes and obesity medicine, was successfully tested for safety in people—a big head start in drug development.

Body Rebuilder

The ability of cells and organs to regenerate after injury is limited under normal circumstances. After a heart attack, for instance, molecules called growth factors and cytokines go to the heart to stimulate new growth, but their signals are blocked by an enzyme. Dead heart cells are not replaced. In tests on mice with damaged hearts, however, an injected compound called MSI-1436 inhibits the trouble-making enzyme. The result is new heart muscle, pumping away.





natives, such as pills, that were easier to take. Pharmaceutical companies did not pursue it.

But for regenerating damaged cells, there are currently not a lot of medical options. There have been many headlines about stem cells, unspecialized cells that can, with the right cues, give rise to the myriad highly differentiated cell types that make up the human body. In theory, they could repair damaged parts. Unfortunately, despite many years of clinical trials and other tests, stem cell transplants remain challenged by a lack of efficacy and other serious concerns. The only wide use now is in bone marrow transplants to treat blood cell diseases. But MSI-1436, which has a proved safety record, could become valuable regenerative medicine for repairing the destruction from heart attacks and potentially from other devastating diseases as well.

RESTORATION PROJECT

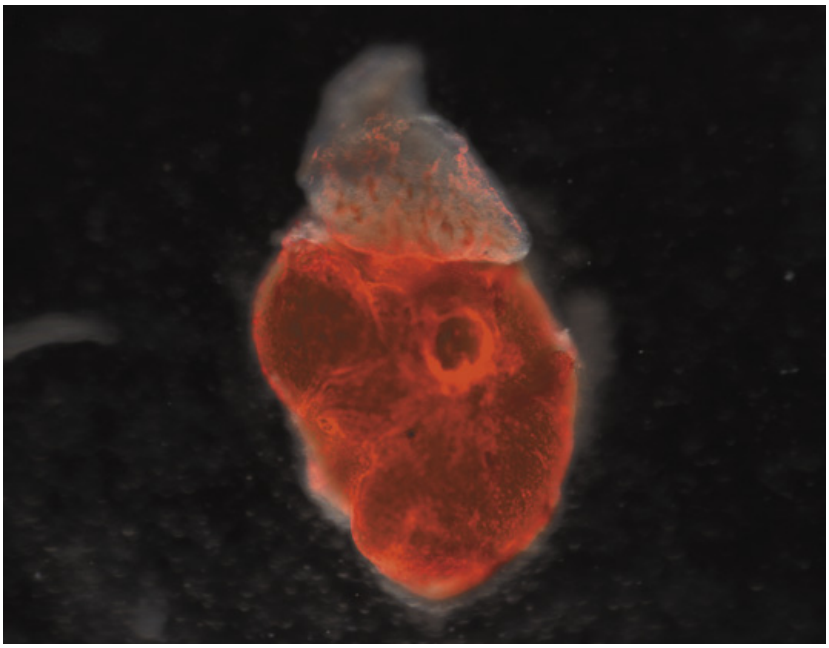
MANY ANIMALS have startling regenerative capabilities. Salamanders regrow entire limbs after amputation. The lamprey, an eel-like fish, can repair a severed spinal cord. Zebra fish, a popular aquarium fish species that is also broadly used in biomedical research, can regenerate damaged hearts, kidneys, pancreases and appendages. Pick almost any tissue or organ,

Illustration by Campbell Medical Illustration

and there is probably an animal that can readily regenerate it.

Even humans are not out of this regrow-and-repair game completely. Our capability appears more limited, but our skin, blood and gut cells regenerate constantly. Muscle can add new cells after some small injuries. And like Prometheus of Greek legend perpetually regenerating his liver, ours, too, can regrow after limited injury. So our cells have these abilities, but they get dialed down and switched off, especially as we grow older. Yet because they exist in the first place, we thought it might be possible to turn them back on with the proper molecular signal. But of course, we first had to find that signal. The fast-healing animal world was the logical place to look.

Zasloff, in his prospecting for antibiotics in animals, had come across a class of molecules called aminosterols—MSI-1436 is one of them—that also had the potential to stimulate regeneration because they could regulate cell activities such as growth. We decided to test their capacities using zebra fish. As vertebrates, the fish have many of the same major organs that people do, and about 70 percent of their genes have human counterparts. They are transparent as embryos, making it easy to study changes in anatomy. We wanted to see if any of the aminosterols made the fish's ability to regrow tissue happen faster and better.



ZEBRA FISH HEART, damaged and then dosed with the compound MSI-1436, quickly regrew muscle and regained blood-pumping ability.

We started with a simple amputation test, cutting off part of the tail and adding various aminosterols to the water in the fish tanks. Nothing happened. That changed, however, when we got some help from Helen Roberts, a recently graduated high school senior working as an intern in Yin's laboratory. Roberts developed methods to inject substances directly into the zebra fish rather than adding them to the water. When she did this with MSI-1436, it stimulated the rate of tail fin regeneration by more than 300 percent. Instead of taking 10 to 12 days to regenerate, the fin took only three to four days, and there were no signs of abnormal growth. We had Roberts and a lab technician independently repeat the experiments, comparing different compounds, and made sure they did not know which one they were injecting into the fish. MSI-1436 worked in each situation; other compounds did not. This was stunning and prompted some exclamations of excitement in Strange's office that are not appropriate to repeat here.

How did MSI-1436 stimulate regeneration in such a dramatic fashion? Some scientists had studied its effects on cells, and after we did more experiments, the answer seemed pretty clear: MSI-1436 hobbled an enzyme named protein tyrosine phosphatase 1B (PTP1B), which has several jobs in the body, one of which is to regulate the growth of new cells. That is an important occupation because widespread uncontrolled growth can make an organ malfunction or become cancerous. PTP1B is essentially a brake on cell regeneration. Our compound released that brake but only at injury sites, in a very local, focused and controlled way.

When PTP1B brakes, it does so by interfering with a crucial class of cell proteins called receptor tyrosine kinases, or RTKs. RTKs are embedded in cell membranes and form parts of signaling pathways that start outside the cell and lead inside; the signals the path carries tell a cell to grow and divide. To become active and pass those signals along, RTKs need to be bound to another type of molecule, called a phosphate group. PTP1B gets in the way because it cuts phosphate groups away. No phosphate, no RTK signaling and no cell regeneration. But our compound, MSI-1436, disables PTP1B's phosphate-cutting ability. And with these brakes disabled, RTKs and cell regeneration run happily along.

HEART DISEASE AND HEART ATTACKS

IN ADDITION TO REGROWTH of the zebra fish tail fin, we found that our PTP1B blocker stimulates regeneration of the zebra fish heart. That is quite important because while humans may not have a tail fin, we do have a heart, and it often needs help. Cardiovascular disease is the leading cause of death worldwide, killing about 18 million people every year, and 85 percent of those deaths are caused by heart attack and stroke. Heart muscle cells that die in an attack do not regenerate but instead form a scar that increases the chances of another attack. A 45-year search for treatments, including stem cell transplants, to help the heart repair itself has failed.

So when we saw that MSI-1436 helped fish, we moved on to test it in mice, an animal model widely used in heart disease research. We induced heart attacks in the rodents and then injected them with MSI-1436 every three days over a span of four weeks. The blood-pumping ability of the organ improved by more than twofold, the amount of scar tissue was reduced by 50 percent, and heart muscle cells at the injury site proliferated by nearly 600 percent. MSI-1436 is the only small molecule known to have this effect.

Recently we began testing the compound in mice with a completely different kind of disease: a rodent version of Du-

CHRISTINA A. DYKEMAN AND YIN LABORATORY *MDI Biological Laboratory*

chenne muscular dystrophy. This is a slow, degenerative muscle-wasting ailment, quite distinct from the sudden damage of a heart attack. Our preliminary data indicate that MSI-1436 prompts enough cell regeneration to keep skeletal and heart muscles ahead of the wasting. It does not stop the disease, but it may mitigate its effects.

ON FROM ANIMALS

WHAT BODES WELL for humans is that the compound stimulates tissue regeneration in both zebra fish and adult mice. These animal species are separated by approximately 450 million years of evolution. Because MSI-1436 works on such distinct creatures, the compound most likely targets cellular pathways that have been strongly conserved, or reused, by evolution in organism after organism. It increases the chances that such pathways exist in people and can be manipulated in a like fashion.

Perhaps animals respond well to MSI-1436 because it evolved in animals in the first place. It was not identified in a genetically engineered lab mouse or from tens of thousands of synthetic chemicals at a drug company.

Testing drug candidates in a diverse population of humans, however, is very different from tightly controlled lab animal studies. The potential for failure in clinical trials is high. And although there are good reasons to be optimistic about MSI-1436, the reality is that we will not really know if it is effective in treating heart attacks until we try it in human patients. As a first step in that direction, we have begun National Institutes of Health–funded tests of this drug candidate in a pig heart attack model. The pig heart is remarkably similar to the human heart, and the size of the animal allows us to mimic a human heart attack and its early-stage treatment much better than we can in mice. If the pig trial results are positive, we will be well positioned to seek permission from the FDA to conduct clinical trials.

In our studies, we are also going to be watching out for signs of cancer. A concern in regenerative medicine is that treatments to stimulate tissue growth and repair may trigger uncontrolled cell proliferation, which is the biological hallmark of a cancerous cell. We believe that this concern is lower with MSI-1436. The extensive toxicity testing already done on the compound during its earlier incarnation as a diabetes and obesity drug was designed to identify problems such as cancer. None were found, and the FDA deemed MSI-1436 safe to use in studies of human patients. Limiting the presence of PTP1B also seems reasonably safe. The gene responsible for making it was first knocked out in mice in 1999. These mice have been studied extensively. They showed no signs of overt tumor growth, which suggests that even long-term inhibition of PTP1B does not cause cancer. Plus, treatment using MSI-1436 to stimulate tissue regeneration would likely last only a few weeks or months.

Finally, our own experiments indicate that MSI-1436 acts only at an injury site and does not send cells in normal tissue into a kind of cancerous overdrive. In zebra fish and mice, we did not observe tissue overgrowth or abnormalities in tissue and organ shapes (a sign of growing malignancy) when injured animals were treated with the compound. We tested this idea in one-cell zebra fish embryos, a highly sensitive point in the development of the fish. Embryos injected with the compound for 14 straight days developed into normal adult animals. Going from a single cell to a full-blown animal is, obviously, a complex process that requires tremendous cell proliferation and differentiation. Many drugs and environmental factors easily send it wildly off-kilter when given at such an early stage. It is reassuring that MSI-1436 does not.

THE NATURAL ADVANTAGE

PERHAPS ANIMALS RESPOND WELL to the compound because it evolved in animals in the first place. It was not identified in a genetically engineered lab mouse or in cells grown in a dish at a medical center or from a screen of tens of thousands of synthetic chemicals at a drug company. Our findings came out of lessons we learned from dolphins, sharks and zebra fish. MDIBL, where we took advantage of those lessons, was founded to do exactly that. Our institution began as a marine research station on the coast of Maine in 1898, when biologists wanted an immediate connection to the natural world they were trying to understand.

This link is, unfortunately, something that the larger biomedical research enterprise, and the pharmaceutical industry in particular, has drifted away from. There is an important role for computer-designed molecules, of course. But regenerative medicine biologist Alejandro Sánchez Alvarado of the Stowers Institute for Medical Research, who is not involved in our research, has told us that MSI-1436 is "a great case study of what happens when scientists choose to walk away from the familiar and search nature for answers to vexing biomedical problems." SA

MORE TO EXPLORE

Observations on the Remarkable (and Mysterious) Wound-Healing Process of the Bottlenose Dolphin. Michael Zasloff in *Journal of Investigative Dermatology,* Vol. 131, No. 12, pages 2503–2505; December 2011.

Rethinking Differentiation: Stem Cells, Regeneration, and Plasticity. Alejandro Sánchez Alvarado and Shinya Yamanaka in *Cell,* Vol. 157, No. 1, pages 110–119; March 27, 2014.

The Protein Tyrosine Phosphatase 1B Inhibitor MSI-1436 Stimulates Regeneration of Heart and Multiple Other Tissues. Ashley M. Smith et al. in *npj Regenerative Medicine,* Vol. 2, Article No. 4; March 3, 2017.

FROM OUR ARCHIVES

A Change of Heart. Ferris Jabr; April 2013.

scientificamerican.com/magazine/sa

ANIMAL PHYSIOLOGY

Investigations into how the electric eel uses electricity have revealed astonishing insights into the creature's physiology and behavior

By Kenneth C. Catania

ELECTRIC EEL wields its superpower to great effect during both hunting and self-defense.

Photograph by David Liittschwager

SHOCK & AWE

Kenneth C. Catania is a professor of biological sciences at Vanderbilt University. He studies comparative neurobiology, with an emphasis on animal sensory systems. This is his fourth article for *Scientific American*.

IT'S NO SECRET THAT ELECTRIC EELS STUN THEIR PREY—ACCOUNTS OF SUCH OCCURRENCES DATE back centuries. But unless you work security on the starship *Enterprise,* "stun" is a vague term. What really happens when these creatures attack? Until recently, biologists knew surprisingly little about the electric eel's superpower. I was not planning to study this phenomenon, and I certainly never imagined I would offer an eel my arm in the name of science, as I eventually did. But as a professor of biological sciences at Vanderbilt University, I teach about electric fish, and when I brought some eels to my laboratory so I could obtain new photographs and slow-motion movies to liven up my lecture, I saw something so strange that I had to drop everything else to investigate.

When an eel attacked a prey fish with high voltage, all the nearby fish in the tank became completely immobile in only three milliseconds. It was as if they had been turned into little statues; they just floated stock-still in the water. At first, I wondered if they had simply been killed. But if the eel missed its target and turned off the high voltage, the fish "unfroze" and took off at full speed. The eel's effect was temporary. I was hooked; I had to know how the eel's electric attack worked.

The most obvious analogy that came to mind was a law-enforcement Taser, which causes neuromuscular incapacitation by interfering with the nervous system's ability to control muscles. Tasers deliver electricity along wires in short, high-voltage pulses at a rate of 19 pulses a second. Electric eels do not need wires, because the water allows current to flow, as happens when a hair dryer falls into a bathtub. But otherwise, the eel's output is reminiscent of a Taser's: it comes in brief pulses, each lasting only about two milliseconds. Eels can give off more than 400 pulses per second during an attack volley, however—a much higher rate than the law-enforcement devices. Could electric eels be souped-up, swimming Tasers?

With this question in mind, I set out on what would become a three-year mission to unravel the mechanism of the eel's attack and the effects of its shocks on both prey and would-be predators. I was surprised at every turn by the eel's sophisticated use of electricity and reminded that humankind's inventions don't hold a candle to nature's.

SHOCK VALUE

YOU MIGHT BE SURPRISED to learn the electric eel is not a true eel but rather belongs to a family of fish known as the Gymnotidae that live in South America. The other members of this group give off very weak electric discharges that they use to sense their surroundings and to communicate. The electric eel has amped up its power over the course of evolution. It can generate a charge of up to 600 volts, thanks to the electric organ that spans nearly the length of their body (the animals can reach eight feet in length and weigh more than 40 pounds). The organ is composed of thousands of special disk-shaped cells called electrocytes that work like batteries to discharge electricity.

To investigate the possibility that the electric eel operates like a Taser to incapacitate its prey, I needed to observe the animal in hunting mode. So I devised an experiment that took advantage of the eel's insatiable appetite for earthworms. First, I placed a dead fish that still had working nerves and muscles in the water with the eel (but separated by an electrically permeable barrier) and attached it with a string to a device for measuring muscle contractions. Then I fed the eel earthworms, which it happily shocked and ate. This setup allowed me to conduct a series of tests on the fish muscle responses to the high-voltage pulses emanating from the hunting eel.

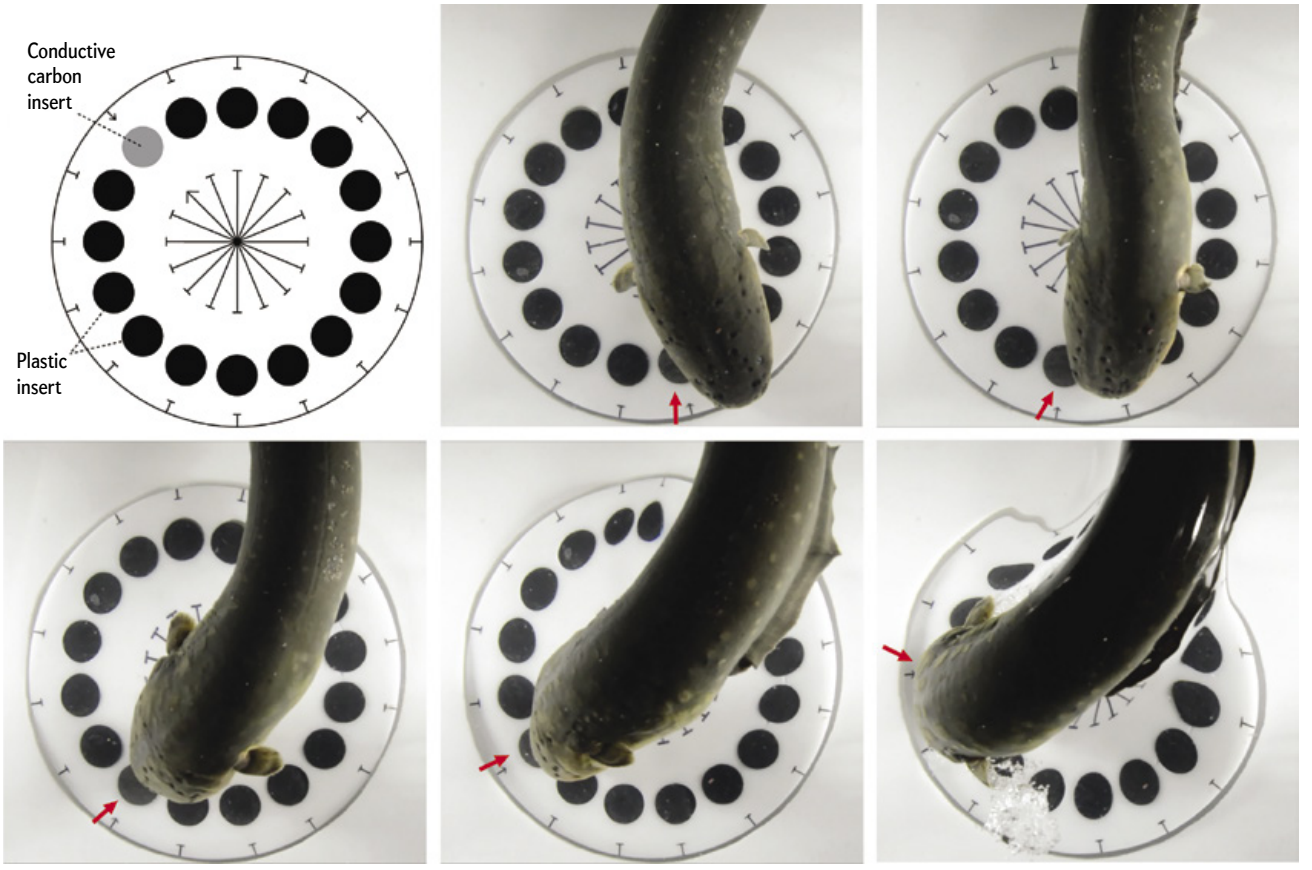
The volleys of high-voltage pulses from the eel caused massive muscle contractions in the fish that started three milliseconds after the electric attack began—exactly the same amount of

IN BRIEF

The electric eel has long been known to stun its prey. But the mechanism of the eel's attack and how the shocks affect prey were a mystery.

A series of laboratory experiments has revealed how the creature uses electric fields to detect, track and immobilize prey.

The eel also uses its electrical powers when threatened, leaping from the water to intensify the current it delivers to potential predators.



TRACKING SYSTEM: The eel can track prey and other conductors using high-voltage electroreception. In experiments with a spinning disk bearing one conductive insert and multiple nonconductive inserts, the eel singled out the conductive insert with remarkable accuracy.

time that passed before the fish were seen to stop moving in the slow-motion movies. Apparently eels invented the Taser long before humans. But the experiments showed much more. Eels do not activate fish muscles directly. Instead their zaps activate the nerves that lead to the fish muscles. Each high-voltage pulse from an eel generates an action potential, or nerve impulse, in the fish's motor nerves.

This finding is remarkable when you consider that the eel's electric organ is a modified muscle activated by the animal's own motor nerves. The motor nerves are, in turn, activated by neurons in its brain. For each high-voltage pulse, the flow of command signals starts in the eel's brain and travels to its motor neurons, which then activate the electric organ. From there the signal passes through the water to trigger the motor neurons, and then muscles, in nearby fish. In other words, the eel immobilizes its prey using a form of high-fidelity remote control.

Intriguingly, this insight suggests the eel's electric output may have been shaped in part by what happens to the muscles of its prey. With this finding in mind, I began considering the eel's high-voltage volley with a new perspective. I was especially intrigued by reports from a previous investigator, Richard Bauer, who in 1979 showed that hunting electric eels often pause to give off pairs of high-voltage pulses, each separated by two milliseconds. These paired pulses are called doublets, and all the eels in my lab exhibited the same behavior. What, I wondered, are doublets for?

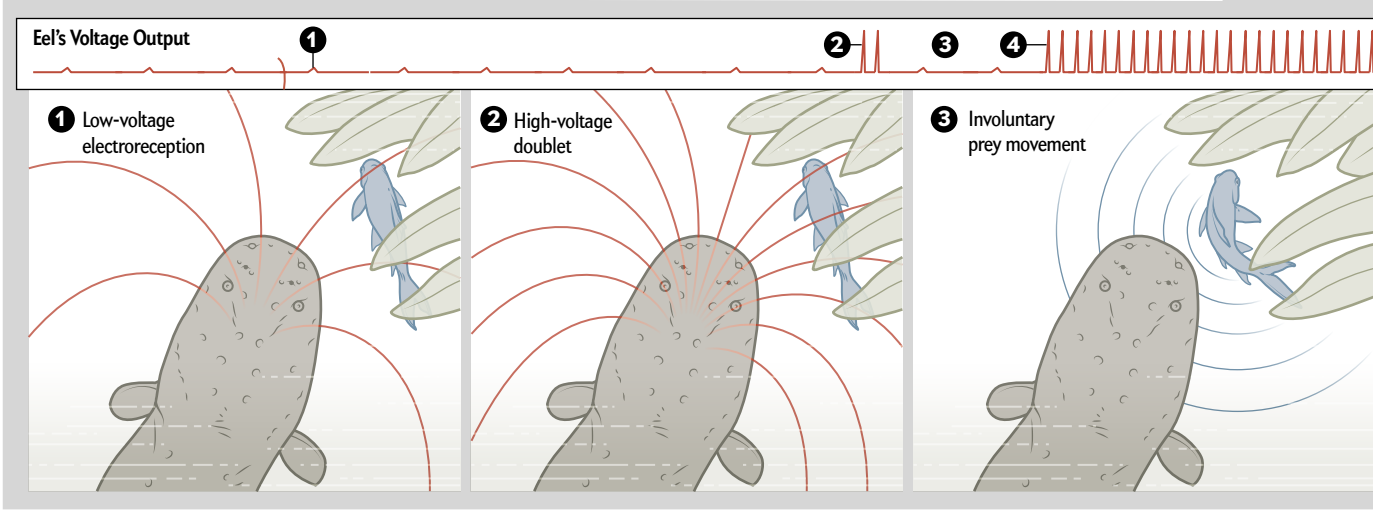
A little research into muscle physiology revealed that doublets—which can also be described as pairs of action potentials—sent from motor neurons to muscles are the best way to generate maximal muscle tension. Accordingly, my experiments showed that eel doublets cause a brief, massive, whole-body twitch in nearby prey, in contrast to the volleys, which cause sustained paralysis. The twitch, in turn, produces a strong water displacement—essentially an underwater sound. Given the eel's exquisite sensitivity to the slightest water movement, an interesting possibility comes to mind. Could doublets be the eel's way of asking, "Are you alive?" After all, wild eels hunt at night in the Amazon, surrounded by a vast diversity of hidden prey—things that are far harder to find than worms and goldfish dropped into a tank.

Supporting this idea: when eels in my lab hunted novel prey, such as crayfish, or prey hidden among plants in the tank, they often gave off doublets while searching and attacked after the prey twitched, as if the prey's movement had tipped them off. These were telling observations, but to provide more direct evidence, I attached the dead fish to an electric stimulator that could be triggered by either me or the eel's doublets. I then placed the wired fish in a ziplock bag so the eel's own doublets would have no effect on it. This setup allowed me to control when the fish's muscles twitched. Sure enough, the eels never followed a doublet with an attack unless the fish twitched. The

KENNETH C. CATANIA

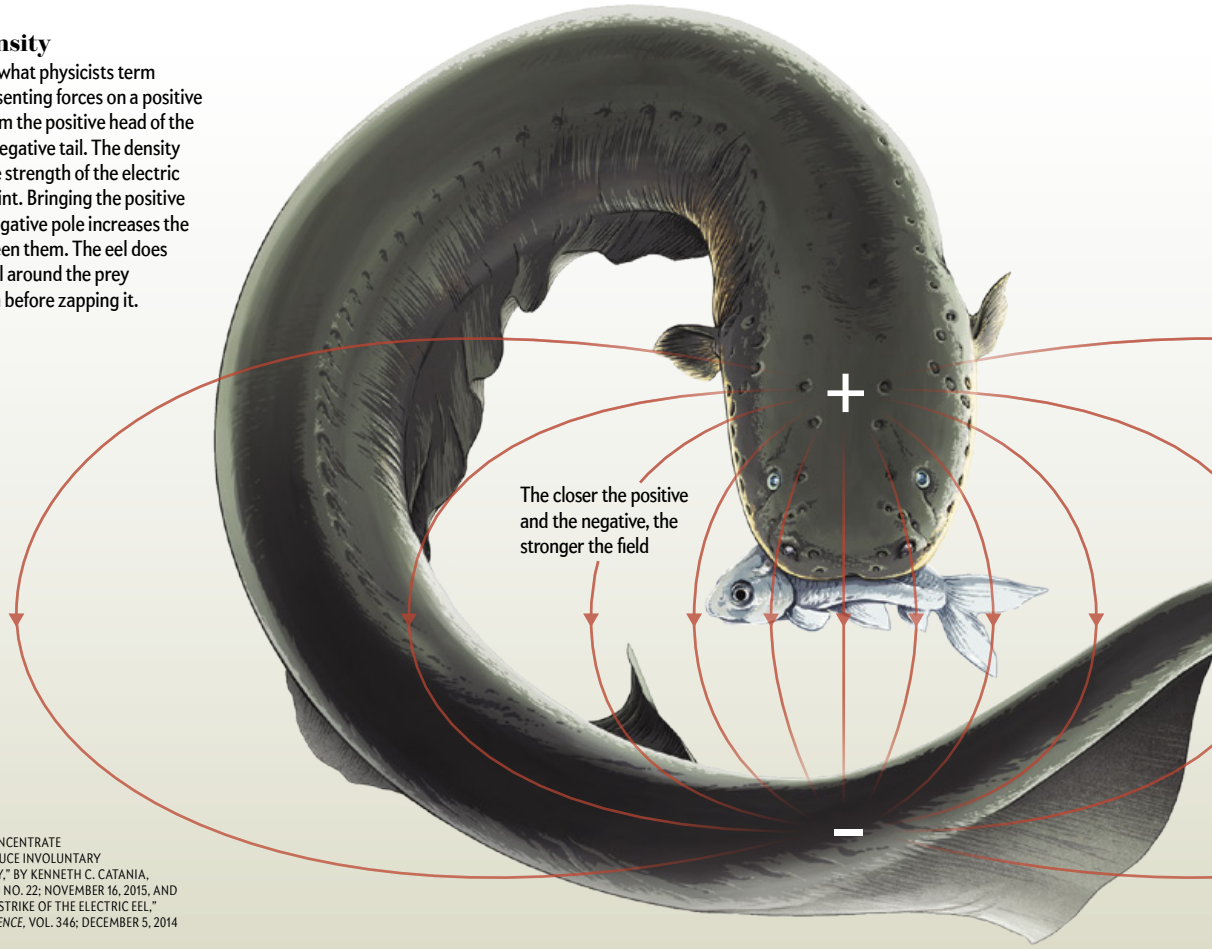
Attack Mode

Like a Taser, an electric eel on the hunt emits pulses of electricity to incapacitate prey. The eel's zaps activate the motor neurons that control the prey's muscles. In this way, the eel can be said to have remote control over prey. It uses this remote control in two ways: to reveal hidden prey by making them twitch and then to freeze the prey once they have been located, preventing escape. The eel can also use its electricity to track moving prey. And it has evolved an ingenious solution to a fundamental challenge of operating in the aquatic realm, where much of the electricity in its stunning strikes would typically be lost to the surrounding water.



Focused Intensity

Eel's electric field is what physicists term a dipole: lines representing forces on a positive charge originate from the positive head of the eel and end on the negative tail. The density of lines indicates the strength of the electric field at any given point. Bringing the positive pole closer to the negative pole increases the field strength between them. The eel does this by curling its tail around the prey gripped in its mouth before zapping it.

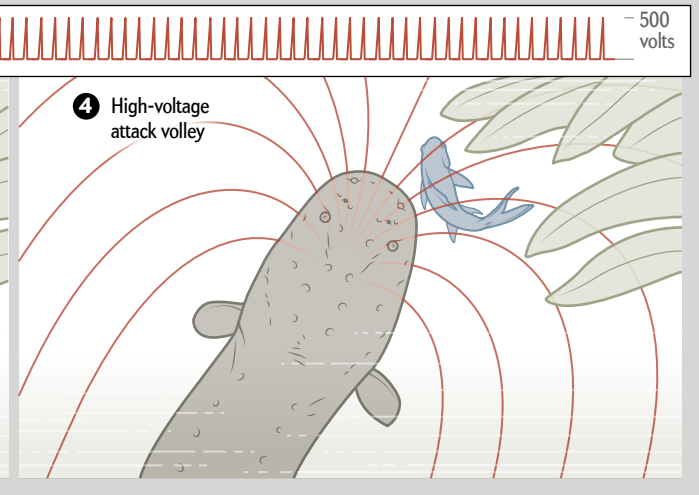


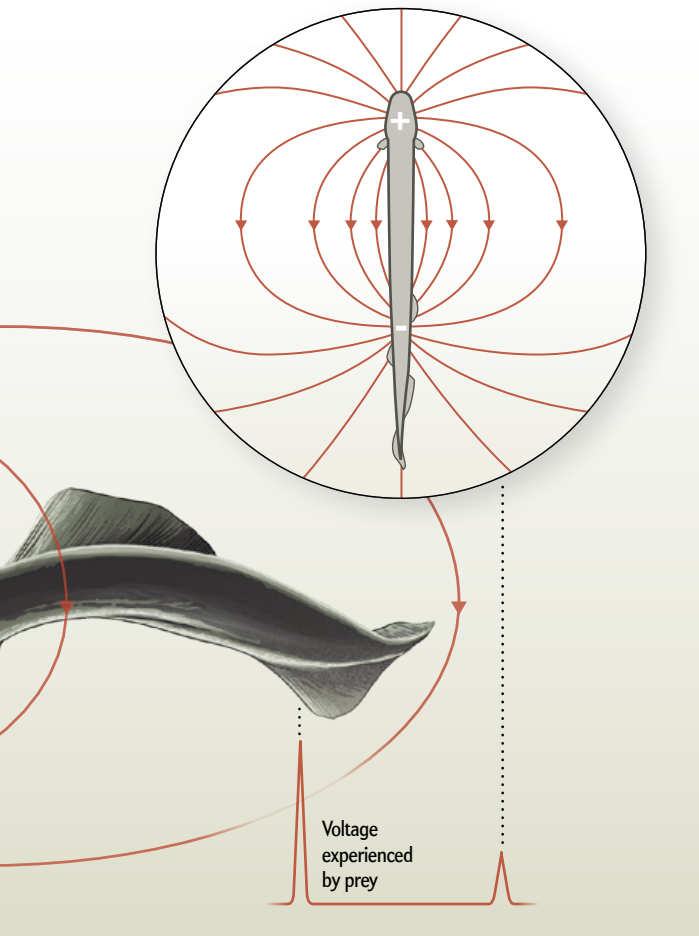
SOURCES: "ELECTRIC EELS CONCENTRATE THEIR ELECTRIC FIELD TO INDUCE INVOLUNTARY FATIGUE IN STRUGGLING PREY," BY KENNETH C. CATANIA, IN *CURRENT BIOLOGY*, VOL. 25, NO. 22; NOVEMBER 16, 2015, AND "THE SHOCKING PREDATORY STRIKE OF THE ELECTRIC EEL," BY KENNETH CATANIA, IN *SCIENCE*, VOL. 346; DECEMBER 5, 2014

Illustrations by Matthew Twombly

Stages of a Kill

Eel uses both low- and high-voltage electric output to sense its surroundings ❶. While searching for prey hidden among plants, the eel gives off pairs of high-voltage pulses called doublets that cause a powerful twitch in nearby prey ❷. The twitch displaces the surrounding water, revealing the prey to the eel ❸. On finding a target, the eel launches a high-voltage attack volley that paralyzes the prey, which the eel then strikes at with a suction-feeding bite ❹.





work showed that the eels were, in fact, attacking in response to doublet-generated fish movements.

Thus, the electric eel has two modes of remote control, which together make for one of the most insidious hunting tactics in the animal kingdom: it can unmask hidden prey by making them move, and it can freeze moving prey once they have been discovered.

DOUBLING DOWN

REMOTELY CONTROLLING another animal is pretty cool, but it is not the eel's only trick. The creature also has an ingenious solution to a fundamental problem with its electric output. Unlike superheroes or wizards who can aim lightning bolts, every time the eel gives off a high-voltage pulse, the electricity is distributed throughout the surrounding water. As a result, only a tiny fraction of the eel's prodigious power is transmitted to prey. English physicist and chemist Michael Faraday, who coincidently worked with electric eels in 1838, gave us a convenient way to visualize the problem: The eel's electric field is a so-called dipole, with lines representing forces on a positive charge emanating from the positive head of the eel and ending on the negative tail. The density of lines reflects the strength of the electric field at any given point; it is strongest at the poles and falls off in strength rapidly with distance. In introductory physics, you learn that bringing a negative pole close to the positive pole greatly increases the field strength in between. Eels have apparently taken physics because they use this move on difficult, struggling prey. The eel holds the victim firmly in its jaws and curls its tail (the negative pole) around the animal before delivering a series of high-voltage volleys.

To measure the effect of the eel's maneuver, I designed an eel "chew toy"—a pair of recording electrodes on a plastic holder inside a dead fish. The eels grabbed the apparatus, and I shook the attaching wires to simulate struggling. The eels obliged, curling around and shocking the electrodes. As expected, the field strength more than doubled. It is a great strategy, allowing the eel to concentrate its otherwise fixed power output on a target, like focusing the fixed power of a flashlight to a single bright spot.

What happened to prey was predictable yet awe-inspiring. Subsequent experiments showed that the eel's amped-up attack causes muscle contractions at abnormally high rates, totally and utterly exhausting prey in just a few seconds. It is the electric analogue of a neurotoxin, allowing the eel to capture and subdue otherwise dangerous animals, such as large, clawed crayfish.

MORE THAN A WEAPON

DURING MY STUDIES of the eel's hunting behavior, I noticed something that made me wonder whether the shocks might function as more than just a weapon. Typically three things happen when electric eels go in for the kill. First, they give off a full volley of high-voltage pulses, then they rapidly strike at the prey and suck it into their mouth. But in my experiments, when the dead fish was made to twitch in the insulated plastic bag, the eel's attack was always cut short. The eel gave off the high-voltage volley and struck toward the fish but missed and aborted the attack without the final suction-feeding bite. Why?

I had assumed the eels' strike was ballistic—a preplanned event that takes place without sensory feedback. But now it occurred to me that the animals might use high-voltage pulses as a tracking system. This would explain why they overlooked prey insulated in plastic. Electric eels evolved from weakly electric

fish that use electricity to probe their surroundings, and they have retained the weak, low-voltage electric output used for sensing. Why not use the high voltage for sensing as well? I decided to put this possibility to a test.

I took advantage of the conductive properties of prey and the eel's aggressive hunting behavior. Submerged animals tend to be more conductive than water, so an electric eel is especially interested in conductors because they have the "signature" of living things. Keep in mind, though, that the eel can and does detect conductors with its low-voltage system, which is always active until the predator switches to high voltage during an attack. To specifically test for high-voltage electroreception, I needed to examine the eel's behavior in slow motion during the strikes, when the low-voltage system was off and only the high-voltage one was active.

The first simple experiment was to add a rod made of carbon, an inert conductor, to the aquarium near the twitching fish in the ziplock bag. Once again, the eel attacked when it detected the water movement from the twitch and struck toward the bag with the insulated fish. But this time, the eel changed course midway and tried to eat the carbon rod with a full-on suction-feeding strike. The eel seemed to interpret the carbon rod as the fish—as one would expect if it was using the high-voltage pulses to track prey.

It was a great start, but I needed more evidence. I developed additional tests with carbon rods and multiple plastic rods to control for vision. Each time, the eels attacked the carbon conductor while giving off high-voltage volleys. The ultimate test was to present the eels with a rapidly spinning disk that had a single small conductor embedded in its surface, along with a series of identical-looking nonconductive control objects. The eels' performance was incredible: they could track and attack the conductor during the high-voltage volley with a speed and accuracy unheard of for animals that employ active electroreception. There was no doubt—they use high voltage simultaneously as a weapon and as part of a sensory system to track prey. My respect for electric eels was growing daily, which was fortunate because their next trick was directed at me.

A STUNNING DEFENSE

IN MARCH 1800 Prussian naturalist Alexander von Humboldt hired villagers in the Amazon to collect some electric eels for experiments. The result became an epic tale. They decided to fish for the eels using horses. They rounded up 30 wild horses and mules and forced them into a shallow pool full of eels, which emerged from the mud to attack the horses, shocking them repeatedly. The villagers yelled and waved branches to corral the terrified horses in the pool until the eels were spent and could be collected safely. Two horses died in the mayhem; others stumbled from the pool and collapsed on the bank. Humboldt published an account of the spectacle in 1807, and the story helped to propel him to fame. But some later scholars were skeptical about Humboldt's claims. Why would eels go on the offensive against large animals that they could not eat, risking injury in the process? No further instances of such behavior were reported for more than 200 years, until I chose the wrong net to catch a large eel in my lab.

As a rule, electric eels do not leap out of their aquarium. But there is an exception: if you approach a cornered eel with a large conductor that is sticking out of the water, it will often respond with an explosive attack. I discovered this literally shocking behavior when I tried to transfer a large eel to a new aquarium using a net with a metal rim and handle. In an instant, the eel turned and leaped from the water with its lower jaw pressed against the metal handle while it gave off a long volley of high-voltage pulses (fortunately, I was wearing a protective rubber glove). It is a daunting defensive behavior exhibited by all the eels I have tested.

As I investigated the electric consequences of the eel's leap and accounts of Humboldt's adventures, many pieces of the biological and historical puzzle fell into place. If eels interpret small conductors as edible prey, it follows that an approaching, partly submerged large conductor would be interpreted as a large threatening animal—perhaps a predatory cat or crocodilian. Why not swim away? During the dry season in the Amazon, electric eels are often trapped in small pools, where they are at risk of predation—exactly the situation reported for Humboldt's eels. Add to this scenario the fact that eels cannot "aim" their electricity when submerged, and you have the recipe for evolving an astonishing defense strategy.

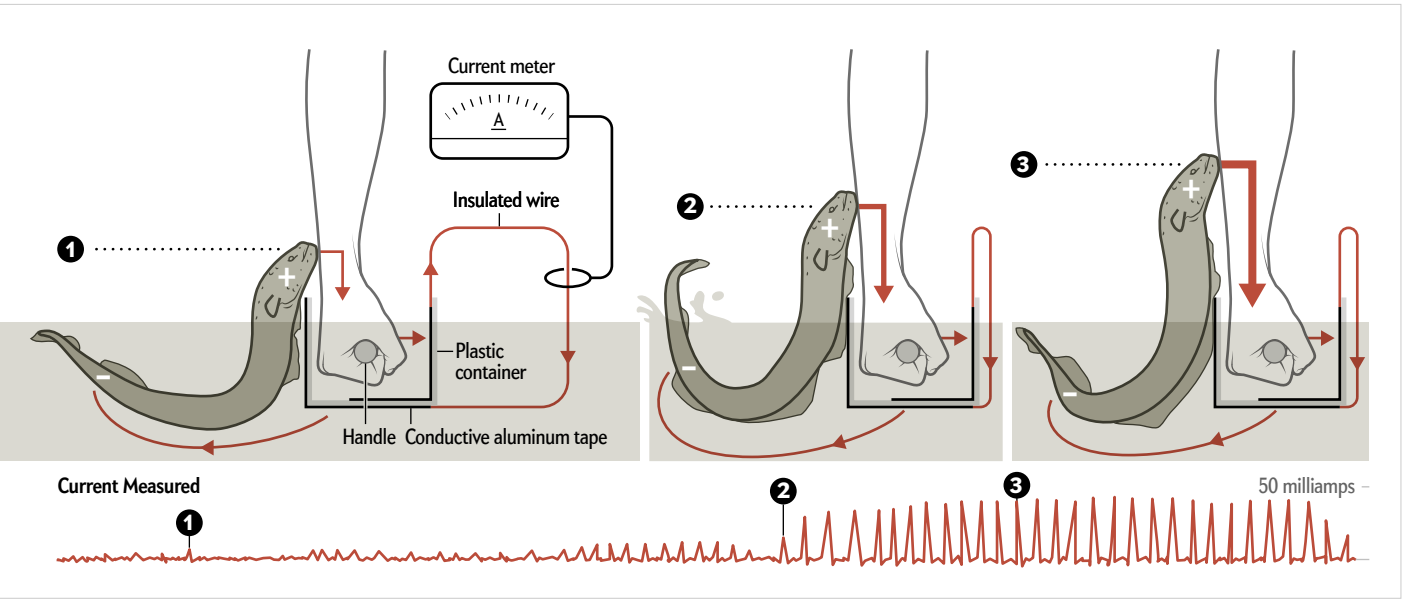
So is Humboldt's dramatic story true? Although he does not provide much detail in his famous account, I was able to find a little-known illustration of the event, which appeared decades later in a book authored by Robert Schomburgk, a British explorer and acquaintance of Humboldt's. The central figure is a horse being shocked by an eel that has jumped out of the water to press its lower jaw against the horse's chest. It is the spitting image of the leaping eels from my lab. As far as I am concerned, if Humboldt reported discovering dinosaurs in the Amazon, I would want to check it out.

BUILDING BUZZ

SOME THINGS ARE HARD TO EXPLAIN to the university's purchasing department, and severed zombie arms fall squarely in this category. So I thought it best to use my own money when I needed fake arms for another set of experiments with the eels aimed at further elucidating their leaping behavior. After scrubbing the fake blood off the arms, I filled them with light-emitting diodes strategically placed to mimic nerve tracts and presented them to

The Best Defense

Eels will jump from the water to electrify a perceived threat. To measure the current through a human during the eel's leaping attack, the author designed an experiment that involved offering his own arm to a juvenile eel ❶. As the eel rises, the usual current path from the eel's head to its tail is replaced by a path via the target, and the current intensifies ❷. At the highest point of the animal's leap, the current it delivered to the subject was about 43 milliamperes—a strongly aversive jolt that prompted the author to reflexively withdraw his arm ❸. A large eel would be expected to deliver substantially more power to its target.



the eels. Bringing an arm close to an eel resulted in a compelling demonstration of the leaping defense. The lights flashed brighter as the eel rose farther out of the water while shocking the arm. But exactly how and why did this happen?

Getting the answers to these questions required working out the so-called equivalent circuit and then determining the voltage, or electromotive force, of the eel's electric organ. I would also need to calculate how much the materials in the circuit reduce the flow of electric current through it—a property known as resistance. So I designed experiments to measure each variable in succession, starting with the eel's electric organ. At slightly more than three feet long, the largest eel in my lab had an electric potential of 382 volts and an internal resistance of only 450 ohms, allowing for currents of nearly one ampere if there were no other resistances. That is quite an electric punch—far greater than a Taser's.

When an eel emerges from the water, pressing its lower jaw against a target, the usual current path for electricity from the eel's head to its tail is progressively shut down—because air is a poor conductor—and is replaced by a path through the target. Remarkably it is similar to a volume-control knob—the eel progressively turns up the volume in the target as it rises from the water. This observation explains how the behavior could have gradually evolved because each increment in height provides an advantage. But how efficient is the eel at turning up the volume?

When working out the details, I ran into the most basic of circuit problems: calculating the electric current in a circuit containing two resistors arranged side by side. It is a favorite challenge in circuit puzzles (that is, physics exams) because you cannot calculate the electric current in the circuit without knowing the value of both resistors. I was able to solve for one resistance—the path from the eel's head to the water—by taking measurements from eels attacking metal plates connected to a voltmeter. The other resistance was the arm—the eel's target. After collecting data for all the other variables, I could only guess at this last value: the complex resistance that developed between the eel's jaw, a living target and the surrounding water.

It was hard to stop working on the circuit without the final answers. In addition, just as my first paper documenting the eel's leaping attack was published in 2016, a video was posted to the Internet showing a very large eel leaping onto a surprised fisherman in South America (he was temporarily immobilized and then recovered, similar to the aftermath of being Tased). Suddenly the circuit I had been studying out of curiosity had real-world consequences.

There was nothing for it but to use my own arm to determine the last variable and test the predictions from all the previous measurements. I used a very small eel with an electromotive force of 198 volts and an internal resistance of 960 ohms. I built a device that measured the current through my arm during the eel's attack, allowing me to finally solve the circuit. I can also report with conviction that eels are very efficient at turning up the volume of their attack.

I may have started this project thinking I would teach about electric eels, but in the end, it was the eels that taught me. It is the same lesson I relearn every time I investigate a new species: the animals are always far more interesting than I could possibly imagine, in ways I could never have predicted at the outset. It keeps me up at night—in a good way—to contemplate all we have yet to discover. SA

SOURCE: "POWER TRANSFER TO A HUMAN DURING AN ELECTRIC EEL'S SHOCKING LEAP," BY KENNETH C. CATANIA, IN *CURRENT BIOLOGY*, VOL. 27, NO. 18, SEPTEMBER 25, 2017

MORE TO EXPLORE

The Shocking Predatory Strike of the Electric Eel. Kenneth Catania in *Science*, Vol. 346, pages 1231–1234; December 5, 2014.

Electric Eels Use High-Voltage to Track Fast-Moving Prey. Kenneth C. Catania in *Nature Communications*, Vol. 6, Article No. 8638; October 20, 2015.

Power Transfer to a Human during an Electric Eel's Shocking Leap. Kenneth C. Catania in *Current Biology*, Vol. 27, No. 18, pages 2887–2891; September 25, 2017.

FROM OUR ARCHIVES

Natural-Born Killer. Kenneth C. Catania; April 2011.

scientificamerican.com/magazine/sa

How calculus helped to drive the fight against HIV

By Steven Strogatz

MATHEMATICS

OUTSMARTING A VIRUS WITH MATH

WORKING BEHIND THE SCENES, CALCULUS IS AN UNSUNG HERO OF MODERN LIFE. By harnessing the forecasting powers of differential equations—the soothsayers of calculus—humans have used an arcane branch of mathematics to change the world. Consider, for instance, the supporting role that calculus played in the fight against HIV, the human immunodeficiency virus.

In the 1980s a mysterious disease began killing tens of thousands of people a year in the U.S. and hundreds of thousands worldwide. No one knew what it was, where it came from or what was causing it, but its effects were clear—it weakened patients' immune systems so severely that they became vulnerable to rare kinds of cancer, pneumonia and opportunistic infections. Death from the disease was slow, painful and disfiguring. Doctors named it acquired immunodeficiency syndrome (AIDS). No cure was in sight.

Basic research demonstrated that a retrovirus was the culprit. Its mechanism was insidious: The virus attacked and infected white blood cells called helper T cells, a key component of the immune system. Once inside, the virus hijacked the cell's genetic machinery and co-opted it into making more viruses. Those new virus particles then escaped from the cell, hitched a ride in the bloodstream and other bodily fluids, and looked for more T cells to infect. The body's immune system responded to this invasion by trying to flush out the virus particles from the blood and kill as many infected T cells as it could find. In so doing, the immune system was killing an important part of itself.

The first antiretroviral drug approved to treat HIV appeared in 1987. It slowed the virus down by interfering with the hijacking process, but it was not as effective as hoped, and HIV often became resistant to it. A different class of drugs called protease inhibitors appeared in 1994. They thwarted HIV by interfering with the newly produced virus particles, keeping them from maturing and rendering them noninfectious. Though also not a cure, protease inhibitors were a godsend.

Soon after protease inhibitors became available, a team of researchers led by David Ho (a former physics major at the California Institute of Technology and so, presumably, someone comfortable with calculus) and a mathematical immunologist named Alan Perelson collaborated on a study that changed how doctors thought about HIV and revolutionized how they treated it. Before the work of Ho and Perelson, it was known that untreated HIV infection typically progressed through three stages: an acute primary stage of a few weeks, a chronic and paradoxically asymp-

Illustration by Amy Martin

tomatic stage of up to 10 years, and a terminal stage of AIDS.

In the first stage, soon after a person becomes infected with HIV, he or she displays flulike symptoms of fever, rash and headaches, and the number of helper T cells (also known as CD4 cells) in the bloodstream plummets. A normal T cell count is about 1,000 cells per cubic millimeter of blood; after a primary HIV infection, the T cell count drops to the low hundreds. Because T cells help the body fight infections, their depletion severely weakens the immune system. Meanwhile the number of virus particles in the blood, known as the viral load, spikes and then drops as the immune system begins to combat the HIV infection. The flulike symptoms disappear, and the patient feels better.

At the end of this first stage, the viral load stabilizes at a level that can, puzzlingly, last for many years. Doctors refer to this level as the set point. A patient who is untreated may survive for a decade with no HIV-related symptoms and no lab findings other than a persistent viral load and a low and slowly declining T cell count. Eventually, however, the asymptomatic stage ends and AIDS sets in, marked by a further decrease in the T cell count and a sharp rise in the viral load. Once an untreated patient has full-blown AIDS, opportunistic infections, cancers and other complications usually cause the patient's death within two to three years.

The key to the mystery was in the decade-long asymptomatic stage. What was going on then? Was HIV lying dormant in the body? Other viruses were known to hibernate like that. The genital herpesvirus, for example, hunkers down in nerve ganglia to evade the immune system. The chicken pox virus also does this, hiding out in nerve cells for years and sometimes awakening to cause shingles. For HIV, the reason for the latency was unknown.

In a 1995 study, Ho and Perelson gave patients a protease inhibitor, not as a treatment but as a probe. Doing so nudged a patient's body off its set point and allowed the researchers—for the first time ever—to track the dynamics of the immune system as it battled HIV. They found that after each patient took the protease inhibitor, the number of virus particles in the bloodstream dropped exponentially fast. The rate of decay was incredible: half of all the virus particles in the bloodstream were cleared by the immune system every *two days*.

FINDING THE CLEARANCE RATE

CALCULUS ENABLED PERELSON AND HO to model this exponential decay and extract its surprising implications. First, they represented the changing concentration of virus in the blood as an unknown function, $V(t)$, where t denotes the elapsed time since the protease inhibitor was administered. Then they hypothesized how much the concentration of virus would change, dV, in an infinitesimally short time interval, dt. Their data indicated that a constant fraction of the virus in the blood was cleared each day, so perhaps the same constancy would hold when extrapolated down to dt. Because dV/V represented the fractional change in the virus concentration, their model could be translated into symbols as the following equation:

$$dV/V = -c\,dt$$

Here the constant of proportionality, c, is the clearance rate, a measure of how fast the body flushes out the virus.

Steven Strogatz is a professor of mathematics at Cornell University. He has blogged about math for the *New York Times* and is a frequent guest on Radiolab and Science Friday.

The equation above is an example of a differential equation. It relates the infinitesimal change of V (which is called the differential of V and denoted dV) to V itself and to the differential dt of the elapsed time. By applying the techniques of calculus to this equation, Perelson and Ho solved for $V(t)$ and found it satisfied:

$$\ln [V(t)/V_0] = -ct$$

Here V_0 is the initial viral load, and ln denotes a function called the natural logarithm. Inverting this function then implied:

$$V(t) = V_0 e^{-ct}$$

In this equation, e is the base of the natural logarithm, thus confirming that the viral load did indeed decay exponentially fast in the model. Finally, by fitting an exponential decay curve to their experimental data, Ho and Perelson estimated the previously unknown value of c.

For those who prefer derivatives (rates of change) to differentials (infinitesimal increments of change), the model equation can be rewritten as follows:

$$dV/dt = -cV$$

Here dV/dt is the derivative of V with respect to t. This derivative measures how fast the virus concentration grows or declines. Positive values signify growth; negative values indicate decline. Because the concentration V is positive, then $-cV$ must be negative. Thus, the derivative must also be negative, which means the virus concentration has to decline, as we know it does in the experiment. Furthermore, the proportionality between dV/dt and V means that the closer V gets to zero, the more slowly it declines.

This slowing decline of V is similar to what happens if you fill a sink with water and then allow it to drain. The less water in the sink, the more slowly it flows out because less water pressure is pushing it down. In this analogy, the volume of water in the sink is akin to the amount of virus in the body; the drainage rate is like the outflow of the virus as it is cleared by the immune system.

Having modeled the effect of the protease inhibitor, Perelson and Ho modified their equation to describe the conditions *before* the drug was given. They assumed the equation would become:

$$dV/dt = P - cV$$

In this equation, P refers to the uninhibited rate of production of new virus particles, another crucial unknown in the early 1990s. Perelson and Ho imagined that before administration of the protease inhibitor, infected cells were releasing new infectious virus particles at every moment, which then infected oth-

er cells, and so on. This potential for a raging fire is what makes HIV so devastating.

In the asymptomatic phase, however, there is evidently a balance between the production of the virus and its clearance by the immune system. At this set point, the virus is produced as fast as it is cleared. That gave new insight into why the viral load could stay the same for years. In the water-in-the-sink analogy, it is like what happens if you turn on the faucet and open the drain at the same time. The water will reach a steady-state level at which outflow equals inflow.

At the set point, the concentration of virus does not change, so its derivative has to be zero: $dV/dt = 0$. Hence, the steady-state viral load V_0 satisfies:

$$P = cV_0$$

Perelson and Ho used this simple equation to estimate a vitally important number that no one had found a way to measure before: the number of virus particles being cleared each day by the immune system. It turned out to be a *billion* virus particles a day.

That number was unexpected and truly stunning. It indicated that a titanic struggle was taking place during the seemingly calm 10 years of the asymptomatic phase in a patient's body. The immune system cleared a billion virus particles daily, and the infected cells released a billion new ones. The immune system was in a furious, all-out war with the virus and fighting it to a near standstill.

TURNING HIBERNATION ON ITS HEAD

THE FOLLOWING YEAR Ho, Perelson and their colleagues conducted a follow-up study to get a better handle on something they could not resolve in 1995. This time they collected viral load data at shorter time intervals after the protease inhibitor was administered because they wanted to obtain more information about an initial lag they had observed in the medicine's absorption, distribution and penetration into the target cells. After the drug was given, the team measured the patients' viral load every two hours until the sixth hour, then every six hours until day two and then once a day thereafter until day seven. On the mathematical side, Perelson refined the differential equation model to account for the lag and to track the dynamics of another important variable, the changing number of infected T cells.

When the researchers reran the experiment, fit the data to the model's predictions and estimated its parameters again, they obtained results even more staggering than before: *10 billion* virus particles were being produced and then cleared from the bloodstream each day. Moreover, they found that infected T cells lived only about two days. The surprisingly short life span added another piece to the puzzle, given that T cell depletion is the hallmark of HIV infection and AIDS.

The discovery that HIV replication was so astonishingly rapid changed the way that doctors treated their HIV-positive patients. Previously physicians waited until HIV emerged from its supposed hibernation before they prescribed antiviral drugs. The idea was to conserve forces until the patient's immune system really needed help because the virus would often become resistant to the drugs. So it was generally thought wiser to wait until patients were far along in their illness.

Ho and Perelson turned this picture upside down. There was no hibernation. HIV and the body were locked in a pitched struggle every second of every day, and the immune system needed all the help it could get and as soon as possible after the critical early period of infection. And now it was obvious why no single medication worked for very long. The virus replicated so rapidly and mutated so quickly, it could find a way to escape almost any therapeutic drug.

Perelson's mathematics gave a quantitative estimate of how many drugs had to be used in combination to beat HIV down and keep it down. By taking into account the measured mutation rate of HIV, the size of its genome and the newly estimated number of virus particles that were produced daily, he demonstrated mathematically that HIV was generating every possible mutation at every base in its genome many times a day. Because even a single mutation could confer drug resistance, there was little hope of success with single-drug therapy. Two drugs given at the same time would stand a better chance of working, but Perelson's calculations showed that a sizable fraction of all possible double mutations also occurred each day. Three drugs in combination, however, would be hard for the HIV virus to overcome. The math suggested that the odds were something like 10 million to one against HIV being able to undergo the necessary three simultaneous mutations to escape triple-combination therapy.

When Ho and his colleagues tested a three-drug cocktail on HIV-infected patients in clinical studies in 1996, the results were remarkable. The level of virus in the blood dropped about 100-fold in two weeks. Over the next month it became undetectable.

This is not to say that HIV was eradicated. Studies soon afterward showed the virus can rebound aggressively if patients take a break from therapy. The problem is that HIV can hide out. It can lie low in sanctuary sites in the body that the drugs cannot readily penetrate or lurk in latently infected cells and rest without replicating, a sneaky way of evading treatment. At any time, these dormant cells can wake up and start making new viruses, which is why it is so important for HIV-positive people to keep taking their meds, even when their viral loads are undetectable.

In 1996 Ho was named *Time* magazine's Man of the Year. In 2017 Perelson received a major prize for his "profound contributions to theoretical immunology." Both are still saving lives by applying calculus to medicine: Ho is analyzing viral dynamics, and some of Perelson's latest work helped to create treatments for hepatitis C that cure the infection in nearly every patient.

The calculus that led to triple-combination therapy did not cure HIV. But it changed a deadly virus into a chronic condition that could be managed—at least for those with access to treatment. It gave hope where almost none had existed before. SA

MORE TO EXPLORE

Rapid Turnover of Plasma Virions and CD4 Lymphocytes in HIV-1 Infection. David D. Ho et al. in *Nature*, Vol. 373, pages 123–126; January 12, 1995.

Modelling Viral and Immune System Dynamics. Alan S. Perelson in *Nature Reviews Immunology*, Vol. 2, pages 28–36; January 2002.

FROM OUR ARCHIVES

The Secret Spiritual History of Calculus. Amir Alexander; April 2014.

scientificamerican.com/magazine/sa

Not your average cruise.

Cruise prices start at $2,809 per person (pp) based on double occupancy. For those attending our SEMINARS, there is a $1,575 fee. Add'l pp fees: gov't taxes and fees ($210), a non-refundable Booking Service Fee ($150), and the Tour Leader gratuities ($10 pp per day). Program, cruise pricing and options are subject to change. Scientific American is a registered trademark of Springer Nature America, Inc.

RECOMMENDED

By Andrea Gawrylewski

Our Planet

by Alastair Fothergill and Keith Scholey, with Fred Pearce. Ten Speed Press, 2019 ($35)

This month the new nature documentary series *Our Planet* will be released on Netflix, from the same team that created *Planet Earth* and *The Blue Planet*. The companion book by co-producers Fothergill and Scholey can certainly stand on its own, with many images leaving the viewer wondering, "How'd they get that shot?": A lone polar bear treks along the ridge of a jagged, blue and glistening ice cap in the Russian High Arctic (*above*). An iridescent turquoise European kingfisher seems frozen in time as it dives for minnows off its mossy perch. A brown bear peeks around the tree in a Slovenian forest—its expression so humanlike, you could dare call it shy. This collection goes beyond photography, though, with a thorough discussion of the conservation challenges facing many ecosystems on Earth. It's not enough to merely look at the planet around us—we must understand how humans impact it.

Eating the Sun: Small Musings on a Vast Universe

by Ella Frances Sanders. Penguin Books, 2019 ($17)

From the atoms that make up our bodies to the galactic supercluster that houses the Milky Way, writer and illustrator Sanders elucidates many of the wonders of our world through drawings and conversational explanations. While describing lunar theory, for example, she compares the moon and Earth's locked synchronous rotation to the movement of dance partners: "How glad we can be, that we have someone to figure out this universe business alongside, to dance with, to gradually lengthen our days and keep us slow." A star's death, trees helping one another survive and the ways our brain rewrites memories are also among the concepts Sanders demystifies. Each inspiring snapshot feeds the curiosity of anyone interested in exploring the universe that we exist in and that exists in us. —*Sunya Bhutta*

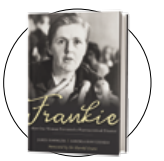
Einstein's Unfinished Revolution: The Search for What Lies beyond the Quantum

by Lee Smolin. Penguin Press, 2019 ($28)

Quantum mechanics—the basis for our understanding of particles and forces—is arguably the most successful theory in all of science. But its success has come at a price: unresolved mysteries at the theory's heart, such as the paradoxical wave-particle duality of quantum objects, can make modern physics seem decidedly metaphysical. Simply put, if mainstream interpretations of quantum mechanics are true, then the central, most cherished tenet of physics—that an objective reality exists independently of our mind but is still comprehensible—must be false. Smolin, a member of the Perimeter Institute for Theoretical Physics in Ontario, argues against this vexing status quo: "It is possible to be a realist while living in the quantum universe." —*Lee Billings*

Frankie: How One Woman Prevented a Pharmaceutical Disaster

by James Essinger and Sandra Koutzenko. Wellspring, 2019 ($24.95)



On March 8, 1962, pharmacologist Frances ("Frankie") O. Kelsey, a medical reviewer at the FDA, received a most unexpected letter. The drug firm that had pressured her to approve the distribution of a sleeping pill was withdrawing its request. For nearly two years she had refused to accede—there was not enough evidence to prove the medication was safe. As it turned out, the drug, thalidomide, which was also used to treat morning sickness in pregnancy, had been linked to birth defects in Europe and elsewhere. In the end, it never pervaded the U.S. market. Writers Essinger and Koutzenko unearth the story of Kelsey, who helped prevent a public health tragedy by standing her ground in the name of scientific proof. —*Emiliano Rodríguez Mega*

Zeynep Tufekci is an associate professor at the University of North Carolina School of Information and Library Science and a regular contributor to the *New York Times*. Her book, *Twitter and Tear Gas: The Power and Fragility of Networked Protest*, was published by Yale University Press in 2017.

YouTube Has a Video for That

But the site's recommendation algorithms have a dark side

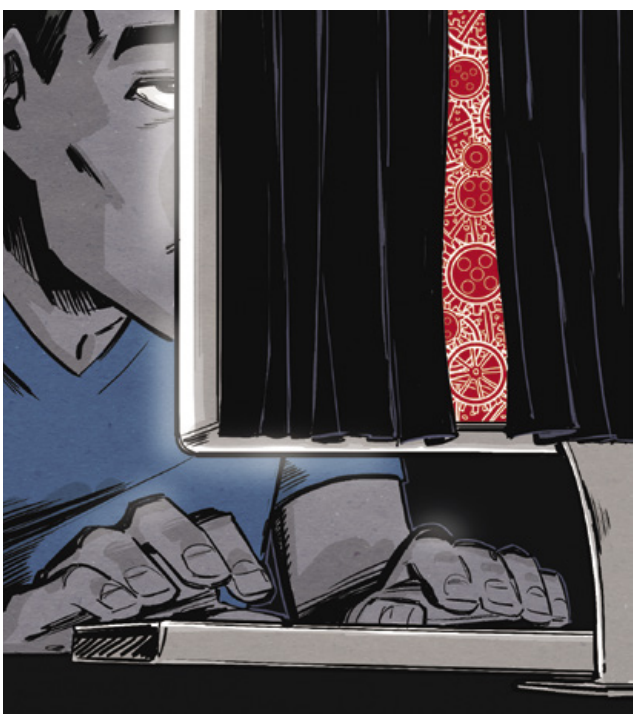
By Zeynep Tufekci

It was 3 A.M., and the smoke alarm wouldn't stop beeping. There was no fire, so I didn't need to panic. I just had to figure out a way to quiet the darn thing and tamp down my ire. I had taken out the battery and pushed and twisted all the buttons to no avail.

Luckily for me, the possible solutions were all laid out in the YouTube tutorial I found. The video helpfully walked me through my options, demonstrating each step. And the fact that it had hundreds of thousands of views reassured me that this might work.

YouTube has become the place to learn how to do anything, from assembling an Ikea cabinet to making a Bluetooth connection with your earbuds. It is a font of tutorials, some very good, some meandering, some made by individuals who have become professionals at it and rake in serious sums through advertising. But many are uploaded by people who have solved something that frustrated them and want to share the answer with the world.

The native language of the digital world is probably video, not text—a trend missed by the literate classes that dominated the public dialogue in the predigital era. I've noticed that many young people *start* their Web searches on YouTube. Besides, Google, which owns YouTube, highlights videos in its search results.



"How do I" assemble that table, improve my stroke, decide if I'm a feminist, choose vaccinations, highlight my cheeks, tie my shoelaces, research whether climate change is real…? Someone on YouTube has an answer. But the site has also been targeted by extremists, conspiracy theorists and reactionaries who understand its role as a gateway to information, especially for younger generations.

And therein lies the dark side: YouTube makes money by keeping users on the site and showing them targeted ads. To keep them watching, it utilizes a recommendation system powered by top-of-the-line artificial intelligence (it's Google, after all). Indeed, after Google Brain, the company's AI division, took over YouTube's recommendations in 2015, there were laudatory articles on how it had significantly increased "engagement": Silicon Valley–speak for enticing you to stay on the site longer.

These "recommended" videos play one after the other. Maybe you finished a tutorial on how to sharpen knives, but the next one may well be about why feminists are ruining manhood, how vaccinations are poisonous or why climate change is a hoax—or a nifty explainer "proving" the *Titanic* never hit an iceberg.

YouTube's algorithms will push whatever they deem engaging, and it appears they have figured out that wild claims, as well as hate speech and outrage peddling, can be particularly so.

Receiving recommendations for noxious material has become such a common experience that there has been some loud pushback. Google did ban a few of the indefensibly offensive high-profile "creators" (though not before helping them expose their views to millions of people), and recently the company announced an initiative to reduce recommending "borderline content and content that could misinform users in harmful ways." According to Google, this content might be things like "a phony miracle cure for a serious illness" or claims that "the earth is flat." The change, they say, will affect fewer than 1 percent of all videos.

While it's good to see some response from Google, the problem is deep and structural. The business model incentivizes whatever gets watched most. YouTube's reach is vast. Google's cheap and nifty Chromebooks make up more than half the computers in the K–12 market in the U.S., and they usually come preloaded with YouTube. Many parents and educators probably don't realize how much their children and students use it.

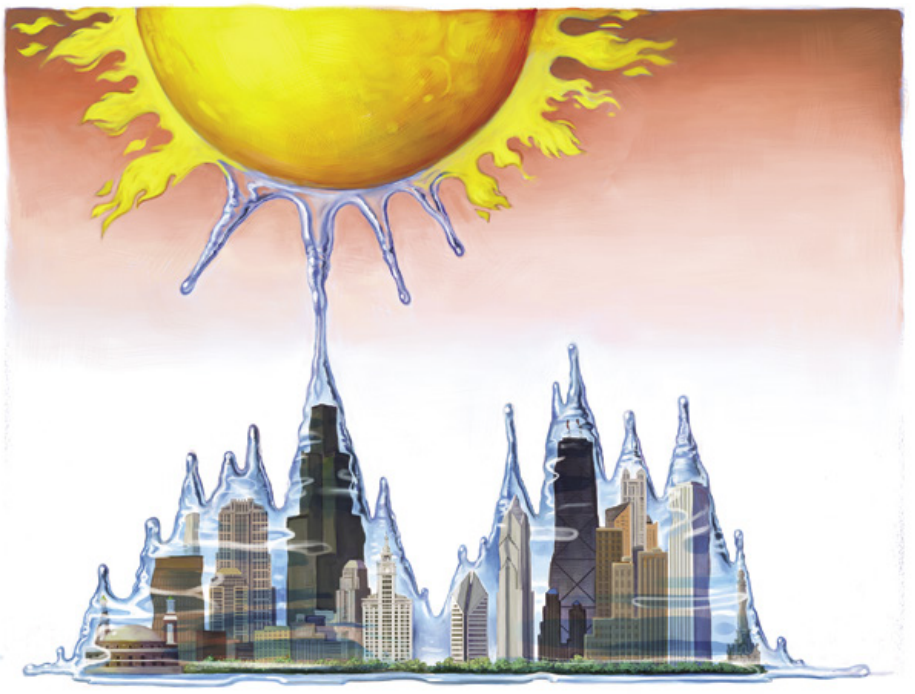
We can't scream at kids to get off our lawn or ignore the fact that children use YouTube for a *reason:* there's stuff there they want to watch, just like I really needed to figure out how to unplug that beeping catastrophe at 3 A.M. We need to adjust to this reality with regulation, self-regulation and education. People can't see how recommendations work—or how they're designed to keep eyes hooked to the screen. We could ask for no YouTube or "no recommendations" for Chromebooks in schools.

This is just tip of the iceberg of the dangerous nexus of profit, global scale and AI. It's a new era, with challenges as real as that iceberg the *Titanic* did hit—no matter what the video claims. SA

JOIN THE CONVERSATION ONLINE
Visit *Scientific American* on Facebook and Twitter or send a letter to the editor: editors@sciam.com

Illustration by Thomas Pitilli

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



Cold Comfort

A look back at winter's wacky weather

By Steve Mirsky

By the time you read these words, winter's grip should have mostly loosened in the Northern Hemisphere. But at its worst, this winter was brutally cold. Here in New York City on January 31, the low temperature snuck down to two degrees Fahrenheit. In Chicago, it was also two degrees—but that was the high. The low plummeted to –20. Which was two degrees warmer than the low the day before. And the wind chill in the Windy City was –51 or –52, depending on which weather station was crying out in agony. As comedian Lewis Black once said of Minnesota (which was similarly afflicted in January), "That is not weather. That's an emergency condition."

When the forecast warned us a couple of days earlier that Arctic air was looming, the president issued a sincere and helpful tweet, which ended with: "What the hell is going on with Global Waming [sic]? Please come back fast, we need you!" And being the most powerful man on Earth, he was successful in his polite imploration. On February 4 the Chicago temperature reached 51 degrees. And the next day the Big Apple basked in a sunny 65.

The Arctic is warming at twice the rate as the global average. This heat can help disrupt the polar vortex, a steady wind pattern that usually stays focused on circling the North Pole. A wobbly jet stream then runs into a brick wall of that Arctic air, which is still pretty frosty by human standards, and both wind up hundreds of miles farther south than they usually belong. And for a few days we in the Deep South—by which I mean Chicago or New York compared with the Arctic—freeze our butts off. But less than a week after this most recent vortex disruption, thanks to some warm air coming up from the *real* South, I was walking outside without a coat. On a date when the average high temperature is about 40.

Like so much else we are currently living through, this kind of thermometer ride is not normal. Or it didn't used to be, anyway.

Of course, scientists have been waming—sorry, warning—that warming can have these very effects. Climate change deniers may sneer, "So when it's warmer than usual, that's because of global warming. And when it's colder, that's also because of global warming?" Well, yes. And anybody who just can't accept these kinds of seemingly paradoxical situations needs to reflect on the expression "freezer burn."

In the midst of this wacky weather came Groundhog Day. And I happened on a 2010 interview with noted climatologist Katharine Hayhoe of Texas Tech University, in which she pointed out: "It's been mathematically proven that it's impossible to predict the evolution of a chaotic system like weather for more than two weeks. As everyone knows, though, the laws of physics don't apply to groundhogs." She also remarked that for groundhog weather forecasting to be truly scientific, its "findings would need to be published in scientific journals such as the *Journal of Groundhog Predictions* where they would be reviewed for accuracy by other groundhogs." How Hayhoe could be understood with her tongue so securely embedded in her cheek is a scientific mystery.

In a completely unrelated development, alligators eat stones. As writer Jake Buehler explains in the journal *Science,* it's long been known that the beasties dine on the rocks. Favored explanations have included the incidental swallowing of mineral while eating animal or vegetable and the ingestion of stones to help mash up the meat in their digestive tracts—akin to what many birds do.

But a new explanation for this gastrolith activity has appeared. Tests with seven captive American alligators found that when they had taken in a bunch of rocks, they were able to hide underwater 88 percent longer. The weight appears to work against the tendency to float back to the surface when the lungs are filled with air. Because if you're going to successfully cope with the laws of physics, it's far better to have stones in your stomach than rocks in your head. SA

JOIN THE CONVERSATION ONLINE
Visit *Scientific American* on Facebook and Twitter or send a letter to the editor: editors@sciam.com

Illustration by Matt Collins

50, 100 & 150 YEARS AGO

INNOVATION AND DISCOVERY AS CHRONICLED IN *SCIENTIFIC AMERICAN*

Compiled by Daniel C. Schlenoff

APRIL

1969 Transuranium Elements

"Up to 1963 the rate of discovery of transuranium elements had been high. Each step forward has required more and more complex apparatus and methods to increase the number of protons in the nucleus, while at the same time the stability of the nuclei produced has decreased, making them difficult to observe and identify. Nonetheless, heavy synthetic elements are a subject of livelier interest than ever because of advances in the theory of nuclear stability, which have given rise to the possibility of synthetic elements beyond the dreams of early workers in the field. Concurrently great progress has been made in manufacturing in quantity the unstable elements through element 98, in enlarging knowledge of their properties and in finding worthwhile applications for them.—Glenn T. Seaborg and Justin L. Bloom"

Seaborg shared the 1951 Nobel Prize in Chemistry for his work in this field.

Knappers at Work

"The only living men who make tools by flaking flint are usually believed to be a few primitive tribesmen who still follow the customs of their forebears and a handful of specialized craftsmen who fashion the flints needed for surviving flintlock firearms. During recent archaeological work in Turkey, Jacques Bordaz of the University of Montreal found this belief to be in error: flint-knappers in the Turkish village of Çakmak produce 500 tons of flint blades every year, enough to provide fresh cutting edges for all the threshing sledges in rural Turkey. Turkish wheat-growers like to separate the grain from the stalk by dragging a sledge over sheaves spread on a threshing floor. Each sledge has 600 to 800 blades of flint, a little less than two inches long, set on edge in a slot. Each knapper can turn out 500 pounds of blades a day from locally quarried nodules of flint."

New agricultural machinery made this craft obsolete in the 1980s.

1919 Airships for Travel

"The substitution of helium for hydrogen, which is one of America's contributions to military aviation, removes one of the greatest prejudices against the lighter-than-air craft. For now that helium gas, which is non-inflammable, is used in place of explosive hydrogen, there is no further need to think of conflagration during flight or on the ground. Engines can be placed anywhere, and so can the galley and stoves and heating plant, since the dirigible is no longer a huge explosive charge held in a silk bag, ready to burst into flames at the slightest spark. Frankly, the airplane as a commercial proposition is today but a poor second to the dirigible. The airplane is to be the competitor of the fast railroad train, while the dirigible [*see illustration*] is destined to be the carrier of passengers and goods over long routes, in competition with the intercontinental steamers."

1919: Elegant dirigibles are the hope for air travel to come. Passengers relax in the stern observation salon of an airship crossing the Atlantic Ocean.

1969

1919

1869

1869 Meat on Ice

"A new invention, in the shape of machinery for making ice and performing the refrigerating process, was tested on board the ship *William Taber,* lying at the foot of Nineteenth Street, East River, New York City, in the presence of a number of scientific and mechanical gentlemen, to whom invitations had been extended. The ship has been thoroughly fitted with this new apparatus for the preservation, during transportation, of fresh beef and other perishable food for a long period, and she will sail for Texas some day next week. The two great principles in the mechanism of the affair seem to be, first, the application of pumps to the liquefaction of carbonic acid [carbon dioxide] gas; and second, the remaking of it into gas over and over again ad infinitum."

The ship failed to make its delivery. The date of the first successful refrigerated ship voyage is usually given as 1877.

High Fashion in Toys

"Not the least interesting of the English reports on the French Exhibition is on toys. The chief French toy is a doll, not a representation of an infant for a child to fondle, but a model of a lady attired in the height of fashion, a leading manufacturer changing the costume every month to ensure accuracy. As an excuse for this apparently early inoculation of childhood with a love for finery, it is explained that these dolls serve as models to colonial and other extra-Parisian milliners before they are handed over to their children. French dolls, unlike our wax-faced natives, have china heads."

SCIENTIFIC AMERICAN, VOL. CXX, NO. 16; APRIL 19, 1919

Text by Mark Fischetti | Graphic by Valentina D'Efilippo

First Words

Scientific American has brought more than 1,000 new terms to light

Words originate everywhere. And *Scientific American* is the place to find the earliest evidence of a surprising number of them. The venerable *Oxford English Dictionary* investigates where each of its multitudinous terms first appears. *Scientific American* has popped up as one of the dictionary's most quoted sources for new words, new meanings of existing words and exemplary uses of novel words (*large graphic*). Since the magazine debuted in 1845, it has provided the first record of 1,056 terms (*smaller graphic*). We tip our hat to *The Times* (London) and William Shakespeare as the top sources. Certainly the advancement of science and technology, as reported in our pages, spawns original language. So does sharing emerging ideas. Our next new word? Stay tuned.

William Shakespeare playwright
Walter Scott novelist
Geoffrey Chaucer poet
John Trevisa translator
Francis Bacon philosopher
Robert Mannyng historian
George Eliot novelist (only female in top 100 sources)
Encyclopædia Britannica
Cursor Mundi historical poem
Wycliffe Bible (early version) group of bible translations
Acts of Parliament, Britain
The Times (London) Most frequently quoted source: 42,840 citations
New York Times
Daily Telegraph
Harper's
Blackwood's
Listener
New Yorker
Philosophical Transactions of the Royal Society
Science
Nature
Today
2000
1800
1600
1400
1200
1000
Year
Word Source
PEOPLE
PUBLICATIONS
Journals
Magazines
Newspapers
Reference works
*Some publications include earlier incarnations with different names.

Top 100 Sources of Words

Key

Number of Times Cited for New Words, New Meanings and Exemplary Uses of Novel Words

3,000
8,000
18,000
30,000
43,000

Life Span of Source
Year born or founded
Year died or ended
Today
First record of a new word
First record of a new meaning

6,200 3,100 1,000 20

Scientific American

The magazine is the earliest record for 208 words (*red*), from "carburetor" in 1862 to "pharm" in 1994: a place that raises genetically modified plants or animals to produce pharmaceuticals. Even more prevalent are 848 new meanings for existing words (*gold*); in 1973 we used "crash" to describe a computer that suddenly quits.

Carburetor
Homogenized
Chassis (motor cars)
Space tourist (pay to go to space)
Pie crimper (baking)
Log-on
Pharm
Fractal
Clone (animals)
Digital cash (money transfer)
Crash (computer)
1860
1880
1900
1920
1940
1960
1980
2000
5,000
4,000
3,000
2,000
1,000
Cumulative New Words, Meanings and Uses

A Closer Look at *Scientific American*

Key

5
3
1
1
3
5

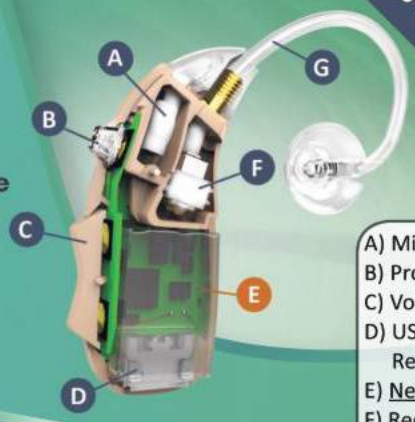
Number of first records of new words
Cumulative times cited for new words, new meanings and exemplary word use
Number of first records of new meanings

SOURCE: OED ONLINE. OXFORD UNIVERSITY PRESS. JANUARY 2019 www.oed.com

NEW Rechargeable Digital Hearing Aid Technology Only $229!*

(*Each when you buy a pair)

The new more powerful HearClear™ **HCR3 rechargeable** hearing aid combines advanced technology with a low price to provide you with outstanding value.



New Improved R3 Digital Processor™!

A) Microphone
B) Program Button
C) Volume Control
D) USB Charging Port & Rechargeable Battery
E) New Digital Processor
F) Receiver (Speaker)
G) Sound Tube

5 Star Reviews! ★★★★★

Outstanding Product! "This product is outstanding. Dad loves it, my mom loves it, and I am grateful! Don't believe that you have to spend a lot of money to get a quality hearing aid" - *Gilmore B.*

HCR3 Features!

- Digital sound processing chip provides **clear sound and makes speech easier to understand** with less feedback than old analog technology
- Don't worry about replacing batteries! **Full Charge Gives 16 Hours of Use! (Charger Included)**
- Easy **On / Off Button**
- Automatic Noise Reduction and Feedback Cancellation
- **100% Money Back Guarantee**
- **4 Programs** for different listening situations
- Helps most **moderate to significant hearing losses** (call us if you need more power)

Even Better In Pairs!

Your brain is designed to use both ears working together. In fact, studies show that you may be able to **hear up to 3 times better** in noisy situations when using two hearing aids. Buy a pair for the best results and maximum savings!

Simple. Affordable. Rechargeable Digital Hearing Aid - For Only $229!*

The new HearClear™ HCR3 Rechargeable Digital Hearing Aids are now available to you for an unbelievably affordable price! The HCR3 is packed with the same key technologies that all high end digital hearing aids share while leaving out the extra bells and whistles that increase cost and require expensive adjustments. This helps you **hear better, while saving you a lot of money.**

NOW ON SALE!
~~List Price: $849~~
Sale Price: $229*

Your new HearClear HCR3 hearing aids work at a fraction of the cost of name-brand hearing aids, and you won't have to keep changing the batteries! You will love the discreet, comfortable, lightweight Open-fit design. The HCR3 is pre-programmed for most moderate to significant hearing losses, so you won't need professional appointments to make costly adjustments. **It is shipped directly to you and will help you hear better right out of the box!**

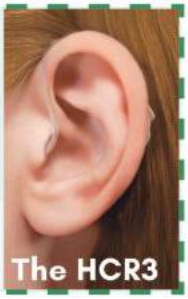
You can spend thousands for an expensive hearing aid, or you can spend just **$249** for a hearing aid that is great for most hearing losses **(only $229 each when you buy a pair – hear up to 3 times better than wearing just one)**. We are so sure you will love your hearing aids that we offer a **100% Money Back Guarantee - Risk Free** if you are not satisfied for any reason.

MONEY SAVING OFFER!

Use Coupon Code: **SA94**

1-888-259-5971

***Only $229 Each When You Buy A Pair!**
(Coupon Code & Price Valid For A Limited Time Only)



Advanced Affordable Hearing™
Affordable Quality Since 1996!

A+ BBB ACCREDITED BUSINESS | 100% MONEY BACK GUARANTEE | RISK • FREE • Trial | US Company Owned And Operated | FDA REGISTERED

Visit and Save: **www.AdvancedHearing.com/SA94**