FOOD
Preserving Wines as Climate Changes

TECHNOLOGY
Motion Microscopes' Powerful New View

EXPLORATION
Precision Tools Find Sunken Treasures

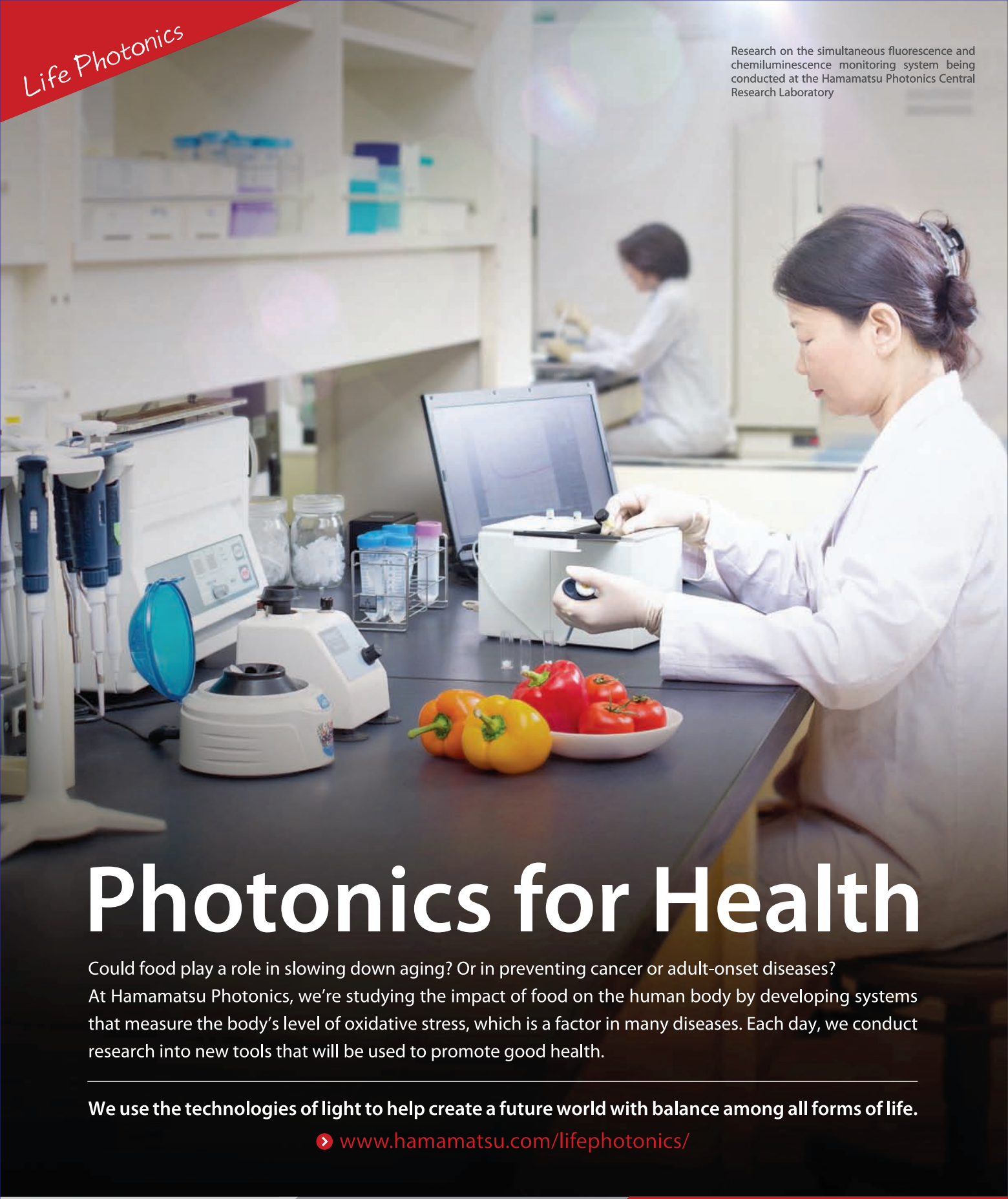
SCIENTIFIC AMERICAN

ScientificAmerican.com
JANUARY 2015

The Hunt for Planets Better Than Earth

"Superhabitable" worlds may be common in our galaxy, making ideal homes for extraterrestrial life

Life Photonics



Research on the simultaneous fluorescence and chemiluminescence monitoring system being conducted at the Hamamatsu Photonics Central Research Laboratory

Photonics for Health

Could food play a role in slowing down aging? Or in preventing cancer or adult-onset diseases?
At Hamamatsu Photonics, we're studying the impact of food on the human body by developing systems that measure the body's level of oxidative stress, which is a factor in many diseases. Each day, we conduct research into new tools that will be used to promote good health.

We use the technologies of light to help create a future world with balance among all forms of life.

www.hamamatsu.com/lifephotonics/

HAMAMATSU
PHOTON IS OUR BUSINESS

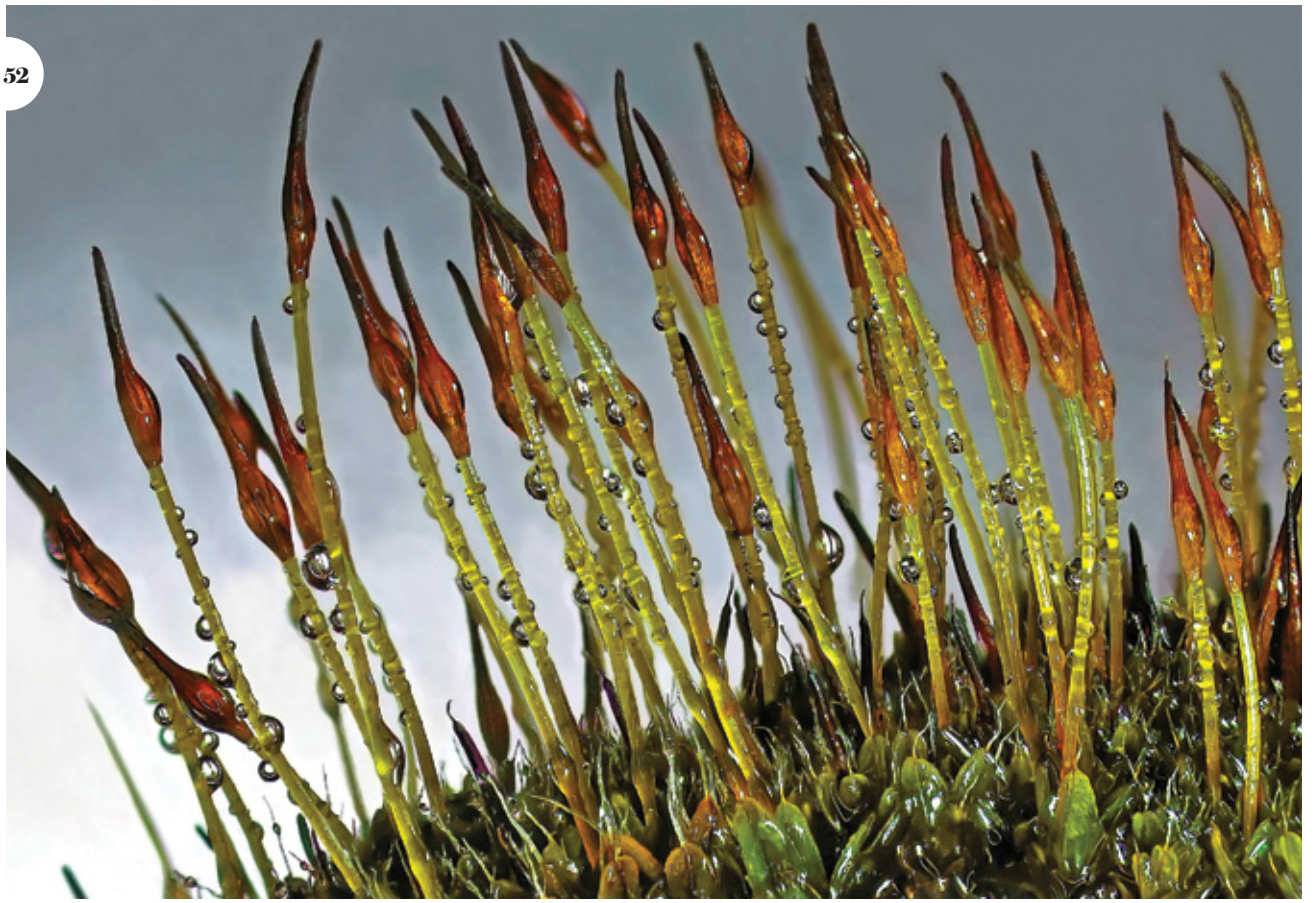
HAMAMATSU PHOTONICS K.K.
325-6, Sunayama-cho, Naka-ku, Hamamatsu City, Shizuoka Pref., 430-8587, Japan
Telephone:(81)53-452-2141, Fax:(81)53-456-7889 **www.hamamatsu.com**

ON THE COVER

Alien life could exist not only on Earth-like planets but also on worlds quite different from our own. The misty world here is an Earth-mass moon of a gas-giant planet, which lurks in the background, accompanied by a smaller, lifeless moon. Light, heat and tidal forces from the giant planet could all sculpt the cloudy moon into a place even more hospitable for life than Earth. Illustration by Ron Miller.

SCIENTIFIC AMERICAN

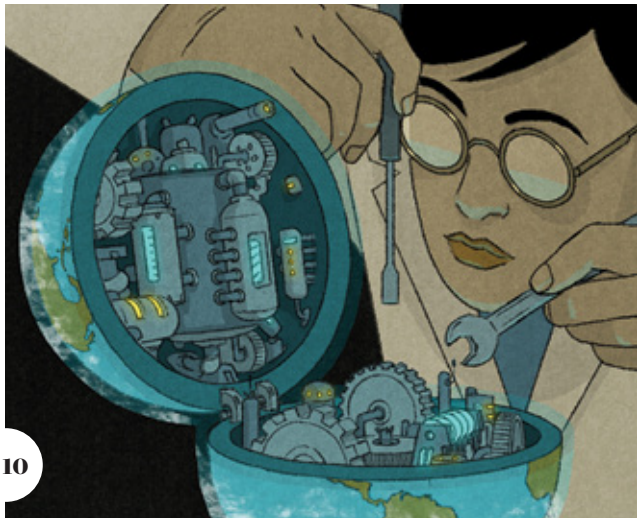
January 2015, Volume 312, Number 1



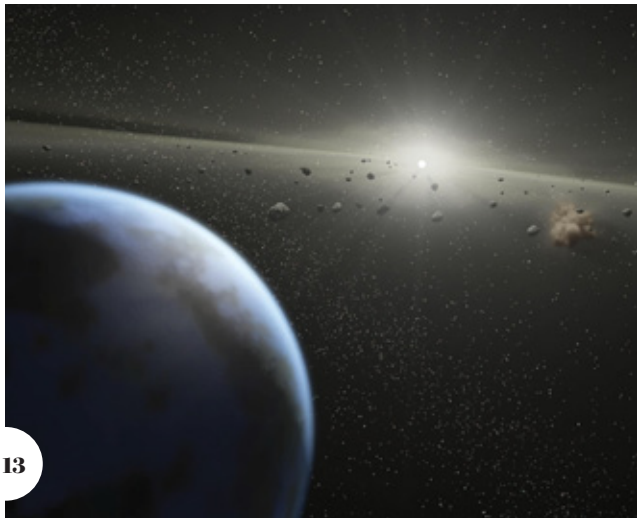
52

COURTESY OF CSABA PINTÉR, 2014 OLYMPUS BIOSCAPES DIGITAL IMAGING COMPETITION (*spore-forming bodies of the moss* Tortula ruralis)

FEATURES



10



13

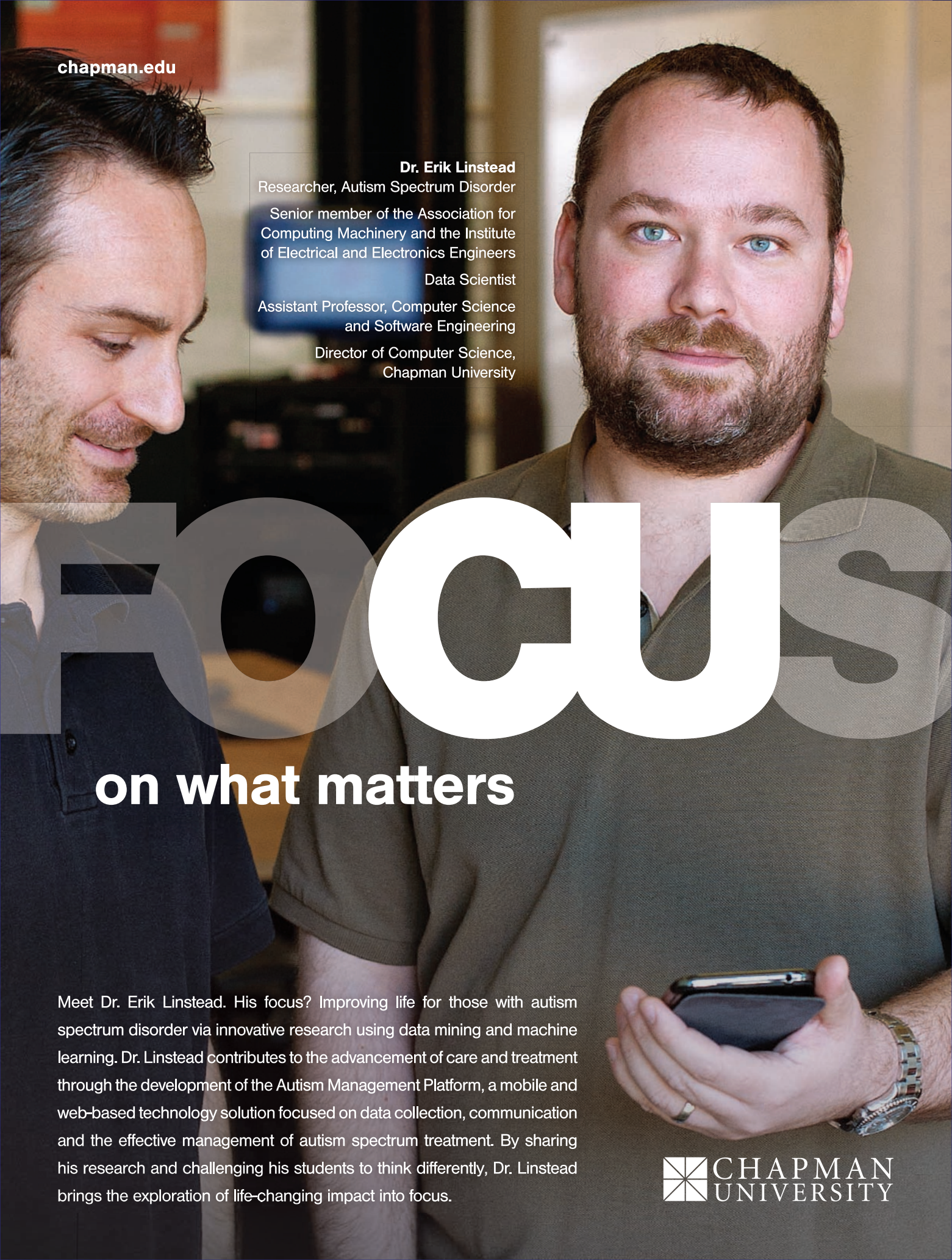
82

SCIENTIFIC AMERICAN

DEPARTMENTS

SPECIAL REPORT

Scientific American (ISSN 0036-8733), Volume 312, Number 1, January 2015, published monthly by Scientific American, a division of Nature America, Inc., 75 Varick Street, 9th Floor, New York, N.Y. 10013-1917. 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 $39.97 (USD), Canada $49.97 (USD), International $61 (USD). **Institutional Subscription rates:** Schools and Public Libraries: 1 year $72 (USD), Canada $77 (USD), International $84 (USD). Businesses and Colleges/Universities: 1 year $330 (USD), Canada $335 (USD), International $342 (USD). Postmaster: Send address changes to Scientific American, Box 3187, Harlan, Iowa 51537. **Reprints available:** write Reprint Department, Scientific American, 75 Varick Street, 9th Floor, New York, N.Y. 10013-1917; fax: 646-563-7138; reprints@SciAm.com. **Subscription inquiries: U.S. and Canada (800) 333-1199; other (515) 248-7684. Send e-mail to scacustserv@cdsfulfillment.com.** Printed in U.S.A.



chapman.edu

Dr. Erik Linstead
Researcher, Autism Spectrum Disorder

Senior member of the Association for Computing Machinery and the Institute of Electrical and Electronics Engineers

Data Scientist

Assistant Professor, Computer Science and Software Engineering

Director of Computer Science, Chapman University

FOCUS

on what matters

Meet Dr. Erik Linstead. His focus? Improving life for those with autism spectrum disorder via innovative research using data mining and machine learning. Dr. Linstead contributes to the advancement of care and treatment through the development of the Autism Management Platform, a mobile and web-based technology solution focused on data collection, communication and the effective management of autism spectrum treatment. By sharing his research and challenging his students to think differently, Dr. Linstead brings the exploration of life-changing impact into focus.

CHAPMAN UNIVERSITY

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

Many Worlds

As I type this essay on a flight from Dubai to Paris, I can see the hazy curve of our blue planet at the horizon. I've just finished the kickoff meeting of the World Economic Forum's Global Agenda Councils, where I served as vice chair of the Meta-Council on Emerging Technologies. I am now headed to the launch of the UNESCO World Library of Science, a set of free science resources for educators and students created by a partnership of UNESCO and Nature Education, with funding support from Roche. (*Scientific American* is part of Nature Publishing Group.) Although they are using different approaches to tackle separate goals, both initiatives share a broader mission: to help improve the state of the world.

I find myself reflecting: Earth is not without its problems, but it's still the most habitable spot in the cosmos. Or is it?

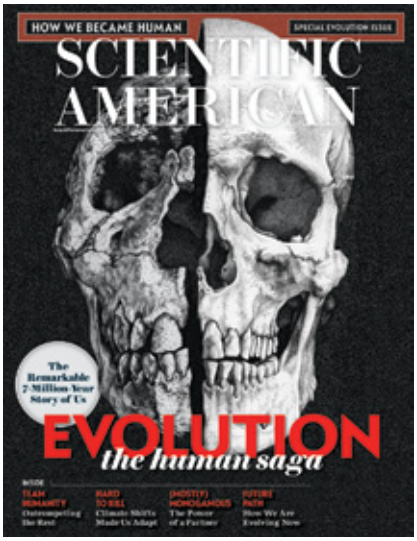
That is the intriguing possibility posed by this issue's cover story, "Better Than Earth," by René Heller. "Over the past two decades astronomers have found more than 1,800 exoplanets [beyond our solar system], and statistics suggest that our galaxy harbors at least 100 billion more," Heller writes.

Some of them may be "superhabitable" worlds—with stable biospheres that may be optimal targets in our search for extraterrestrial life in other corners of the galaxy. They may even surpass the ability to nurture life that we see on Earth, with its vast deserts, frigid polar regions and nutrient-poor open oceans. In our planet's past, it was warmer, wetter and more oxygen-rich than today, and the future will be less life-friendly. Heller's feature story looks at how astronomers are searching for such worlds and what they may be like. Turn to page 32.

Back on Earth, you can expect to see our Meta-Council on Emerging Technologies 2015 list in late January, during the World Economic Forum's meeting in Davos. And you don't have to wait at all to dip into the rich knowledge resources in the UNESCO Library of Science: just point your browser to www.unesco.org/wls. A world of possibility awaits. SA

Illustration by Ron Miller (cover image), Illustration by Nick Higgins (DiChristina)

editors@sciam.com



September 2014

QUESTIONS OF LOGIC

Throughout the special issue on evolution, a question based on a false premise is asked: What makes human special? As a minor branch on a vast evolutionary bush, modern humans have been roaming the earth for no more than a few hundreds of thousands of years—too little time to demonstrate if the evolution of large brains is a successful strategy for long-term survival of the species. If any life-form were special, it would be bacteria, which will be here long after the human experiment is a distant memory.

Jeff Schweitzer
Spicewood, Tex.

I find myself likening the attempt to pinpoint where humanity began to preschoolers theorizing about candy they've found scattered about a picnic area. A Hershey bar in the grass suggests chocolate grows there, whereas a Butterfinger by the table surely fell out of a pocket.

Inventing scenarios to try and fit observations are where theories come from. Still, beware that in our eagerness to explain, we risk elevating accidents of the discovery process to primary evidence.

David K. Elliott
Oxford, Mass.

MODERN EVOLUTION

As John Hawks states in "Still Evolving (After All These Years)," human populations continue to evolve today. But Hawks does not discuss the possible consequences of some of the evolutionary pressures that have been altered in the past century by medicine and public health. Could modern medical intervention inadvertently result in the survival and spread of genetic mutations that would otherwise have been eliminated or in the loss of protective genes?

Martin J. Greenwood
Stirling, Western Australia

"If any life-form were special, it would be bacteria, which will be here long after the human experiment is a distant memory."
Jeff Schweitzer *Spicewood, Tex.*

HAWKS REPLIES: A bit of thinking about genetic drift and mutation shows that we need not worry about future generations being "genetically weaker" because of medical technology and other modern advances. If selection is relaxed on a deleterious mutation, its frequency can change only because of random genetic drift. Under drift alone, most rare mutations will become extinct over many generations. A few may increase in frequency, but the speed of genetic drift in a large population is very slow. In our large populations, it would take many thousands of generations for any of today's rare mutations to become common.

I look with wonder and joy on people today living happy lives by managing once fatal genetic disorders. If we can advance medical technology and public health in ways that release people from such lethal disorders for the next few thousand generations, I think we have little to fear from genetic drift.

CURIOUS CREATURE

In "If I Had a Hammer," Ian Tattersall cites our capacity for symbolic reasoning as one of the traits unique to humans that led to the rise of our species' dominant position on the earth. I believe that our highly developed curiosity is another key, uniquely human trait. Without motivation, our capacity for symbolic reasoning would be of little use, and curiosity could have provided it.

Leon M. Rosenson
via e-mail

TATTERSALL REPLIES: Human "curiosity," in the sense in which we understand it today, is clearly enabled by our symbolic capacity to imagine that the world could potentially be different from the one we immediately experience.

CONTRADICTORY VIEWS?

I am confused by the apparent contradiction between statements in two articles.

In his article, Tattersall writes that "a population needs to be small if it is to incorporate any substantial innovation, genetic or cultural. Large, dense populations simply have too much genetic inertia to be nudged consistently in any direction." But in his article, Hawks asserts that "the huge and rapidly increasing population size of our ancestors gave them many more rolls of the dice. As human populations have spread into new parts of the world and grown larger, they have rapidly adapted to their new homes precisely because those populations were so big."

Mel Tremper
Berwyn Heights, Md.

THE EDITORS REPLY: Although Tattersall's and Hawks's statements might appear contradictory, they actually refer to different evolutionary scenarios.

Tattersall's article focuses on evolution in small populations of early human ancestors that were isolated from one another and lived in different environments. Under such conditions, random genetic and cultural changes (both beneficial and neutral) could have accumulated rapidly, thereby leading such populations to differentiate and, ultimately, speciate.

In contrast, Hawks's article focuses specifically on adaptive genetic changes within large populations of Homo sapiens. *Large populations have more matings and hence more chances for beneficial genetic changes to arise, thus facilitating adaptation to the novel environments our species encountered as it spread out from Africa across the world.*

WE'RE LOOKING AT CANCER IN A WAY THE WORLD NEVER HAS BEFORE.

Cancer can't hide anymore. That's because a new nanotechnology-based imaging system is helping our surgeons pinpoint the exact location of a tumor so they can remove it more precisely than they ever have. By improving the way we see cancer, we're seeing new possibilities for our patients.
Learn more at MSKCC.ORG/MORESCIENCE

MORE SCIENCE. LESS FEAR.

1884

Memorial Sloan Kettering Cancer Center

MANHATTAN • BROOKLYN • LONG ISLAND • WESTCHESTER COUNTY • BASKING RIDGE, NJ
In-network with most health plans. Ask about financial assistance.

SEX AND THE EXPERIMENT

In criticizing the National Institutes of Health's new policy requiring the scientists it funds to use equal numbers of male and female animal subjects in their research ["Vive la Différence," Forum], R. Douglas Fields claims that doing so would create problems because it would increase data variability. That is balderdash.

First, differences between male and female participants can be captured by many different statistical treatments, which allows researchers to compare groups without increasing error variability.

Second, the idea that reduced variability is the aim of all scientists is scary. I could reduce data variability on chairs by only studying purple ones that were 0.5 meter high. Then I could make only generalizations about those particular chairs.

Cynthia Whissell
Laurentian University, Ontario

Fields incorrectly states that when sex is added to an experiment, it cuts the sample size in half and increases variation. In research or experimental design, one reduces variance by eliminating differences within the sample or by building differences into the design. Thus, at the postassessment phase, one might have a "two-by-two design" (experimental group versus control group and male versus female).

David Lopez-Lee
Professor Emeritus
University of Southern California

FIELDS REPLIES: The essence of experimental research is careful discrimination. Comparing similar groups enables more discerning distinctions. There is no magic statistical method that can overcome the realities that variances add: increasing the number of categories from two to four makes it more difficult to draw conclusions without increasing the sample size.

The scientific method uses deductive reasoning to reject a specific hypothesis. Unlike Whissell's assertion, it does not permit any generalization. Further, only a small fraction of NIH grant applications are funded. The mandate imposes a specific hypothesis to test in every grant and circumvents the normal peer review that considers whether testing a hypothesis in each case is, for instance, prudent or practical.

LETTERS TO THE EDITOR

Scientific American
75 Varick Street, 9th Floor
New York, NY 10013-1917
or editors@sciam.com

Letters may be edited for length and clarity. We regret that we cannot answer each one. Post a comment on any article at ScientificAmerican.com/jan2015

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, 75 Varick Street, 9th Floor, New York, NY 10013-1917; 212-451-8877; reprints@SciAm.com. For single copies of back issues: 800-333-1199.

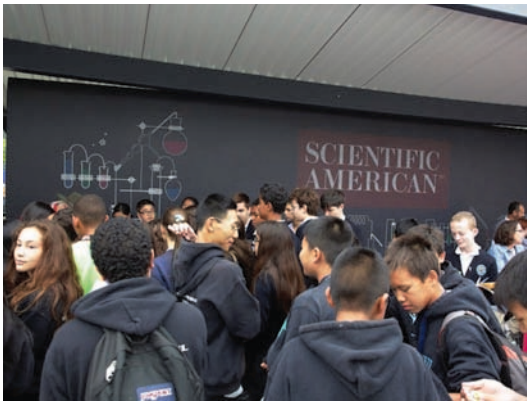
Permissions
For permission to copy or reuse material: Permissions Department, Scientific American, 75 Varick Street, 9th Floor, New York, NY 10013-1917; randp@SciAm.com; www.ScientificAmerican.com/permissions. Please allow three to six weeks for processing.

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.

PROMOTION

The Agenda Setters

Bringing Science to Life



Google Science Fair 2014

Googleplex | Mountain View, CA | September 22, 2014

In support of the next generation of science enthusiasts, SCIENTIFIC AMERICAN has been a key partner of the global Google Science Fair competition since it launched in 2011. Each year, Editor in Chief Mariette DiChristina heads up the judging team and we award the SCIENTIFIC AMERICAN Science in Action Award to honor a project that makes a practical difference by addressing an environmental, health or resources challenge. This year's $50,000 award went to Kenneth Shinozuka (pictured in the center of the photo on the upper right) for his wearable sensors for an aging society. SCIENTIFIC AMERICAN received national media attention for this, including a segment on NBC's Nightly News.

At this year's event at the Google campus in California, we and the other Google Science Fair partners – LEGO Education, National Geographic and Virgin Galactic – hosted science activities for literally thousands of children and their families.

A Hacker's Guide to Planet Cooling

"Geoengineering" our climate sounds like an idea from the mind of Dr. Strangelove, but tests of the methods may save us from disaster

In 2009 biological oceanographer Victor Smetacek tried to sink our global warming problem in the sea. The researcher, his scientific team and the crew of the ship RV *Polarstern* sailed to the Southern Ocean and poured a solution of iron into a small eddy. Iron, a nutrient, triggered a phytoplankton bloom, and the tiny photosynthesizers sucked carbon dioxide from the sky as they grew. When the plankton died, they drifted like snow to the bottom of the ocean, entombing CO_2 in their tiny corpses.

Although the technique, if used widely, could bury a billion metric tons of this greenhouse gas every year, the experiment drew the ire of environmentalists. Such iron fertilization was condemned by organizations such as the World Wide Fund for Nature and the ETC Group, some other scientists, and Germany's environment minister, who worried about unforeseen and toxic side effects, such as plankton growth harming the food chain. Smetacek, who had received prior approval from the governments of Germany and India, eventually stopped pursuing the idea after an international treaty against ocean dumping added cautions about such experiments.

We need to get over the environmentalist skittishness that thwarts these small tests of climate manipulation. Civilization may depend on such geoengineering methods as the planet keeps warming. We need tests to get them right—and stop people from doing them wrong.

Humanity is on pace to raise the planet's thermostat by four degrees Celsius by 2100, according to the Intergovernmental Panel on Climate Change. Its latest report states that technology to pull CO_2 from the air will be needed to avoid that rise.

There are at least two families of geoengineering ideas: those that get rid of CO_2, the primary greenhouse gas, and those that seek to block sunlight, which buys time. Scientists and engineers have proposed various approaches besides iron fertilization, such as hazing the skies with sulfates to mimic the cooling effects of a volcanic eruption or even launching a fleet of mirrors to deflect sunlight away from the planet. The problem with any of these approaches is that scientists do not know much about potential side effects. Could plants genetically engineered for supercharged photosynthesis kick off another Ice Age by drawing down too much CO_2? Would artificial volcanoes shut off crucial Asian monsoon rains by altering cloud and wind patterns? Would any of these world-changing ideas work in the first place, and are some too crazy to pursue?

The only way to find out for sure is to do what Smetacek did: test them, in a contained, rigorous, transparent manner. Not only did the oceanographer obtain government permission, he published the findings and data in a scientific journal so all could see. Yet even small tests like this are taboo. When U.K. researchers announced plans to spray a few tubs of water into the sky in 2011, more than 70 organizations from around the world signed a protest petition. The scientists backed off. These attitudes need to change, and scientific funding agencies need to support such research. The small but discernible effects of a restricted test should do no long-lasting damage. Smetacek's plankton bloom faded quickly. The eruption of Mount Pinatubo in 1991—a large-scale geoengineering "experiment"—did not have lasting climate effects.

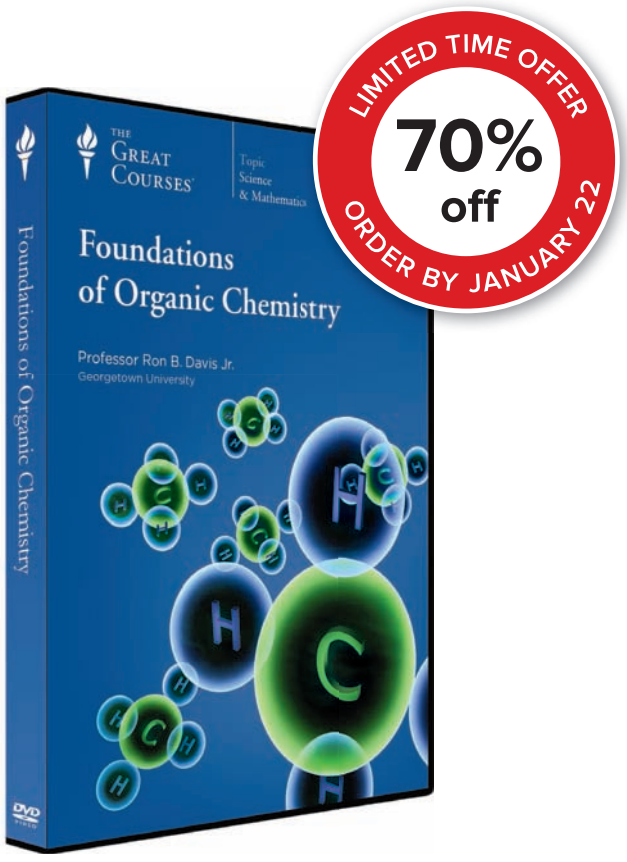
Geoengineering experiments do carry risks: setting off artificial volcanoes all over the globe, for instance, might destroy the ozone layer. That is another reason why geoengineering concepts need testing: so people know what *not* to do.

After all, Smetacek and his crew are not the only people to try out iron fertilization. In 2012 independent entrepreneur Russ George dumped iron overboard with the idea of restoring salmon fisheries and selling carbon credits. That is the kind of rogue geoengineering that we cannot afford. SA

SCIENTIFIC AMERICAN ONLINE
Comment on this article at ScientificAmerican.com/jan2015

Illustration by Morgan Schweitzer

THE GREAT COURSES®



Master Organic Chemistry with a World-Class Teacher

As a field, organic chemistry is just a few hundred years old, yet it is already at the heart of modern advances in energy, nanotechnology, and medicine. For all its far-reaching applications, however, organic chemistry is a challenging subject that is feared by many students.

Foundations of Organic Chemistry is taught by award-winning Professor Ron B. Davis, Jr. of Georgetown University, who has the ability to make clear even the most complex concepts. Professor Davis's expert instruction and demonstrations will give you a solid grasp of organic chemistry—what it is, how it works, and why it's so important.

By the time you finish this course, you'll have a basic understanding of the scientists, theories, and concepts involved in the field; grasp the impact of organic chemistry on both today's world and tomorrow's; and launch yourself into bold new areas of study in a branch of science that's a lot less intimidating—and more exciting—than you imagined.

Offer expires 01/22/2015

THEGREATCOURSES.COM/4SA

1-800-832-2412

Foundations of Organic Chemistry

Taught by Professor Ron B. Davis, Jr.
GEORGETOWN UNIVERSITY

LECTURE TITLES

1. Why Carbon?
2. Structure of the Atom and Chemical Bonding
3. Drawing Chemical Structures
4. Drawing Chemical Reactions
5. Acid–Base Chemistry
6. Stereochemistry—Molecular Handedness
7. Alkanes—The Simplest Hydrocarbons
8. Cyclic Alkanes
9. Alkenes and Alkynes
10. Alkyl Halides
11. Substitution Reactions
12. Elimination Reactions
13. Addition Reactions
14. Alcohols and Ethers
15. Aldehydes and Ketones
16. Organic Acids and Esters
17. Amines, Imines, and Nitriles
18. Nitrates, Amino Acids, and Amides
19. Conjugation and the Diels-Alder Reaction
20. Benzene and Aromatic Compounds
21. Modifying Benzene—Aromatic Substitution
22. Sugars and Carbohydrates
23. DNA and Nucleic Acids
24. Amino Acids, Peptides, and Proteins
25. Metals in Organic Chemistry
26. Synthetic Polymers
27. UV-Visible Spectroscopy
28. Infrared Spectroscopy
29. Measuring Handedness with Polarimetry
30. Nuclear Magnetic Resonance
31. Advanced Spectroscopic Techniques
32. Purifying by Recrystallization
33. Purifying by Distillation
34. Purifying by Extraction
35. Purifying by Chromatography
36. The Future of Organic Chemistry

Foundations of Organic Chemistry
Course no. 1185 | 36 lectures (30 minutes/lecture)

SAVE $270

DVD ~~$384.95~~ NOW $114.95
+$15 Shipping, Processing, and Lifetime Satisfaction Guarantee
Priority Code: 105526

For 24 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 mobile apps for iPad, iPhone, or Android. Over 500 courses available at www.TheGreatCourses.com.

Commentary on science in the news from the experts

Carl Benedikt Frey is a research fellow of the Oxford Martin School at the University of Oxford and a member of the department of economic history at Lund University in Sweden. He is also a specialist adviser to the Digital Skills Committee at the House of Lords of the U.K. Parliament.

The End of Economic Growth?

How the digital economy could lead to secular stagnation

Last September e-commerce giant Amazon acquired Twitch, a live-streaming video company, for $970 million. Not long ago a new billion-dollar company would have been a boon to job creation. Yet Twitch employs just 170 workers.

The story of Twitch illustrates an important lesson about the digital economy: at the same time it has generated enormous wealth for shareholders and entrepreneurs, it has resulted in few new jobs. In fact, the digitization of the economy may have far-reaching implications for the future of growth and employment.

In a series of recent articles on the state of the digital economy, former U.S. treasury secretary Lawrence Summers revived the notion of secular stagnation, an idea first presented by economist Alvin Hansen during the Great Depression. Hansen's theory suggested that as population growth slows and the rate of capital-absorbing innovation (that is, investment opportunities created by the arrival of new technologies) tapers off, investment will fall, leading to slower economic growth and fewer new jobs.

During the growth miracle of the postwar period, Hansen's theory proved spectacularly wrong. Technological advances during the 1930s and the increase in capital investment associated with World War II did enough to stave off stagnation. After that, the baby boomer generation entered the workforce, pushing the economy ahead. Then, in the 1980s and 1990s, investment in computer and information-processing equipment surged, facilitating a wide range of entirely new computer-related occupations.

But after 2000, when the first wave of IT investment peaked, the demand for new work in the U.S. declined. Hansen famously wrote that "when a revolutionary new industry … reaches maturity and ceases to grow, as all industries finally must, the whole economy must experience a profound stagnation…. And when giant new industries have spent their force, it may take a long time before something else of equal magnitude emerges." Without new job-creating industries to take the place of those that came before, the economy might stagnate.

The problem is that most industries formed since 2000—electronic auctions, Internet news publishers, social-networking sites, and video- and audio-streaming services, all of which appeared in official industry classifications for the first time in 2010—employ far fewer people than earlier computer-based industries. Whereas in 2013 IBM and Dell employed 431,212 and 108,800 workers, respectively, Facebook employed only 8,348 as of last September.

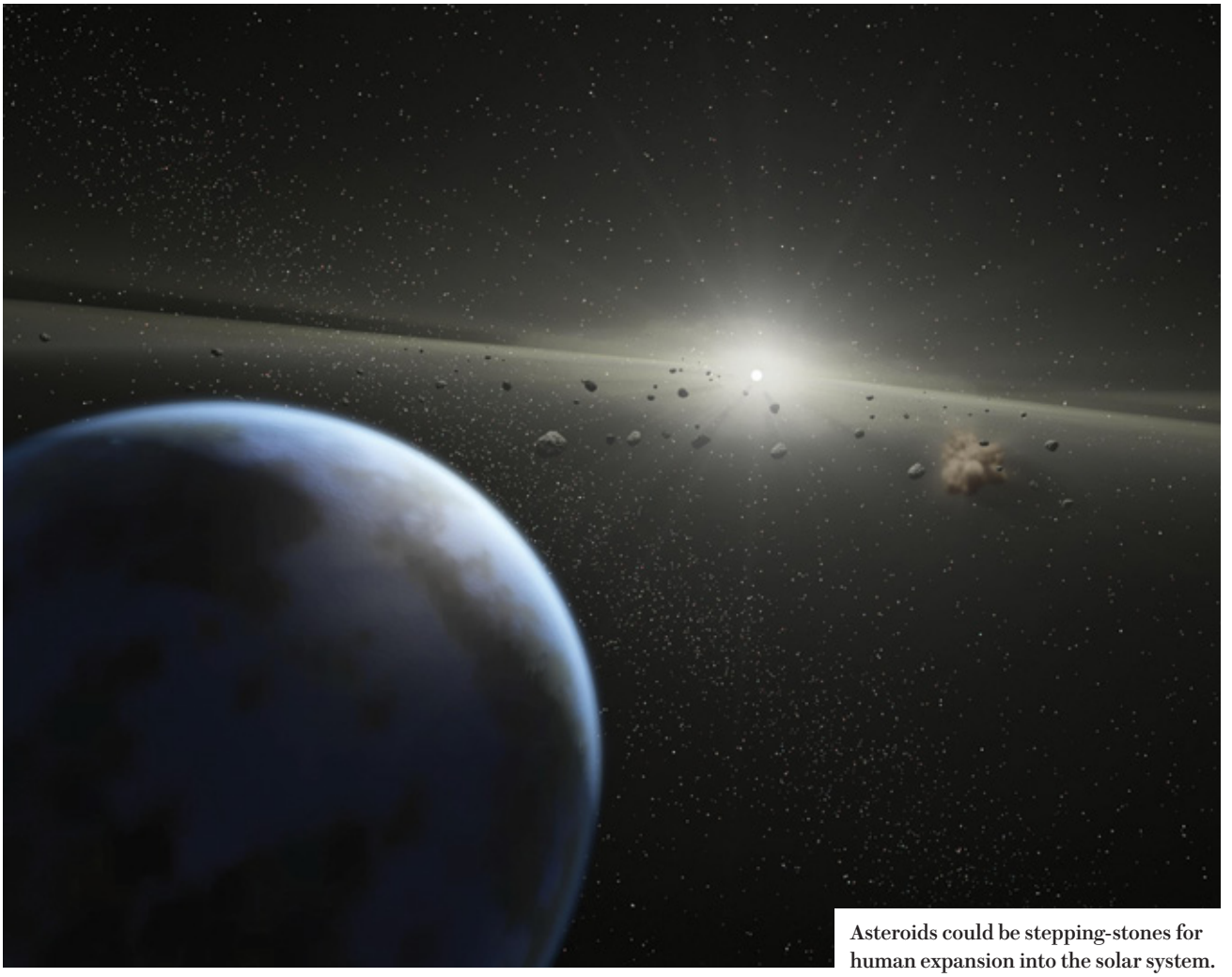
The reason these businesses spin off so few jobs is that they require so little capital to get started. According to a recent survey of 96 mobile app developers, for example, the average cost to develop an app was $6,453. Instant-messaging software firm WhatsApp started with a relatively meager $250,000; it employed just 55 workers at the time Facebook announced it was buying the company for $19 billion. All of which explains why new technologies throughout the 2000s have brought forth so few new jobs. According to my own research with Thor Berger of Lund University in Sweden, in 2010 only about 0.5 percent of the U.S. workforce was employed in industries that did not exist a decade earlier.

Summers is likely to be proved right as digital technologies lead to insufficient investment and growing inequality reduces spending. Yet there is much that governments can do to prevent stagnation. They can redistribute income to those with a higher propensity to spend. They can also support investment into industries that might foster more new jobs than digital technologies—jobs for solar photovoltaic installers, wind energy engineers, biofuels production managers and transportation planners.

Finally, while digital technologies may create fewer jobs than previous innovations, they also substantially reduce the amount of money it takes to start a new digital business—and that will make it possible for more people to become entrepreneurs. Indeed, self-employment might become the new normal. The challenge for economic policy is to create an environment that rewards and encourages more entrepreneurial risk taking. A basic guaranteed income, for instance, would help by capping the downside to entrepreneurial failure while boosting spending and combating inequality. SA

SCIENTIFIC AMERICAN ONLINE
Comment on this article at ScientificAmerican.com/jan2015

Illustration by Nick Ogonosky



Asteroids could be stepping-stones for human expansion into the solar system.

COURTESY OF NASA AND JPL/CALTECH

AEROSPACE

Dancing with the Asteroids

NASA's proposed human mission to a space rock has a bumpy road ahead

The Obama administration wants to send humans to Mars in the 2030s. Of course, such a mission requires a lot of advance engineering, and as a first step, NASA plans to send astronauts to a small asteroid that would be brought into a stable orbit around the moon. To achieve that mechanical feat, a solar-powered robotic probe is being designed to capture a space rock and slowly push it into place. A target asteroid has yet to be announced, and the robotic space tug has yet to be built, but the parties involved hope to have the rock relocated to the moon's vicinity as soon as 2021. NASA calls this concept the Asteroid Redirect Mission (ARM) and is marshaling resources across the entire agency to support it.

Michele Gates, the agency's program director for ARM, says that its advanced propulsion technology and crew activities would give NASA the capability and experience needed to someday reach Mars. The trip would demonstrate spacecraft rendezvous procedures and establish protocols for sample collection and extravehicular movements. And it would do all of this while keeping astronauts relatively safe, staying sufficiently close to home so that if something went wrong, the crew could potentially make an emergency return to Earth.

ARM's critics are loud and legion, however. In June the prestigious National Research Council issued a report stating that the mission could divert U.S. resources

FURTHER READINGS AND CITATIONS ScientificAmerican.com/jan2015/advances

and attention from more worthy space exploration, highlighting parts of ARM as dead ends on the path to Mars. The harshest criticisms have come from asteroid scientists. Mark Sykes, director of the Planetary Science Institute in Tucson, Ariz., ridiculed ARM last September while testifying to a congressional committee, saying that the agency's tentative cost estimate of less than $1.25 billion for the concept's robotic component strained credulity.

"It doesn't advance anything," Sykes says, "and everything that could benefit from it could be benefited far more by other, cheaper, more efficient means."

The mission's detractors miss the point that it represents the nation's best opportunity in the foreseeable future to maintain its momentum in human spaceflight, says Louis Friedman, a space policy expert who helped to conceive ARM.

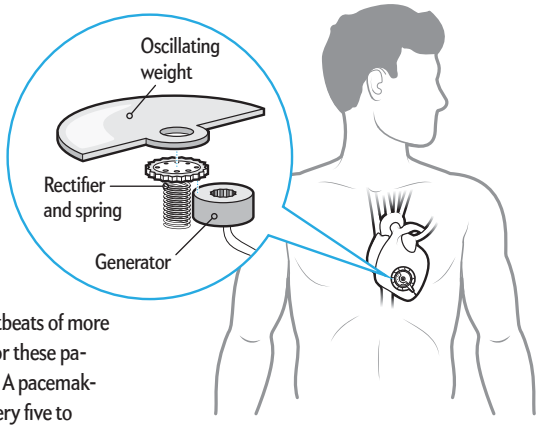
To this point, planetary scientist Richard Binzel of the Massachusetts Institute of Technology argues that NASA needs to look for more asteroids before it leaps into ARM. A robust asteroid survey, he says, would discover suitable targets for a crewed mission that would not require an expensive orbital relocation. "By the time we would tow a tiny rock into lunar orbit, we could be discovering more attractive, larger objects passing through the Earth-moon system that are easy to reach," Binzel notes.

NASA plans to conduct a formal review of the ARM concept in February, and the Obama administration's next budget proposal is expected to request more funding for ARM. But the redirect's fate may have already been sealed by 2014's midterm elections, in which Republicans, who are largely opposed to the mission, took full control of Congress. With this latest blow to NASA's post–Space Shuttle plans for human spaceflight, the agency's astronauts may end up boldly going nowhere for many years to come—regardless of the approach. *—Lee Billings*

TECHNOLOGY

The Pulse of Pacemakers

An automatic wristwatch mechanism harnesses heartbeats



Electronic pacemakers time the heartbeats of more than three million people in the U.S. For these patients, surgery is a regular occurrence. A pacemaker's batteries must be swapped out every five to eight years, and the electric leads that connect the device to the heart can wear out, too.

In an effort to eliminate the batteries and leads altogether, biomedical engineers at the University of Bern in Switzerland have built a heartbeat-powered pacemaker, assembled from self-winding clockwork technology that is more than two centuries old.

Automatic wristwatches, invented in 1777, contain a weighted rotor that turns when a wearer's wrist moves. The rotor winds up a spring, and when the fully coiled spring unwinds, it turns the watch's gears. In modern versions, the gears drive a tiny current-producing generator.

Like the jostling of a wrist, a beating heart can also wind a spring, the Swiss team found. The researchers stripped an automatic wristwatch of its time-indicating parts, enclosed the winding mechanism in a three-centimeter-wide case and sutured it to a live pig's heart. The prototype produced 50 microwatts of power; pacemakers need about 10.

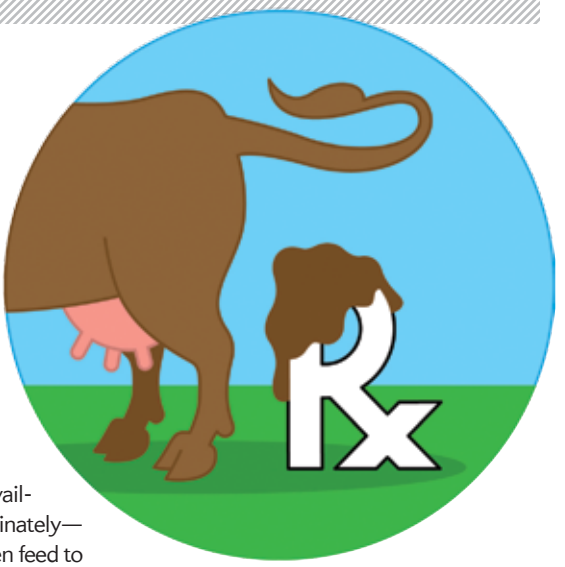
The device currently has a "messy setup," says Adrian Zurbuchen, who presented details about it at the European Society of Cardiology Congress late last summer. Wires connect the watch parts to a box containing electronics and a pacemaker. The goal is to have everything in one device. It will not be ready for prime time soon, predicts Spencer Rosero, who is director of the pacemaker clinic at the University of Rochester Medical Center and was not involved in the project. He says if tests are successful, medicine will most likely first see a pacemaker with both a battery and energy-harvesting components. *—Prachi Patel*

Graphic by Brown Bird Design

BIOLOGY

Bacteria? They Love All Manure

Cow dung encourages antibiotic resistance, even if it comes from drug-free cows



When antibiotics first became available, farmers used them indiscriminately—dribbling streptomycin into chicken feed to boost growth and doling out low doses to fatten pigs. Now scientists know that the overuse of antibiotics in livestock can foster drug-resistant bacteria that are dangerous to human health. Amid debates over what kinds of restrictions should be put in place, figuring out how antibiotic-resistant bacteria evolve and make their way to humans remains an area of intense interest.

Jo Handelsman is tracing one such pathway that, as she puts it, travels from "barn to table." Handelsman, a microbiologist who is now associate director for science at the White House Office of Science and Technology Policy, looked into dairy cows, which are often treated with antibiotics and produce manure that farmers use on their crops. In addition to nutrients, that fragrant fertilizer may harbor antibiotic-resistant bacteria—a problem because the microbes can come into contact with plants that are subsequently shipped to supermarkets and sometimes eaten raw.

To tease out how those antibiotic-resistant bacteria come to exist, Handelsman and her colleagues at Yale University added manure from a nearby Connecticut farm to raised beds of soil in 2013. In this case, the manure specifically came from cows that were not treated with antibiotics. The researchers unexpectedly found that soil bacteria carrying antibiotic-resistant genes became more abundant when they were grown with the manure than when they were grown with synthetic nitrogen-based fertilizer—even though the cows were drug-free. The team published its work in October in the *Proceedings of the National Academy of Sciences USA*.

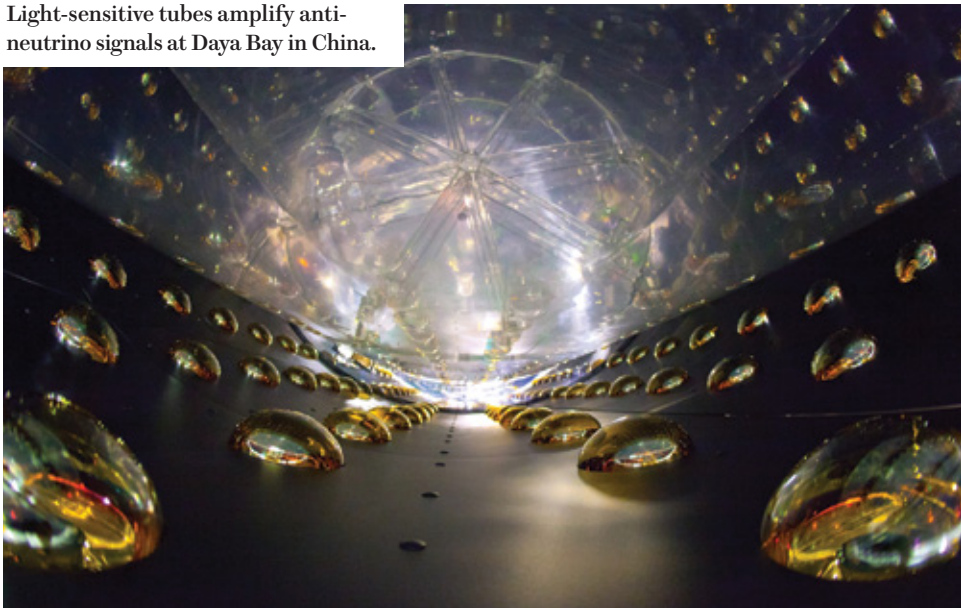
Previous research has found that manure from pigs treated with antibiotics contains resistant bacteria, including *Escherichia coli*, but the cow-pie results suggest there are more factors promoting resistance besides antibiotic use. Something about manure itself may encourage naturally resistant bacteria to proliferate.

> The cow-pie results suggest there are more factors promoting resistance besides antibiotic use.

The findings should not, however, give the perception that resistance is everywhere, notes Lance Price, a microbiologist at George Washington University (who was not involved in the study). Widespread resistance is not inevitable, he says. "We can control this. There's very clear evidence that when we turn off the antibiotic spigot, we bring down drug-resistant bacteria."

Next on the farm-to-table agenda, Handelsman will test whether radishes grown in soil treated with cow manure are capable of taking up resistant genes from bacteria via their vascular system. "They have veins just like us," she says. "We don't have any evidence yet that they're taking up the bacteria, but it's a really interesting possibility." —*Peter Andrey Smith*

Illustrations by Thomas Fuchs



Light-sensitive tubes amplify anti-neutrino signals at Daya Bay in China.

COURTESY OF ROY KALTSCHMIDT *Lawrence Berkeley National Laboratory*

PHYSICS

Theoretical Particles, Still Theoretical

No signs of the rumored "sterile" neutrino

Neutrinos come in three types, or flavors: electron, muon and tau. But physicists suspect that others may be out there and that they will be weird—almost never interacting with other particles. These "sterile" neutrinos may resolve some of physics' biggest mysteries. For example, they could contribute to the befuddling dark matter that apparently pervades the universe and exerts a gravitational pull on regular matter.

Despite decades of looking, however, sterile neutrinos remain elusive, and the latest attempt to catch them in action recently turned up empty, too. Physicists running the international Daya Bay Reactor Neutrino Experiment in China, which studies neutrino behavior, found no evidence for sterile neutrinos after a seven-month-long hunt.

This particular search took place underground: Daya Bay's neutrino detectors are buried at various depths below a group of nuclear power reactors in the province of Guangdong. That is because the fission reactions that take place at the plant naturally produce lots of the antimatter counterparts of electron-flavored neutrinos. Neutrinos, strangely enough, can switch flavors in a process called oscillation, so as these antimatter particles go flying, some of them change into muon or tau antineutrinos, hitting the detectors along the way. Scientists know roughly how many of the electron antineutrinos should change into the other flavors, and they use this calculation to figure out if any electron antineutrinos are missing at the deepest detectors. Missing particles would mean the originals probably turned into sterile neutrinos.

The absence of missing neutrinos at Daya Bay "leaves no room open in this particular territory for having a sterile neutrino," says Brookhaven National Laboratory physicist Milind Diwan, a member of the experiment's team. The results, published in October in *Physical Review Letters,* rule out the particles only in a certain range of masses and characteristics, however, so the ultimate truth about sterile neutrinos is still out there. Physicists at the site will continue looking for the particles within a broader range of characteristics. After all, the first 30 years' worth of searches for the Higgs boson turned up nothing.

—Clara Moskowitz

COMMENT AT ScientificAmerican.com/jan2015

CONSERVATION

Monikers Matter

An animal's name could determine its fate

If all goes according to plan, cement and concrete maker Lafarge will continue turning a limestone hill in Malaysia into a quarry. It would be business as usual for Lafarge, but bad news for *Charopa lafargei*, a recently discovered snail that lives only on that hill. The gastropod's name is no coincidence. For the first time, taxonomists have named a species after the entity that could cause the creature's extinction.

Whether this guilt trip will work remains to be seen (Lafarge has said it will avoid certain areas of the hill), but there is something to be said for choosing the name of a species carefully. Research has shown that an animal's common name can affect whether people want to protect it. In a 2012 study, George Mason University researchers found that species with patriotic or cute names are more likely to inspire public support for their conservation. The team that described the snail hopes that the same principle will help persuade Lafarge to protect *C. lafargei*.

—*David Shiffman*

WHAT'S IN A NAME?

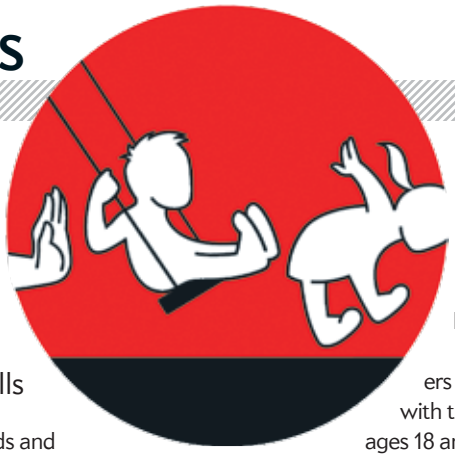
Survey respondents deemed an animal with a positive name (*green*) more conservation-worthy than its negatively named self (*red*).

	RATING (*percent*)*
Patriot falcon	68
Killer falcon	53
American eagle	77
Sheep-eating eagle	46
Great American wolf	66
Eastern coywolf	48
American otter†	68
Hairy-nosed otter†	41
Furry-nosed otter†	63
Sharp-clawed otter†	34

*Percent of study participants who wanted to conserve the animal. All names are fictional.

†From an unpublished follow-up study by Caitlyn Scott and Chris Parsons of George Mason University.

SOURCE: "WHAT'S IN A NAME? DO SPECIES' NAMES IMPACT STUDENT SUPPORT FOR CONSERVATION?" BY PAUL T. KARAFFA, M. M. DRAHEIM AND E.C.M. PARSONS, IN *HUMAN DIMENSIONS OF WILDLIFE: AN INTERNATIONAL JOURNAL*, VOL. 17, NO. 4, 2012



PSYCHOLOGY

Parental Controls

Pushy parents could harm kids' social skills

As countless unmade beds and unfinished homework assignments attest, kids need rules. Yet how parents make demands can powerfully influence a child's social skills, psychologists at the University of Virginia recently found after the conclusion of a study investigating the notorious transition from adolescence to adulthood.

Initially 184 13-year-olds filled out multiple surveys, including one to assess how often their parents employed psychologically controlling tactics, such as inducing guilt or threatening to withdraw affection. The kids rated, for example, how typical it would be for Dad to suggest that "if I really cared for him, I would not do things that caused him to worry" or for Mom to become "less friendly [when] I did not see things her way."

The researchers followed up with the subjects at ages 18 and 21, asking the young adults to bring along a close friend and, later, a romantic partner if they had one. These pairs were asked to answer hypothetical questions that were purposefully written to provoke a difference of opinion. "We wanted to see whether they could navigate a disagreement in a healthy way," says study leader Barbara Oudekerk, now at the U.S. Department of Justice's bureau of statistics.

In the October issue of *Child Development*, Oudekerk and her colleagues report that the 13-year-olds who had highly controlling parents floundered in friendly disagreements at age 18. They had difficulty asserting their opinions in a confident, reasoned manner in comparison to the kids without controlling parents. And when they did speak up, they often failed to express themselves in warm and productive ways.

The researchers suspect that manipulative parents undermine their child's ability to learn how to argue his or her own viewpoint in other relationships. Although parents do need to set boundaries, domineering tactics imply that any disagreement will damage the bond itself. Separate findings suggest that parents who explain the reasons behind their rules and turn disagreements into conversations leave youngsters better prepared for future disputes.

The consequences of tense or domineering relationships appear to compound with time. This study also found that social difficulties at 18 predicted even poorer communication abilities at age 21. Psychologist Shmuel Shulman of Bar-Ilan University in Israel, who did not participate in the work, thinks these conclusions convincingly reveal how relationship patterns "carry forward" into new friendships. —*Daisy Yuhas*

JOHANNES EISELE Getty Images

HEALTH

EBOLA SUITS

WHERE THEY ARE MADE

Approximately 12,500 Ebola virus capsules can fit side by side through a hole the size of a pinprick in a piece of clothing, and because exposure to just a few of the capsules can cause infection, protective barriers are a must for those who come into contact with patients. Lakeland Industries, a global manufacturer of protective clothing based in Ronkonkoma, N.Y., is one of a few companies that sews the plastic ChemMAX and MicroMAX suits that health care workers wear as shields.

As a result of the recent Ebola outbreak, Lakeland estimates that it received orders for about one million suits between late September and early November—a number that does not include requests for hoods, foot coverings and gloves. To accommodate the demand, its primary factory in Shandong Province, China (*above*), has hired more employees and invested in new machinery. By January the company expects its typical monthly production will have doubled. ***—Julia Calderone***

Brown bears hibernate for as long as eight months.

PHYSIOLOGY

Health Advice from a Grizzly

What humans can learn from animals that sleep for months on end

Hibernation is a complex solution to a simple problem. In winter, food is scarce. To survive this seasonal famine, animals, such as the arctic ground squirrel and black bear, induce a sedentary state under which physiological shifts keep them alive despite the lack of food, water and movement. Researchers and doctors alike are interested in how these hibernation tricks could help humans with their own health.

—Amy Nordrum

THREAT: **Stroke**
INSIGHT: Blood flow in the brain of a hibernating arctic ground squirrel drops to a tenth of normal. Typically such oxygen deprivation would cause a stroke. But these squirrels can survive all winter because their metabolism lowers to 2 percent of its summer rate—requiring much less oxygen to maintain. If paramedics could similarly lower the metabolism of a human patient immediately after a stroke—perhaps by cooling the body—they might prevent permanent brain damage, says Brian Barnes, a biologist at the University of Alaska Fairbanks.

THREAT: **Diabetes**
INSIGHT: People who gain a lot of weight often stop responding to insulin. The hormone regulates the amount of glucose that cells take up from the blood; too much sugar in the blood results in type 2 diabetes. Yet grizzly bears gain 100 pounds or more each autumn and somehow avoid diabetes. A recent study found that the grizzlies' fat cells become more sensitive to insulin as they prepare for the winter, allowing the bears to keep processing and storing sugar. Scientists at biotechnology company Amgen are now testing whether tweaking the same protein that controls sensitivity in diabetic humans could have similar results.

THREAT: **Osteoporosis**
INSIGHT: If a human were to lie still for long periods without food, his or her bones would slowly degrade. A black bear, however, emerges from its den after winter just as strong as ever because its bone is recycled at 25 percent of normal levels during hibernation. Researchers at Colorado State University are now trying to identify the hormones that control this extreme limit on bone turnover. They aim to create a drug for people at risk for osteoporosis that similarly protects bone density.

THREAT: **Heart Disease**
INSIGHT: During cardiac surgery, a patient becomes oxygen-deprived when the heart stops beating. To cope, the body switches from aerobic to anaerobic metabolism. Unfortunately, the change creates lactic acid, which can kill cells if it builds up. Damage of this kind does not occur in hibernating arctic ground squirrels, likely because they break down more fats than sugars even after the heart has slowed to just one beat per minute. Collaborating researchers at Duke University and the University of Alaska Fairbanks are now working to identify how this species prioritizes fat as fuel in low-oxygen conditions. Finding a way to coax cardiac surgery patients to do the same may reduce injury to organs during procedures.

ALAMY

COMMENT AT ScientificAmerican.com/jan2015

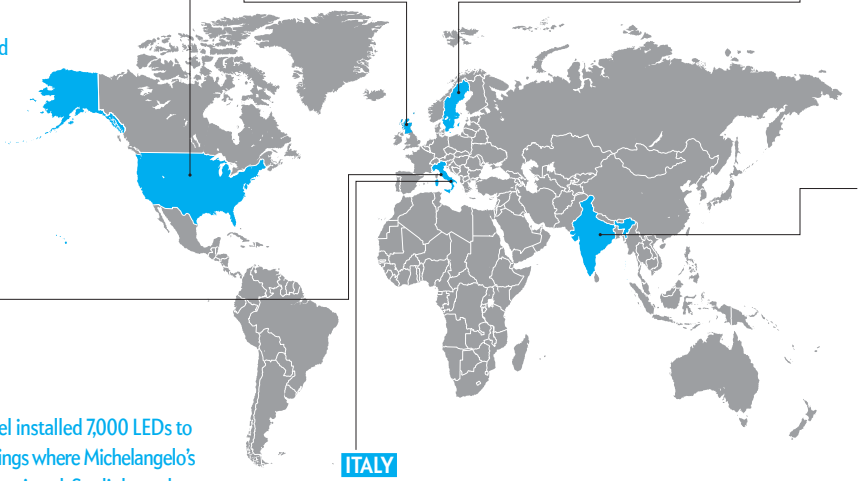
IN THE NEWS

Quick Hits

U.S.
Two leading groups of physicians now recommend hormonal implants and intrauterine devices (IUDs) as first-line birth control for teen girls. These long-acting methods have a higher success rate than daily birth-control pills.

SCOTLAND
Police officers began enforcing a new blood alcohol limit for drivers in December. The legal maximum dropped from 0.8 to 0.5 milligram per milliliter—essentially a zero-tolerance policy that rules out even a single glass of wine for those planning to get behind the wheel.

SWEDEN
Örnsköldsvik is set to become the world's first remotely controlled airport. Air-traffic controllers are testing a system of cameras and sensors that replaces humans and issues commands across multiple airports at once.



INDIA
The government introduced its first national mental health policy as part of a plan to increase access to resources for psychological well-being. With a suicide rate that is double the global average, India currently has only about 3,500 psychiatrists for its 1.2 billion citizens.

VATICAN CITY
The Sistine Chapel installed 7,000 LEDs to illuminate the ceilings where Michelangelo's masterpieces are painted. Sunlight and halogen bulbs were fading the frescoes.

ITALY
The military will start growing marijuana this year in an effort to make prices competitive with imported supplies. The country legalized marijuana for medicinal use in 2013.

For more details, visit www.ScientificAmerican.com/jan2015/advances

GEOLOGY

From Rain to Ranges

Rain that fell millions of years ago on the American West helps to sketch a long-gone landscape

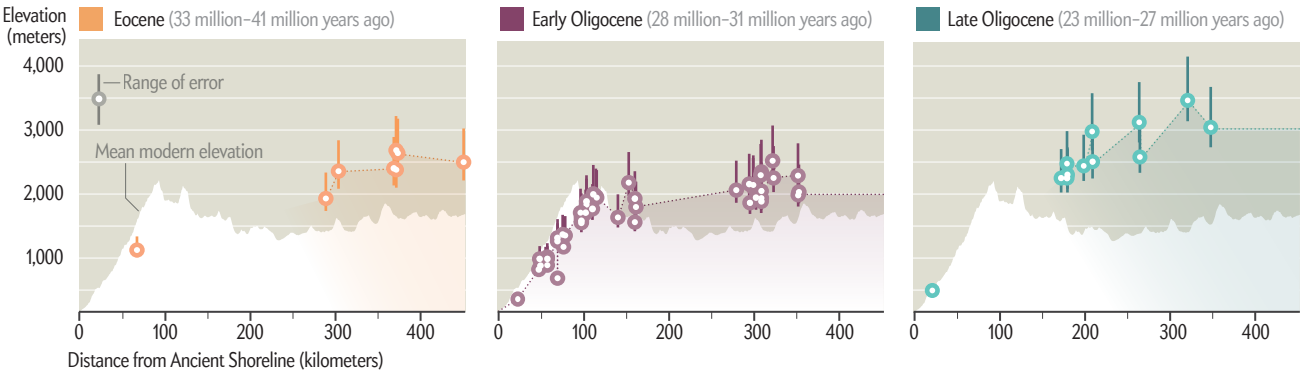
From atop California's Sierra Nevada Mountains, it is a downhill trek into Nevada. But back in the Oligocene, you would have had a climb ahead of you. During that epoch and the latter part of the Eocene before it, the West Coast was host to a broad band of mountains resembling the modern South American Andes. Over time, the earth's crust in this region, known as the Basin and Range Province, stretched until it cracked into blocks, tilting like thick volumes between sliding bookends. Geologists are now mapping that long-ago transformation by using a phenomenon that has spanned geologic time: rain.

Twenty-three million to 40 million years ago a series of volcanic eruptions in eastern Nevada produced rolling clouds of hot ash and cinders that coursed downhill all the way to the Pacific Ocean, leaving a trail behind them. For the following few millennia, rain diffused into these porous volcanic deposits—a mix of ash and rock particles—leaving behind clues about the ground's altitude.

Those clues come in the form of hydrogen isotopes: rainwater molecules with heavier hydrogen atoms, which leave clouds at lower altitudes, become scarcer as rain clouds move to higher ground. Following that logic, University of Idaho geologist Elizabeth Cassel and her colleagues measured the isotope ratios in rock samples between the Sierra Nevada and eastern Nevada to

Nevada's Rocky Past

Reconstructed mountain scapes based on rainwater isotopes reveal the state's ups and downs



ERIC LO Getty Images

Graphic by Tiffany Farrant-Gonzalez

map the mountain scapes of yesteryear (*below left*). Their results were published in November in the journal *Geology*.

Experts had thought that the state was a plateau 25 million years ago, rising no higher than the Sierra Nevada, but the rainwater isotopes reveal that the peak elevation in eastern Nevada rose more than 1,200 meters above the Sierra Nevada—roughly 2,100 meters higher than it sits today.

Rock samples of different ages testify that Nevada's mountains stood tall for more than 20 million years, ruling out fleeting geologic activity as the source of the area's drastic transformation. Instead the continental crust must have thickened there, squeezed by the colliding North American and Pacific plates. When that collision ceased (eventually birthing the San Andreas Fault), the compressed crust spread out between its loosened bookends—yielding the more expansive view today.

—*Scott K. Johnson*

SOURCE: "PROFILE OF A PALEO-OROGEN: HIGH TOPOGRAPHY ACROSS THE PRESENT-DAY BASIN AND RANGE FROM 40 TO 23 MA," BY ELIZABETH J. CASSEL ET AL., IN *GEOLOGY*, VOL. 42, NO. 11; NOVEMBER 2014

ASTRONOMY

The Dust Belt Next Door

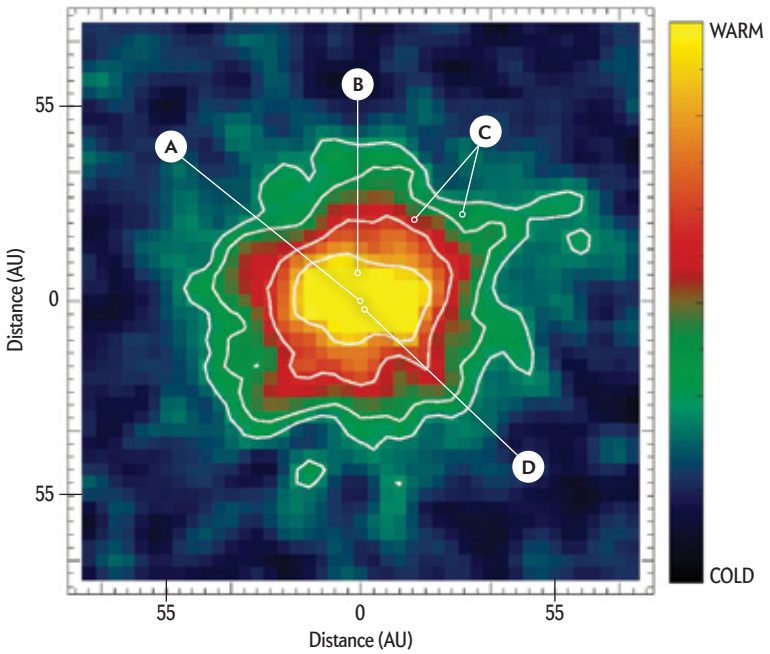
A nearby solar system shares features with our own

Shining just 12 light-years from Earth, the star Tau Ceti so resembles the sun that it has appeared in numerous science-fiction stories and was the first star astronomers ever searched for signs of intelligent life, half a century ago. In 2012 Tau Ceti grew still more intriguing when astronomers reported five possible planets somewhat larger than Earth circling closer to the star than Mars orbits the sun—one of which is in the star's habitable zone. Newly released far-infrared images taken by the Herschel Space Observatory yield even more insight about Tau Ceti's solar system: greater detail about its dust belt.

Dust arises when asteroids and comets collide, so its location reveals where these dust-creating objects—which are too small to be seen directly—orbit a star. In Tau Ceti's case, "it's quite a wide dust belt," says Samantha Lawler of the University of Victoria in British Columbia. As her team reported in November, the belt's inner edge is roughly two to three astronomical units (AUs) from the star, which is the position of our own sun's asteroid belt. (An AU is the distance from Earth to the sun.) Tau Ceti's dust belt extends out to 55 AU, which would be just beyond our system's main Edgeworth-Kuiper belt, the zone of small bodies whose largest member is probably Pluto. Presumably full of asteroids and comets, Tau Ceti's dust belt most likely lacks a planet as large as Jupiter, Lawler says. The gravity of such a massive planet would have ejected most small space rocks.

Within a year a new array of radio telescopes in Chile called ALMA should provide a sharper view of the disk, especially of its inner edge. The ALMA images will help astronomers deduce whether the star's five proposed planets are indeed real. If the disk overlaps the planets' hypothesized orbits, then they probably do not exist; they would have expelled most asteroids near the star, removing the source of dust.

If those planets do exist, however, Lawler's team suggests that Tau Ceti's planetary system may resemble what our solar system would have looked like had the four giant planets—Jupiter, Saturn, Uranus and Neptune—never formed: small planets orbiting close to the star, and nothing but asteroids, comets and dust beyond. —*Ken Croswell*



COURTESY OF GRANT KENNEDY *University of Cambridge* AND SAMANTHA LAWLER *University of Victoria*

A Look at Tau Ceti

Published in the November 1, 2014, issue of *Monthly Notices of the Royal Astronomical Society,* the far-infrared image above reveals Tau Ceti's dust belt at a previously unseen level of detail. —*K.C.*

A TAU CETI. The star, located at the image's center, heats the dust particles that orbit it.

B WARM DUST. The dust radiates that heat at far-infrared wavelengths, picked up by the Herschel Space Observatory. Yellow denotes the brightest radiation, which comes from the particles orbiting closest to the star because they are warmest.

C COOL DEBRIS. Red indicates cooler dust, and green indicates the coldest and most faraway particles.

D PLANETS. The five possible planets orbiting Tau Ceti are so close to the star that their orbits would be difficult to see at this scale.

COMMENT AT ScientificAmerican.com/jan2015

SCIENTIFIC AMERICAN™ Travel

BRIGHT HORIZONS™ 26

NORWAY & ICELAND, AUGUST 1 – 15, 2015

For information on more trips like this, please visit **www.ScientificAmerican.com/Travel**

Experience lands of fire, ice, and sea on Bright Horizons 26. Absorb the shared Viking/Nordic heritage that lives on in distinctively different ways in our Shetland Islands, Faroe Islands, Iceland, and Norway ports of call. Enjoy vibrant cultures, traditional hospitality, natural beauty, and outdoor adventure.

Keep up on science with seminars and discussions aboard Holland America's Ryndam while we're at sea. Consider the nuances of neuroscience. Engineer a new understanding of architecture. Gather new findings on geologic hazards. Deepen your knowledge of Viking anthropology. Explore oceanography and the tectonics of the North Atlantic.

Chase Iceland's rainbows or soak in the Blue Lagoon. Hike Norway's fjordlands with a friend. Spot Arctic birds! Come along with us and celebrate the moment by charting new territory.

Cruise prices vary from $2,539 for an Interior Stateroom to $7,349 for a Pinnacle Suite, 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 ($255), booking service fee ($100), cruiseline gratuities ($11.50 per day), and Tour Leader gratuities ($129). The Program, cruise pricing, and options are subject to change. For more information email us at Info@InsightCruises.com.

LONDON (HARWICH) – Saturday, August 1st

Find your own version of London amidst its many layers and neighborhoods. Museums and parks, tradition and innovation, urban vitality and peaceful corners are all up for your exploration.

EARTH SCIENCE

- The End of the World: Everything
- The Biggest Bangs Since the Big One
- How a Changing Climate Triggers Earthquakes, Tsunamis and Volcanoes
- Surviving Armageddon: Solutions For a Threatened Planet

ARCHITECTURE AND ENGINEERING

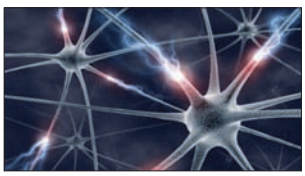
- A Field Guide to Great Structures
- The Norwegian Stave Church
- Saint Paul's Cathedral: Evolution of the First Modern Dome
- A Structural Retrospective

ANTHROPOLOGY

- Why Was There a Viking Age?
- Viking Voyages of Discovery
- The Icelandic Republic: A Frontier Society
- Poetry and Saga of the Viking Age
- Vikings in Hollywood

OCEANOGRAPHY

- Dynamics of the Mid-Atlantic Ridge
- Exploring Undersea Earthquakes, Landslides, and Tsunami
- The Gulf Stream, North Atlantic Deep Water, and the Global Heat Conveyor Belt
- The Global Ocean, Climate Change, and Sea Level Rise



NEUROSCIENCE

- The Neuroscience of Boosting Your Brainpower
- Wellbeing and the Brain
- Neurolaw
- How Genes and Experience Make Us Who We Are

SPEAKERS

Harold Tobin, Ph.D.
Bill McGuire, Ph.D.
Stephen J. Ressler, P.E., Ph.D.
Kenneth W. Harl, Ph.D.
Martha J. Farah, Ph.D.

For more info please email Info@InsightCruises.com or visit ScientificAmerican.com/travel

SCIENTIFIC AMERICAN™ Travel

BRIGHT HORIZONS™ 27

AUSTRALIA & NEW ZEALAND, OCT. 25 – NOV. 8, 2015

For information on more trips like this, please visit **www.ScientificAmerican.com/Travel**

Chart new science territory in Oceania with Scientific American Travel. Adventure calls, and scientific inquiry beckons on the Bright Horizons 27 cruise conference on Holland America Line's Noordam, sailing from Sydney Australia to Auckland New Zealand. Exercise your curiosity, celebrate the moment, and join a floating community of keen minds amidst the scenic splendor of Australia and New Zealand.

Learn about research on the self, social motivation, and society. Multiply your mental math abilities, and see the calculations that tip gaming odds. Explore the state of astronomy in Australia. Tap the energy and excitement of contemporary science aboard Bright Horizons 27.

Then head ashore and discover why New Zealand's Maori culture, period architecture, hiking tracks, wildlife, and food and wine are the stuff of legends. Stroll Sydney's beaches, walk Melbourne's urban lanes and arcades, hike Tasmania's outback in one seamless journey.

Cruise prices vary from $1,859 for an Interior Stateroom to $7,199 for a Neptune Suite, 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 ($389), booking service fee ($100), cruiseline gratuities ($11.50 per day), and Tour Leader gratuities ($140). The Program, cruise pricing, and options are subject to change. For more information email us at Info@InsightCruises.com.

Mathematics

Speaker: Arthur Benjamin, Ph.D

The Secrets of Mental Math

Dr. Benjamin will demonstrate and explain how to perform amazing feats of mental calculation. You'll improve your ability to manipulate and memorize numbers, learn how to figure out the day of the week of any date in history, and other astounding feats of mind.

The Mathematics of Games and Gambling

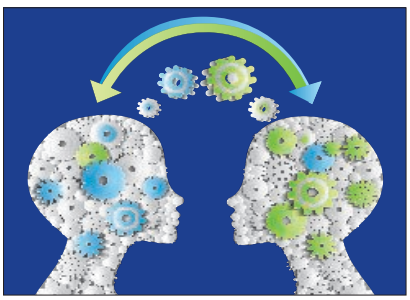
What are the best and worst games to play at the casino? When should you hit, split, or double down in blackjack? How much should you bet? Learn the answer to these questions, along with some games you can't lose, once you know the secret.

My Favorite Numbers

What makes the number 9 so magical? Explore the beauty of the Fibonacci Numbers 1, 2, 3, 5, 8, 13, 21, … and the golden ratio 1.618 … Is it irrational to be in love with Pi?

Discrete Mathematics

Learn the mathematics that underlie computer science and cryptography. Topics include combinatorics (the art of counting), number theory, and graph theory. But don't let the names of these topics scare you. You don't need much more than arithmetic and a logical mind to enjoy this lecture.



Psychology

Speaker: Jennifer Crocker, Ph.D.

Does Self-Esteem Matter?

Despite a huge volume of studies, researchers hotly debate whether self-esteem is actually important to well-being. We'll consider some of the major controversies in the field, such as whether high self-esteem people are happier, more successful, or more popular than low self-esteem people, and what factors actually affect our self-esteem.

For more info please email Info@InsightCruises.com or visit ScientificAmerican.com/travel

Pursuing Self-Esteem

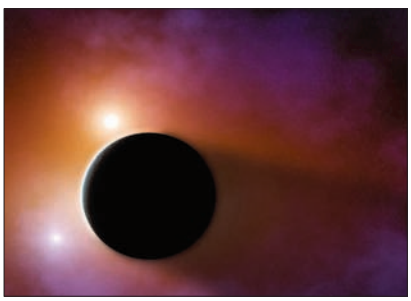
People tend to invest their self-esteem in just a few endeavors, such as academics, appearance or sports. Learn what research tells us about the benefits and pitfalls of pursing self-esteem by striving for success and avoiding failure in these domains, as well as successful strategies for avoiding the downsides of pursuing self-esteem.

Principles of Close Relationships

Many scientists assume that people in relationships are fundamentally self-interested, and aim to promote their own ends. Yet people can also transcend self-interest and care about relationship partners as much as themselves. Learn which relationships are likely to be governed by which set of principles, and what factors prompt these principles to shift.

The Key to Good Relationships

Learn how to create relationships that are good for your health and well-being through positive intentions. Evidence shows that when people strive to be supportive and constructive toward their partners, they tend to become so. Their partners notice and respond in kind, and the relationships tend to improve for everyone.



Astronomy

Speaker: Edwin L. Turner, Ph.D.

Exoplanets: Strange New Worlds

The first planet-sized body orbiting a star beyond the sun was discovered two decades ago. Since then, a torrent of new finds has come. Today we have catalogued and studied a few thousand exoplanets. Take a tour of these strange new worlds and learn about the future outlook for finding more.

The Quest for Earth's Twin

Is life on Earth unique in the universe? If not, our best hope for finding extraterrestrial organisms is to find a planet resembling our own, with the conditions and liquid water we think life probably requires. Learn how we search for Earth twins, and the prospects for detecting alien life from afar.

Life as We Don't Know It

Astrobiologists tend to search for extraterrestrial organisms resembling those found on Earth. But it's quite plausible that the universe contains life that is radically different from ours. Learn how scientists are beginning to study this topic, and how we might eventually hope to recognize life beyond our ability to imagine it.

Abiogenesis: Life's Origins

The biggest mystery about life is how it got started—that is, how it arose from a completely abiotic, or sterile, environment. Scientists have proposed radically different scenarios for this spark, and so far we have no way to discriminate between them. We'll discuss the latest thinking on the perplexing origins of life.

Evolution

Speaker: Spencer C.H. Barrett, Ph.D.

The Evolution Revolution

Evolution provides an explanation for all biodiversity on Earth, including human origins. Learn how and why evolution occurs, and why understanding the process of evolution is not only of profound biological importance but is also crucial for many contemporary issues affecting society.

Plant Sex for Grown-ups

The reproductive strategies of plants exhibit greater variety than those of any other group of organisms. Why should this be so? We'll address a variety of fundamental questions about plant sex, highlight some of the bizarre floral adaptations associated with pollination, and discuss how experimental studies can yield insight.

Evolution On Islands

Islands can act as "evolutionary laboratories," providing some of the clearest evidence for natural selection. We'll contrast the case histories of Australia and New Zealand, highlighting the similarities and differences between the floras and faunas of the two regions, and discuss why islands provide such a rich source of biological novelty.

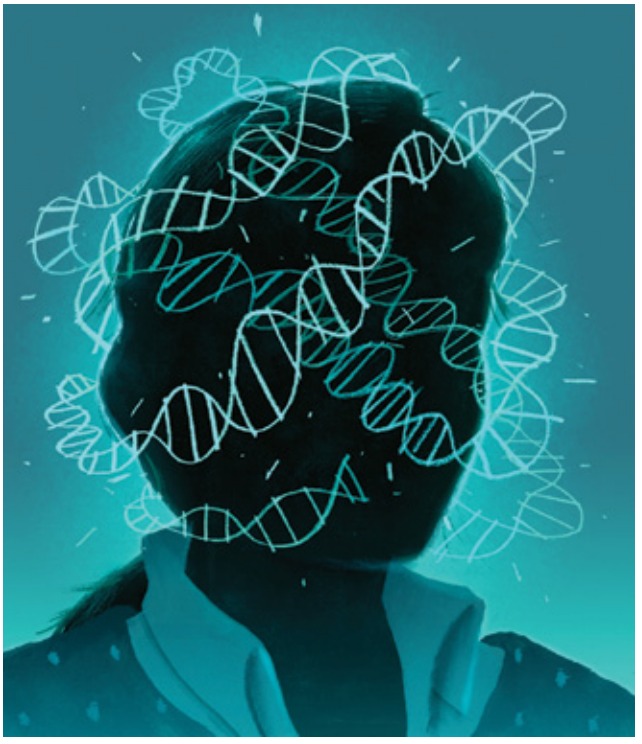
Biological Invaders

Invasive species can cause huge economic losses and threaten biodiversity and ecosystem function. We'll discuss the fascinating new field of applied science known as invasion biology. Learn why some invasive species have the capacity to evolve rapidly in response to local environmental conditions in their adopted homes, whereas others are characterized by genetic uniformity.

Dina Fine Maron is an associate editor at *Scientific American*.

When DNA Means "Do Not Ask"

As comprehensive genetic tests become more widespread, patients and experts mull how to deal with unexpected findings



Last spring Laura Murphy, then 28 years old, went to a doctor to find out if a harmless flap of skin she had always had on the back of her neck was caused by a genetic mutation. Once upon a time, maybe five years ago, physicians would have focused on just that one question. But today doctors tend to run tests that pick up mutations underlying a range of hereditary conditions. Murphy learned not only that a genetic defect was indeed responsible for the flap but also that she had another inherited genetic mutation.

This one predisposed her to long QT syndrome, a condition that dramatically increases the risk of sudden cardiac death. In people with the syndrome, anything that startles them—say, a scary movie or an alarm clock waking them from a deep slumber—might kill by causing the heart to beat completely erratically.

Doctors call this second, unexpected result an "incidental finding" because it emerged during a test primarily meant to look for something else. The finding was not accidental, because the laboratory was scouring certain genes for abnormalities, but it was unexpected.

Murphy, whose name was changed for this story, will most likely have plenty of company very soon. The growing use of comprehensive genetic tests in clinics and hospitals practically guarantees an increasing number of incidental discoveries in coming years. Meanwhile the technical ability to find these mutations has rapidly outpaced scientists' understanding of how doctors and patients should respond to the surprise results.

UNKNOWN UNKNOWNS

INCIDENTAL FINDINGS from various medical tests have long bedeviled physicians and their patients. They appear in about a third of all CT scans, for example. A scan of the heart might reveal odd shadows in nearby lung tissue. Further investigation of the unexpected results—either through exploratory surgery or yet more tests—carries its own risks, not to mention triggering intense anxiety in the patient. Follow-up exams many times reveal that the shadow reflects nothing at all—just normal variation with no health consequences.

What makes incidental findings from genetic tests different, however, is their even greater level of uncertainty. Geneticists still do not know enough about how most mutations in the human genome affect the body to reliably recommend any treatments or other actions based simply on their existence. Furthermore, even if the potential effects are known, the mutation may require some input from the environment before it will cause its bad effects. Thus, the presence of the gene does not necessarily mean that it will do damage. Genetics is not destiny. In Murphy's case, her mutation means that she has a roughly 50 to 80 percent chance of developing long QT syndrome, and the presence of the mutation alone is not a sure indicator she will be afflicted, says her physician, Jim Evans, a genetics and medicine professor at the University of North Carolina School of Medicine. To be safe, he has advised her to meet with a cardiac specialist to talk about next steps, including possibly starting beta-blocker drugs to regularize her heart rate.

The incidence of hard-to-interpret results is expected to rise because the cost of surveying large swaths of the genome has dropped so low—to around $1,000. It is typically less expensive to get preselected information about the 20,000 or so genes that make up a person's exome—the section of the genome that provides instructions for making proteins—than to perform a more precision-oriented test that targets a single gene. As a consequence, scientists and policy makers are now scrambling to set up guidelines for how much information from such testing to

Illustration by Skip Sterling

DiamondAura®

Does This Ring Make My Wallet Look Fat?

Spend 100% LESS on Luxury with FREE Jewelry... only from Stauer*

Buy now, pay never. Call us today and we'll send you the .925 sterling silver and Diamond*Aura*® ***Mirador Marquise Ring*** (a $395 value†) for **FREE!**** That's right... **FREE**. It's true. We cut the ring price 100% and you pay only $19.95 for shipping & processing *(*see details below)*. There are no tricks. You aren't obligated to spend another dime... although we make it VERY hard to resist.

Why give away jewelry? We want your attention. We want you to take a closer look at our 8 million carats of rubies, emeralds and sapphires and vintage-inspired watches. Once you discover "Luxury for Less," we're betting that you'll fall in love with Stauer.

COMPARE FOR YOURSELF AND SEE!		
	Mined D-Flawless Diamond	DiamondAura Compares to:
Hardness	Cuts Glass	Cuts Glass ✓
Cut (58 facets)	Brilliant	Brilliant ✓
Color	"D" Colorless	Colorless ✓
Clarity	"IF" Flawless	Clear ✓
Dispersion/Fire	0.044	0.066 ✓
1 ctw ring price	$22,000+	FREE

If we had our way, we'd send your ***Mirador Marquise Ring*** with no shipping charge. Unfortunately, the rising cost of gas and freight makes that impossible. But, to sweeten the deal, we'll include a **$20 Stauer Gift Coupon** with your **FREE** ring. More proof that true luxury is money in the bank!

Mirador Marquise Ring (1 ¼ ctw)
Appraised at $395†
Your Cost With Offer Code*—FREE
***pay only shipping & processing of $19.95.**

Stauer®
14101 Southcross Drive W.,
Dept. FMR211-01
Burnsville, Minnesota 55337
www.stauer.com

ACCREDITED BUSINESS
BBB Rating of A+

† For more information concerning the appraisal, visit ***http://www.stauer.com/appraisedvalues.asp.***

You must use the offer code below to receive this special free ring.

1-888-324-2060

Offer Code FMR211-01
Please mention this code when you call.

Smart Luxuries—Surprising Prices™

* This offer is valid in the United States (and Puerto Rico) except in TX, FL, CO, OK, RI, NH, WV, OR, SC, VA and ID. These state residents will be charged one cent ($.01) + shipping & processing for the item. Void where prohibited or restricted by law. Offer subject to state and local regulations. Not valid with any other offers and only while supplies last. This offer is limited to one item per shipping address. ** *Free is only for customers who use the offer code versus the original Stauer.com price.*

The Best Gene Screen

Information about most rare genetic mutations is so uncertain as to be meaningless. As a result, geneticists recommend testing only for genes that clearly increase the risk of developing certain conditions. A list of these ailments and their associated genes appears below.

CANCERS AND PRECANCEROUS CONDITIONS

- Familial adenomatous polyposis—*APC*
- Familial medullary thyroid cancer—*RET*
- Hereditary breast and ovarian cancer—*BRCA1, BRCA2*
- Li-Fraumeni syndrome—*TP53*
- Lynch syndrome—*MLH1, MSH2, MSH6, PMS2*
- Multiple endocrine neoplasia type 1—*MEN1*
- Multiple endocrine neoplasia type 2—*RET*
- MYH-associated polyposis and related conditions—*MUTYH*
- Peutz-Jeghers syndrome—*STK11*
- PTEN hamartoma tumor syndrome—*PTEN*
- Retinoblastoma—*RB1*
- Von Hippel–Lindau syndrome—*VHL*
- WT1-related Wilms tumor—*WT1*

HEART AND VASCULAR DISORDERS

- Arrhythmogenic right ventricular cardiomyopathy—*PKP2, DSP, DSC2, TMEM43, DSG2*
- Certain other cardiomyopathies—*MYBPC3, MYH7, TNNT2, TNNI3, TPM1, MYL3, ACTC1, PRKAG2, GLA, MYL2, LMNA*
- Catecholaminergic polymorphic ventricular tachycardia—*RYR2*
- Ehlers-Danlos syndrome (vascular type)—*COL3A1*
- Long QT syndromes and Brugada syndrome—*KCNQ1, KCNH2, SCN5A*
- Marfan syndrome and related conditions—*FBN1, TGFBR1, TGFBR2, SMAD3, ACTA2, MYLK, MYH11*

NONCANCEROUS GROWTHS

- Hereditary paraganglioma-pheochromocytoma syndrome—*SDHD, SDHAF2, SDHC, SDHB*
- Neurofibromatosis type 2—*NF2*
- Tuberous sclerosis complex—*TSC1, TSC2*

OTHER

- Familial hypercholesterolemia—*LDLR, APOB, PCSK9*
- Malignant hyperthermia susceptibility—*RYR1, CACNA1S*

share with patients and for how best to help them deal with the inevitable incidental findings.

Before making any definitive recommendations, however, they need to know how often genetic results produce such findings. To that end, Evans is heading up the NCGENES clinical trial, part of a larger effort by three organizations, including the University of North Carolina School of Medicine. Of the roughly 300 patients who have received genetic information since Evans started ordering whole exome tests a couple of years ago, he says, six of them (or 2 percent) had incidental findings that required further testing or decisions about treatment.

Separately, Christine Eng, medical director of the DNA Diagnostic Laboratory at the Baylor College of Medicine, says her team has conducted more than 2,000 whole exome tests since October 2011 with about 95 incidental findings. "That's an incidence of about 5 percent," she notes. Most of the findings did not require immediate action. Usually they prompt more frequent screening tests, often for breast cancer or colorectal cancer.

BALANCING ACT

IN THE HOPE OF MINIMIZING the number of people forced to cope with incidental findings, the American College of Medical Genetics and Genomics (ACMG) in 2013 proposed regularly returning results on 56 genes from comprehensive genetic tests. The professional group felt that there was enough—though by no means conclusive—information about these specific mutations to merit letting patients know if they had tested positive for them. In other words, the mutations "met a standard of relatively high likelihood of being disease-causing." The list included genetic variants that have been strongly linked to retinoblastoma (cancer of the eye), hereditary breast cancer and long QT syndrome. The ACMG believed that its guidance would give physicians a shortcut so they would not need to haphazardly guess which mutations had a strong enough link to a given malady to tell patients about the results.

Such advice is particularly important given how often children undergo genetic tests nowadays. "About 80 percent of our cases are pediatric-aged, so the incidental findings are being found in the children, and many of the conditions are adult-onset conditions," Eng says. Families given such information about their children then may have to wait decades before they can do anything about it or decide when, if ever, to start considering treatment for a disorder that may not ever develop.

Yet a year after issuing its guidance, the ACMG produced an addendum: patients should have the opportunity to opt out of having information about even that short list of analyzed genes. "When families are given a choice, a very large percentage of them want this information, but there are some individuals who feel they do not want this information, so I think this option is a good one," says Eng, who was not on that decision-making board.

For her part, Murphy is still grappling with how to respond to her incidental finding. She is not yet 30, and she finds it hard to imagine being young and carefree and on beta blockers. "Generally, I'm a very healthy person. I was doing just fine until now, so why does it matter that I found this out?" she asks. "I've been giving it a lot of thought, and if I hadn't gotten [the test] done, I might never have known about this. Now I'm wondering if I really want a lifestyle change. It's a lot to think about." Yet the hope is that Murphy's experience, and those of other patients, will help geneticists decide which tests to include in future gene scans and better prepare patients and health care workers for dealing with any unwelcome surprises. SA

SCIENTIFIC AMERICAN ONLINE
Comment on this article at ScientificAmerican.com/jan2015

SOURCE: "ACMG RECOMMENDATIONS FOR REPORTING OF INCIDENTAL FINDINGS IN CLINICAL EXOME AND GENOME SEQUENCING," BY ROBERT C. GREEN ET AL., IN *GENETICS IN MEDICINE*, VOL. 15, NO. 7, JULY 2013

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

You: By the Numbers

Can personal fitness monitors whip us—and health research—into shape?

You may have heard of the Fitbit or the UP band: $50-ish to $100-ish wristbands that measure your steps throughout the day, like a high-tech pedometer, and display your progress as a graph on your smartphone.

But this product category has exploded well beyond those common names. There's the Nike+ FuelBand, Garmin Vivofit, the Basis Peak, the Magellan Echo, the Misfit Shine, and on and on. Health tracking is also built into the Apple Watch and the Samsung Gear watches. Wearable fitness monitoring has become a $1.15-billion industry.

All these gadgets count steps. Most also measure sleep, revealing fascinating details about the one third of your life that you spend unconscious. The fancier models can also tabulate other metrics, including heart rate, blood oxygen level, skin temperature, perspiration, body weight and body mass.

That's the great appeal. These gadgets allow us, mere untrained mortals, to gauge what only doctors used to measure. We gain knowledge about the workings of our own bodies—by monitoring measurements *continuously,* not once a year at a physical.

Meet the quantified-self movement. It's a Web site, it's a conference, it's communities of people, some of whom are raising self-monitoring to the level of obsession.

Millions of people making a greater effort to get healthy and fit—who could argue with that?

There are a couple of obvious problems with the mad rush to quantify ourselves, though—and to sell us gadgets for it.

First, we're almost certainly ascribing more precision to these devices than they deserve. If you wear three brands of fitness band, you'll rack up three different step counts by the end of each day. And don't get sleep scientists started on the accuracy of those sleep graphs; according to researchers, it's brain waves, not wrist movement, that indicate what stage of sleep you're in.

But you know what? It doesn't matter. These devices are succeeding not because of their scientific qualities but because of their *motivational* ones. We all know we should move more and sleep better—but with slow decline, most of us don't bother.

What the fitness bands do is to keep these issues front-of-mind. There it is, every time you turn on your phone: the latest stats on your progress. Most also show the results of friends who wear the same brand; it's fitness through humiliation.

In other words, the accuracy really makes little difference; the point is to keep us aware, to gamify our efforts. In that way, these bands really work. You wind up parking farther away, getting off the bus a stop earlier, going for a walk down the block to bring your 9,374 daily step count up to your 10,000-step goal.

The other concern is less easily dismissed: the data. Terabytes of personal health data, amassed daily in stunning quantities. It's the world's biggest health study—and nobody's running it.

Researchers would love to get their hands on that information. So would advertisers. Insurance companies would have a field day; they could offer active members lower rates than sedentary sloths. (Our rates are already higher if we're smokers or drivers with bad records.)

Who owns the data? Will the makers of the fitness bands sell personal information? Will it be anonymous and aggregated or associated with us by name? What if we want to contribute our data—to a doctor? To a research study?

It's the Wild West at the moment. We're collecting mountains of personal health data and just shoving them into underground caverns. The real promise of the quantified-self movement may not be fulfilled until we determine how to find the gold in those data—and who gets to do the looking. SA

SCIENTIFIC AMERICAN ONLINE
Health-monitoring socks and more: ScientificAmerican.com/jan2015/pogue

Illustration by Rebekka Dunlap

ASTRONOMY

BETTER THAN EARTH

Planets quite different from our own may be the best homes for life in the universe *By René Heller*

Illustration by Ron Miller

LARGE, ROCKY "superhabitable" world orbiting a star smaller than our sun might be both familiar and alien. The landscape would be flattened by higher surface gravity, and plants there could be tinted darker than Earth's greenery to better absorb the faint starlight.

René Heller is a postdoctoral fellow at the Origins Institute at McMaster University in Ontario and a member of the Canadian Astrobiology Training Program. His research focuses on the formation, orbital evolution, detection and habitability of extrasolar moons. He is informally known as the best German rice pudding cook in the world.

DO WE INHABIT THE BEST OF ALL POSSIBLE WORLDS? German mathematician Gottfried Leibniz thought so, writing in 1710 that our planet, warts and all, must be the most optimal one imaginable. Leibniz's idea was roundly scorned as unscientific wishful thinking, most notably by French author Voltaire in his magnum opus, *Candide.* Yet Leibniz might find sympathy from at least one group of scientists—the astronomers who have for decades treated Earth as a golden standard as they search for worlds beyond our own solar system.

Because earthlings still know of just one living world—our own—it makes some sense to use Earth as a template in the search for life elsewhere, such as in the most Earth-like regions of Mars or Jupiter's watery moon Europa. Now, however, discoveries of potentially habitable planets orbiting stars other than our sun—exoplanets, that is—are challenging that geocentric approach.

Over the past two decades astronomers have found more than 1,800 exoplanets, and statistics suggest that our galaxy harbors at least 100 billion more. Of the worlds found to date, few closely resemble Earth. Instead they exhibit a truly enormous diversity, varying immensely in their orbits, sizes and compositions and circling a wide variety of stars, including ones significantly smaller and fainter than our sun. Diverse features of these exoplanets suggest to me and to others that Earth may not be anywhere close to the pinnacle of habitability. In fact, some exoplanets, quite different from our own, could have much higher chances of forming and maintaining stable biospheres. These "superhabitable worlds" may be the optimal targets in the search for extraterrestrial, extrasolar life.

AN IMPERFECT PLANET

OF COURSE, our planet does possess a number of properties that, at first glance, seem ideal for life. Earth revolves around a sedate, middle-aged star that has shone steadily for billions of years, giving life plenty of time to arise and evolve. It has oceans of life-giving water, largely because it orbits within the sun's "habitable zone," a slender region where our star's light is neither too intense nor too weak. Inward of the zone, a planet's water would boil into steam; outward of the area, it would freeze into ice. Earth also has a life-friendly size: big enough to hold on to a substantial atmosphere with its gravitational field but small enough to ensure gravity does not pull a smothering, opaque shroud of gas over the planet. Earth's size and its rocky composition also give rise to other boosters of habitability, such as climate-regulating plate tectonics and a magnetic field that protects the biosphere from harmful cosmic radiation.

Yet the more closely we scientists study our own planet's habitability, the less ideal our world appears to be. These days habitability varies widely across Earth, so that large portions of its surface are relatively devoid of life—think of arid deserts, the nutrient-poor open ocean and frigid polar regions. Earth's habitability also varies over time. Consider, for instance, that during much of the Carboniferous period, from roughly 350 million to 300 million years ago, the planet's atmosphere was warmer, wetter and far more oxygen-rich than it is now. Crustaceans, fish and reef-building corals flourished in the seas, great forests blanketed the continents, and insects and other terrestrial creatures grew to gigantic sizes. The Carboniferous Earth may have supported significantly more biomass than our present-day planet, meaning that Earth today could be considered less habitable than it was at times in its ancient past.

Further, we know that Earth will become far less life-friendly in the future. About five billion years from now, our sun will have largely exhausted its hydrogen fuel and begun fusing

IN BRIEF

Astronomers are searching for twins of Earth orbiting other sunlike stars. **Detecting Earth-like twins** remains at the edge of our technical capabilities. **Larger "super-Earths"** orbiting smaller stars are easier to detect and may be the most common type of planet. **New thinking suggests** that these systems, along with massive moons orbiting gas-giant planets, may also be superhabitable—more conducive to life than our own familiar planet.

more energetic helium in its core, causing it to swell to become a "red giant" star that will scorch Earth to a cinder. Long before that, however, life on Earth should already have come to an end. As the sun burns through its hydrogen, the temperature at its core will gradually rise, causing our star's total luminosity to slowly increase, brightening by about 10 percent every billion years. Such change means that the sun's habitable zone is not static but dynamic, so that over time, as it sweeps farther out from our brightening star, it will eventually leave Earth behind. To make matters worse, recent calculations suggest that Earth is not in the middle of the habitable zone but rather on the zone's inner cusp, already teetering close to the edge of overheating [*see box on page 38*].

Consequently, within about half a billion years our sun will be bright enough to give Earth a feverish climate that will threaten the survival of complex multicellular life. By some 1.75 billion years from now, the steadily brightening star will make our world hot enough for the oceans to evaporate, exterminating any simple life lingering on the surface. In fact, Earth is well past its habitable prime, and the biosphere is fast-approaching its denouement. All things considered, it seems reasonable to say our planet is at present only marginally habitable.

Earth is past its prime, and the biosphere is nearing its end. All things considered, our planet is only marginally habitable.

SEEKING A SUPERHABITABLE WORLD

IN 2012 I FIRST BEGAN THINKING about what worlds more suitable to life might look like while I was researching the possible habitability of massive moons orbiting gas-giant planets. In our solar system, the biggest moon is Jupiter's Ganymede, which has a mass only 2.5 percent that of Earth—too small to easily hang on to an Earth-like atmosphere. But I realized that there are plausible ways for moons approaching the mass of Earth to form in other planetary systems, potentially around giant planets within their stars' habitable zones, where such moons could have atmospheres similar to our own planet.

Such massive "exomoons" could be superhabitable because they offer a rich diversity of energy sources to a potential biosphere. Unlike life on Earth, which is powered primarily by the sun's light, the biosphere of a superhabitable exomoon might also draw energy from the reflected light and emitted heat of its nearby giant planet or even from the giant planet's gravitational field. As a moon orbits around a giant planet, tidal forces can cause its crust to flex back and forth, creating friction that heats the moon from within. This phenomenon of tidal heating is probably what creates the subsurface oceans thought to exist on Jupiter's Europa and Saturn's moon Enceladus. That said, this energetic diversity would be a double-edged sword for a massive exomoon because slight imbalances among the overlapping energy sources could easily tip a world into an uninhabitable state.

No exomoons, habitable or otherwise, have yet been detected with certainty, although some may sooner or later be revealed by archival data from observatories such as NASA's Kepler space telescope. For the time being, the existence and possible habitability of these objects remain quite speculative.

Superhabitable planets, on the other hand, may already exist within our catalogue of confirmed and candidate exoplanets. The first exoplanets found in the mid-1990s were all gas giants similar in mass to Jupiter and orbiting far too close to their stars to harbor any life. Yet as planet-hunting techniques have improved over time, astronomers have begun finding progressively smaller planets in wider, more clement orbits. Most of the planets discovered over the past few years are so-called super-Earths, planets larger than Earth by up to 10 Earth masses, with radii between that of Earth and Neptune. These planets have proved to be extremely common around other stars, yet we have nothing like them orbiting the sun, making our own solar system appear to be a somewhat atypical outlier.

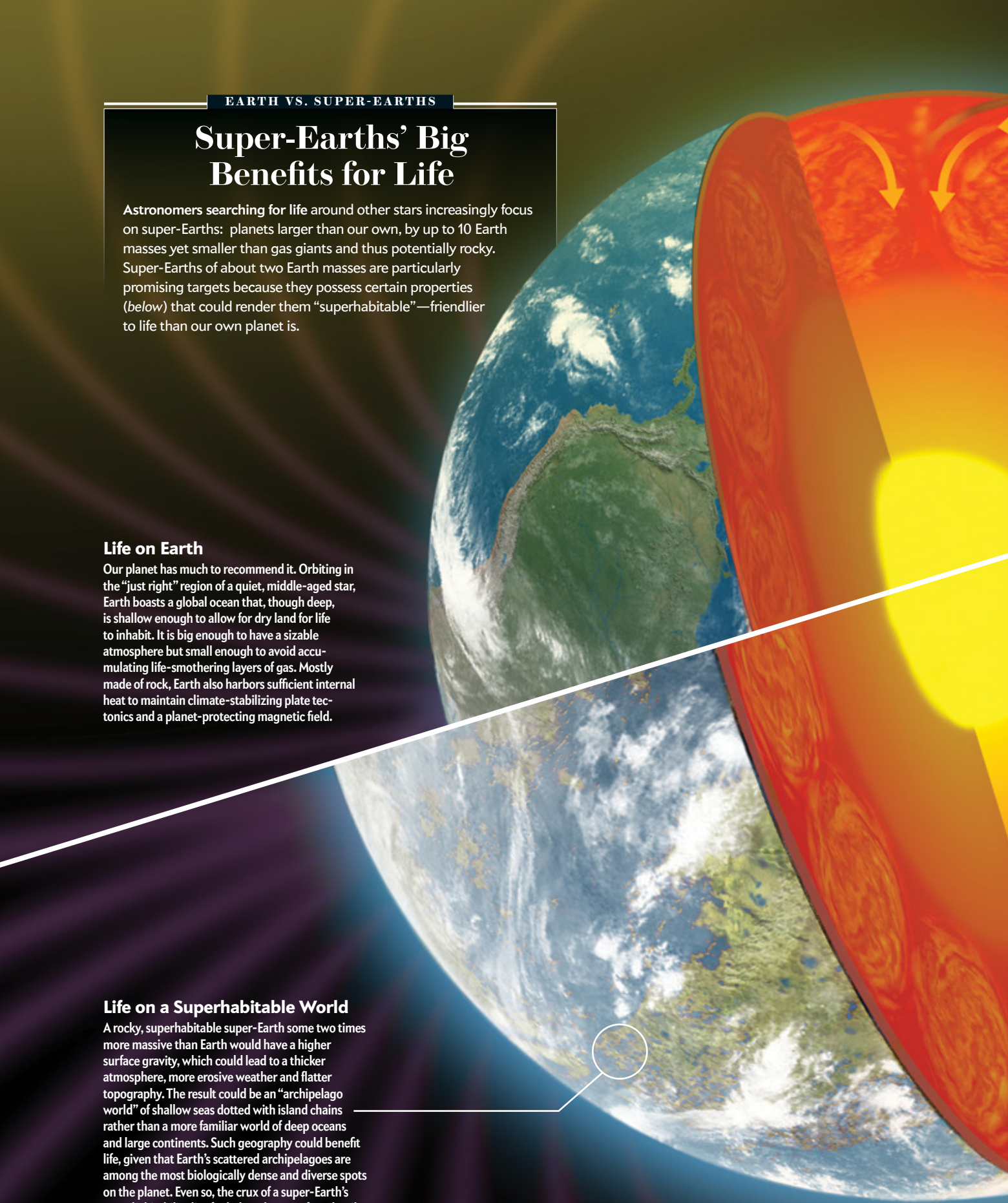
Many of the bigger, more massive super-Earths have radii suggestive of thick, puffy atmospheres, making them more likely to be "mini Neptunes" than super-sized versions of Earth. But some of the smaller ones, worlds perhaps up to twice the size of Earth, probably do have Earth-like compositions of iron and rock and could have abundant liquid water on their surfaces if they orbit within their stars' habitable zones. A number of the potentially rocky super-Earths, we now know, orbit stars called M dwarfs and K dwarfs, which are smaller, dimmer and much longer-lived than our sun. In part because of the extended lives of their diminutive stars, these super-sized Earths are currently the most compelling candidates for superhabitable worlds, as I have shown in recent modeling work with my collaborator John Armstrong, a physicist at Weber State University.

THE BENEFITS OF LONGEVITY

WE BEGAN OUR WORK with the understanding that a truly long-lived host star is the most fundamental ingredient for superhabitability; after all, a planetary biosphere is unlikely to survive its sun's demise. Our sun is 4.6 billion years old, approximately halfway through its estimated 10-billion-year lifetime. If it were slightly smaller, however, it would be a much longer-lived K dwarf star. K dwarfs have less total nuclear fuel to burn than more massive stars, but they use their fuel more efficiently, increasing their longevity. The middle-aged K dwarfs we observe today are billions of years older than the sun and will still be shining billions of years after our star has expired. Any potential biospheres on their planets would have much more time in which to evolve and diversify.

Super-Earths' Big Benefits for Life

Astronomers searching for life around other stars increasingly focus on super-Earths: planets larger than our own, by up to 10 Earth masses yet smaller than gas giants and thus potentially rocky. Super-Earths of about two Earth masses are particularly promising targets because they possess certain properties (*below*) that could render them "superhabitable"—friendlier to life than our own planet is.



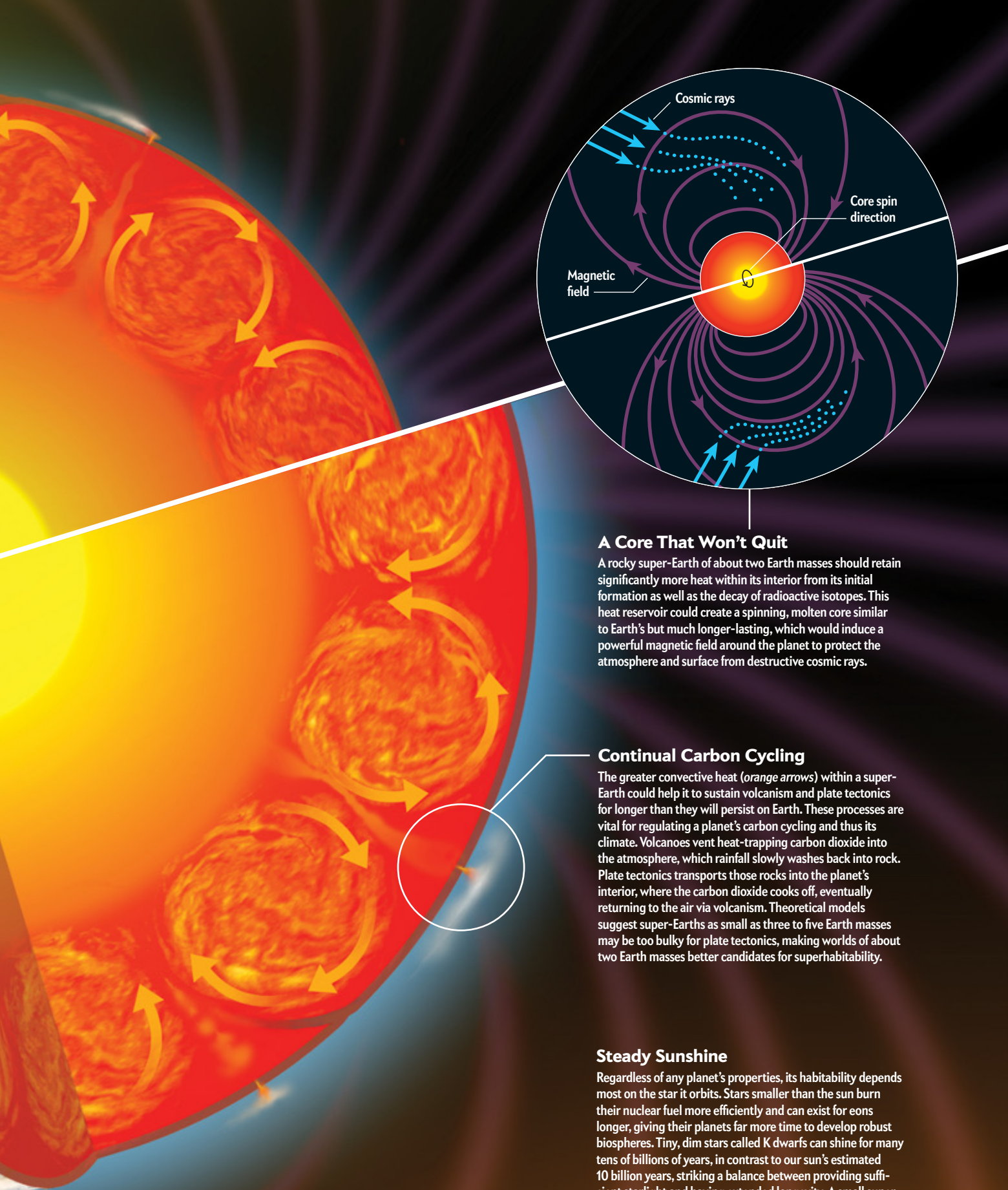
Life on Earth

Our planet has much to recommend it. Orbiting in the "just right" region of a quiet, middle-aged star, Earth boasts a global ocean that, though deep, is shallow enough to allow for dry land for life to inhabit. It is big enough to have a sizable atmosphere but small enough to avoid accumulating life-smothering layers of gas. Mostly made of rock, Earth also harbors sufficient internal heat to maintain climate-stabilizing plate tectonics and a planet-protecting magnetic field.

Life on a Superhabitable World

A rocky, superhabitable super-Earth some two times more massive than Earth would have a higher surface gravity, which could lead to a thicker atmosphere, more erosive weather and flatter topography. The result could be an "archipelago world" of shallow seas dotted with island chains rather than a more familiar world of deep oceans and large continents. Such geography could benefit life, given that Earth's scattered archipelagoes are among the most biologically dense and diverse spots on the planet. Even so, the crux of a super-Earth's superhabitability lies far below these surface details, in the planet's interior (*opposite page*).

Illustration by Ron Miller (planets) and Jen Christiansen (inset)



A Core That Won't Quit

A rocky super-Earth of about two Earth masses should retain significantly more heat within its interior from its initial formation as well as the decay of radioactive isotopes. This heat reservoir could create a spinning, molten core similar to Earth's but much longer-lasting, which would induce a powerful magnetic field around the planet to protect the atmosphere and surface from destructive cosmic rays.

Continual Carbon Cycling

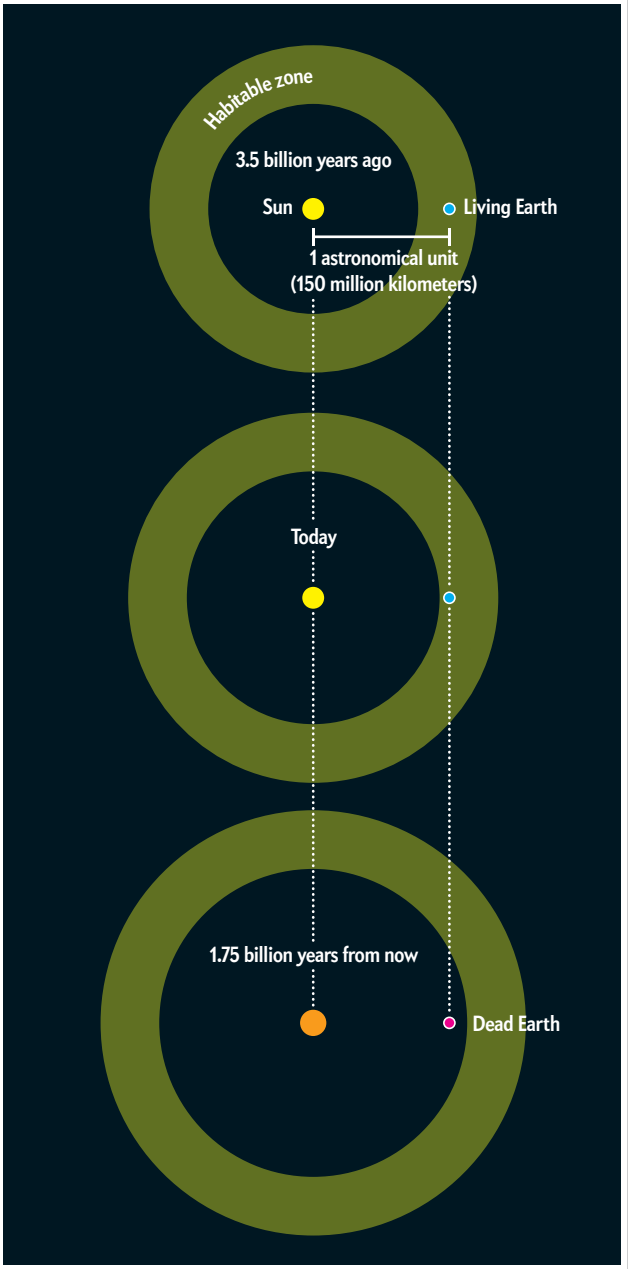
The greater convective heat (*orange arrows*) within a super-Earth could help it to sustain volcanism and plate tectonics for longer than they will persist on Earth. These processes are vital for regulating a planet's carbon cycling and thus its climate. Volcanoes vent heat-trapping carbon dioxide into the atmosphere, which rainfall slowly washes back into rock. Plate tectonics transports those rocks into the planet's interior, where the carbon dioxide cooks off, eventually returning to the air via volcanism. Theoretical models suggest super-Earths as small as three to five Earth masses may be too bulky for plate tectonics, making worlds of about two Earth masses better candidates for superhabitability.

Steady Sunshine

Regardless of any planet's properties, its habitability depends most on the star it orbits. Stars smaller than the sun burn their nuclear fuel more efficiently and can exist for eons longer, giving their planets far more time to develop robust biospheres. Tiny, dim stars called K dwarfs can shine for many tens of billions of years, in contrast to our sun's estimated 10 billion years, striking a balance between providing sufficient starlight and having extended longevity. A small super-Earth orbiting in the habitable zone of a K dwarf may reside in the sweet spot of superhabitability.

As Stars Age, They Turn Up the Heat on Habitable Planets

On human timescales, a star's habitable zone appears to be static. But because stars brighten as they age, over eons the zone sweeps outward, eventually leaving living worlds behind. Earth is poised near the inner edge of the sun's habitable zone and will become too hot to harbor liquid water in some 1.75 billion years. Smaller stars shine dimmer and longer than the sun, scarcely budging their habitable zones over tens of billions of years, potentially extending their planets' lives.



A K dwarf's light would appear somewhat ruddier than the sun's, as it would be shifted more toward the infrared, but its spectral range could nonetheless support photosynthesis on a planet's surface. M dwarf stars are smaller and more parsimonious still and can steadily shine for hundreds of billions of years, but they shine so dimly that their habitable zones are very close-in, potentially subjecting planets there to powerful stellar flares and other dangerous effects. Being longer-lived than our sun yet not treacherously dim, K dwarfs appear to reside in the sweet spot of stellar superhabitability.

Today some of these long-living stars may harbor potentially rocky super-Earths that are already several billion years older than our own solar system. Life could have had its genesis in these planetary systems long before our sun was born, flourishing and evolving for billions of years before even the first biomolecule emerged from the primordial soup on the young Earth. I am particularly fascinated by the possibility that a biosphere on these ancient worlds might be able to modify its global environment to further enhance habitability, as life on Earth has done. One prominent example is the Great Oxygenation Event of about 2.4 billion years ago, when substantial amounts of oxygen first began to accumulate in Earth's atmosphere. The oxygen probably came from oceanic algae and eventually led to the evolution of more energy-intensive metabolisms, allowing creatures to have bigger, more durable and active bodies. This advancement was a crucial step toward life's gradual emergence from Earth's oceans to colonize the continents. If alien biospheres exhibit similar trends toward environmental enhancement, we might expect planets around long-lived stars to become somewhat more habitable as they age.

To be superhabitable, exoplanets around small, long-lived stars would need to be more massive than Earth. That extra bulk would forestall two disasters most likely to befall rocky planets as they age. If our own Earth were located in the habitable zone of a small K dwarf, the planet's interior would have grown cold long before the star expired, inhibiting habitability. For example, a planet's internal heat drives volcanic eruptions and plate tectonics, processes that replenish and recycle atmospheric levels of the greenhouse gas carbon dioxide. Without those processes, a planet's atmospheric CO_2 would steadily decrease as rainfall washed the gas out of the air and into rocks. Ultimately the CO_2-dependent global greenhouse effect would grind to a halt, increasing the likelihood that an Earth-like planet would enter an uninhabitable "snowball" state in which all of its surface water freezes.

Beyond the potential breakdown of a planet-warming greenhouse effect, the cooling interior of an aging rocky world could also cause the collapse of any protective planetary magnetic field. Earth is shielded by a magnetic field generated by a spinning, convecting core of molten iron, which acts like a dynamo. The core remains liquefied because of leftover heat from the planet's formation, as well as from the decay of radioactive isotopes. Once a rocky planet's internal heat reservoir became exhausted, its core would solidify, the dynamo would cease, and the magnetic shield would fall, allowing cosmic radiation and stellar flares to erode the upper atmosphere and impinge on the surface. Consequently, old Earth-like planets would be expected to lose substantial portions of their atmospheres to space, and higher levels of damaging radiation could harm surface life.

Illustration by Jen Christiansen

Rocky super-Earths as much as twice our planet's size should age more gracefully than Earth, retaining their inner heat for much longer because of their significantly greater bulks. But planets larger than about three to five Earth masses may actually be too bulky for plate tectonics because the pressures and viscosities in their mantles become so high that they inhibit the required outward flow of heat. A rocky planet only two times the mass of Earth should still possess plate tectonics and could sustain its geologic cycles and magnetic field for several billion years longer than Earth could. Such a planet would also be about 25 percent larger in diameter than Earth, giving any organisms about 56 percent more surface area than our world on which to live.

LIFE ON A SUPERHABITABLE SUPER-EARTH

WHAT WOULD A SUPERHABITABLE PLANET look like? Higher surface gravity would tend to give a middling super-Earth planet a slightly more substantial atmosphere than Earth's, and its mountains would erode at a faster rate. In other words, such a planet would have relatively thicker air and a flatter surface. If oceans were present, the flattened planetary landscape could cause the water to pool in large numbers of shallow seas dotted with island chains rather than in great abyssal basins broken up by a few very large continents [*see box on pages 36 and 37*]. Just as biodiversity in Earth's oceans is richest in shallow waters near coastlines, such an "archipelago world" might be enormously advantageous to life. Evolution might also proceed more quickly in isolated island ecosystems, potentially boosting biodiversity.

Of course, lacking large continents, an archipelago world would potentially offer less total area than a continental world for land-based life, which might reduce overall habitability. But not necessarily, especially given that a continent's central regions could easily become a barren desert as a result of being far from temperate, humid ocean air. Furthermore, a planet's habitable surface area can be dramatically influenced by the orientation of its spin axis with respect to its orbital plane around its star. Earth, as an example, has a spin-orbit axial tilt of about 23.4 degrees, giving rise to the seasons and smoothing out what would otherwise be extreme temperature differences between the warmer equatorial and colder polar regions. Compared with Earth, an archipelago world with a favorable spin-orbit alignment could have a warm equator as well as warm, ice-free poles and, by virtue of its larger size and larger surface area on its globe, would potentially boast even more life-suitable land than if it had large continents.

Taken together, all these thoughts about the features important to habitability suggest that superhabitable worlds are slightly larger than Earth and have host stars somewhat smaller and dimmer than the sun. If correct, this conclusion is tremendously exciting for astronomers because across interstellar distances super-Earths orbiting small stars are much easier to detect and study than twins of our own Earth-sun system. So far statistics from exoplanet surveys suggest that super-Earths around small stars are substantially more abundant throughout our galaxy than Earth-sun analogues. Astronomers seem to have many more tantalizing places to hunt for life than previously believed.

One of Kepler's prize finds, the planet Kepler-186f, comes to mind. Announced in April 2014, this world is 11 percent larger in diameter than Earth and probably rocky, orbiting in the habitable zone of its M dwarf star. It is probably several billion years old, perhaps even older than Earth. It is about 500 light-years away, placing it beyond the reach of current and near-future observations that could better constrain predictions of its habitability, but for all we know, it could be a superhabitable archipelago world.

Closer superhabitable candidates orbiting nearby small stars could soon be discovered by various projects, most notably the European Space Agency's PLATO mission, slated to launch by 2024. Such nearby systems could become prime targets for the James Webb Space Telescope, an observatory scheduled to launch in 2018, which will seek signs of life within the atmospheres of a small number of potentially superhabitable worlds. With considerable luck, we may all soon be able to point to a place in the sky where a more perfect world exists. SA

Superhabitable worlds are slightly larger than Earth and orbit stars that are somewhat smaller and dimmer than the sun.

MORE TO EXPLORE

Habitable Climates: The Influence of Obliquity. David S. Spiegel, Kristen Menou and Caleb A. Scharf in *Astrophysical Journal,* Vol. 691, No. 1, pages 596–610; January 20, 2009. http://iopscience.iop.org/0004-637X/691/1/596/article

Exomoon Habitability Constrained by Illumination and Tidal Heating. René Heller and Rory Barnes in *Astrobiology,* Vol. 13, No. 1, pages 18–46; 2013. http://arxiv.org/abs/1209.5323

Habitable Zone Lifetimes of Exoplanets around Main Sequence Stars. Andrew J. Rushby, Mark W. Claire, Hugh Osborn and Andrew J. Watson in *Astrobiology,* Vol. 13, No. 9, pages 833–849; September 18, 2013.

Superhabitable Worlds. René Heller and John Armstrong in *Astrobiology,* Vol. 14, No. 1, pages 50–66; January 16, 2014. http://arxiv.org/abs/1401.2392

FROM OUR ARCHIVES

Planets We Could Call Home. Dimitar D. Sasselov and Diana Valencia; August 2010.
The Dawn of Distant Skies. Michael D. Lemonick; July 2013.
The Search for Life on Faraway Moons. Lee Billings; January 2014.

SCIENTIFIC AMERICAN ONLINE Learn more about superhabitable super-Earths at ScientificAmerican.com/jan2015/heller

MEDICINE

A Weakness in Bacteria's Fortress

Evolutionary biologists are trying to attack bacteria in a new way: by short-circuiting their social life

By Carl Zimmer

AT THE UNIVERSITY OF ZURICH, ROLF KÜMMERLI INVESTIGATES NEW DRUGS TO STOP DEADLY infections. He spends his days in a laboratory stocked with petri dishes and flasks of bacteria—exactly the place where you would expect him to do that sort of work. But Kümmerli took an odd path to get to that lab. As a graduate student, he spent years hiking through the Swiss Alps to study the social life of ants. Only after he earned a Ph.D. in evolutionary biology did he turn his attention to microbes.

IN BRIEF

Researchers from an emerging field called sociomicrobiology believe they have a new approach to fight antibiotic resistance among illness-causing bacteria.

They want to disrupt the processes that allow bacteria to communicate and cooperate with one another.

Evolutionary theory predicts that acquiring resistance to such "antisocial" drugs should be difficult. Not everyone is convinced, however, that this new strategy for developing antibiotics will work.

Photography by Zachary Zavislak

Carl Zimmer is a columnist at the *New York Times* and author of 13 books, including *Evolution: Making Sense of Life*. His last article for *Scientific American* was about the oldest rocks on the earth.

The path from ants to antibiotics is not as roundabout as it may seem. For decades scientists have studied how cooperative behavior evolves in animal societies such as ant colonies, in which sterile female workers raise the eggs of their queen. A new branch of science—sometimes called "sociomicrobiology"—is revealing that some of the same principles that govern ants can explain the emergence of bacterial societies. Like ants, microbes live in complex communities, where they communicate with one another to cooperate for the greater good. This insight of social evolution suggests a new strategy for stopping infections: instead of attacking individual bacteria, as traditional antibiotics do, scientists are exploring the notion of attacking entire bacterial societies.

New strategies are exactly what is needed now. Bacteria have evolved widespread resistance to antibiotics, leaving doctors in a crisis. For example, the Centers for Disease Control and Prevention estimates that 23,000 people die in the U.S. every year of antibiotic-resistant infections. Strains of tuberculosis and other pathogens are emerging that are resistant to nearly every drug. "It already is a substantial problem," says Anthony S. Fauci, director of the National Institute of Allergy and Infectious Disease. "And there's every reason to believe it's going to get even worse."

The standard response to this crisis has been to slow the evolution of resistance and find new drugs to replace old ones as they grow weak. But this is only a treadmill solution. Bacteria are relentlessly evolving resistance and will continue to do so unless we find a different way to fight them. "Every time we develop a new drug, it fails," says John Pepper, a theoretical biologist at the National Cancer Institute. "So the solution is, 'Quick! Make another antibiotic!' That helps for a few months. But that's just not good enough any more."

Many infectious species of bacteria depend on their collective behavior to make us sick. Sociomicrobiologists are looking for opportunities to disrupt their societies—by interfering with their communication, for example, or blocking their cooperative efforts to gather nutrients. Evolutionary theory predicts that the collective behavior of bacteria should be a ripe target for medicine. Attacking the social life of bacteria may not be a completely evolution-proof strategy. But at the very least, it might slow down the evolution of resistance dramatically.

Sociomicrobiologists have a lot of skepticism to overcome. Although they have presented detailed theoretical arguments and a few promising experimental results, some researchers doubt that their evolution-inspired drugs will be able to stop the rise of resistance. And pharmaceutical companies, which have shied away from antibiotics in general, are not yet ready to push such drugs through the approval pipeline and into the marketplace.

Still, the sociomicrobiologists are getting some attention. The National Institutes of Health has been laying plans for research into antibiotic resistance, and investigators have made the social life of bacteria a top priority. If the work pans out, they will have succeeded in reversing the relation between medicine and evolution. Traditionally an enemy in the fight against bacteria, evolution would become a friend.

THE EVOLUTION OF DRUG RESISTANCE

THE CRISIS of antibiotic resistance has been long in the making. A few years after the first antibiotics were introduced in the mid-1900s, doctors had already discovered some bacteria that could withstand them. At the time, it was not entirely clear what was happening. Today, of course, scientists can probe the evolution of resistance in all its molecular details.

Penicillin, for example, kills bacteria by grabbing onto a protein that helps in building the bacteria's cell membranes. Without this protein, a bacterium will spring a leak and die. In any population of bacteria, a few mutants will be able to defend themselves against penicillin. Bacteria, for example, have pumps to flush toxic chemicals out of their interior. A mutant microbe may produce extra pumps, allowing it to rid itself of penicillin quickly, freeing up its proteins to build its membranes.

Normally such a mutation does not provide any evolutionary advantage to a microbe. If a patient takes a dose of penicillin to clear an infection, suddenly those extra pumps can make a huge difference. Bacteria without the extra pumps die, whereas many mutants manage to survive. The survivors multiply, increasing the proportion of mutants in the population. In subsequent generations, the descendants of the original mutants may evolve even better defenses, sometimes by picking up genes from other bacterial species.

For decades new drugs came out of the development pipeline quickly enough to replace the old ones that failed. But now that pipeline is drying up. As the expense of developing new antibiotics has cut into profits, many pharmaceutical companies have bailed out of the antibiotics business and invested instead in more profitable drugs for cancer or hepatitis.

As the crisis deepened, scientists yearned for an antibiotic that would not become obsolete. And sometimes they did find what they believed to be an evolution-proof drug. In 1987, for example, Michael Zasloff, then at the NIH, discovered that African clawed frogs produce a powerful toxin against bacteria in their skin. Zasloff and other researchers soon found that the amphibians were not the only toxin makers. Just about every animal they looked at made small, positively charged proteins that could kill bacteria—a class of molecules that came to be known as antimicrobial peptides.

In journal reviews and in news reports, Zasloff predicted that bacteria would be unlikely to evolve resistance against the drugs. Animals, he pointed out, had been using antimicrobial peptides to kill bacteria for hundreds of millions of years, and yet bacteria today remain vulnerable to the peptides. In 2003 Graham Bell, an evolutionary biologist at McGill University, predicted that Zasloff would be proved wrong. Penicillin and many other drugs had also been discovered being made in nature. But modern medicine delivered them in huge concentrations to patients—thereby creating a tremendous evolution pressure that drove the rise of resistant mutants. As soon as doctors started giving pills packed with antimicrobial peptides to patients, history would repeat itself.

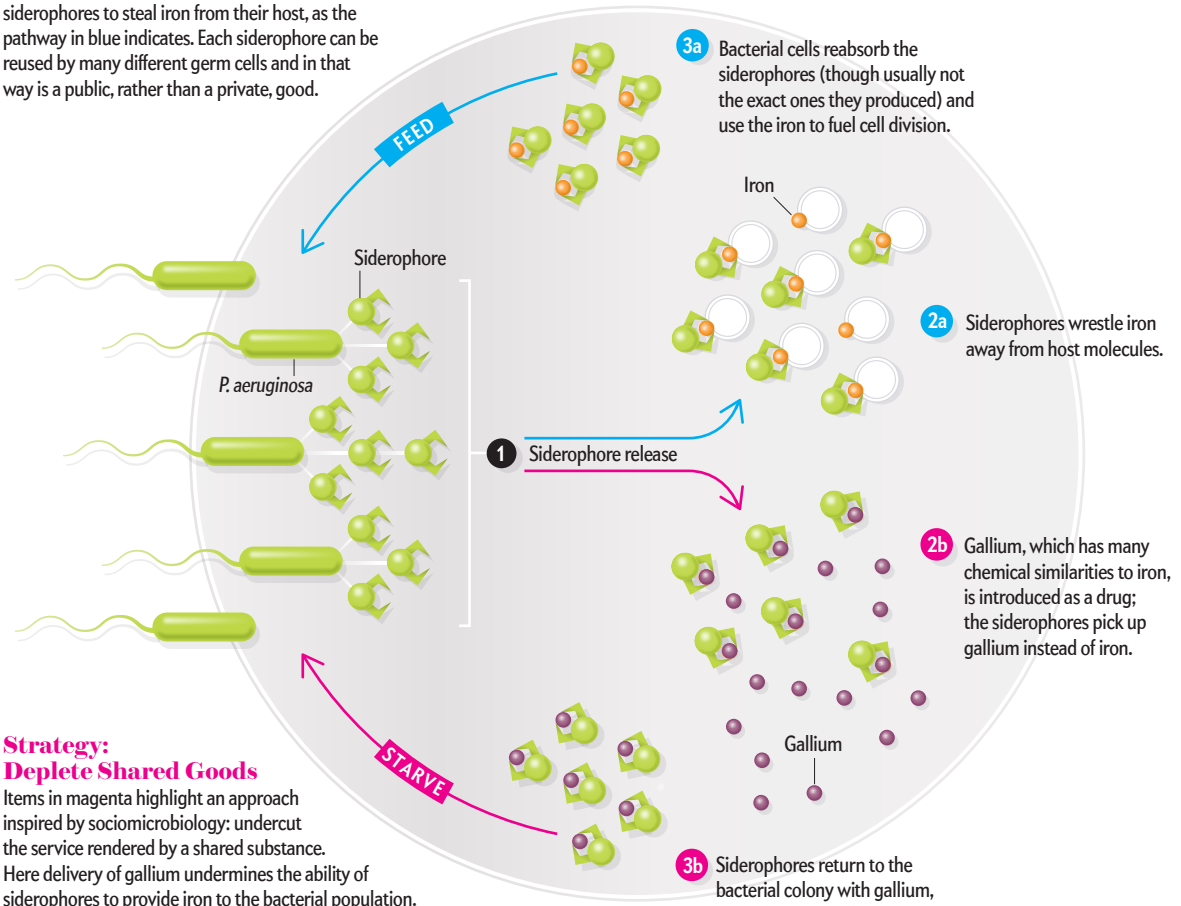
Zasloff challenged Bell to see if bacteria could become resis-

Lessons from Evolutionary Biology

Researchers hope to develop more effective antibacterial treatments by interfering with the way various germs communicate and cooperate with one another. Such an approach should trigger less drug resistance, in theory, because no single cell should be able profit by changing the way it responds. One idea, which targets a molecule that *Pseudomonas* bacteria use to scavenge iron, is shown below.

The Target: Communal Nutrient Gathering

Pseudomonas bacteria produce molecules called siderophores to steal iron from their host, as the pathway in blue indicates. Each siderophore can be reused by many different germ cells and in that way is a public, rather than a private, good.



Strategy: Deplete Shared Goods

Items in magenta highlight an approach inspired by sociomicrobiology: undercut the service rendered by a shared substance. Here delivery of gallium undermines the ability of siderophores to provide iron to the bacterial population. Even if a single cell develops a favorable siderophore mutation, that cell will still probably starve because it is likely to take up siderophores made by other bacteria.

tant to pexiganan, one of his best-studied peptides. Bell and his then graduate student Gabriel Perron reared a batch of *Escherichia coli* and exposed it to a low dose of pexiganan. Then they took some of the surviving bacteria to start a new colony, which they exposed to a higher dose of the drug. Increasing the dose over a few weeks, the scientists watched the bacteria evolve to be completely resistant to pexiganan, just as Bell had predicted.

Zasloff immediately acknowledged that Bell had been right. The experiment made him far more cautious about antimicrobial peptides. "If something can happen in a test tube, it is very likely that it can happen in the real world," Zasloff told *Nature*. (*Scientific American* is part of Nature Publishing Group.)

Today we do not know for sure if that is actually true, and we will not unless antimicrobial peptides are eventually approved for use for infections. Currently pharmaceutical companies are running several clinical trials, but 28 years after their discovery, not a single antimicrobial peptide has been approved for use for infections. They are victims of a slow pipeline.

COOPERATION AMONG BACTERIA

CHARLES DARWIN COULD HAVE had no idea that bacteria would become one of the best illustrations of his theory of natural selection. He and other scientists of his day knew very little about how microbes grow. When he presented his theory in *On the Ori-*

Illustration by John Grimwade

gin of Species in 1859, he instead wrote about traits that were familiar to his fellow Victorians, like the fur on mammals and the colors of feathers.

Darwin also wrote about familiar features of nature that had initially made him worry that his idea might be wrong. One of them was that in many species of ants, female workers are sterile. In Darwin's theory, natural selection emerged from the competition between individuals to survive and reproduce. But worker ants, which do not reproduce themselves, seemed to be dropping out of the competition altogether. Their existence, Darwin wrote, seemed to be "actually fatal to my whole theory."

Darwin suspected that a solution to the worker ant paradox lay in kinship. An ant colony is not just a random jumble of strangers. It is more like an extended family. Together a group of related ants may be able to produce more offspring than if they all try to breed on their own.

Darwin's ideas on cooperation have inspired generations of evolutionary biologists to explore them further. That is how Kümmerli got his start as a scientist. He would sequence DNA from ants in different nests, for example, to see how their kinship influenced their behavior toward one another. The research was fascinating but also slow and limited. As Kümmerli got closer to earning his Ph.D., he discovered some evolutionary biologists who were switching from social animals to social bacteria.

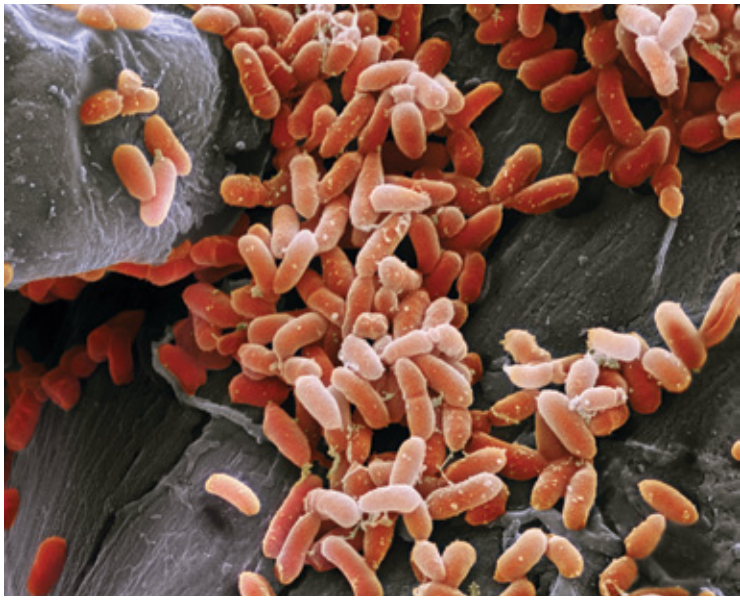
The words "social" and "bacteria" may not be tightly joined in most people's minds, but it turns out that microbes live in intimate communities full of conversation and cooperation. Take *Pseudomonas aeruginosa,* a species that can cause serious lung infections. When one of the microbes invades a host, it sends out signaling molecules. Other members of its species can grab those molecules with special receptors. Releasing and grabbing these molecules is a way for bacteria to say, "I'm here—is anyone else here?"

If the bacteria sense that they do have enough members, they will begin to cooperate to build a shelter. They spray out gooey molecules that grow into a mat, inside of which the bacteria embed themselves. This so-called biofilm can stick to the lining of the lungs or other organs. Nestled deep inside the biofilm, the bacteria are shielded from the attacks of immune cells.

Pseudomonas bacteria also work together to gather nutrients. Bacteria cannot grow without iron, for example, but the human body is a tough place to find it because our cells snap up iron and lock it away in hemoglobin and other molecules. To get an iron supply, each microbe releases molecules called siderophores. The siderophores can wrest the atoms away from our own molecules. "They basically steal the iron," says Sam Brown, an evolutionary biologist at the University of Edinburgh. The bacteria can then absorb the iron-bearing siderophores and use the iron to grow.

The effort is deeply cooperative because each siderophore that a microbe takes in was probably made by one of its millions of neighbors. "One cell will pay a cost that will benefit the whole infection, not that one cell," the NCI's Pepper says. Evolutionary theorists have a name for such molecules: public goods. These molecules are good for the public at large—in this case, the community of bacteria. They are the opposite of private goods, which only benefit the individual bacteria that made them.

Public goods represent a Darwinian paradox. Natural selection should, in theory, wipe them out. Mutants that do not make their own public goods can still use the public goods made by others. This imbalance should put the freeloader at an evolutionary advantage. A mutant that does not make siderophores can still get iron without paying the cost of making siderophores. It should reproduce faster than cooperative bacteria and become more common. And yet it is the cooperators that dominate species such as *P. aeruginosa,* not the freeloaders.



ENEMY GROUP: The collective activities of *Pseudomonas aeruginosa* bacteria, pictured in the electron micrograph above, allow them to trigger hard-to-eradicate infections.

STEVE GSCHMEISSNER *Science Source*

In the mid-2000s a small group of evolutionary biologists began to turn their attention to these intriguing questions about the social life of bacteria. The University of Edinburgh emerged as a leading center for sociomicrobiology, which is why Kümmerli went there in 2007. He did not immediately start running experiments, though. Years of studying ants had not yet prepared him for the hard work of microbiology. Kümmerli and other aspiring sociomicrobiologists had to apprentice themselves in the microbiological arts. They learned how to rear bacteria, how to prevent their stocks from getting contaminated, how to manipulate their genes and how to run experiments. "It took years to learn all the methods," Kümmerli says. "Sometimes we were not taken seriously by the classical microbiologists."

Eventually they got results. They began uncovering tricks that social bacteria use to keep freeloaders at bay. Working with Brown, for example, Kümmerli found that *Pseudomonas* bacteria do not produce a steady stream of siderophores. Instead they churn them out suddenly, in an initial burst. Once the bacteria have created a supply of siderophores, they can recycle the molecules. They absorb iron-bearing siderophores, pull away the iron atoms and then spit the siderophores back out. Thanks to the durability of siderophores, the bacteria do not have to use up much energy making new siderophores to replace old ones. Recycling thus lowers the cost of cooperation. It also helps to cut down the advantage of being a freeloader.

As the sociomicrobiologists discovered more about the social evolution of bacteria, they began to wonder if they could apply their insights in a very practical way: by finding new kinds of drugs to fight infections.

SCIENTIFIC AMERICAN ONLINE Watch a video about the social life of bacteria at ScientificAmerican.com/jan2015/social-bacteria

TIPPING POINT

TO AN EVOLUTIONARY BIOLOGIST, all antibiotics in use today are basically the same. Each attacks bacteria's private goods. If a microbe mutates to protect its own private goods, it will outcompete other bacteria that cannot. Sociomicrobiology reveals a different target for stopping infections. "Instead of targeting the individual cells, target their public goods," Pepper says.

Evolutionary theory predicts that bacteria will be less likely to evolve resistance to drugs that go after public goods. Imagine, for example, that researchers were to develop a drug that attacked siderophores. As a result, bacteria would become starved of iron.

Now imagine that an individual microbe acquired a mutation that protected its siderophores from the drug. That mutant would not gain any advantage. Bacteria collectively release all their siderophores into their host, where the molecules get mixed up. When a microbe takes up an iron-bearing siderophore, it is almost certainly not one of its own. As a result, mutants cannot outreproduce their fellow bacteria.

Sociomicrobiologists first developed this argument in the abstract, through mathematical equations and computer simulations. "We devise all these theories and say look, this ought to work if you just try it," Pepper says. "But all that effort is useless if no one is going to try it." Those experiments are now under way. Recently, for example, Kümmerli, Brown and their colleagues tried out a drug that attacks siderophores. Previous research had revealed that siderophores made by *Pseudomonas* grab a metal called gallium just as easily as they grab iron. The researchers wondered if they could use gallium as a drug to starve the bacteria of iron.

To find out, they ran an experiment on caterpillars. They infected the insects with *Pseudomonas* and let the infection run its course in some of the insects, which all died. But the infected caterpillars that were given gallium all recovered.

Having shown that gallium could act as an antibacterial drug, the scientists ran another experiment to see if the bacteria could evolve resistance to it. Evolutionary theory predicted that they should not. "We were quite nervous doing the experimental evolution," Kümmerli says. He and his colleagues knew very well how other promising drugs had been crushed by the power of evolution. "We were just hoping no evolution came up," he adds.

For their new experiment, the scientists reared *Pseudomonas* in a broth that included iron. But the iron was bound up in molecules that the bacteria could not absorb. They needed to use their siderophores to pry the iron away from the molecules to survive. In one set of trials, the scientists exposed the bacteria to some conventional antibiotics. At first, the drugs rapidly slowed down the growth of the bacteria. But after 12 days of exposure, the bacteria became completely resistant to the antibiotics.

Then they ran the experiment all over again, this time exposing the bacteria to gallium instead of conventional antibiotics. The gallium drastically slowed down the growth of the bacteria. After 12 days, the bacteria were just as vulnerable to gallium as they had been at the start. The experiment met the predictions of the sociomicrobiologists. A drug that targeted public goods had prevented bacteria from evolving resistance.

Pepper, who was not involved in the experiment, considers the gallium experiment a major success for sociomicrobiology. "I think it's exactly what was needed as a next step," he observes. "I hope this will be a tipping point for people."

Kümmerli hopes that other scientists will start testing gallium in infected mice and, perhaps in a few years, in humans. Such trials would be relatively easy to run because gallium has already been extensively tested in humans for a number of medical treatments.

POTENTIAL DRUGS

SIDEROPHORES are just one of a number of public goods that sociomicrobiologists are studying as potential targets for drugs. Some bacteria, for example, make us sick by releasing toxins. But they only do so once their population is big enough to deliver a potent wallop. Then they unleash toxins that cause our cells to rupture, spilling out molecules that the bacteria can feed on. Drugs that can disarm toxins may be able to render bacteria helpless without even killing them.

Other researchers are investigating the signals that bacteria send to one another. They are discovering molecules that can jam this communication in various ways, such as blocking the receptors that usually grab signaling molecules. If bacteria cannot communicate with one another, then they cannot cooperate.

Antisocial drugs could have another advantage over conventional antibiotics: instead of wiping out lots of species of bacteria at once, they may be able to narrow their targets. That is because the public goods made by one species are typically only useful to that species alone. Thus, antisocial drugs might be less likely to wipe out good germs along with the bad.

As promising as this research may be, however, some scientists are skeptical that antisocial drugs will avoid resistance. Thomas Wood of Pennsylvania State University and his colleagues have been investigating a few of the most promising of these compounds. And their results are sobering. In an experiment on a drug that interferes with bacterial signaling, for example, they found mutants that could grow in spite of the drug. In other words, the bacteria evolved a way to live without a public good. "I'm not hopeless," Wood says. "I just don't think this one class of drugs is a panacea."

It is possible that Wood's results mean that certain public goods are not truly essential. If that is so, then evolution-based drugs will have to target only the essential ones.

Even if antisocial drugs turn out only to slow down resistance, Pepper says, they will be an important advance. "We're losing this race, and lives are at stake," he declares. "Even if we can just gain an edge against our opponent, that's going to save a lot of lives." SA

MORE TO EXPLORE

Hacking into Bacterial Biofilms: A New Therapeutic Challenge. Christophe Bordi and Sophie de Bentzmann in *Annals of Intensive Care,* Vol. 1, Article No. 19; June 13, 2011. www.ncbi.nlm.nih.gov/pubmed/21906350

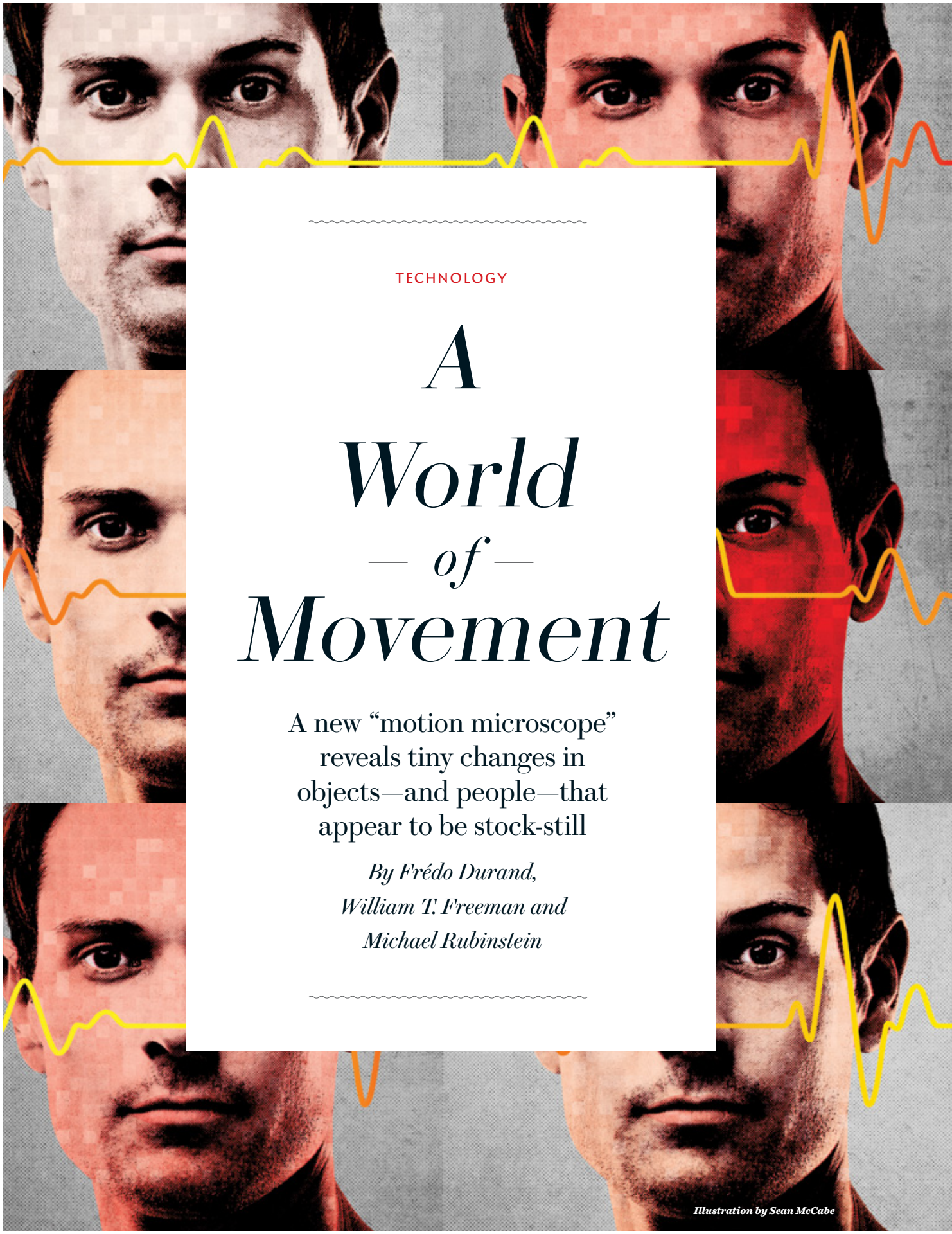
Gallium-Mediated Siderophore Quenching as an Evolutionarily Robust Antibacterial Treatment. Adin Ross-Gillespie et al. in *Evolution, Medicine, and Public Health,* Vol. 2014, No. 1, pages 18–29; 2014. www.ncbi.nlm.nih.gov/pubmed/24480613

FROM OUR ARCHIVES

The Challenge of Antibiotic Resistance. Stuart B. Levy; March 1998.

Battling Biofilms. J. W. Costerton and Philip S. Stewart; July 2001.

scientificamerican.com/magazine/sa



TECHNOLOGY

A World of Movement

A new "motion microscope" reveals tiny changes in objects—and people—that appear to be stock-still

By Frédo Durand, William T. Freeman and Michael Rubinstein

Illustration by Sean McCabe

Frédo Durand works on computational photography as a professor of electrical engineering and computer science at the Massachusetts Institute of Technology.

William T. Freeman, a professor of electrical engineering and computer science at M.I.T., studies how machine learning can be applied to computer vision.

Michael Rubinstein is a research scientist at Google, working on computer vision. His motion microscope work was done while he was at Microsoft Research and M.I.T.

THE FIRST MICROSCOPES, IN THE 1500S AND 1600S, TRANSFORMED GLASS PANES THAT LOOKED completely transparent into a universe teeming with bacteria, cells, pollen and intricate crystals. These visionary aids were the first devices to show people that there were cells within a drop of blood. Since then, microscopes have opened up other invisible worlds for scientists, going within cells or down to the scale of atoms.

We believe a new kind of microscope is about to unveil another fascinating new world: a world of motion and color change too minute for the eye to catch. Blood pulsing through one's face makes it redder and then lighter, the wind can cause construction cranes to sway by a tiny amount, and a baby's breathing is often too subtle too be seen. These movements are almost unimaginably small, yet their importance looms large. They can reveal the state of our health or the vibrations of a crucial machine about to fail. With our students and collaborators, we have developed what we call a motion microscope, a tool that couples a video camera with specialized computation. Together they amplify movements in people and objects that seem, to the naked eye, to be standing absolutely still.

CALCULATING COLOR

OUR MOTION MICROSCOPE was discovered serendipitously. We had been working on a video project to measure tiny color changes, too small to be seen by the unaided eye. Scientists Ming-Zher Poh, Daniel McDuff and Rosalind W. Picard of the M.I.T. Media Lab had shown, in 2010, that they could use a video camera to measure a pulse by detecting minuscule color variations caused by blood flowing to and from the face in rhythm with the beats of the heart. (They have turned the technique into a pulse-measuring smartphone app called Cardiio.) We felt the calculations were tricky and more complex than they needed to be, involving advanced linear algebra. We began searching for a simpler way to carry out the process.

The main challenge is the low degree of the color change in any individual video pixel caused by blood flow—it varies by just 0.2 percent over the course of a pulse. Unfortunately, camera sensors do not record exact values and always contain random noise, typically higher than 0.2 percent. This noise vastly overshadows the variation in redness.

In our search for a simpler route, we, along with our then student Hao-Yu Wu, researcher John Guttag of the Massachusetts Institute of Technology and Eugene Shih, then at Quanta Research Cambridge, decided to replace the number representing the color of each pixel with an average of all nearby pixels. This method dramatically reduced the noise because these random fluctuations tend to cancel one another out within a large enough pixel group. We also filtered out color changes that occurred over a longer or shorter period than the range typical of the resting pulse for adults.

Our simple approach proved successful at converting the pixel changes into the number of beats per minute. But these color changes were invisible to us, and we wanted to see what they

IN BRIEF

Although they appear to be absolutely still, objects and people move in ways imperceptible to normal vision. These movements can be as small, and as important, as a baby's breaths.

By amplifying color changes in video pixels as they change moment by moment, researchers have created a "motion microscope" that makes these small motions very visible.

These magnified movements can show crucial health indicators such as changes in pulse or blood flow or looming safety problems such as abnormal vibrations in heavy machinery.

looked like. By using these calculations to compute changes in redness at each pixel in a video over time and then amplifying them by a factor of 100, we were able to clearly see the face of an adult man getting redder every time his heart beat.

This technique also works for babies. In a test on newborns, performed with physicians Donna Brezinski and Karen McAlmon, both then at Winchester Hospital in Massachusetts, we shot a video with a regular digital camera. After amplification, we found the pulse shown by the video and a traditional pulse meter attached to a tiny finger matched closely. This observation raises the possibility of measuring a pulse without contact, which is important for fragile premature neonates because touching such infants can be harmful. For adults, in the future, these visualizations may help reveal abnormalities in blood flow that could have health implications, such as asymmetries in circulation between the left and right sides of the body.

NOT SO STILL LIFE

OUR VIDEOS, however, presented us with a puzzle. To simplify the color processing, we had asked the adults in front of our cameras to hold very still, and their heads really looked motionless in the original videos. But as we watched the color-amplified results, we noticed that their heads were moving. Our technique seemed to enhance not only color changes but also tiny motions.

In earlier work with other colleagues, we had created videos that amplified small movements. But that involved specialized software that computed motion directions—vectors—for each pixel at each point and moved them around to new locations. It turned out to be complicated and prone to errors. We were astounded that our new approach could achieve a similar effect with a simple computation and without calculating any tricky motion vectors.

Why did bigger color changes also magnify these small motions? To find out, we had to review how movement in a video results in local color changes. Imagine an object like a ball that is lit from the right, making the right side of the ball bright and the left side dark. If the ball is flying from left to right across a video screen, a pixel at one fixed location on the screen will get darker and darker as time ticks on because it depicts points farther and farther to the left on the ball. The variation depends on how fast the ball is moving and how sharp the brightness transition is between the left and right sides of the ball, the so-

BASICS

Turning Color Changes into Motion

In a video, each pixel represents a point on an object, such as a leaf or branch on a tree. As time ticks ahead, the color in that pixel changes as the leaf moves, even a tiny bit, because the leaf moves in relation to the light hitting it. A computer program that amplifies the color variation from one frame to the next also exaggerates the tiny motions so they become obvious to the naked eye. Researchers can isolate and amplify one particular time frequency—say, the speed of leaves shaking—and the result will make leaf movement stand out against the rest of the tree.

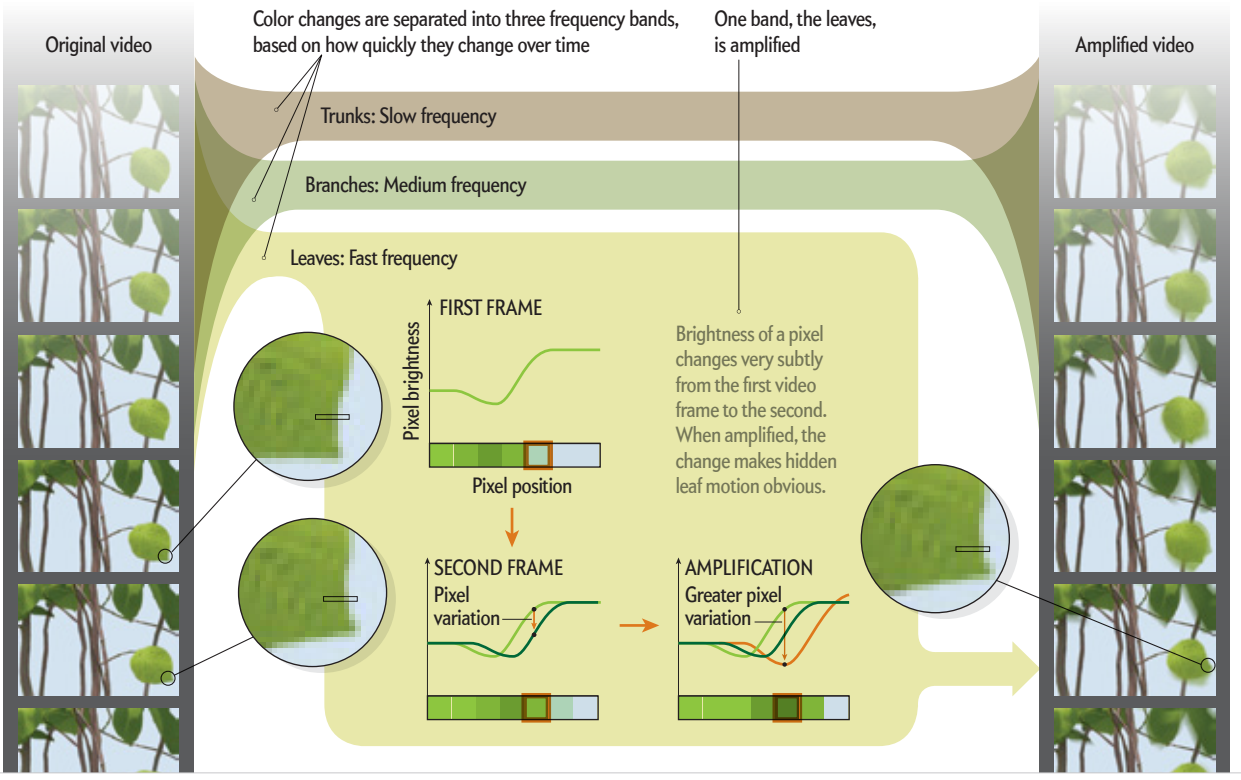
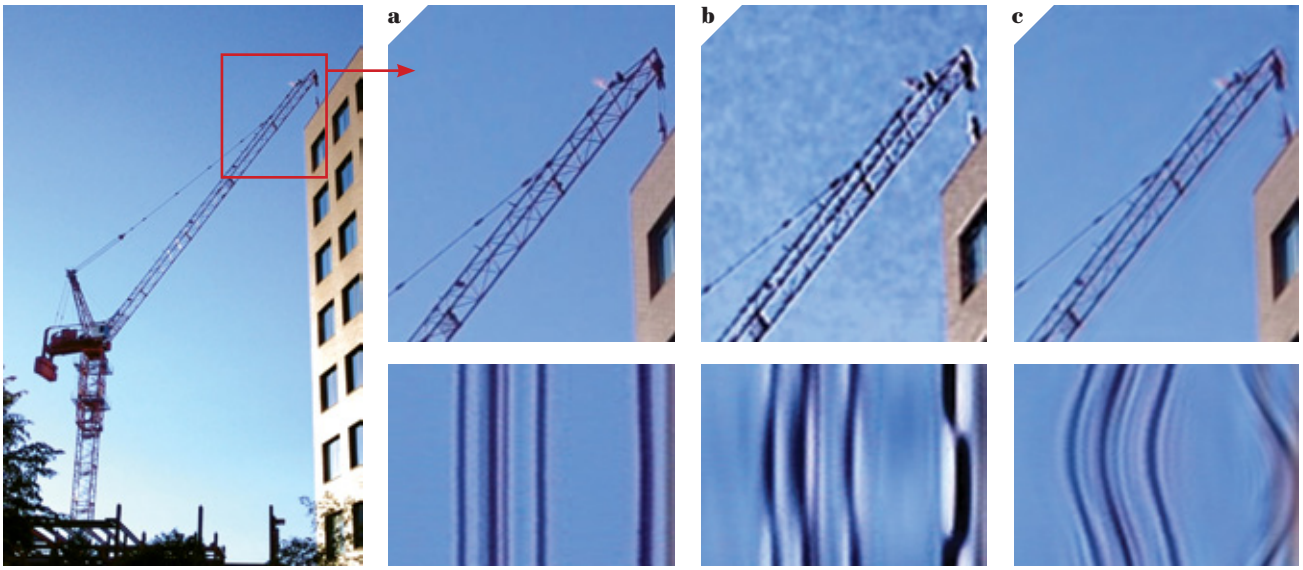


Illustration by Jen Christiansen



MOVING TARGET: **This construction crane seems motionless (*a*). Amplifying video color changes reveals swaying, but pixels look jagged (*b*). A computer smooths pixel transitions, showing motion (*c*). The bottom images show one crane feature moving over time.**

called color gradient. Mathematically, we can say that the change of a pixel's color over time is the product of the speed of the object multiplied by this color gradient.

Our algorithm, of course, does not know about speed or color gradients. Nevertheless, because it amplifies the color change at any particular point as the ball moves a fraction of an inch to the right, it also amplifies that fractional motion of the ball for your eyes to see. In a similar way, the colors of pixels representing specific points on a baby's chest will change as the baby breathes, and making the color change more dramatic also makes the tiny movement of the chest more obvious.

A FLUID LOOK

THE DIFFERENCES BETWEEN our earlier work that used vectors and our new approach based on color changes over time are a matter of perspective. It is the difference between going with the flow and standing still amid the current, and that change in viewpoint is what makes our newer calculations simpler to do. The idea comes from scientists who watch fluids and model how they move. There are two contrasting ways to do this: Lagrangian and Eulerian methods. Lagrangian approaches track a given portion of fluid as it travels through space, like an observer on a boat following the flow of a river. In contrast, Eulerian approaches use a fixed location in space and study the fluid passing by it, as if the observer was standing on a bridge.

Our earlier work followed a Lagrangian philosophy, acting like the observer on a boat, where pixels are tracked in the input video and then moved—as the boat moves—according to magnified vectors from point to point to point. In contrast, our new approach considers color changes only at a fixed location, similar to the observer who stays on the bridge. This local perspective applies to only small motions but makes it much simpler and robust. A computer can quickly process a video using this technique, whereas our earlier work required a lot of computer-processing time and often contained mistakes.

In 2012 we published a paper on this new method, called Eulerian video magnification. It showed how the blood flow changed a face. It also contained a variety of other examples, such as the breathing motions of an infant, which can be amplified so that parents of newborns could check an enhanced video signal to see if the baby was moving. We also took a high-speed video of a guitar where all the strings were vibrating and selected narrow bands of frequencies around given notes, such as 72 to 92 hertz for a low E string vibrating at 82 Hz. This amplified the motion of a single string, whereas the others looked like they were absolutely still.

We created a Web site where people could upload their videos and run them through this motion-magnification process. (See the videoscope at https://videoscope.qrilab.com.) People used it in ways we had not thought about, which was exciting. One person posted a video showing fetal movements in a late-term pregnancy. Another person amplified the breathing motion of her pet guinea pig. An art student made a video showing the imperceptible movements and expressions of her friends trying to stay still.

We also learned, however, that our Eulerian approach does have limits. If a given input pixel gets much darker from one frame to the next, the computer will enhance this change to an excessive degree, producing a fully black pixel, kind of a runaway amplification effect. This type of issue can cause dark or bright halos around motion areas. Input color variations from sensor noise are also a challenge because—even though we smooth them out by averaging many local pixels—the noise still gets magnified.

This result prompted us and our graduate student, Neal Wadhwa, to develop a new algorithm that preserves the benefits of simple Eulerian approaches but provides a better view when changes get more extreme.

We realized that the root of our original method's limitations is a false assumption. It acted as if the color difference between each pixel and all its neighbors—pixels to the left, the right, above, below—was the same, which unfortunately is not always true. Edges, for example, correspond with much bigger pixel differences (higher gradients) than their surrounding smooth areas. So if

COURTESY OF NEAL WADHWA *Massachusetts Institute of Technology*

SCIENTIFIC AMERICAN ONLINE Watch motion microscope videos at ScientificAmerican.com/jan2015/motion-microscope

you try and amplify all the pixels by the same amount at the same time, you get distortions that do not reveal actual movements.

Instead of amplifying by the same amount, we decided to represent each segment of an image—a local group of pixels—mathematically as a sine wave. A sine wave goes up and down, and the steep slope shows fast variation, whereas the top and bottom show a slow change. In a video image, edges mimic the fast varying part, and smooth areas look like the slow part. We can represent the change in an area of an image over time as the change in what is known as the phase of the wave. Moving from a fast varying phase to a slower varying phase helps us characterize how much movement happened between two frames of a video, and it does not create video artifacts such as halos. We reported this advance in 2013.

SMALL MOTIONS, BIG IMPLICATIONS

AFTER WORKING OUT these kinks, we found that we could process videos to see infinitesimal movements that had previously been predicted only by equations or by computer simulations. For instance, the shell surrounding the round frame of a PVC pipe is a simple object. When hit by a hammer or something similar, the shell bends and rebounds in specific patterns that oscillate at different time frequencies. Patterns that vibrate up and down quickly are tightly bunched, whereas those that shift more slowly are bigger, and they force the shell into different shapes. These patterns appear as equations in engineering textbooks, but seeing the actual deformations in the pipe was difficult because the changes are so small.

We took high-speed videos of pipes being hit. In the unprocessed video, any change in the circular shape is barely visible. Then Justin Chen, a graduate student of Oral Buyukozturk at M.I.T., working on a project with scientists at Shell International E&P, ran the video through our motion microscope, telling the computer to pull out the three lowest-frequency modes of oscillation. (This is the same principle we used to visualize a human pulse, by looking for only the pixel changes that corresponded to the heartbeat rate per minute.) Amplifying those frequencies showed the pipe cross section flexing inward and out, revealing the actual movements.

Watching a wineglass break under sound pressure—vibrating at high frequency—is another great example of how dramatic this visualization can be. We have all seen Hollywood movies when a soprano hits a high note and shatters glass. But none of us had ever seen the actual deformation of the glass because it is usually both too small in amplitude and too fast, typically around 300 to 500 Hz. We wanted to show the glass bend in and out in real time.

To do this, we used an old trick from Harold Edgerton, a pioneer of strobe-light, stop-motion photography. He showed that when a fast periodic motion is recorded with short exposures for each frame, the motion extends for several periods between frames and appears much slower than in real life. We used a regular video camera to grab short bursts of images of the glass. When we magnified the video through our motion microscope, this strobelike effect allowed us to see a glass vibrate in front of our eyes as soon as we hit it with the proper note.

The structural failure of wineglasses can disrupt a dinner party, but we hope that the motion microscope can reveal more serious effects, such as a large, potentially dangerous machine that is beginning to fail. The microscope can take small motions that may be characteristic of mechanical failure and make them visible. We showed this principle in a high-speed video of a car idling normally. As with the pipe, the raw video shows absolutely no movement of any mechanical parts. We then filtered the video to focus on engine vibrations at 22 Hz, blocking out all other frequencies. Magnifying the filtered changes by a factor of 30 revealed that different components of the engine were shaking back and forth. This was not abnormal for an engine, but it shows that the motion microscope can pick out particular bands that might be anomalous, in addition to amplifying small changes until they look big enough to see. Such videos could highlight and help diagnose malfunctioning mechanical parts in rotating or vibrating machinery.

We used a similar approach to show a giant construction crane shaking in the wind. Though appearing rigid to observers, the motion microscope shows the crane bending. There is a normal range of motion for such cranes. If the crane exceeded that range, it could spell trouble. We are exploring structure monitoring with Shell scientists Dirk Smit and Sergio Kapusta.

We can also reverse-engineer the process. By using the motion microscope to highlight tiny vibrations of objects such as the leaves of a plant, we, along with Wadhwa and Abe Davis of M.I.T. and Gautham Mysore of Adobe Research, reconstructed the type of sound that was causing them to shake. If this method was applied to, say, the concrete ramp of a bus terminal, it might identify the sources of vibrations that could weaken the structure.

The motion microscope can also be used to reveal problems in fluid flow. When the smooth flow of air or water in two adjacent layers changes into turbulent mixing, an unstable wave can form where the two layers meet. When this turbulence forms around vehicles, ranging from cars to airplanes to submarines, it has dramatic effects on how fast they move. So studying them is quite important. The waves cannot be seen in unprocessed video, but when particular motion frequencies are magnified by a factor of 40 in our video microscope, signs of wave instability pop out at the viewer.

Using the software to reveal the unseen can feel like putting on magic glasses or suddenly acquiring superhuman vision. Yet it is not magical or the dream of a comic-book creator; it is the result of basic research into video processing and mathematical representation of images. Already it has shown scientists phenomena we knew about intellectually but had never seen with our own eyes. It could, like the first optical microscopes centuries ago, help people identify threats to health and safety. Right now it makes us feel like explorers, marveling at a whole new world of phenomena that have always been around us, hidden in plain sight. SA

MORE TO EXPLORE

Eulerian Video Magnification for Revealing Subtle Changes in the World. Hao-Yu Wu et al. in *Proceedings of ACM SIGGRAPH 2012*, Vol. 31, No. 4, Article No. 65; July 2012. Preprint available at http://people.csail.mit.edu/mrub/vidmag

2012 International Science & Engineering Visualization Challenge. *Science*, Vol. 339, pages 518–519; February 1, 2013. www.sciencemag.org/content/339/6119/518.full

Videoscope. Quanta Research Institute. Upload your own videos to the motion microscope: https://videoscope.qrilab.com

FROM OUR ARCHIVES

Vision by Man and Machine. Tomaso Poggio; April 1984.

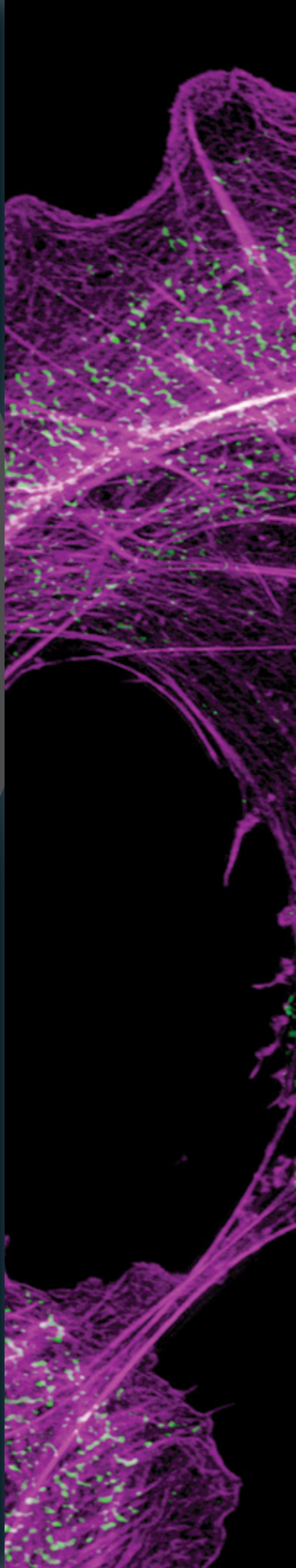
scientificamerican.com/magazine/sa

BIOLOGY

LIVING LARGE

Microscopes find beauty in the most unexpected places

By Kate Wong

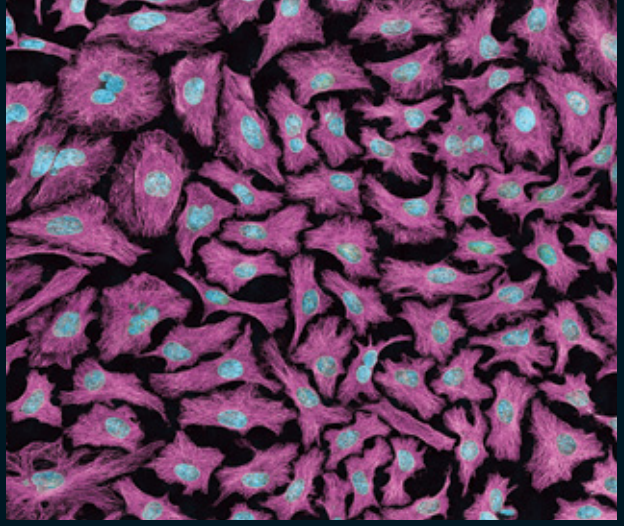


THE YEAR WAS 1665. A YOUNG ENGLISH SCIENTIST NAMED ROBERT HOOKE HAD published a book called *Micrographia* that was soon to become a best seller. The book contained Hooke's descriptions and exquisite illustrations of previously invisible details of the natural world, made using the compound microscope he invented: the jointed legs of a flea, the many-lensed eyes of a drone fly, the stellar shapes of snowflakes. Perhaps most remarkable of all were his observations of thin slices of cork (a plant material), which, his microscope revealed, were composed of a honeycomblike array of compartments. He named these structures "cells."

Three hundred and fifty years later microscopy continues to expose the extraordinary in the mundane, deepening our understanding of the world we live in—sometimes to great aesthetic effect. In the pages that follow, SCIENTIFIC AMERICAN celebrates that marriage of science and art with a selection of images from the 2014 Olympus BioScapes International Digital Imaging Competition. From the Kraken-like armor of a marine plankton dating to 37.6 million years ago (*page 57*) to the seemingly machine-tooled gearwheels that power a young plant hopper insect's jumbo jumps (*page 55*), these images affirm that beauty can be found all around us—we have only to look through the right lens.

CANCER ON THE MOVE

Some 90 percent of cancer-related deaths occur not as a result of the initial tumor itself but because cells migrate from that tumor to other parts of the body. This image of a bone cancer cell, by cell biologist Dylan Burnette of Vanderbilt University, shows the machinery that cancer cells use to spread into surrounding tissue. The cell's skeleton (*purple*) pushes the cell forward with the aid of a molecule known as myosin II (*green*). The cell's DNA appears in yellow.

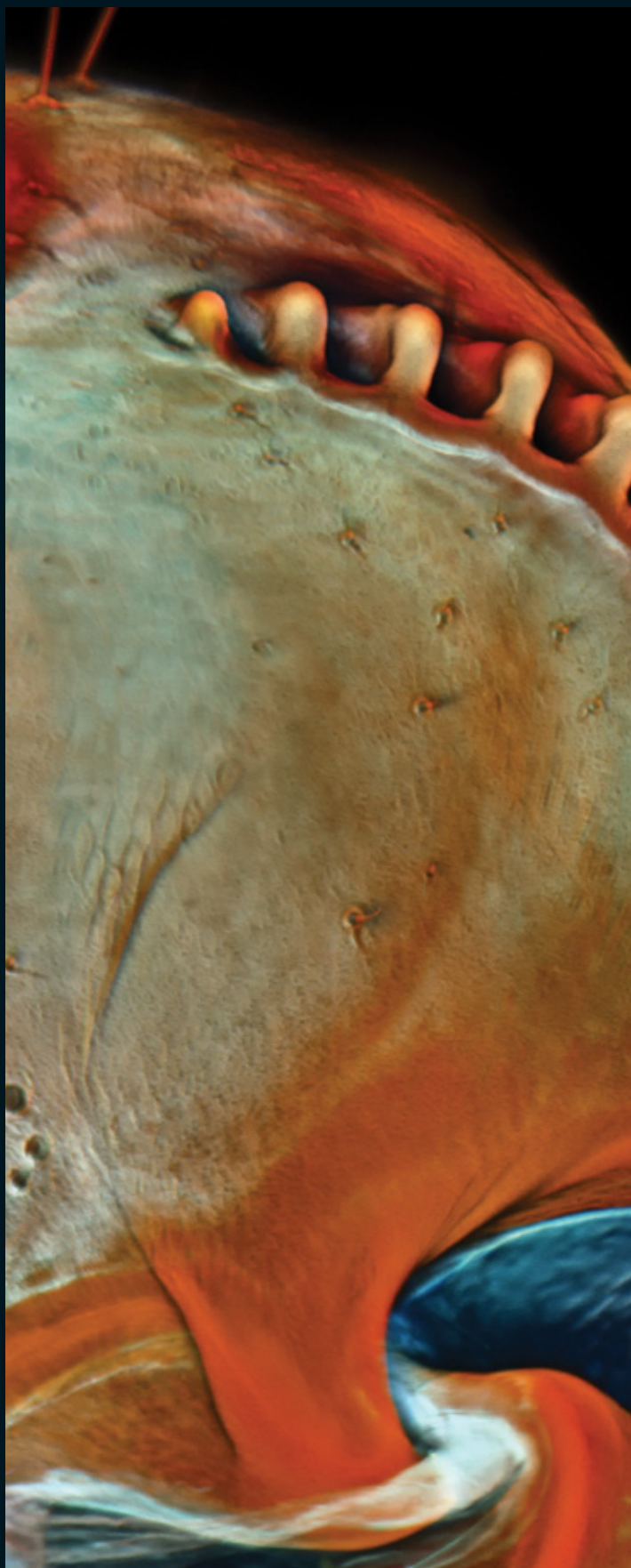


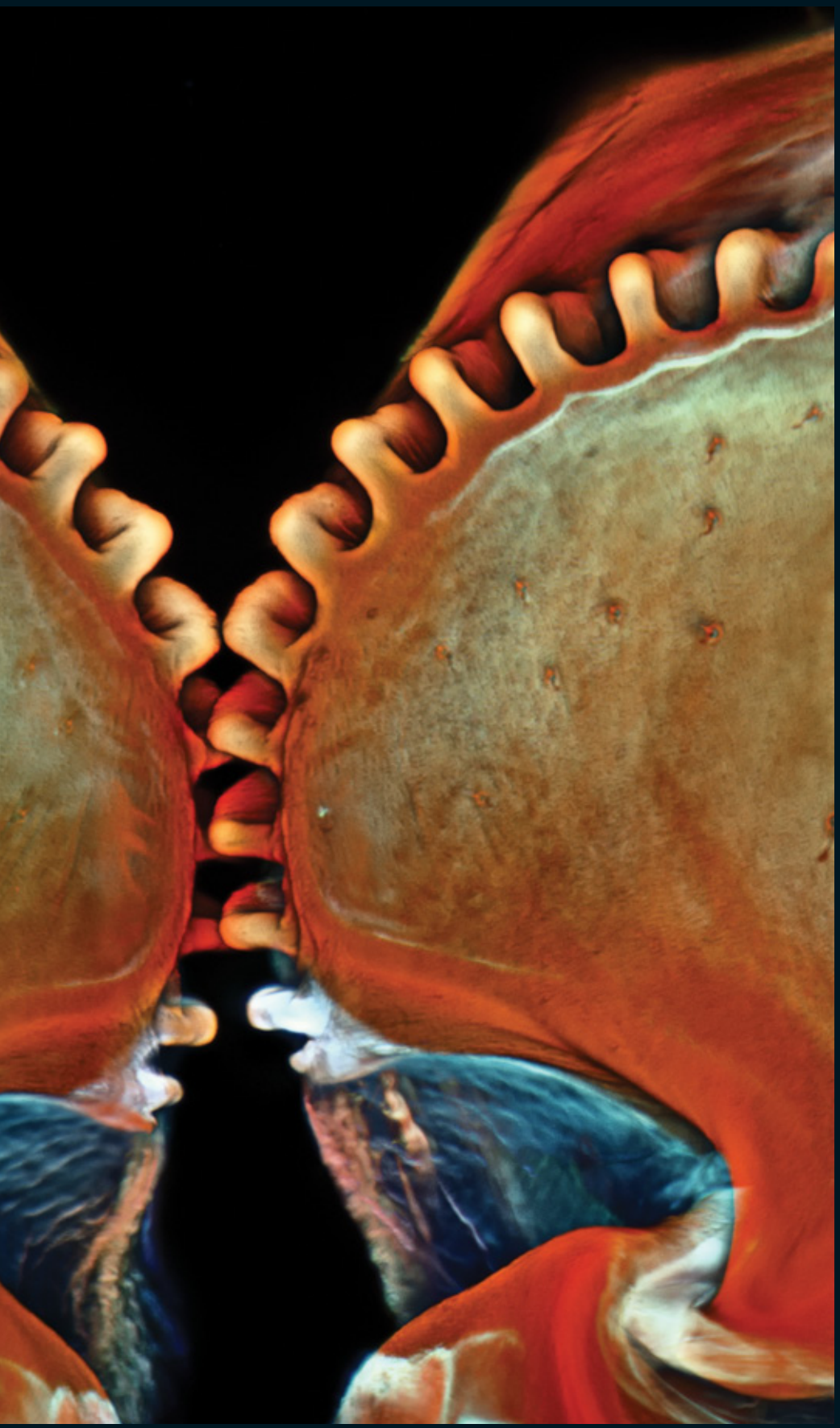
IMMORTAL CELLS

Cervical cancer cells from a patient named Henrietta Lacks were the first human cells to be cloned. Scientists have used these HeLa cells, as they are commonly known, extensively in biomedical research because they propagate readily in culture and are hence "immortal," as opposed to most other human cells, which tend to die in a matter of days. Thomas Deerinck of the National Center for Microscopy and Imaging Research at the University of California, San Diego, labeled the cells using fluorescent dye. The protein tubulin, which forms structures that are integral to cell division, appears in pink; the DNA is in blue.

BARNACLE APPENDAGES

The pesky white crusts that collect on boat hulls conceal remarkably intricate creatures, as this photograph of a barnacle's legs reveals. Neurobiologist Igor Siwanowicz of the Howard Hughes Medical Institute produced the image by removing the animal's soft tissues and staining the remaining exoskeleton with dyes that bind to a polymer known as chitin. "I was always fascinated with the diversity and versatility of crustaceans' appendages—the filter-feeding legs of barnacles are just one example of what can evolve from the common ancestral limb design," he observes.



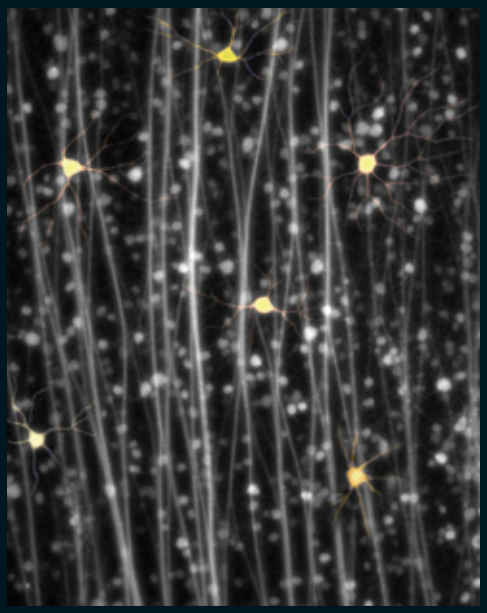


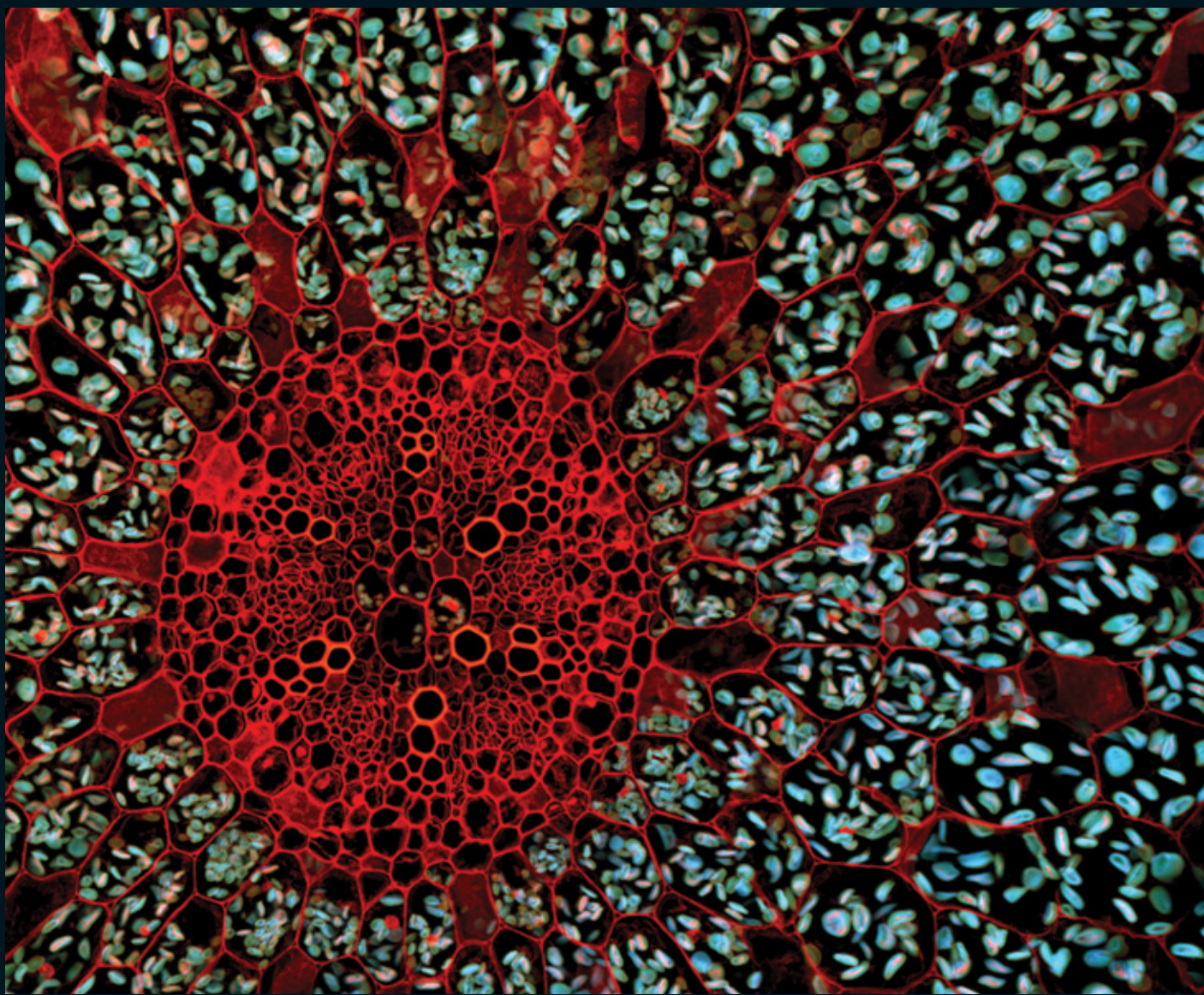
STEAMPUNK INSECT

The rear legs of insects called plant hoppers, known for their jumping ability, contain interlocking gear wheels that synchronize the leg movements of the peppercorn-size juveniles when they leap. This mechanism, described by Malcolm Burrows of the University of Cambridge and his colleagues in 2013, is the first known example of a mechanical gear system in nature. Siwanowicz visualized the plant hopper's 0.75-millimeter-diameter gears using the same techniques he applied to the barnacle at the far left.

RETINAL CELLS

The retina is a sheet of neurons lining the back of the eye that captures light from the outside world and translates it into electrical signals. In this image, produced by neuroscientist Chris Sekirnjak during his postdoctoral research at the Salk Institute for Biological Studies in La Jolla, Calif., a guinea pig's retinal ganglion cells, which send impulses to the brain when light is detected, appear in yellow. "The vertical streaks are axon bundles, which carry information from these neurons to the brain via the optic nerve for further processing," Sekirnjak explains. Each cell body is approximately 10 microns in diameter.





MINI KRAKEN

Fossil marine plankton in a cyst phase of life was found in a drill core from hundreds of meters below the floor of the Greenland Sea. "I was impressed by the fact that after millions of years, the microscopic structure of the cyst was so well preserved," says Stanislav Vitha of Texas A&M University, who imaged the organism. The plankton, which measures around 80 microns across, emitted the green glow when exposed to blue laser light.

CRAB SPIDER

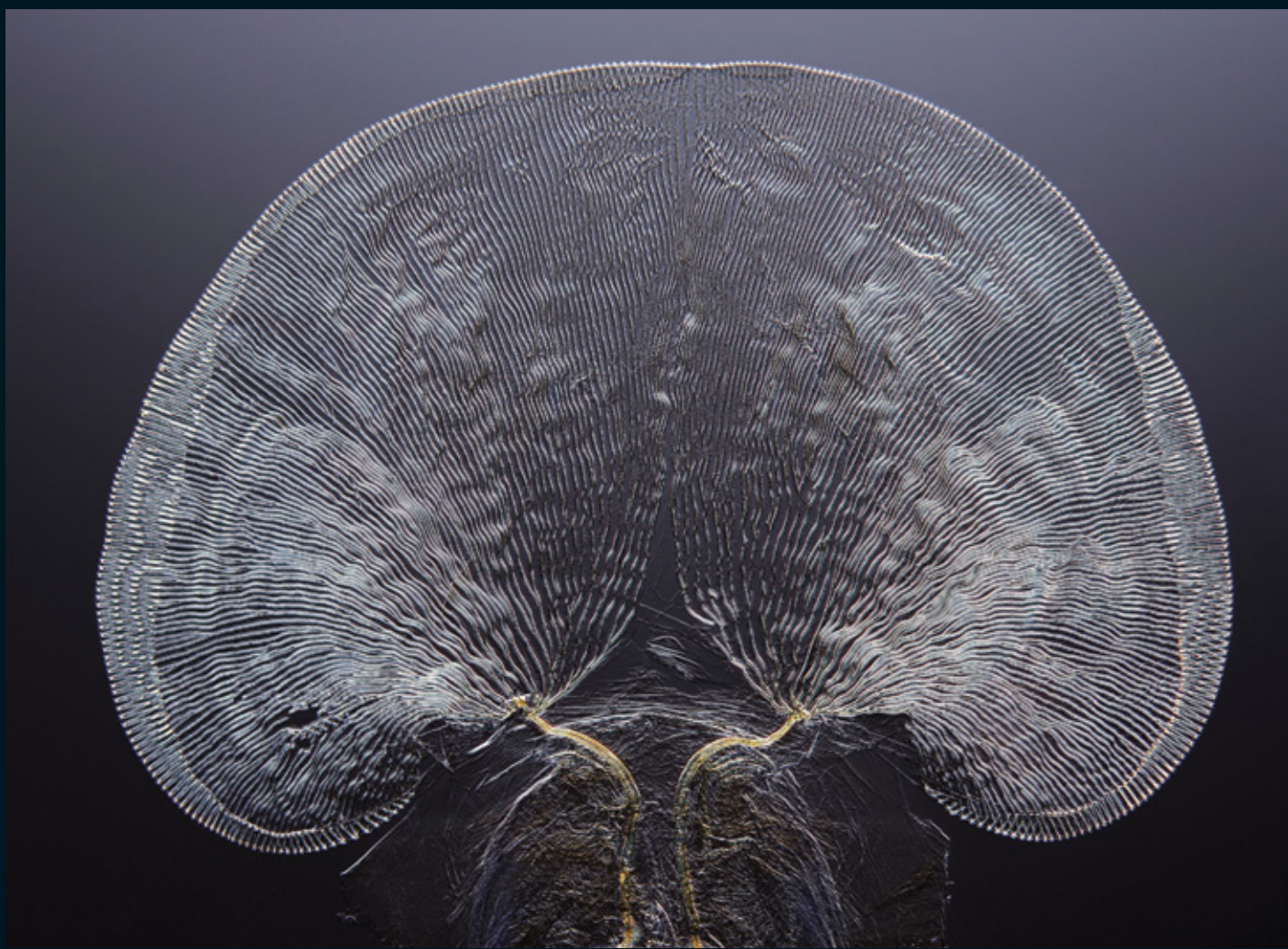
Amateur microscopist Geir A. M. Drange captured this close-up of the crab spider *Misumena vatia*, which he staged on a piece of dried maple leaf. In life, this arachnid can change color to blend in with its setting (frequently a flower of some kind)—a helpful trick for an ambush predator.

PLANT VASCULATURE

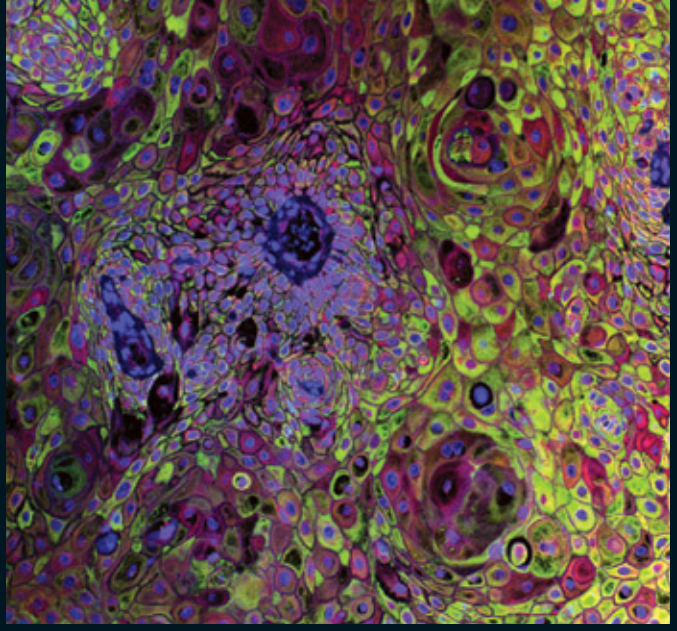
A transversal section of the stem of a flowering plant of the *Ranunculus* genus reveals the elaborate patterning of the plant's vasculature. Cell walls appear in red, and chloroplasts—cell structures that capture energy from the sun—are in white. Biologist Fernán Federici of the Pontifical Catholic University of Chile created the image by staining the plant tissues with fluorescent dyes, exposing the sample to a trio of laser wavelengths and viewing it with a confocal microscope.

JAPANESE EEL DEVELOPMENT

Stained tissue highlights the maturation of the Japanese eel, which is naturally transparent as a juvenile, from hatching (*far left*) through the first eight days. The head (*top*) grows rapidly, with the eyes and mouth appearing to be sufficiently developed by day eight (*far right*) for the young eel to begin hunting for food. By that stage, the yolk sac that provides nutrition to the baby eel has diminished correspondingly. Tora Bardal of the Norwegian University of Science and Technology in Trondheim produced the image.



SCIENTIFIC AMERICAN ONLINE See more images and videos from the 2014 Olympus BioScapes competition at ScientificAmerican.com/jan2015/bioscapes

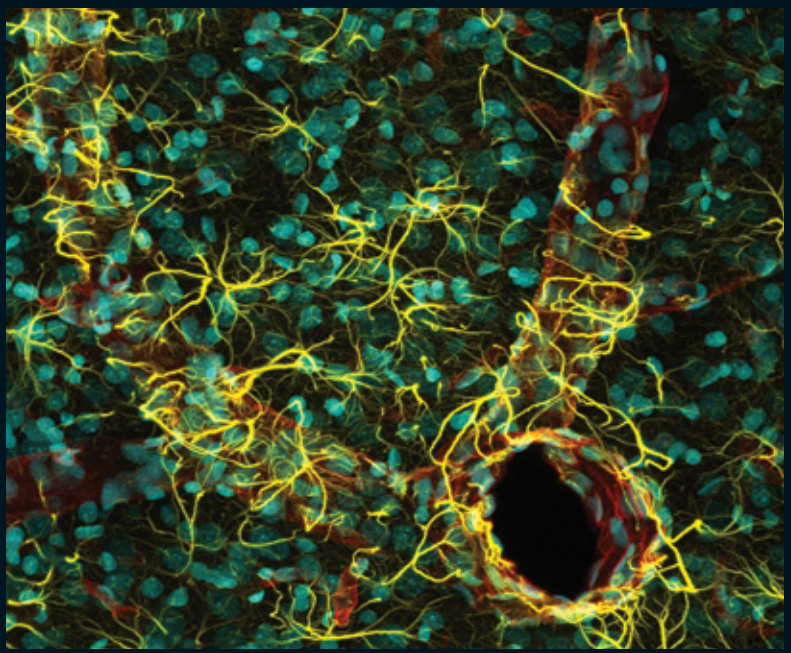


SKIN CANCER

In a form of skin cancer called cutaneous squamous cell carcinoma, keratinocytes—the cells in the top-most layer of the skin—produce a protein known as DIAPH1 that may help promote the spread of the cancer to lymph nodes and lungs. This image, produced by Gopinath Meenakshisundaram and Prabha Sampath of the Institute of Medical Biology in Singapore, shows human cutaneous squamous cell carcinoma tissue with keratinocytes that are producing high levels of DIAPH1 (*red*). The protein keratin, a marker for keratinocytes, appears in green; cell nuclei are blue.

RAT BRAIN

Madelyn E. May visualized the cerebral cortex, or gray matter, of a rat when she was an undergraduate at Rensselaer Polytechnic Institute, as part of a larger effort to map in subcellular detail the glial cells that support and protect neurons. The image highlights the intimate association between the star-shaped glial cells, also called astrocytes (*yellow*), and blood vessels (*red*).



HOUSE CRICKET TONGUE

The tip of a house cricket's tongue is incredibly elaborate, with air-filled tubes (*silver*) that inflate the tongue and hoops made of the compound chitin that keep the tubes open. The exact function of this complex structure is unclear, says photographer David P. Maitland, but he "was gobsmacked by the delicate and beautiful architectural design and wanted to photograph it as if it were an exquisite sculpture."

MORE TO EXPLORE

For more information about the Olympus BioScapes competition, visit www.OlympusBioScapes.com

FROM OUR ARCHIVES

Life under the Lens. Ferris Jabr; January 2014.

scientificamerican.com/magazine/sa

FOOD

Will We Still Enjoy Pinot

Winegrowers are trying to preserve the flavor of your favorite reds and

By Kimberly A. Nicholas

IN BRIEF

Climate change is raising air temperatures in many wine-growing regions. Because temperature drives the accumulation of chemical compounds in grapes, if it keeps rising, wine from a given region may not have the same flavor.

Higher temperature increases a grape's sugar content, which means higher alcohol during fermentation. Temperature also affects trace compounds that create aromas, crucial to our flavor perception.

Winegrowers are taking a range of steps to try to adapt, from reorienting rows of vines to rearranging leaves to provide more shade. Moving a vineyard north or even uphill to lower heat is expensive and may not duplicate flavor because of different moisture and soil conditions.

Noir?

whites as climate change alters the compounds in grapes

Kimberly A. Nicholas is an associate professor of sustainability science at Lund University in Sweden and advises grape growers and winemakers worldwide. She grew up on her family's Cabernet Sauvignon vineyard in Sonoma, Calif. Follow her on Twitter @KA_Nicholas

IT WAS A HOT DAY IN THE VINEYARD, and I was covered in dust, sweat and sticky juice from the grapes I had been collecting for my research on how grape biochemistry is affected by light and temperature. Suddenly, I saw something that made me stop short. Tucked in one corner of this 6.5-acre plot in Carneros, in California's fabled Sonoma Valley, with row after neat row of Pinot Noir grapes, were a handful of alien vines. I had studied the arcane art of ampelography—the practice of identifying grapevines by the shape of their leaves and clusters, as part of my graduate training in viticulture—so I took an educated guess at what they were: the red varieties Cabernet Franc, Petit Verdot, Syrah and Malbec, plus a white, Sauvignon Blanc.

The next time I saw Ned Hill, an old friend from high school in nearby Napa who now managed some of the finest vineyards in the region, including this one, I asked him about those strange vines. "That's an experiment I'm doing," he said. "We're already pretty warm around here for growing Pinot. The price is good right now, so I don't want to make any changes. But pretty soon we might do better growing something else, so I'm trying out some warmer-climate varieties."

A Cabernet in Carneros? That sounded heretical. Upvalley in Napa is famous for its Cabernet, but here, where the Sonoma and Napa valleys broaden and join to meet the San Francisco Bay, it is cooler Pinot territory. The region's mild days, cool nights, fresh sea breezes and clay soils produce Pinots with the flavor of fresh red strawberries and spices like cardamom and cinnamon. It is the flavor of where I am from, and this fingerprint is what makes the wine unique and valued.

If temperatures keep rising, however, wine from those Pinot grapes will not be the same. Growers might indeed have to switch to Syrah or even Cabernet but risk ending the Carneros tradition, perhaps hurting sales. Maybe my friend could move his operation farther north, seeking cooler climates, but Pinot grapes at a different site would be influenced by the soil, humidity and rainfall there; they would not have the Carneros Pinot flavor. Or my friend could apply emerging know-how and try to adapt his growing techniques to preserve the signature flavor, a tricky task.

Climate change is beginning to affect the singular flavors that people expect from different wines from around the world—the experience you have come to know and trust from your favorite reds and whites. As a result, grape growers and winemakers are beginning to make some difficult and intriguing decisions about how to respond. Whether they can adapt enough to make sure that a Carneros Pinot retains the flavor of a Carneros Pinot or a French Burgundy that of a French Burgundy, and whether long-time wine regions fade and new ones arise, will depend on the rate of climate change and the rate of innovation.

GRAPE GROWERS can try to combat higher temperatures by increasing leaf cover or reorienting rows to enhance shade.

GREAT WINE IS GROWN, NOT MADE

WHEN IT COMES TO STAPLE CROPS such as wheat, corn and rice, scientists worry about the effects of rising temperatures on yields. For grapes, temperatures do not threaten the quantity produced so much as the quality of the grapes themselves.

Certain vineyards in warm regions are indeed looking for high volume at low cost. In California's Central Valley, for example, growers in Fresno aim for a yield of about 12 tons an acre. In 2013 they sold these grapes for an average of $340 a

PRECEDING PAGES: GETTY IMAGES (*wine stains*); TRAVIS RATHBONE *Trunk Archive (glass)*; THIS PAGE: COURTESY OF ROBERT SINSKEY VINEYARDS

ton, which mostly end up in bottles of wine costing less than $7.

The more romantic version of wine growing takes place on the cooler fringes of land hugging the California coast. Just 200 miles north of Fresno, skilled workers in Napa Valley raise grapes by hand, touching each vine up to a dozen times over the course of the growing season. Workers deliberately limit yields by pruning vines in the winter so each shoot produces only a few clusters, and they routinely pass through again in the summer, cutting any suboptimal clusters to the ground.

The intent is that the money lost in quantity will be made up in quality—that the vine will concentrate its resources in investing those few clusters with deeper, more complex flavors and aromas. The goal is to produce around four tons per acre, which fetched $3,680 a ton in 2013. Careful vineyard management certainly contributed to this 10-fold increase in price, compared with that of Fresno, but most of the premium is related to climate—a large effect from a seemingly subtle difference in annual average temperatures, just 4.5 degrees Fahrenheit cooler. As one grower told me, "Even a genius can't grow good Pinot Noir in Fresno. It's too hot."

"Too hot" is a problem because all plants are regulated by temperature. Wine grapes are especially sensitive. Wine is so shaped by the environment in which it is grown that the French have a word for it: *terroir*. Wine, like coffee and other geographically distinct products, reflects the place of its origin. The grapevine makes sugar through photosynthesis, then modifies and recombines this one starting ingredient to produce myriad compounds that might ultimately smell like raspberries or fresh-cut grass in your glass. Temperature, moisture, light and the soil itself alter how the vine orchestrates this ballet. Wine is more than 80 percent water and typically 12 to 15 percent alcohol, leaving only about 5 percent for everything else. This small fraction of other elements creates the unique flavor of a local wine, and changes in climate are putting this flavor at risk.

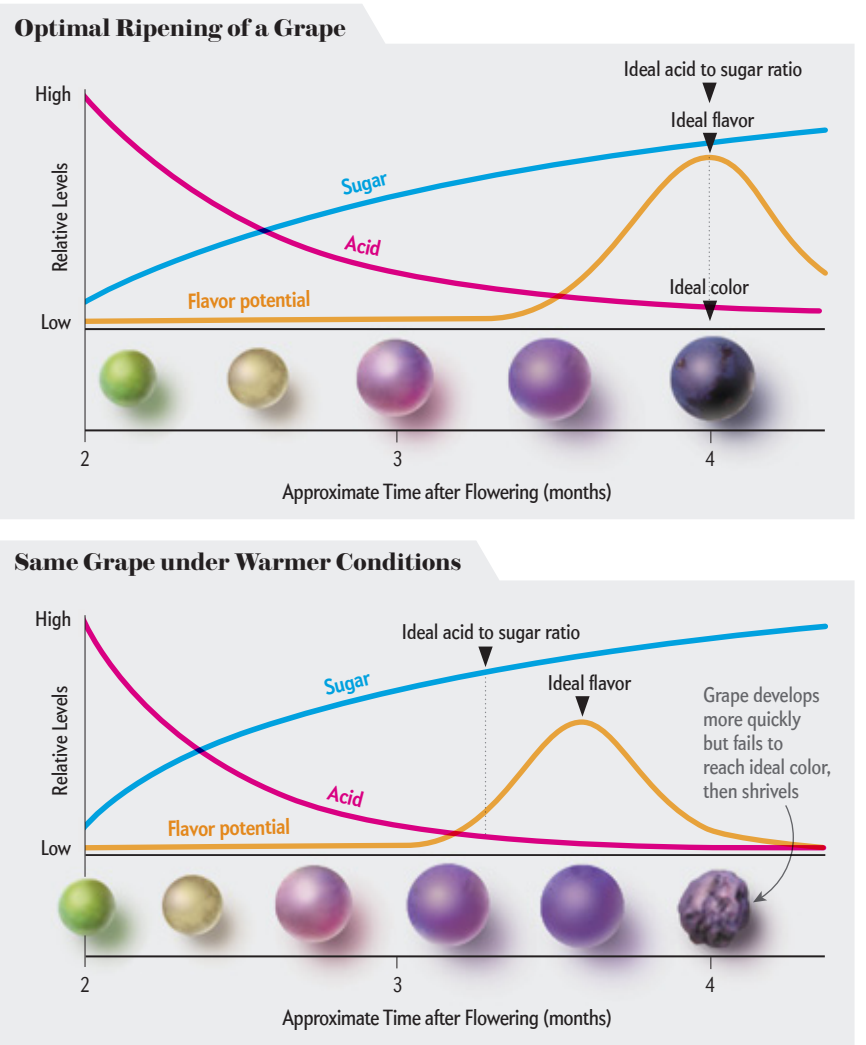
Although wine making requires great skill, nearly all the winemakers I have interviewed for my research on how the industry is responding to environmental challenges readily admit that most of the potential quality of a wine is already determined when the grapes are delivered to the winery. Some of the potential flavors come from the wine-making process, such as the yeasts used in fermentation or aging in oak barrels, but as one well-known wine-

STRATEGY

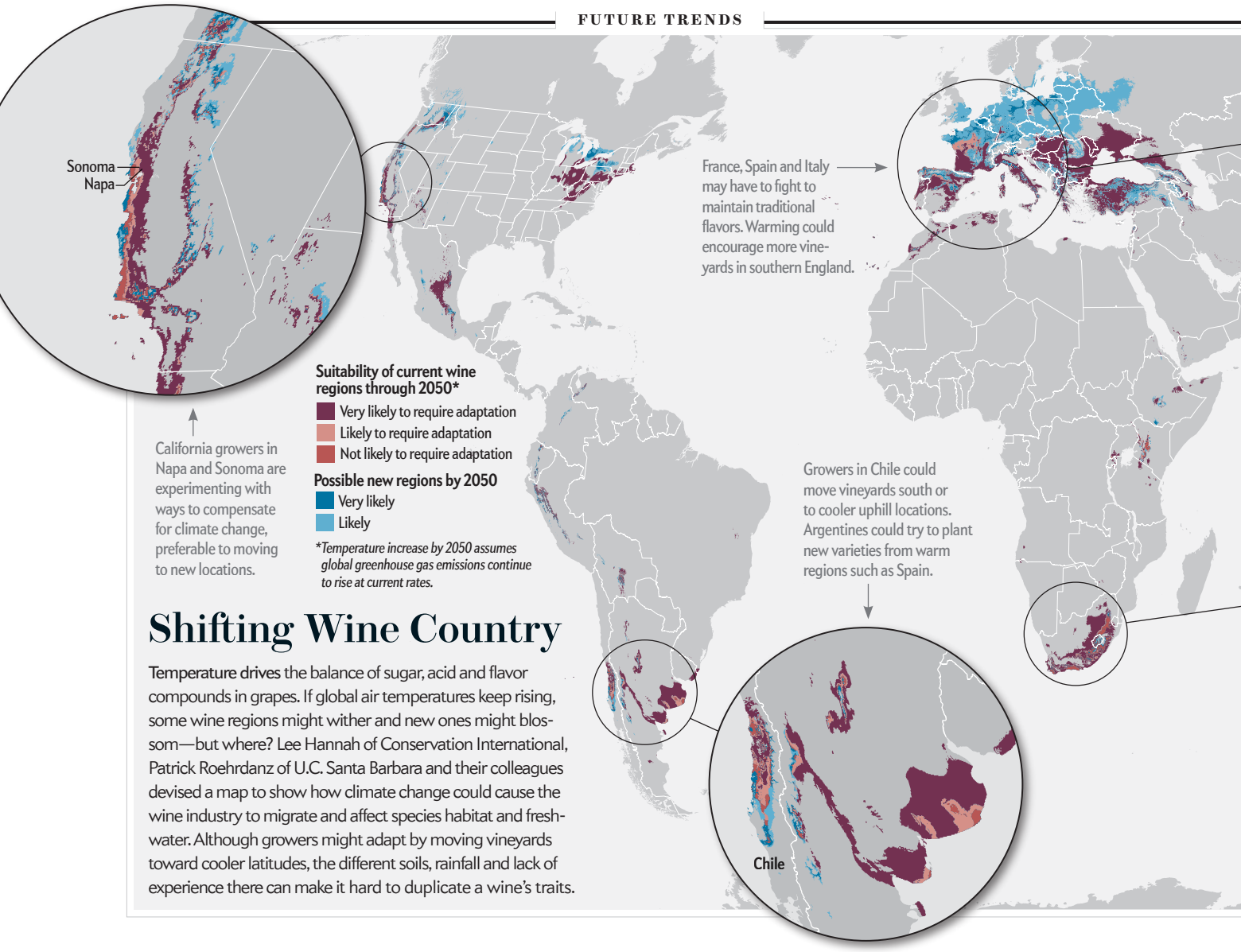
When to Pick Grapes Will Get Harder

Wine grapes take three to four months to ripen, but when to harvest them is a delicate decision. As a grape matures (*top*), its sugar level rises and its acid level falls (*blue* and *red curves*). The ideal ratio for a good wine occurs at around four months. Overall flavor (*orange curve*), influenced by other compounds, also peaks near that time, creating a tight window for the best harvest time.

The decision will get tougher. As the atmosphere warms (*bottom*), the desired ratio of acid to sugar occurs sooner in the growing season. The optimal flavor moment may occur earlier, too, but not shift as much, leaving a gap of time between ideal balance and ideal flavor and making it difficult to find the best combination. The grapes may also ripen too fast to accumulate as much potential flavor (the peak is lower in the orange curve) or to reach ideal color.



Graphic by Jen Christiansen



Shifting Wine Country

Temperature drives the balance of sugar, acid and flavor compounds in grapes. If global air temperatures keep rising, some wine regions might wither and new ones might blossom—but where? Lee Hannah of Conservation International, Patrick Roehrdanz of U.C. Santa Barbara and their colleagues devised a map to show how climate change could cause the wine industry to migrate and affect species habitat and freshwater. Although growers might adapt by moving vineyards toward cooler latitudes, the different soils, rainfall and lack of experience there can make it hard to duplicate a wine's traits.

maker told me, "If everything in the vineyard is done correctly, my job is just not to screw it up." Great wine is grown, not made.

DIFFERENT CLIMATE, DIFFERENT FLAVOR

CLIMATE GREATLY AFFECTS THAT GROWING. Winegrowers think of climate on three levels: the macroclimate of a region like Carneros or Burgundy; the mesoclimate of a vineyard parcel; and the microclimate of a cluster of grapes within a canopy of leaves.

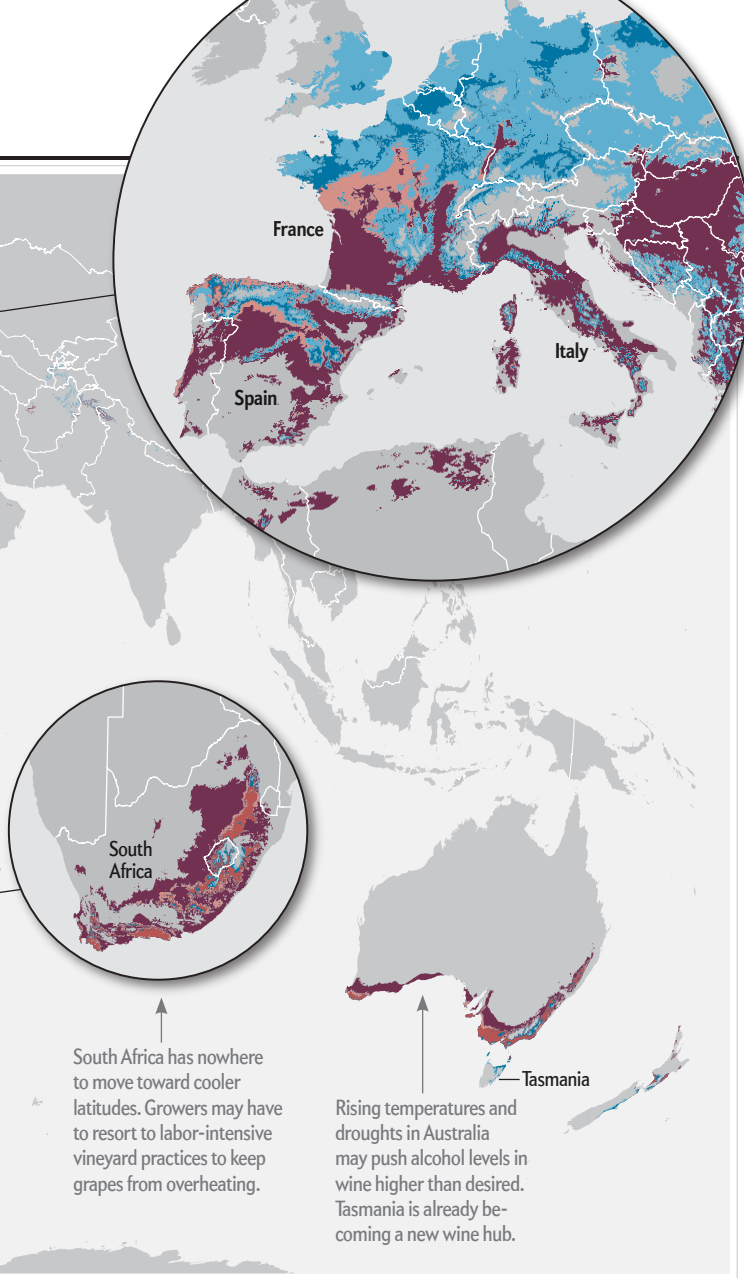
The macroclimate is influenced by broad geographical forces that set the growing season and the temperature and rainfall patterns. Temperature mostly determines which of the thousands of varieties of wine grapes can be grown optimally in a given place, from crisp whites suited to the short growing season and cool temperatures of Germany to bold reds that can maintain their flavors through a long, hot, dry summer in Spain. Temperature controls when vines wake up in the spring after winter dormancy and drives the growth and ripening process. As global temperatures rise, new regions such as southern England are becoming more suitable for wine growing, whereas some warm wine regions, notably parts of Australia, are struggling with high temperatures and regular droughts that contribute to uneven yields, overly high alcohol levels and unbalanced flavors.

Changes in the amount and timing of rainfall in a region can alter grape quality in various ways, and excessive humidity can hasten fungal rot. Drought can severely stress a plant. Many New World wine-growing areas, including California, are widely irrigated, but research I conducted in a team led by my colleagues at Stanford University showed that even in irrigated regions, natural precipitation affects yields.

How a vineyard's mesoclimate affects the taste in your glass is less obvious, but it starts with the balance of sugar and acid in the grapes, the components that form the foundation of a wine's taste. Fruits accumulate sugar through ripening, which is directly controlled by temperature. Ripe wine grapes are especially high in sugar, about a quarter by weight—twice as much as a sweet, juicy peach. Heat increases sugar at a predictable rate, usually by a percentage point or two every week during ripening. Sugar is converted to alcohol in fermentation, so sweeter grapes mean

SOURCE: "CLIMATE CHANGE, WINE, AND CONSERVATION," BY LEE HANNAH ET AL., IN *PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES USA* VOL. 110, NO. 17; APRIL 23, 2013 (STUDY BY A TEAM LED BY LEE HANNAH AT CONSERVATION INTERNATIONAL AND PATRICK ROEHRDANZ AT U.C.S.B.); DATA PROVIDED BY P. ROEHRDANZ

Map by XNR Productions



South Africa has nowhere to move toward cooler latitudes. Growers may have to resort to labor-intensive vineyard practices to keep grapes from overheating.

Rising temperatures and droughts in Australia may push alcohol levels in wine higher than desired. Tasmania is already becoming a new wine hub.

higher-alcohol wines. Over the past few decades rising temperatures have influenced a global trend toward higher-alcohol wines. Higher alcohol is often perceived as "hot" and more bitter and can overpower or alter the perception of more subtle flavors.

Acids are the yin to sugar's yang. Present in large quantities in unripe grapes, they are partially broken down as the grapes ripen. Acids in wine provide a sharp, refreshing taste. Cooler wine regions have planted varieties that can ripen quickly over the short growing season yet still have pleasing acid levels that are not too high. Cool-climate wines such as German Riesling may get less refreshing with warming temperatures as the crisp taste of acids is lost with heat.

Winemakers have studied sugar and acids for a long time, but in recent years they have begun to learn more about how critical less prevalent elements in wine are to our drinking experience. For example, phenolic compounds are important for wine color. Before we sip wine, we see it in the glass, where its color inevitably shapes our overall perception. In one test, even experienced wine tasters used red wine characteristics to describe the flavor of a white wine that had been tinted red. Juice from classic (Old World) wine grapes is not pigmented; the color in the wines comes from phenolic compounds called anthocyanins in the skins. These compounds occur widely in nature; they make blueberries blue and eggplants purple. When grapes are crushed after harvest, the red varieties are left in contact with the skins through weeks of fermentation to transfer the color to the juice. White wine grapes have a lower concentration of phenolics to begin with and are usually pressed away from the skins immediately.

Phenolics in a grape are induced by sun exposure, but wines from warmer climates are generally lower in desirable color. Research suggests that changes in average temperature are not all that matter, however; an increase over certain limits can result in nonlinear consequences that will decrease anthocyanins.

That vineyard microclimate also affects tannins, which give wine texture (like "chewy" or "smooth"). Tannins are another phenolic compound and get their name from their ancient use to tan leather. Tannins are so unpalatable that they protect fruit from being eaten by animals or pests before it is ripe. In your mouth, they bind with proteins in your saliva, drying out your tongue and gums, a sensation that affects your perception of wine flavor. They also have a bitter taste. Good tannin balance helps wine compliment food; the tannins physically cleanse your palate, removing fat from taste receptors so you can taste each bite more fully. Excessive warmth or light can decrease tannins, leading to potentially less balanced wines.

RIPE FOR SMELL

AT THIS POINT, we are down to the trace compounds that account for most of a wine's unique character. These bits are crucial, most of all for smell. When we taste wine, we often swirl it first and smell the aroma. The swirling volatizes compounds in the wine so they bind with receptors in our nose, sending signals to our brain that it interprets as flavor—the integration of many sensory inputs. Most of what we commonly perceive as taste is provided by our exquisite sense of smell. That is why food seems so bland when you have a cold; your stuffy nose does not allow the aroma compounds to reach your nose from inside, at the back of your mouth. Try eating a skinless piece of firm apple and a raw potato with your nose plugged; it is surprisingly difficult to distinguish the difference. Wine tasting might better be named wine smelling, although that sounds less appealing.

Winemakers and researchers are still developing better insights into the trace flavor and aroma compounds, which can arise in many ways. Those found in grapes usually accumulate in the late stages of ripening, and we know that their formation is sensitive to temperatures at that time. This so-called flavor ripening may occur at a different rate than the predictable sugar ripening that traditionally governs harvest decisions. Instead of picking grapes when they reach a given sugar level, many winemakers are making harvest decisions based on tasting grapes in the field, looking for flavors they believe will translate into great wines. The flavors usually progress along a continuum, from tasting like green fruits and vegetables to red fruits like raspberries, black fruits like blackberries and, finally, jammy fruits like raisins.

In some regions this strategy has led to a trend toward greater "hang time"—leaving the fruit on the vine longer for better flavor ripening. Some growers may not like this approach, because the

grapes lose water, which can mean less weight and less income. The longer hang time also increases sugar levels in the grapes, perhaps forcing winemakers to later add water to the juice to ultimately get the right alcohol level.

Researchers are trying to better understand the influences that the more than 1,000 aroma compounds in wine have on flavor perception. This is difficult to predict because some compounds are present at very low concentrations, and human sensitivity to them can vary by hundreds or thousands of times among different people. For example, more than 200 compounds may contribute to strawberry smell, and your trigger for "strawberry" might be different from mine. (So don't worry that you won't get the "right" answer when tasting wines—there is none!)

Sometimes one "impact" compound is the prime force behind a characteristic smell, and understanding its effects on our senses can help growers craft a better product. In the 1980s Hildegarde Heymann of the University of California, Davis, followed a hunch and discovered that a compound called methoxypyrazine, which caused the undesirable bell pepper aroma in Cabernet Sauvignon, was destroyed by light. Growers changed their trellising practices to reduce shade on the fruit, and California Cabernet got a lot better. More recent investigation led by Claudia Wood and her colleagues in Australia, Chile and Germany identified a single compound, rotundone, as the source of the desirable black pepper aroma in Syrah, and other work suggests that rotundone accumulation is likely higher at cooler sites and in cooler years.

GROWERS FIGHT BACK

UNDERSTANDING ALL THE INFLUENCES on a wine's flavor helps growers assess possible adaptations to a changing climate. The most dramatic action would be to move between regions, say from California to Oregon, or less dramatically, move within a region, perhaps from warmer valleys to cooler hillsides. A few studies have assessed these options, but they are based primarily on predicted temperature changes, without accounting for other important environmental factors. Articles in the popular press based on these limited analyses have gone so far as to declare certain wine regions at risk, anticipating decreased grape production and quality.

Several complicating factors make the simplistic notion of moving difficult in practice. Suitable soils that provide the right nutrients and water supply are required for high-quality wines, and these may not exist in new places. Appropriate, undeveloped land may not even be available. Uprooting an entire industry and its infrastructure is difficult and expensive; new vineyards take five or six years to generate full yields and may take 20 years to make a profit. Many growers also have a strong sense of place from farming land for generations that they may not want to lose. And consumers may feel strong ties to that place. New regions that are getting warm enough to grow wine will need time to develop the cultural know-how to solve the particular challenges of planting productive sites, managing pests and disease, and developing the regional style and identity that buyers prize.

What about selecting or breeding different vines to match changing conditions? One Old World grape species, *Vitis vinifera,* accounts for essentially all the grapes used for making what most people call wine, yet it comes in thousands of strains, known as varieties. Growers have selected varieties for their desirable qualities in a particular environment, the same way that people have selected varieties of dog to pull sleds in the Iditarod or to fit in Paris Hilton's purse.

But simply taking a grape that has good characteristics in one place and growing it somewhere else often will not provide the same delicious flavor. For example, clones—genetically identical cuttings from a single mother vine—of Pinot Noir grapes from Dijon, France, were selected to ripen quickly and produce high-quality wines in cool Burgundy, where they gained a reputation for producing great wines. They have now been widely planted in warmer California, yet with faster ripening in a different environment, they do not always produce the same prized flavor profile. Planting varieties from warm regions such as Spain in new places that are warming up might produce tasty wines, but this trial and error can take many years.

Breeding new varieties to better withstand increasing temperatures is an area of active research with some staple food crops, but it has more limited potential for wine grapes. Breeding can take a decade or more, but the main limitations are cultural. French appellation law, for example, specifies that only certain varieties can be grown in certain locations, if they are to carry the protected label of the region, such as Bordeaux (although one more recently bred variety, Marselan, a cross of Cabernet Sauvignon and Grenache, was successfully legalized in the 1990s in the

DO-IT-YOURSELF

The At-Home Wine-Tasting Test

Anyone can learn to taste wine more analytically, without following professional critics. It is mostly a matter of learning to identify elements in wine and to associate them with the relevant descriptive term. Because different people may have different initial perceptions of a certain flavor, panelists in wine-tasting experiments first smell physical samples such as blackberries so they agree on what "blackberry" means. Panelists then go into individual booths, dimly lit with red light to make all wines appear the same color. A researcher slides a tray with numbered wines through the wall, and the panelists rate them on a computer screen.

At home you can simplify this procedure and make it more fun. First, tell a group of friends to bring a particular variety of wine, such as Syrah. Your job, as host, is to find samples of flavors commonly found in Syrah: black pepper, blackberries, clove. Put each one in a glass and cover it with a muffin liner to hold the aroma compounds in. Once your guests are settled, pass around and smell the standards. Then taste each wine and see which flavors you recognize and how strongly.

If you want help, consider the Aroma Wheel developed by Ann Noble. The center of the wheel establishes broad categories of aroma, such as fruity or spicy. Each category gets more refined toward the edge of the wheel: first fruity, then berry, then raspberry. Learning to experience the sensory world in more detail can make the hours a day we spend preparing and eating food a lot more enjoyable. —*K.A.N.*

SCIENTIFIC AMERICAN ONLINE Details about wines made by five different scientists are at ScientificAmerican.com/jan2015/nicholas

WINEMAKERS at Robert Sinskey Vineyards in Napa ensure that fermenting wine stays in contact with grape skins to extract maximum color and tannins.

COURTESY OF ROBERT SINSKEY VINEYARDS

Côtes du Rhône appellation). Worldwide, consumers are often well entrenched in their favorite varieties, and a new breed could have a very difficult time breaking into the market.

Within an existing vineyard, growers can try to combat climate change with planting decisions. For example, they can change the direction of plant rows or how vines are trained as they grow and how they are held up by trellises to provide more shade as temperatures rise. Or growers can graft existing rootstock over to a new fruiting variety that tolerates heat better. These big decisions are usually made once, however, at the beginning of a vineyard's long life cycle.

Less dramatic decisions can still have great adaptation potential. Growers cannot control the air temperature in the macroclimate of their region, and they have only limited options for controlling the temperature at the mesoclimate vineyard scale, like overhead sprinklers or shade cloth. But they can use the number and position of leaves to cool the microclimate of the ripening grape so it better holds on to flavor and aroma compounds.

For example, in vineyards around Carneros in California my measurements revealed very high levels of sunlight (more than three times the levels previously reported) on grapes hanging from more than 500 Pinot Noir vines. All the shoots and leaves were held rigidly above the grape clusters by catch wires to provide more air circulation to reduce disease. In analyses conducted with my colleagues at Stanford and U.C. Davis, we showed that for every 1 percent increase in light, there was a more than 2 percent decrease in desirable tannins and anthocyanins. Easing off the vertical trellising style to allow more shade on the fruit could help preserve these compounds and, of course, cool the fruit.

Although most of a wine's flavor comes from the grape, winemakers can take steps in the processing phase to try to preserve a local wine's taste. If acids are lost too quickly as regions warm, they can add acid in the winery. If grapes accumulate too much sugar, which would ferment into high-alcohol levels that can overwhelm finer flavors, they can use reverse osmosis or other techniques to remove excess alcohol. These options are rather blunt tools, however; they cannot completely correct for flavors that originate in the vineyard.

Coaxing the best flavor from the land is a craft that takes years of hard work. Some industry experts think that New World regions such as Napa and Sonoma are still finding their best *terroir*. Jason Kesner told me several years ago when he was manager of a premium Napa-Carneros vineyard that the most outstanding vineyards in the region may still be generations away. It takes a generation to grow a vineyard, he said, "and then it takes your kids to figure out how to plant it differently, and it takes their kids to really get it dialed in. That's why the French have such incredible vineyards; it's just that they've had more time learning." And yet because great grapes are so sensitive to climate, if the climate changes even a little bit, the local knowledge and skills that have taken generations to hone can become less relevant, even in familiar territory.

CHANGING PLACES

EVEN IF THEY ARE RELATIVELY YOUNG, a Napa Cabernet and a Carneros Pinot have their own profiles and their own devotees. "I opened up the bottle of wine, and it smelled like Carneros," Debby Zygielbaum of Robert Sinskey Vineyards in Napa told me poetically. Climate change, if it alters the aroma and flavor of those grapes, could hurt those regions. Although warming might improve wine growing in some cooler areas, such as Tasmania, changes will most likely disrupt the major wine centers, which have tailored their industries to current conditions. For example, springtime warming greater than 1.8 degrees F is likely to reduce yields of California wine grapes, according to my research. Another example: the price of California Pinot Noir grapes drops steeply when they ripen above an optimal temperature threshold.

Growers and winemakers have some technical options for adapting, as we have seen, but whether these will always be enough remains to be tested. And at what point does applying know-how lead to a wine that is manufactured rather than one that brings out the unique flavor of a place? Ultimately there are biophysical and economic limits to adaptation.

The latest scientific reports say that if the world stays on its current trajectory of fossil-fuel use, the global average temperature will increase 4.7 to 8.6 degrees F in the next few generations. That rise may not sound like much, but consider that the low end of this range is roughly the difference between Napa and Fresno today; the high end is the difference between the Californian Central Valley wine town of Lodi and Houston. Although winegrowers are resourceful and creative, it is hard to imagine Houston becoming the next Napa Valley.

Wine is a literal message in a bottle, captured for our enjoyment. It lets us visit parts of the world we may never see in person. It reflects the fabulous environmental and cultural diversity of the planet, as well as humankind's deep reliance on nature to provide us with everything we need to live and many of the things that make life worth living. Today we are on course to fundamentally disrupt life on earth. Unless we make major changes very soon, the lost flavor of my hometown wines will likely be one of the less serious casualties. SA

MORE TO EXPLORE

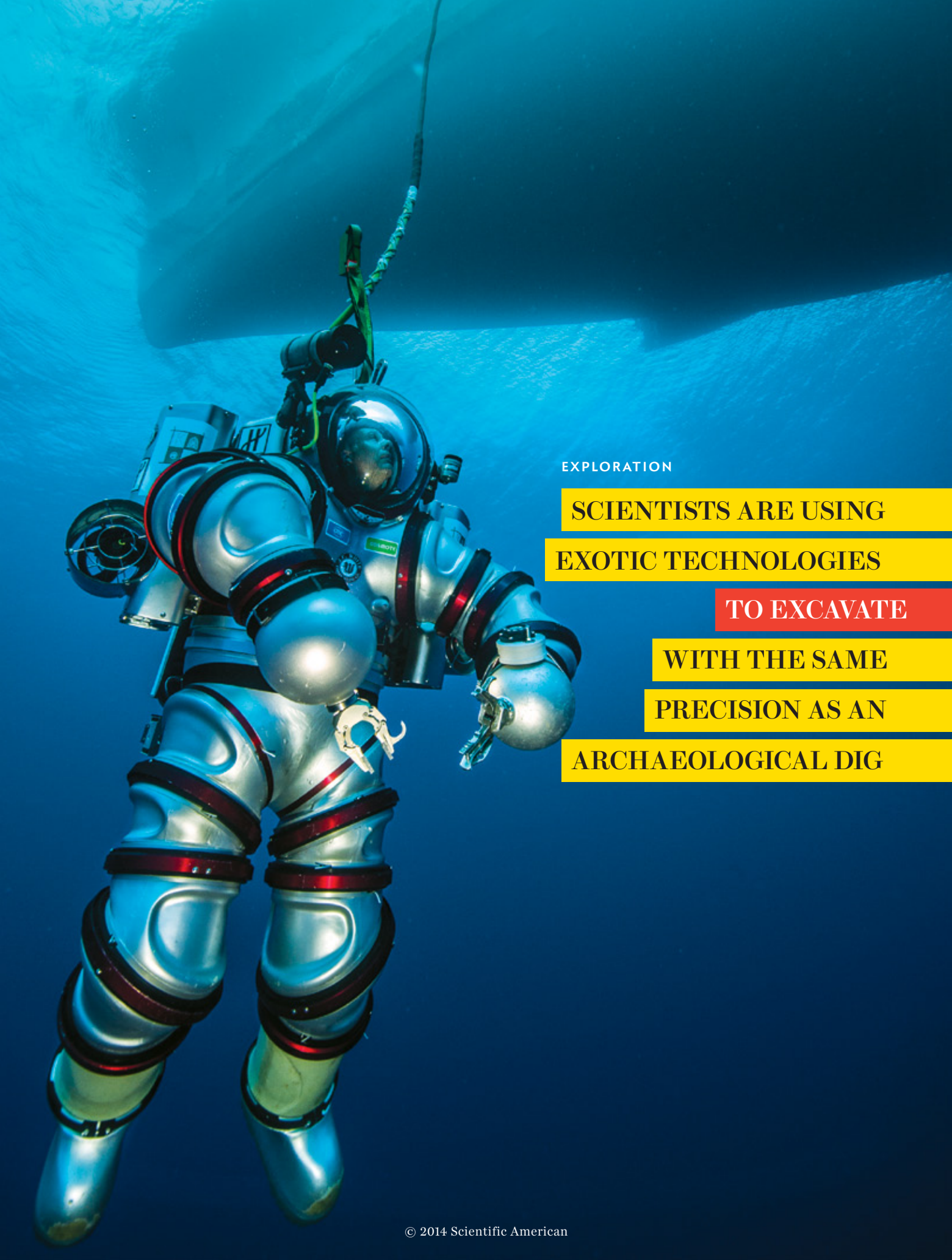
Farm-Scale Adaptation and Vulnerability to Environmental Stresses: Insights from Winegrowing in Northern California. Kimberly A. Nicholas and William H. Durham in *Global Environmental Change*, Vol. 22, No. 2, pages 483–494; 2012.

Climate Change, Wine, and Conservation. Lee Hannah et al. in *Proceedings of the National Academy of Sciences USA*, Vol. 110, No. 17, pages 6907–6912; April 23, 2013.

FROM OUR ARCHIVES

Saving Coffee. Hillary Rosner; October 2014.

scientificamerican.com/magazine/sa



EXPLORATION

SCIENTISTS ARE USING EXOTIC TECHNOLOGIES TO EXCAVATE WITH THE SAME PRECISION AS AN ARCHAEOLOGICAL DIG

EDWARD O'BRIEN becomes the first human to explore the ocean in an Exosuit, which maintains sea-level air pressure inside for many hours, down to 1,000 feet.

UNDERWATER SHIPWRECKS

In Search of Sunken Treasure

By Philip J. Hilts

Philip J. Hilts is a freelance science writer, author of six books, and a former prizewinning reporter for the *New York Times* and the *Washington Post*. He was director of the Knight Science Journalism program at the Massachusetts Institute of Technology from 2008 to 2014.

Two thousand years ago a storm drove a Roman ship against a sheer rock wall on the north side of the remote Greek island of Antikythera. The boat sank, along with tons of treasure: coins, gold jewelry, dozens of large marble and bronze statues, and an extraordinary, bronze clockwork device now counted as the first analog computer.

The wreck lay at the sea bottom, 165 feet down, untouched until 1900, when one day sponge divers came upon it. The divers were equipped with little more than a helmet and a long hose to the surface for air; they struggled just to reach the decayed vessel. One of them died, and two others were paralyzed.

The next expedition did not come until 1976. Jacques Cousteau and his crew explored the site using standard scuba gear. To leave time for the ascent, which had to be slow to avoid "the bends"—the fast expansion of nitrogen in the body that can destroy nerves and kill—the divers could stay on the bottom only for a few precious minutes during each dive.

Limited time on the seafloor evaporated last October during a new expedition to Antikythera. Explorer Phillip Short stepped off the stern of a borrowed boat, *Petros Iro,* wearing a computerized breathing system with multiple tanks called a closed-circuit rebreather. The gear cut down on the rate at which nitrogen builds up in the tissues, allowing him to prod the shipwreck for an hour and a half before turning back. The return ascent still had to be slow after such a long submersion; Short brought along a magazine so he could read at the planned stops upward. During two weeks of dives, Short and his fellow explorers uncovered all kinds of encrusted objects, from double-handled ceramic jars to a seven-foot-long bronze spear.

After Short and others had made several round-trips, Edward O'Brien of the Woods Hole Oceanographic Institution put an even more exotic technology to the test. Onboard a Greek navy ship, *Thetis,* he climbed inside a glistening, muscle-bound shell called the Exosuit, making him appear like something between Iron Man and Buzz Lightyear. At 10:40 on a sunny morning he was lowered from *Thetis* into the surf and descended to 200 feet, just adjacent to the wreck site. The suit maintains surface air pressure, allowing divers to stay submerged for many hours and to come right back up, without the need to stop … or read. "You don't have any sense of pressure or depth," O'Brien exclaimed after his exuberant return to the ship. "Fifty feet feels the same as 200 feet, except maybe it's darker at 200."

The equipment that Short and O'Brien used is emblematic of the powerful technologies that marine scientists now have at their disposal. They are quickly and cleverly adapting innovations from other professions to bolster their own capabilities. The Exosuit, for example, was designed for workers who have to tread through water and sewer tunnels that can be miles long, but now J. F. White Contracting has altered it for ocean archaeology.

As a result, many valuable sites that have been difficult to reach are now opening up to exploration, yielding finds in a matter of weeks that might have taken years not long ago. At Pavlopetri, Greece, for example, the site of the oldest submerged harbor town ever found, divers swimming just a few feet under the surface pushed a small optical mapper that took thousands of digital, three-dimensional photographs. Software stitched them together, revealing submerged houses, streets, trading centers and tombs that made up a full, shore-side town from 4,000 years ago. At excavations near the Egadi Islands off Sicily, where in 241 B.C. Roman and Carthaginian ships sank during the last battle of the first Punic War, sonar scanners pinpointed more than a

IN BRIEF

New technologies are allowing explorers to quickly find and map shipwreck sites and to excavate them with the precision used in archaeological digs.

At the Antikythera wreck off Greece, divers wearing rebreathers could stay at the 165-foot depth for up to 90 minutes instead of only eight minutes with regular scuba gear.

The metallic Exosuit allows divers to work underwater at surface air pressure, eliminating the slow ascents divers must make to avoid "the bends."

Technology perfected at two other Mediterranean dive sites—Pavlopetri and the Egadi Islands—is also making underwater exploration faster and less expensive, helping more adventurers to unearth ancient shipwrecks and submerged towns.

PAGE 68: COURTESY OF BRETT SEYMOUR *Woods Hole Oceanographic Institution;* PRECEDING PAGE: COURTESY OF BRETT SEYMOUR *ARGO*

THREE ANCIENT WRECK SITES have served as proving grounds for advanced gear that is making ocean archaeology much faster and more accurate. The Exosuit (*shown on pages 68 and 69*) was deployed in October 2014 at the Antikythera site.

dozen submerged wrecks. Robot submarines with strong, nimble pincers snared a variety of battle gear and raised it to the surface.

I spent more than a week with divers and expedition members at Antikythera, shuttling back and forth between the boats and the shore. On one evening Brendan Foley, the Woods Hole marine archaeologist who led the excursion, sat for an interview at a breezy cliffside storeroom above the docks. Behind him on a wall was a trophy of the first few days—a large printout of the first photomap ever made of the site. "We are at the beginning of a new era," he told me.

"We can cover more area, faster and more accurately. And remember," he continued, "shipwrecks are archaeological sites frozen in a moment of time. They are unlike land sites," which are constantly raided, rebuilt and ravaged in other ways. Bronze statues, for example, were routinely melted in bygone eras to make cannons, but on the ocean floor they can be found whole; most of the best ancient statuary in museums has come not from land but from the sea.

Because time stops on shipwrecks, objects untouched for thousands of years can provide great cultural and scientific insights into past societies. The chance of realizing that promise is greater now. "It used to be that in marine archaeology, working underwater was a problem," says Jon Henderson, an archaeologist at the University of Nottingham in England who co-led the Pavlopetri expedition. "It's no longer the problem. We've moved on."

AUTOMAPPING AT ANTIKYTHERA

THE NEW TECHNOLOGY is so empowering that it is launching grand new dreams. One of them is mapping entire regions of deep seafloor relatively quickly, using a small fleet of autonomous underwater robot vehicles. Foley, for one, would like to chart the entire Aegean Sea bottom between Crete and the Greek mainland. The area has been a busy maritime traffic corridor for 5,000 years, and sonar-toting robots should be able to readily see bounty on the bottom. In one experiment, Foley found, confirmed and videotaped 10 possible shipwrecks in just 10 days.

In the past, marine archaeologists have had to painstakingly map out a prospective site using hand tools: tape measures and wood frames with string to make grids that indicated where objects might lie and how they might relate to one another. Mapping or digging deeper than 100 feet quickly became problematic because divers could stay submerged for only a few minutes before having to ascend again.

At Antikythera, a team of engineers at the University of Sydney lowered a tandem of yellow torpedoes from the stern of a modest boat into the clear Aegean waters. The researchers then let the robot loose to find the bottom. Team leader Oscar Pizarro did not have to operate the autonomous, underwater vehicle, named Sirius, because it followed a preprogrammed mission on its own. Sirius glided 10 feet above the wreck site, making 40 parallel, overlapping runs—lawn-mower-like—firing strobe lights along the way to brighten the bottom for its stereo cameras. The vehicle knew its location to within three feet or so, thanks to a GPS signal, but it obtained far more precise location information for every rock, dip and protrusion by combining the data from each image with data about its own speed, depth and orientation. Each bit of information was used to make corrections and adjustments. If in one image there was a shadow behind a rock, for

Map by Laszlo Kubinyi

example, another image from another angle filled the shadow.

Although one three-hour session, followed by a few more hours of computer work, would have been enough to take the old wreck's full portrait, the team did two more passes for additional accuracy. The final, composite image contains 50,000 individual photographs, each accurate to tenths of an inch. And the image is three-dimensional, so it can be tilted and viewed from the side.

Team member Stefan Williams says that a survey of similar scope done elsewhere a few years ago took more than a month to complete. His group did it three times, in a single weekend.

BREATHE AND REBREATHE

ONCE THE MAPPING WAS FINISHED, divers could descend to specific spots, repeatedly if desired. The sponge divers who did reach bottom in 1900 spent barely three minutes there, although even that was enough to recover an ancient analog computer, now called the Antikythera mechanism. Deep diving is dangerous because the great water pressure compresses gases in human tissue to a mere fraction of their usual volume. The body's cells compensate by using air from tanks breathed in by divers to pack tissue and resist the pressure. That means the body must cope with a large volume of air, mostly nitrogen. The longer a person is underwater, the more the gases build up.

The biggest threat is that when divers start to ascend, the gases in the tissues can release and expand, like fizz from an opened soda bottle. It is essential that divers rise slowly so the gases escape slowly; if they emerge too fast, they can form bubbles in the blood that can block circulation in small blood vessels and cripple nerves and organs. Nitrogen is particularly troublesome.

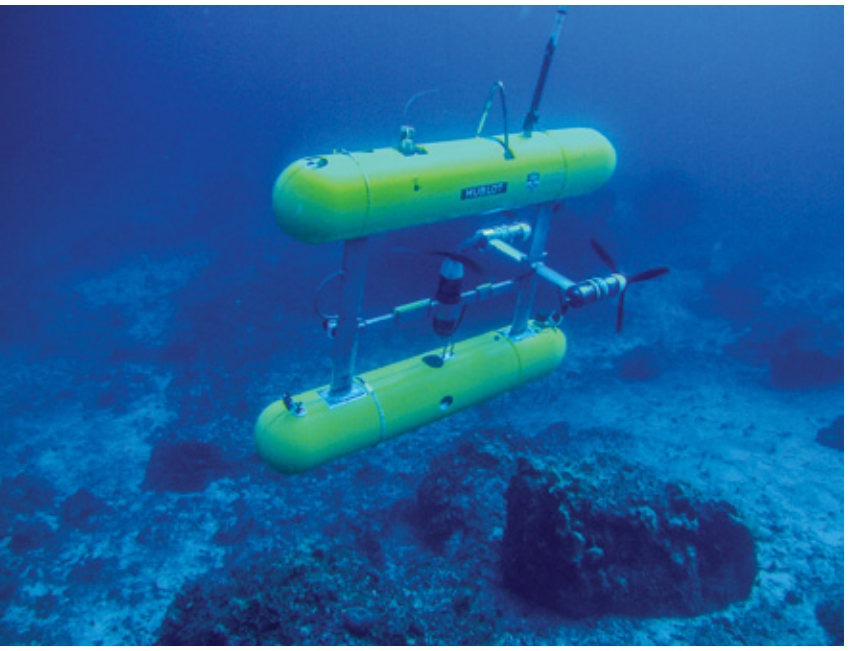
On the cramped dive boat, Short wrestled with about twice as much gear as he would on a regular scuba mission, twisting and turning to get all of it on his body. Instead of a simple metal bottle of air, as in standard scuba, the rebreather draws from two cylinders that Short pulled up onto his back, one containing oxygen and one a "trimix" cocktail of helium, oxygen and nitrogen. The rebreather takes the diver's exhalations, scrubs out the carbon dioxide, then injects oxygen to replace what the diver has used. Software monitors the oxygen level, in effect creating a custom mix of gases for all phases of the dive.

Each evening there was also an hour's work dismantling, cleaning and reassembling the high-tech equipment. "I admit to being completely OCD about this stuff. It's got to be just right," Short said, as he knelt beside the tanks and the wrist-mounted computer display that controls them. "When everything's working well, it's no problem. But you have to be alert and prepared for what to do when something goes wrong, say, with the electronics. That's what you need training for—possible emergencies."

SOTIRIOU'S SPEAR

LESS HIGH-TECH but very helpful during the early dives was an underwater metal detector. After 2,000 years, the wood parts of ships have largely dissolved, and most artifacts have been buried in sand and sediment, many of them "concreted"—encased in calcium carbonate and other minerals so they look like big, white rocks.

Just as on land, the wandlike detector sounds off with a whine when it finds a metallic object. In the first few days, the divers detected several strong signals and laid down stones painted yellow to identify the hotspots for later searches.



REBREATHER worn by Phillip Short (*red tank, above left*) reduces nitrogen buildup that can cripple divers, giving Short's team time to excavate a seven-foot-long bronze spear (*below left*). Autonomous vehicles (*above*) can precisely map large areas of seafloor quickly, guiding explorers to treasure.

After waiting out a few subsequent days of 30-mile-an-hour winds and eight-foot waves, diver Alex Sotiriou went back to the tagged areas and began to dig. Here is where the disadvantages of water turned to an advantage. Dry ground is often hard, demanding that land archaeologists slowly pick away at a site with shovels, trowels and finally brushes to unearth artifacts. But at sea the "ground" is soft and easily swept away by the pass of a diver's hand. Trenches can be dug with ease, and suction hoses can draw up silt and sand and dump it elsewhere. With a single swoosh of his glove, Sotiriou whisked away inches of silt. Another swipe, and the butt end of a bronze spear appeared. He kept fanning along the shaft and finally found the large, sharp tip. In all, the intact spear was seven feet long.

Archaeologists on the team think that the spear is too heavy to have been a weapon and that it was probably once in the grip of a great, bronze warrior statue still buried at the site. The divers also brought up a red terra-cotta jug about a foot and half high, probably used to serve wine. They found a bronze ring for tying up the ship's rigging, as well as two decorative rings from a Roman bed. The divers hauled up the smaller objects in handheld bags. For larger items such as the spear, they unpacked flat tubes they had carried down with them, inflated them with air from one of the breathing tanks and tied them on the objects, gently floating them up to the boat.

The most intriguing discoveries, however, were 600 feet away—far enough from the main wreck that the divers think they found a second ship, which might have been traveling with the first. There they uncovered a second anchor, a piece of lead pipe that might have been from the vessel's bilge pump, and a stack of jars that looked as if it had never been disturbed. Their shapes and markings indicated that they had come from four ports: Pergamon, Ephesus, Kos and Rhodes—the same four varieties that had been found on the main ship.

Excited when the origins were confirmed onshore, Theotokis Theodoulou, an expedition leader at the Greek Ephorate of Underwater Antiquities, declared that "this place still has many secrets. And we want to come back again and again to uncover them."

THE EXCELLENT EXOSUIT

PROGRESS ON THE NEXT TRIP, if it happens, could be quicker still, thanks to the most talked about new technology that was rolled out during the Antikythera dives: the Exosuit.

After two weeks of delays because of nasty winds, on October 7 O'Brien, inside his Exosuit, was swung off the deck of *Thetis* and lowered by cable into the surf. It was the first mission for the suit, built by Nuytco Research. "The first time in saltwater," exclaims Jim Clark of J. F. White Contracting, which owns the armor.

When O'Brien was in the water, operators detached the cable, and he dropped to the bottom 200 feet below, close to the wreck. There he put the suit through its paces. It has 18 flexible joints that allow natural movements of the arms, legs and torso. If needed, O'Brien could kneel down, lie prone on the ocean floor and contort into the many postures working divers find themselves in.

The real excitement came not from the suit's strength and nimbleness but from the fact that it keeps its human occupant at surface pressure all through a dive—no compressed gases in the body and no decompression sickness.

After coming back to the surface in mere minutes and climbing out of the suit on deck, O'Brien told me while standing at the boat's railing that the experience was completely unlike scuba diving. Officer Fotis Lazarou of the Greek navy piloted the suit down to 200 feet later the same day.

On land the suit, made of metal and synthetic materials, weighs more than 500 pounds, but it is light as a feather in the water, almost neutrally buoyant. It can keep a diver at surface air pressure down to 1,000 feet, greatly extending the depths at which humans can work without being trapped inside a submersible.

Archaeologists are already talking about using the Exosuit to search large areas of undisturbed sea bottom—below the depths that fishers trawl, about 300 feet. On future dives the suit will have a specially designed suction hose that will allow its human pilot to vacuum up sand and silt from a wreck for hours at a time. Researchers hope to use the Exosuit on a new mission this year to continue the Antikythera excavation.

PROTOTYPE AT PAVLOPETRI

EARLIER CAMPAIGNS set the stage for Antikythera. The precursor to the Sirius robot vehicle was actually developed for the Pavlopetri expedition, which was designed to survey unusual structures under 10 to 15 feet of water along a southern shore of Laconia, at the end of the Greek Peloponnesian peninsula. The ruins had been discovered in 1968 but had only been crudely mapped and partial-

OPPOSITE PAGE: COURTESY OF BRETT SEYMOUR *ARGO*; THIS PAGE: COURTESY OF PHILLIP SHORT *ARGO*

TIMELINE

Diving into Underwater Exploration

1531

DIVING BELL DEBUTS

Treasure hunters don crude diving bells to scour the bottom of a lake near Rome for two bejeweled ships built for Roman emperor Caligula. The barrel-shaped bell is worn over the neck and shoulders, trapping enough air for divers to search for up to an hour.

1620

FIRST SUBMARINE BUILT

A dozen men power the world's first submarine with oars protruding through holes in the sides of the vessel that are sealed with leather. Dutch inventor Cornelis Drebbel conducts trials in the Thames River for the king of England.

1691

BARRELS DELIVER OXYGEN

Englishman Edmond Halley, better known for Halley's Comet, extends the air supply for diving bells by sending down weighted barrels of oxygen as refills.

1715

SUIT SUFFERS FLAWS

Englishman John Lethbridge creates an early diving suit that looks like a horizontal barrel with armholes sealed with leather. He fails to reach great depths because of a difference in pressure between his torso and limbs.

1788

DIVING BELL GETS UPGRADE

American John Smeaton adds an air storage tank fitted with a hand pump that pulls air through a hose to the surface. A one-way valve prevents air from returning up the hose.

1864

STEEL LUNG INSPIRES SCUBA

Frenchmen Benoit Rouquayrol and Auguste Denayrouse patent the Aerophore, an early form of scuba. A diver inhales air from a tank through a membrane and valve. Air at the surface is pumped down a hose into the tank to refill it.

1870s

REBREATHER RECYCLES AIR

Englishman Henry Fleuss invents a rebreather, a closed-circuit system that supplies compressed oxygen to the diver while absorbing exhaled carbon dioxide, using a rope soaked in caustic potash.

ly excavated. In 2009 archaeologist Jon Henderson arrived for a detailed look.

Engineers mounted two high-resolution cameras on a boxlike frame, which divers pushed in overlapping paths above the submerged structures below. Software combined the thousands of pictures with information about the speed and position of the rig, creating an exact photomosaic of the bottom—all without strings and measuring tapes.

The photomosaic created the first real representation of what was on the bottom: an entire town with streets among 15 buildings, rooms filled with jars, and tombs, all covering more than two acres. Dating of objects that were excavated put the oldest part of the city of Pavlopetri at about 4,000 years ago. It was the first underwater settlement to be digitally mapped and then modeled in 3-D. Henderson brought in Simon Clarke, a computer animation expert who had worked on the *Harry Potter* movies, for the final touch—he created a video animation that used the survey data to re-create a walking and gliding tour through the town as it had once been.

CARNAGE FROM CARTHAGE

ANOTHER MARINE ARCHAEOLOGY EXPEDITION that pioneered new technology to achieve its goals involved a series of trips to the Egadi Islands from 2005 to 2013.

For years the ancient city of Carthage had controlled vital trade routes between Africa and what is now Italy. Its big, hand-rowed boats had defeated Rome's vessels again and again, mainly by bludgeoning the opposing hulls with a great bronze ram fixed to the bow. In 241 B.C. the Romans built their own ramming fleet for a counterattack. Some 200 Roman warships bore down on several hundred Carthaginian warships and cargo ships. Historian Polybius said the confrontation was "the most severely contested war in history." But he did not specify where it happened.

The Superintendent's Office of Underwater Archaeology in Sicily brought in Italian archaeologist Sebastiano Tusa and Jeffrey Royal of the RPM Nautical Foundation in Florida to search for the battlefield. Old documents hinted at a place just east of Levanzo Island, but the wreckage could have been strewn anywhere across 100 square miles of seafloor at depths down to 300 feet.

Tusa and Royal began their multiyear exploration with a research ship that sailed in a back-and-forth search pattern, fitted with an echo-sounding device on its hull. This "multibeam sonar" fired out 500 different pings at a time, at rates up to 40 pulses a second. By reflecting off the seafloor, the sound waves created a rough map of the huge area. Researchers analyzed echoes that seemed to indicate objects and could discern an array of wrecks, from modern airplanes to old ships. But the accuracy of any one location was relatively low.

After much analysis, the team returned with a more precise sonar imager, called a sector scanner. The scientists lowered it on a tripod to the bottom of a prospective site to get a closer and clearer sound image, producing ghostly shapes that were easier to identify. If the team deemed certain objects as important, it sent a remotely operated robotic submarine with cameras to locate it. Members onboard the ship saw what the robot was seeing through a video link. If they found an object, they would remotely manipulate mechanical arms on the robot, which had pincers

SCIENTIFIC AMERICAN ONLINE For a blog and photographs from the Antikythera expedition, go to ScientificAmerican.com/jan2015/hills

1900
NAVY BUILDS SUBMARINE
Irish immigrant John Holland constructs a modern submarine powered by gasoline and electricity for the U.S. Navy. His model, the *Holland,* quickly catches on, and similar vessels debut in navies worldwide during World War I.

1919
WAR SPURS SONAR
The British and French navies devise a sonar system to detect submarines. It is installed on destroyers over the next two decades.

1934
EXPLORERS SINK IN STEEL BALL
Two men inside a two-and-a-half-ton hollow steel ball called a bathysphere set a diving record of a half-mile deep. A steel cable from a mother ship lowers and lifts them, a second cable powers a telephone and lights, and a tube provides air.

1943
DIVERS BREATHE DEEPLY
The Aqua-Lung goes on sale, fashioned by explorer Jacques Cousteau and engineer Emile Gagnan. This scuba technology incorporates an automatic demand valve to supply fresh air to the diver with each breath. It remains the basic system that scuba divers use today.

1955
SEARCH FOR METALS FINDS PLATES
Scientists survey the seafloor using an underwater metal detector called a magnetometer, towed behind a ship. The surveys reveal a striped pattern of subsurface metals that date the sea bottom and provide evidence for the theory of plate tectonics.

1960
HUMANS REACH MAXIMUM DEPTH
The U.S. Navy's *Trieste,* a 6.5-foot-diameter bathyscaphe with a 50-foot tank of gasoline on top, reaches the deepest point in any ocean, the bottom of the Mariana Trench seven miles down—despite a cracked window.

1960s
SCIENTISTS DEPLOY ROBOTS
The U.S. Navy funds development of remotely operated vehicles: underwater robots that researchers on a ship above maneuver by remote control to collect data or virtually explore shipwrecks.

1970s
MACHINES GO IT ALONE
The University of Washington deploys an autonomous underwater vehicle to the Arctic. It is preprogrammed to gather data and complete tasks without a human operator. Progress with autonomous and remotely operated vehicles has brought 98 percent of the ocean floor within reach of scientists.

1980
VIDEO EMERGES FROM BELOW
Robert Ballard, discoverer of the RMS *Titanic,* creates an underwater camera that streams live video via optical fiber to the surface for scientists and educators to watch.

2014
DIVERS FIND NEW FLEXIBILITY
A team excavating a shipwreck in Greece tests the Exosuit, an armored suit that maintains sea-level pressure inside, allowing divers to reach depths of 1,000 feet for up to 40 hours.

—Amy Nordrum

at the ends, to try to pluck the relic from the muck and bring it to the surface—an unusual use of robots to fetch artifacts from ancient shipwrecks.

It was not until the very end of the search season in 2010, however, that Tusa and Royal came across what they were looking for: a wreck with a battering ram. Over the next three years they found eight more boats with rams, some Roman and some Carthaginian, and they retrieved all nine of the bronze batterers. The rams have markings that link them to the era of the naval battle. They also reveal a great deal about ocean warfare at the time: they were mounted on the bow of the oared ships, right at the water line, and they had three broad horizontal blades designed to cut through a boat's hull when they struck.

UNFREEZING TIME

THE CAPABILITIES of high-tech ocean archaeology are expanding quickly. Divers with rebreathers or Exosuits can sink to hundreds of feet and stay for hours. Robot vehicles piloted from ships or programmed to swim on their own can quickly cover not square yards but square miles, capturing digital imagery precise to fractions of an inch. In the future, explorers may operate entire underwater robotic stations that do not require expensive boats and crews. In his grandest dreams, Woods Hole's Foley imagines charting the bottom of the entire Mediterranean Sea and cataloguing thousands of wrecks that could provide keen insight into diverse cultures through the ages.

At a conference on marine archaeology in the fall of 2014, Royal also noted that the array of new technology makes exploration much cheaper and easier: scientists with a few thousand dollars could go to sites and return with 3-D images of striking objects. "More people can do this in more places," he said. "And because there is very little money available, it's the way marine archaeology has to go."

The entire history of seagoing humankind, frozen in time on the seafloor, has become accessible. As Foley noted to me on remote Antikythera before we departed, "98 percent of all the oceans depths are now in range for the first time." SA

MORE TO EXPLORE

Decoding the Heavens: A 2,000-Year-Old Computer—and the Century-Long Search to Discover Its Secrets. Jo Marchant. Da Capo Press, 2009.

Egadi Islands battleground mapping site: www.nottingham.ac.uk/news/pressreleases/2013/november/ancient-naval-battle-site-relics-of-war.aspx

Return to Antikythera expedition Web site, including videos and photographs: http://antikythera.whoi.edu

FROM OUR ARCHIVES

Decoding an Ancient Computer. Tony Freeth; December 2009.

scientificamerican.com/magazine/sa

NEUROSCIENCE

why we have free will

Neurons fire in your head before you become aware that you have made a decision. But this discovery does not mean you are a "biochemical puppet"

By Eddy Nahmias

One night last fall I lay awake wondering how I should begin this essay. I imagined a variety of ways I could write the first sentence and the next and the one after that. Then I thought about how I could tie those sentences to the following paragraph and the rest of the article. The pros and cons of each of those options circled back and forth in my head, keeping me from drifting off to sleep. As this was happening, neurons were buzzing away in my brain. Indeed, that neural activity explains *why* I imagined these options, and it explains why I am writing these very words. It also explains why I have free will.

Increasingly, neuroscientists, psychologists and pundits say that I am wrong. Invoking a number of widely cited neuroscientific studies, they claim that unconscious processes drove me to select the words I ultimately wrote. Their arguments suggest our conscious deliberation and decisions happen only after neural gears below the level of our conscious awareness have already determined what we will choose. And they conclude that because "our brains make us do it"—choosing for us one option over another—free will is nothing more than an illusion.

Illustration by Simon Prades

Eddy Nahmias is a professor in the department of philosophy and the Neuroscience Institute at Georgia State University.

The experiments most often cited to show that our brains take charge behind the scenes were carried out by the late Benjamin Libet in the 1980s at the University of California, San Francisco. There he instructed study participants outfitted with electrodes on their heads to flick their wrists whenever they felt like it. The electrodes detected fluctuations in electrical activity called readiness potentials that occurred about half a second before people made the flicking motion. But participants became aware of their intentions to move only about a quarter of a second before the movement, leading to the conclusion that their brains had decided before they became aware of what had happened. In essence, unconscious brain processes were in the driver's seat.

More recent studies using functional MRI have suggested the unconscious roots of our decisions begin even earlier. In research published in 2013, neuroscientist John-Dylan Haynes of the Bernstein Center for Computational Neuroscience Berlin and his colleagues had volunteers decide whether to add or subtract two numbers while in the fMRI scanner. They found patterns of neural activity that were predictive of whether subjects would choose to add or subtract that occurred four seconds before those subjects were aware of making the choice—a rather long lag time.

Indeed, both these studies—and others like them—have led to sweeping pronouncements that free will is dead. "Our decisions are predetermined unconsciously a long time before our consciousness kicks in," Haynes commented to *New Scientist,* while adding that "it seems that the brain is making the decision before the person." Others share his opinion. Evolutionary biologist Jerry Coyne has written: "So it is with all of our … choices: not one of them results from a free and conscious decision on our part. There is no freedom of choice, no free will." Neuroscientist Sam Harris has concluded from these findings that we are "biochemical puppets": "If we were to detect [people's] conscious choices on a brain scanner seconds before they were aware of them … this would directly challenge their status as conscious agents in control of their inner lives."

But does the research really show that all our conscious deliberation and planning is just a by-product of unconscious brain activity, having no effect on what we do later on? No, not at all. For many reasons, others, such as philosopher Alfred R. Mele of Florida State University, and I argue that people who insist free will is a mirage are misguided.

NOT SO FAST

I CALL THOSE who contend that science shows that free will is an illusion "willusionists." There are many reasons to be wary of the willusionists' arguments. First, neuroscience currently lacks the technical sophistication to determine whether neural activity underlying our imagining and evaluating of future options has any impact on which option we then carry out minutes, hours or days later. Instead the research discussed by willusionists fails to clearly define the border between conscious and unconscious actions.

Consider the Libet experiment. It began with study participants preparing consciously to make a series of repetitive and unplanned actions. When the experiment began, they flexed their wrists when a desire arose spontaneously. The neural activity involved in the conscious planning presumably influenced the later unconscious initiation of movements, revealing an interaction between conscious and unconscious brain activity.

Similarly, the Haynes study, in which people randomly picked whether to add or subtract over the course of many trials, fails to provide convincing evidence against free will. Early brain activity that occurred four seconds before participants were aware of making a choice may be an indication of unconscious biases toward one choice or the other.

But this early brain activity predicted a choice with an accuracy only 10 percent better than could be forecast with a coin flip. Brain activity cannot, in general, *settle* our choices four seconds before we act, because we can react to changes in our situation in less time than that. If we could not, we would all have died in car crashes by now! Unconscious neural activity, however, can prepare us to take an action by cuing us to consciously monitor our actions to let us adjust our behavior as it occurs.

Willusionists also point to psychological research showing that we have less conscious control over our actions than we think. It is true that we are often influenced unknowingly by subtle features of our environment and by emotional or cognitive biases. Until we understand them, we are not free to try to counteract them. This is one reason I think we have less free will than many people tend to believe. But there is a big difference between having less and none at all.

The Libet and Haynes research deals with choices that people make without conscious deliberation at the time of action. Everyone performs repetitive or habitual behaviors, sometimes quite sophisticated ones that do not require much thought because the behaviors have been learned. You put your key in the lock. A shortstop dives for a ground ball. A pianist becomes immersed in playing Beethoven's *Moonlight Sonata.*

The reflexive turning of the key, the lunging for the ball, or the depressing of the white and black keys requires a particular type

IN BRIEF

A major question in neuroscience, in philosophy and in broader public debate is whether the assumption that we have free will is fundamentally misconstrued. If it is, many legal and moral precepts that are the basis for our social institutions are subject to challenge.

Doubts exist because of sophisticated experiments in recent decades that have shown that the brain initiates at least some actions before we become consciously aware that a decision has been made. If this is so, what role, if any, does free will play?

People may have less free will than they think, but that does not mean they have none at all. A number of recent experiments by social psychologists have shown that conscious reasoning and intentions have a significant impact on our actions.

of mental processing. What I was doing on that sleepless night—conscious consideration of alternative options—is a wholly different activity from engaging in practiced routines. A body of psychological research shows that conscious, purposeful processing of our thoughts really does make a difference to what we do.

This work indicates that intentions we formulate to carry out specific tasks in particular circumstances—what psychologists call "implementation intentions"—increase the likelihood that we will complete the planned behavior. A study performed by psychologist Peter Gollwitzer of New York University and his colleagues revealed that dieters who consciously formed an intention to ignore thoughts about tempting foods whenever they came to mind then ate less of those foods than those dieters who simply set the goal to lose weight.

Psychologist Roy F. Baumeister of Florida State University and his colleagues have demonstrated that conscious reasoning improves performance on logical and linguistic tasks and that it helps in learning from past mistakes and overriding impulsive behaviors. In addition, psychologist Walter Mischel of Columbia University has found that our ability to willfully distract ourselves from a temptation is crucial for self-control.

Every one of us takes actions every day that we have consciously planned for ourselves. It is possible that the neural activity that carries out this planning has no effect on what we do or that it just concocts stories after the fact to explain to ourselves and others what we did. But that would make little evolutionary sense. The brain makes up only 2 percent of the human body's weight but consumes 20 percent of its energy. There would be strong evolutionary pressure against neural processes that enable intricate conscious thought yet are irrelevant to our behavior. The brain circuits responsible for my imagining that this is the best way to write this essay are likely causing it to turn out this way.

FREE WILL IN THE BRAIN?

WILLUSIONISTS, however, suggest this internalized brain processing simply cannot count as free will. They often say that people who believe in free will must be "dualists" who are convinced that the mind somehow exists as a nonphysical entity, separate from the brain. "Free will is the idea that we make choices and have thoughts independent of anything remotely resembling a physical process," wrote neuroscientist Read Montague in 2008. And Coyne has claimed that "true 'free will' … would require us to step outside of our brain's structure and modify how it works."

It is true that some people think of free will in this way. But there is no good reason to do so. Most philosophical theories develop a view of free will that is consistent with a scientific understanding of human nature. And despite willusionists' claims, studies suggest that most people accept that we can have free will even if our mental activity is carried out entirely by brain activity. If most people are not dualists about free will, then it is a mistake to tell them that free will is an illusion based on the scientific view that dualism is false.

One way to test people's assumptions about free will is to describe the possibility of brain-imaging technology that would allow perfect prediction of actions based on information about prior brain activity. In fact, Harris has suggested this scenario "would expose this feeling [of free will] for what it is: an *illusion*."

To see whether people's belief in free will would be challenged by the knowledge that the brain is engaged in unconscious information processing that predicts behavior, Jason Shepard of Emory University, Shane Reuter of Washington University in St. Louis and I recently performed a series of experiments in which we presented people with detailed scenarios describing futuristic brain-imaging technology, as posited by Harris.

Hundreds of students at Georgia State University participated in the studies. They read about a woman named Jill who, in the distant future, wore a brain-imaging cap for a month. Using information from the brain scanner, neuroscientists predicted everything she thought and did, even when she tried to fool the system. The scenario concluded that "these experiments confirm that all human mental activity just *is* brain activity such that everything that any human thinks or does could be predicted ahead of time based on their earlier brain activity."

More than 80 percent of the participants reported that they believed that such future technology was possible, yet 87 percent of them responded that Jill still had free will. They were also asked whether the existence of such technology would indicate that individuals lack free will. Roughly 75 percent disagreed. Further results showed that a significant majority felt that as long as the technology did not allow people's brains to be manipulated and controlled by others, they would have free will and be morally responsible for their behavior.

Most participants in the experiments seem to think that the hypothetical brain scanner is just recording the brain activity that is Jill's conscious reasoning and consideration about what to decide. Rather than taking this to mean that Jill's brain is making her do something—and that she has no free will—they may just be thinking that the brain scanner is simply detecting how free will works in the brain.

Why, then, do willusionists believe the opposite? It may have to do with the current state of knowledge. Until neuroscience is able to explain consciousness—which will require a theory to explain how our minds are neither reducible to, nor distinct from, the workings of our brain—it is tempting to think, as the willusionists seem to, that if the brain does it all, there is nothing left for the conscious mind to do.

As neuroscience advances and imaging technology improves, these developments should help reveal more precisely how much conscious control we have and to what extent our actions are governed by processes beyond our control. Finding resolutions for these questions about free will is important. Our legal system—and the moral basis for many of our society's institutions—requires a better understanding of when people are—and are not—responsible for what they do. SA

MORE TO EXPLORE

Do Conscious Thoughts Cause Behavior? Roy F. Baumeister, E. J. Masciampo and Kathleen D. Vohs in *Annual Review of Psychology*, Vol. 62, pages 331–361; January 2011.

Predicting Free Choices for Abstract Intentions. Chun Siong Soon et al. in *Proceedings of the National Academy of Sciences USA*, Vol. 110, No. 15, pages 6217–6222; April 9, 2013.

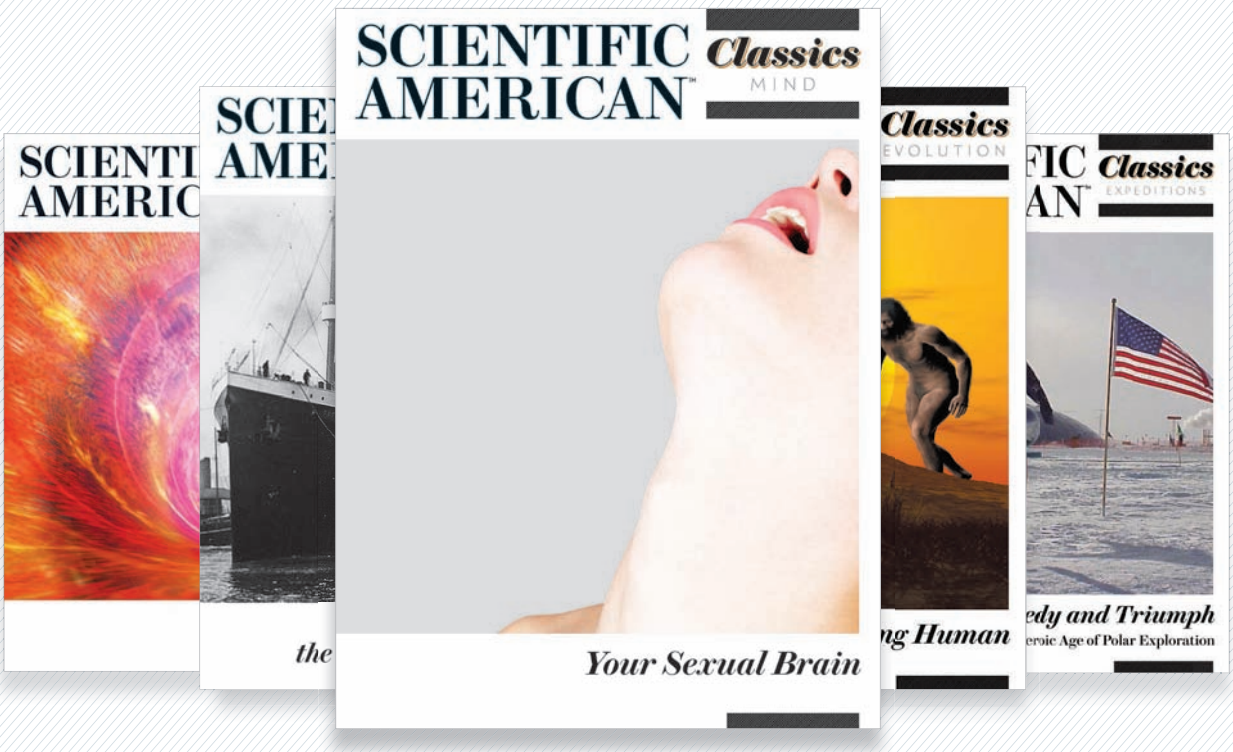
It's OK If "My Brain Made Me Do It": People's Intuitions about Free Will and Neuroscientific Prediction. Eddy Nahmias, Jason Shepard and Shane Reuter in *Cognition*, Vol. 133, No. 2, pages 502–516; November 2014.

FROM OUR ARCHIVES

Thought Experiments. Joshua Knobe; November 2011.

SCIENTIFIC AMERICAN™ *Classics*

Discover the Future through Our Past.

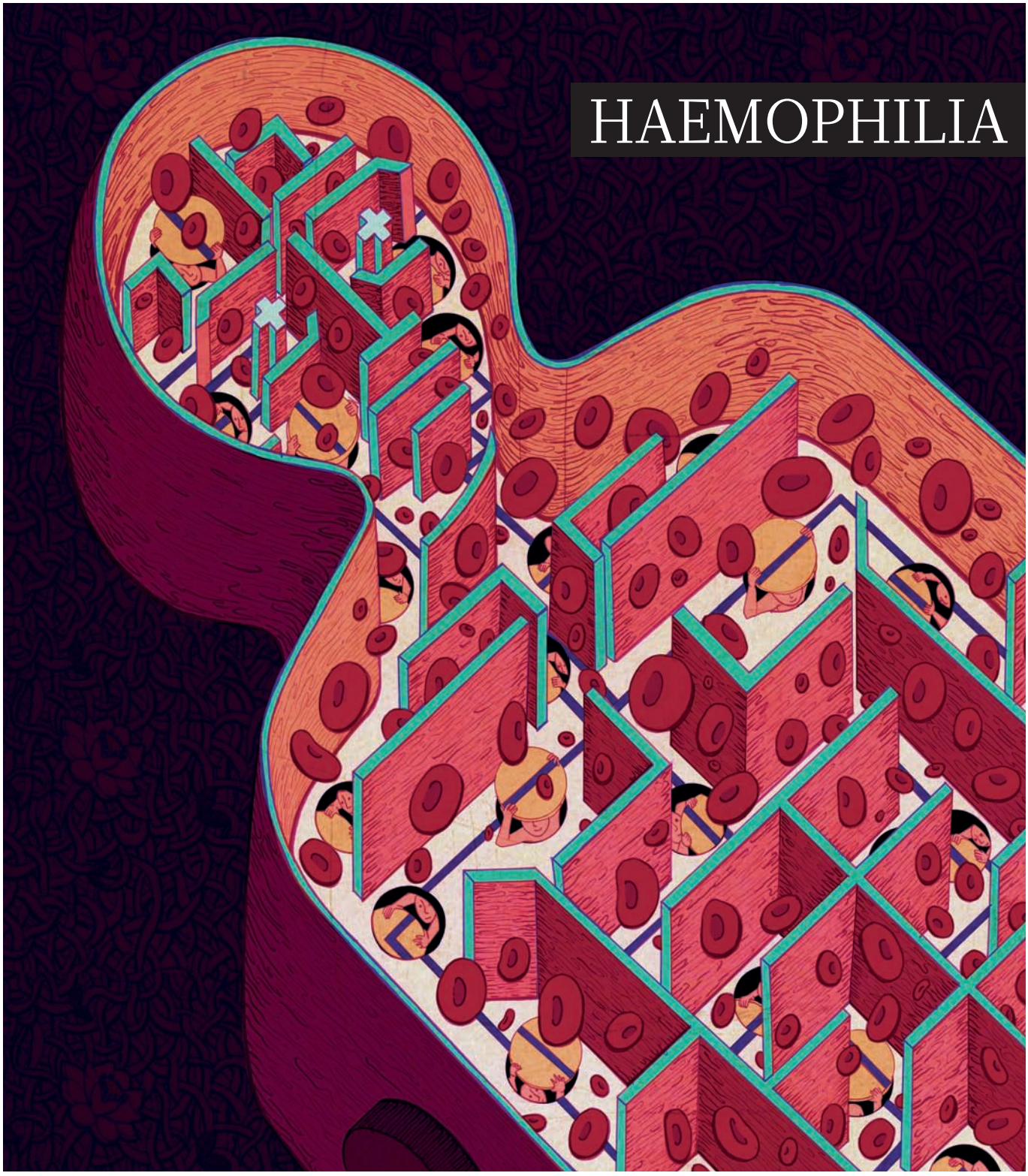


SCIENTIFIC AMERICAN Classics are single-topic anthologies compiled from SCIENTIFIC AMERICAN's 169 years of extensive historical archives as 70+ page PDFs.
New Classics are priced at $9.99 per issue

Learn more at ScientificAmerican.com/Classics and start your collection today.

Collection includes: A New Look at Human Evolution, The Hidden Mind, Birth of Flight, Reality-Bending Black Holes, Tragedy and Triumph, Your Sexual Brain, The Titanic and Age of the Transatlantic Steamship

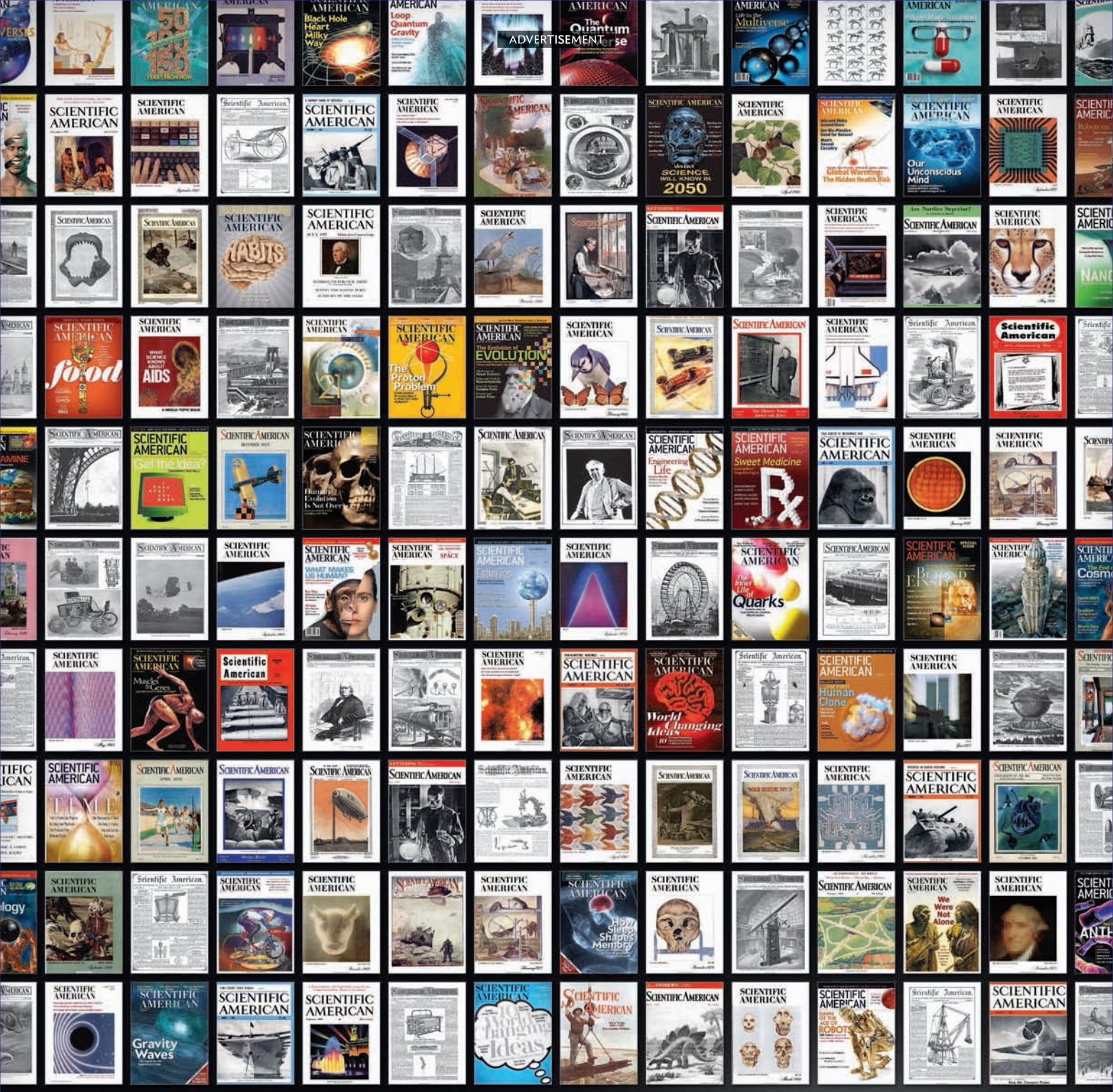
nature OUTLOOK
in association with SCIENTIFIC AMERICAN™



HAEMOPHILIA

Editorially independent report produced with support from Baxter Healthcare Corporation

A flow of ideas to stop the bleeding



What issue are you looking for?

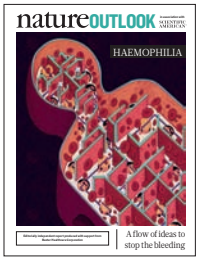
We discovered a lot in our long history. Now our award-winning Archives are available for purchase in digital format. Browse and download any single issue from any year—1845 to the present.

www.scientificamerican.com/archives

SCIENTIFIC AMERICAN™ | THE ARCHIVES

nature OUTLOOK

HAEMOPHILIA



Cover art: Jessica Fortner

In any complex machine, the lack of a single part can lead to big trouble. That is the problem faced by the 170,000 people globally who have the bleeding disorder known as haemophilia. A genetic mutation (usually inherited) suppresses the production of proteins that make blood coagulate (see page S4). Internal bleeding into the joints causes bone degradation and excruciating pain (S16), and even mild injuries can be life-threatening.

The standard therapy is frequent infusions with blood-clotting promoters. These treatments are uncomfortable and expensive, so it is welcome news that several longer-lasting clotting factors have been developed (S8). Many people develop an immune resistance to these infused factors, but relief may be on the way in the form of anti-inhibitory pills made from plants (S12). Development of these pills depends on colonies of haemophilic dogs that serve as cooperative test subjects (S18).

Clotting-factor infusions treat symptoms of haemophilia, but gene therapy could provide a cure (S6). Research is also moving ahead on an alternative treatment strategy to remove or disable the body's anticoagulants (S14) rather than adding clotting factors.

The haemophilia community is still haunted by the traumas of blood supplies that were contaminated with HIV and hepatitis C. These experiences have led to reluctance to accept the good news that may soon be on offer, says medical historian Stephen Pemberton (S11).

This Outlook, which is being published in *Scientific American* and *Nature,* is sponsored by Baxter Healthcare Corporation. It was produced independently by editors of *Nature,* who have sole responsibility for all editorial content. Beyond the choice to sponsor the particular topic of haemophilia, Baxter Healthcare Corporation had no input into the editorial content of this package.

Herb Brody
Supplements Editor

CONTENTS

Nature Outlooks are sponsored supplements that aim to stimulate interest and debate around a subject of interest to the sponsor, while satisfying the editorial values of *Nature* and our readers' expectations. The boundaries of sponsor involvement are clearly delineated in the Nature Outlook Editorial guidelines available at go.nature.com/e4dwzw.

CITING THE OUTLOOK
Cite as a supplement to *Nature*, for example, Nature **Vol. XXX**, No. XXXX Suppl., Sxx–Sxx (2014).

VISIT THE OUTLOOK ONLINE
The *Nature Outlook Haemophilia* supplement can be found at http://www.nature.com/nature/outlook/haemophilia
The website features all newly commissioned content as well as a selection of relevant previously published material.

All featured articles will be freely available for 6 months.

SUBSCRIPTIONS AND CUSTOMER SERVICES
For UK/Europe (excluding Japan): Nature Publishing Group, Subscriptions, Brunel Road, Basingstoke, Hants, RG21 6XS, UK. Tel: +44 (0) 1256 329242. Subscriptions and customer services for Americas — including Canada, Latin America and the Caribbean: Nature Publishing Group, 75 Varick St, 9th floor, New York, NY 10013-1917, USA. Tel: +1 866 363 7860 (US/Canada) or +1 212 726 9223 (outside US/Canada). Japan/China/Korea: Nature Publishing Group — Asia-Pacific, Chiyoda Building 5-6th Floor, 2-37 Ichigaya Tamachi, Shinjuku-ku, Tokyo, 162-0843, Japan. Tel: +81 3 3267 8751.

CUSTOMER SERVICES
Feedback@nature.com

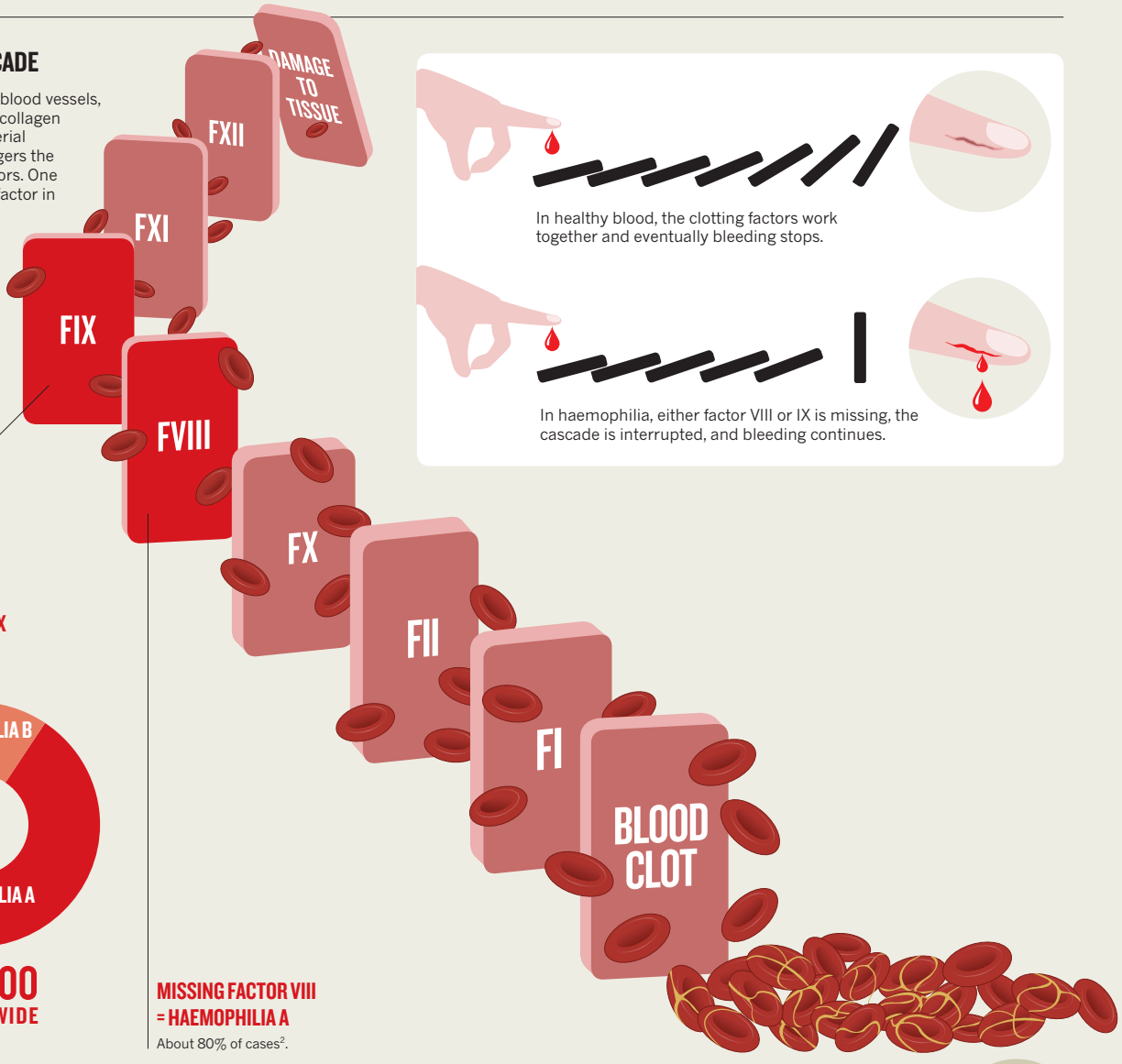
This special report first appeared in *Nature* [27 November 2014 | Vol. 515 | Issue No. 7528]. Internal references may vary from original version.

BORN IN THE BLOOD

People with the inherited bleeding disorder haemophilia lack factors that cause the blood to clot. The disease affects thousands of people around the world and has even played a part in historic events. By **Neil Savage**.

COAGULATION CASCADE

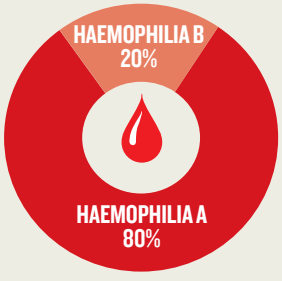
When damage occurs to blood vessels, exposure of the blood to collagen in the cell walls and material released by the cells triggers the activation of clotting factors. One factor activates the next factor in a series of events (some not depicted here) that eventually produces fibrin. Fibrin forms a mesh to hold together a plug of platelets to form a clot (platelets are a type of cell that circulates in the blood to help coagulation)[1].



In healthy blood, the clotting factors work together and eventually bleeding stops.

In haemophilia, either factor VIII or IX is missing, the cascade is interrupted, and bleeding continues.

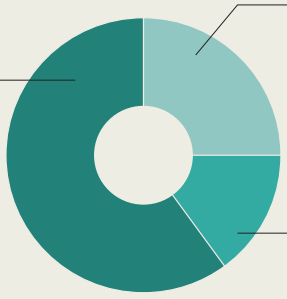
MISSING FACTOR IX = HAEMOPHILIA B
About 20% of cases[2].



AT LEAST 172,000 PEOPLE WORLDWIDE HAVE HAEMOPHILIA

MISSING FACTOR VIII = HAEMOPHILIA A
About 80% of cases[2].

OF ALL THE PEOPLE WITH HAEMOPHILIA...



60%
Have severe haemophilia (clotting factor in the blood is less than 1% of the level in normal, healthy people)[3]
Bleeding after injury, spontaneous bleeding, risk of joint damage. Median age at diagnosis is one month.

25%
Have mild haemophilia (clotting factor levels of 6–30%)[3]
Bleeding only after serious injury, accidents or surgery. Heavy menstrual bleeding in women. Median age at diagnosis is 36 months, though it is often not diagnosed until after a serious injury.

15%
Have moderate haemophilia (clotting factor levels of 1–5%)[3]
Bleeding after injury, some spontaneous bleeding, risk of joint damage. Median age at diagnosis is eight months.

TREATMENT TIMELINE

About two-thirds of the world's population lacks access to prophylaxis with clotting factors because the cost of treatment is too high.

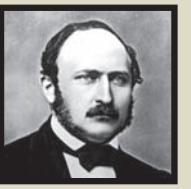
1840

1840s
First blood transfusions for bleeding episodes.

THE ROYAL DISEASE

Queen Victoria became a carrier of haemophilia through what is believed to have been a spontaneous genetic mutation[4].

Queen Victoria
1819–1901



Prince Albert
1819-1861

Victoria passed it on to one son, who died of bleeding, and two daughters.

Victoria

Edward VII

Alice
1843–1878

Alfred

Helena

Louise

Arthur

Ludvig IV

Leopold
1853–1884

Beatrice
1857–1944

Haemophilia spread throughout European royalty, including Victoria's great-grandson, Alexei Romanov, son of the last Russian tsar, Nicholas II.

The 'mad monk' Rasputin claimed to be able to treat Alexei's haemophilia, and his influence with the tsar's family is credited with contributing to the Russian revolution.

In 2009, DNA tests on Alexei's remains showed that Victoria carried haemophilia B.

Alexandra
1872–1918

Alexei
1904–1918

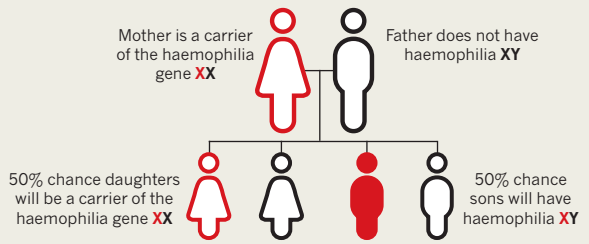
Nicholas II of Russia

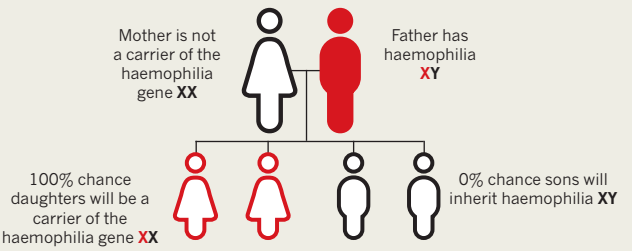
HULTON/GETTY; THE PRINT COLLECTOR/GETTY; IMAGEPAST/ALAMY; FINE ART IMAGES/HERITAGE IMAGES/GETTY; HERITAGE IMAGE PARTNERSHIP LTD/ALAMY

INHERITANCE PATTERN

The mutations causing haemophilia are carried on the X chromosome. Woman are usually carriers, with a 50% chance of having sons with haemophilia or daughters who are carriers. Men with haemophilia will have no sons who are haemophiliacs, but all their daughters will carry the gene. In rare cases, female carriers or girls with both X chromosomes affected will have haemophilia; fewer than 10% of cases occur in females. Approximately one-third of cases arise from spontaneous mutation[5].

Does not have haemophilia
Carrier of haemophilia gene
Has haemophilia





An estimated 40,000 haemophiliacs worldwide were infected with HIV, including 70–90% of those with severe haemophilia[6].

40,000 HIV

The cost of prophylaxis treatment could reach $300,000 per child per year[7].

$300,000

1900

1923 First use of plasma replacement therapy

1950s–1960 Fresh frozen plasma requires large volume transfusions

Mid-1960s Cryoprecipitate (a concentrate of blood components made from frozen plasma) allows smaller transfusions

1970 Freeze-dried clotting factors allow home-based prophylaxis

1970s–early 1980s Haemophiliacs contract hepatitis and HIV from blood products

1987 Heat-treated factor VIII reduces risk of blood-born pathogens

1989 Genetically engineered factor VIII, no risk of HIV or hepatitis

2000

1997 Genetically engineered factor IX

2014 First extended-life clotting factors approved

Future Gene therapy

References: 1. Pipe, S. W. (Ed.) The Hemophilia Report (2014) available at: www.hemophiliareport.com 2. 2012 World Hemophilia Foundation Survey, covering 91% of the world's population; 3. US National Hemophilia Foundation 4. Rogaev, E. I. *et al. Science* **326,** 817 (2009). 5. US Centers for Disease Control and Prevention 6. Starr, D. *Blood: An Epic History of Medicine and Commerce*, p346, Harper Perennial (2000). 7. Manco-Johnson, M. A. *et al. N. Engl J. Med.* **357,** 535–544 (2007).

JESSICA FORTNER

GENE THERAPY

Genie in a vector

Repairing the faulty genes that cause haemophilia could ultimately cure the disease, but it will be a tough challenge.

BY JULIE GOULD

Martin never learned to ride a bike, could not play football with his friends and wore a crash helmet when playing in the garden, just in case he bumped his head. His parents had good reason to be protective: his severe haemophilia B meant that the gentlest touch could lead to a serious, debilitating bleed. "It's very frustrating, growing up with haemophilia," says Martin. "You want to be like the other kids, but you can't."

As a result of an inherited genetic mutation, people with haemophilia B lack a protein called factor IX that is crucial for forming blood clots (see page S4). Currently, patients are treated several times a week with infusions of a concentrated version of the protein. This stops the bleeding, but it does not address the underlying cause of the disease nor does it fully remove its debilitating symptoms.

A few years ago, Martin had to stop his work as a truck driver. "I was letting the company down because I couldn't make it into work," he says. "The bleeding into my joints had made it very painful for me to move." In 2011, after 37 years of pain and joint degeneration caused by internal bleeding, Martin signed up for a clinical trial of a gene-therapy treatment at the Royal Free Hospital in London, hoping that it would provide some relief.

Rather than infusing functional clotting factors, the therapy aims to get the body to create its own. DNA with a functional factor IX gene was bundled into the molecular wrapper of a virus — known as AAV8 — then shuttled into liver cells, where factor IX is normally made.

Of the six patients who enrolled, four were able to discontinue their infusion treatments after the therapy[1]. Martin was one of them: his factor IX levels increased significantly, taking him out of the severe haemophiliac range and into the moderate group. His clotting factor levels have remained stable ever since.

The success was a crucial stepping stone for Edward Tuddenham, emeritus professor of haemophilia at University College London, who led the clinical trial. He wants to find a treatment not just for haemophilia B but for the much more common haemophilia A — but that is turning out to be a challenge.

FREEDOM OF EXPRESSION

The viral vehicle AAV8 is ideal for treating haemophilia B, but it works less well for haemophilia A. This is because the DNA encoding the clotting factor that is missing in the latter — factor VIII — is about six times larger than for factor IX, so it doesn't fit into AAV8. To make it fit, researchers often cut 4,500 base pairs out of the factor VIII gene sequence. The section they delete encodes a specific region of the protein — called the B-domain — that ensures efficient secretion of factor VIII. In its place, Tuddenham and his colleagues tried inserting a DNA sequence that is one-fiftieth of the size, but has the same function. But in a 2010 study of haemophiliac mice, these B-domain-modified treatments did not increase the level of factor VIII expressed in the blood[2]. Since then, Tuddenham has not only been trying to fix the gene but also to improve its expression.

The rate at which the factor VIII gene produces its protein is affected in part by the placement of the triplets of DNA bases — codons — that dictate where translation of the genetic material into protein should start and stop. The start and stop codons in the DNA sequence of a normal mouse or human factor VIII gene, did not promote vigorous protein production. "So we replaced them with better ones," says Tuddenham. When that was done, expression levels in a mouse model of haemophilia went from about 2% of that found in healthy mice to about 2,000%. The increase produced by the codon optimization was "enormous, truly stunning", he says.

In 2015, Tuddenham and his team hope to lead trials to test safety

➲ NATURE.COM
Meet people living with haemophilia in our film:
go.nature.com/dzyned

DAVID A. WILCOX & PAQUITA NURDEN

and efficacy of their optimized factor VIII gene therapy for people with haemophilia A. The number of people in the trials is likely to be between 10 and 20, but even if the factor is expressed effectively in humans, there are still hurdles to overcome.

DELIVERY ON A PLATELET

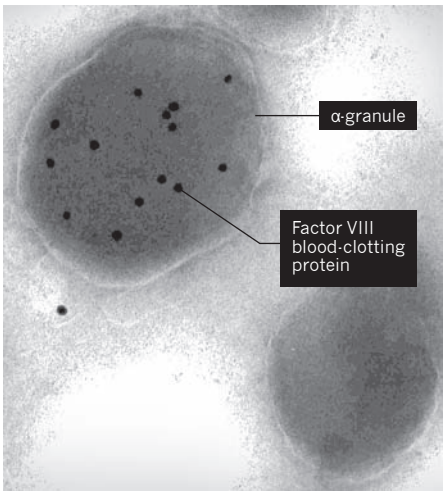
One hurdle is that AAV8 can be administered only once, because the virus triggers a strong immune response. "After one treatment with AAV8, you can't ever have a repeat dose. You are immunized against it," says Tuddenham. So although gene therapy could be a one-off cure, if the immune response is triggered before the therapy reaches the target, it is useless.

David Wilcox at the Children's Hospital of Wisconsin Research Institute in Milwaukee, hopes to get around this problem by using the body's own cells to deliver factor VIII. He is developing a way to insert functional factor VIII into structures called α-granules, which are found inside blood cells called platelets (see image, right). Platelets are the first cells to arrive at a wound site, where they rapidly begin to help form blood clots by releasing chemical messengers. Wilcox is working on modifying platelets to also release functioning factor VIII. "This removes the problem of having AAVs and factor VIII proteins floating around the rest of the body," says Wilcox, "thus avoiding any immune reactions."

"We've still got a lot to learn about gene editing in large animals before we even think about trying it in adult humans."

First, however, Wilcox has to harvest blood stem cells from the patient. He uses growth factors to coax stem cells in the bone marrow out into peripheral blood vessels, where they can easily be collected. The stem cells, which make up 2–5% of the peripheral blood sample, are then separated out in a procedure called peripheral blood stem cell apheresis and undergo gene therapy so that they contain the working factor VIII. The patient then has chemotherapy to partially suppress their existing bone-marrow stem cells before receiving a transfusion of the engineered stem cells into the blood. These cells find their way back to the bone marrow, where they will eventually produce platelets that contain functioning factor VIII.

In 2013, Wilcox tested the procedure on three dogs with severe haemophilia A, using a human factor VIII gene — and two of the dogs no longer require the usual treatment with infused factor VIII[3]. As predicted, none of the dogs showed signs of developing antibodies to the human factor VIII proteins — when the dogs received a cut, blood clots formed faster than they had without the gene therapy. "We think that the factor VIII is secreted from the platelets so quickly at the trauma site that the immune system does not have time to react before the factor VIII can start repairing the vascular injury," says Wilcox. Like Tuddenham, Wilcox's team hopes to start clinical trials inext year.



Researchers are modifying platelets to release factor VIII from α-granules at the site of injury.

But even if platelets can offer an alternative delivery vehicle, it could be an unpleasant one for patients. "I think they have a viable approach for patients with antibodies to AAVs or those affected by HIV and hepatitis," says Tuddenham, "but the doses of chemotherapy treatment before the stem-cell transplant aren't a walk in the park".

CORRECTING IN PLACE

So far, gene-therapy trials have focused on adults with the disease, but haemophilia is an inherited disease, affecting a person from birth. Unfortunately, the technique is not a viable option for children. If a child's liver were to be infused with factor VIII genes introduced through AAV, there would be an initial increase in the levels of clotting factor in the blood, as with the adults in Tuddenham's 2011 trial. But as the child grows, the expression levels would decrease when new liver cells are produced without the functioning factor VIII gene are produced, says haematologist Katherine High, at the Children's Hospital of Philadelphia in Pennsylvania.

In theory, Wilcox's method might work in children because the functional clotting-factor genes have been integrated into the stem cell's genome and will be passed on to daughter cells. In practice, however, no responsible physician would expose an infant or child with a non-lethal disease such as haemophilia to chemotherapy.

A promising way to avoid these problems is *in vivo* genome editing, in which mutant genes are corrected *in situ* rather than replaced. This could potentially work at any age — but the earlier in life such a treatment is available, the better, as the benefit would be lifelong.

Conceptually, this approach is as simple as setting up a biological tool to cut out the mutated area of the genome, then another to insert a corrected template, says Merlin Crossley of the University of New South Wales, Sydney, Australia. Crossley sees gene-editing therapies as the best potential tool for curing haemophilia.

This could be particularly beneficial for children: as the liver grows, the new daughter cells would contain the functioning clotting-factor gene. The clotting factor would then be recognized as part of the body, and could ultimately eliminate the child's haemophilia. "The replacement template is cloned from healthy patients and wouldn't be attacked by the immune system because it isn't considered as foreign," Crossley says.

A 2011 study in mice[4] by High provided strong evidence that genome editing is a viable option. Immediately after birth, one set of mice was given Tuddenham's style of gene-transfer therapy; a second set was given the genome-editing treatment. High discovered that the levels of functioning clotting proteins in mice receiving the genome-editing treatment stayed high even after a portion of their liver was surgically removed; in the mice receiving gene therapy, by contrast, factor levels decreased. "This is the advantage of this treatment, especially for children," says High.

Genome editing has to be precisely targeted to the mutation to be repaired, and the sheer number of mutations for haemophilia A — more than 2,000 — makes this a challenge.

Both High and Tuddenham believe that in the short term, genome editing is not the answer. "The gap between proof-of-principle experiments in mice to clinical trials in humans for gene-transfer therapy was 14 years," says High. "And we've still got a lot to learn about gene editing in large animals before we even think about trying it in adult humans, let alone infants."

Having his haemophilia reduced to a moderate level has improved Martin's quality of life tremendously. He has needed the standard infusion treatment fewer than ten times since the gene therapy, and says that "only one of those occasions was a serious bleed". He says that signing up for the trial was not an easy decision, because there were not any other similar trials on which to base his decision. But he believes that his successful experience should help to encourage people to participte in future studies. "You go from a position of knowing what you are, how you are and how to deal with it, to a position of complete uncertainty," he says. "So I hope that the uncertainty is reduced for other patients when they hear about our experiences." ■

Julie Gould *is the editor of Naturejobs.*

1. Nathwani, A. C. *et al. N. Engl. J. Med.* **365,** 2357–65 (2011).
2. McIntosh J. *et al. Blood.* **117,** 798–807 (2011).
3. Du, L. M. *et al. Nature Comm.* 4, 2773 (2013).
4. Li, H. *et al. Nature* **475,** 217–21 (2011).

WORLD FEDERATION OF HEMOPHILIA

Boys with haemophilia receive a blood-clotting factor by intravenous injection (also referred to as an infusion).

CLOTTING FACTORS

Stretching time

Extending the life of clotting factors may improve quality of life for people with haemophilia.

BY NEIL SAVAGE

For the parents of a child born with haemophilia, the diagnosis comes with both good and bad news. The good news is that the child, at least if he (or rarely, she) is born in the developed world, can expect a near-normal lifespan, up from a mere 20 years in 1970. The bad is that the parents must teach themselves to find their child's veins, insert a needle and infuse him with a clotting factor to replace what he lacks. Parents must infuse a toddler as often as every other day, and children with haemophilia will have to continue that treatment for the rest of their lives.

But treatment is getting easier. Down the road, gene therapy and other approaches look likely to bring longer-term treatments for patients with the rare bleeding disorder. For now, improvement in treatment lies in the emergence of new, longer-lasting replacements for the blood-clotting factors missing from the blood of people with the condition. These therapies could stretch the time between infusions to days or even weeks. The first two such treatments were approved by the US Food and Drug Administration (FDA) earlier this year, and more are in the pipeline, with some expected to be approved in 2015. As these therapies emerge, dealing with haemophilia will become less troublesome (see 'Drugs to help the blood'). This could increase compliance with treatment, reduce complications — and perhaps even allow some people to live almost as if they were free of the disease.

Replacing the clotting ability lacking in haemophilia has been the treatment since the 1840s, when attempts were made to treat people with the disease by transfusion with whole blood from people with normal clotting. By the end of the 1960s, freeze-dried concentrates of clotting factors were available for home use, to prevent spontaneous bleeding. In the 1990s, treatment leapt forward again, with donated plasma being replaced by clotting factors manufactured through recombinant DNA-technology, eliminating the transmission of viral diseases that had devastated the haemophiliac community in the 1970s and 1980s.

But prophylactic treatment still has its problems. The clotting factors do not last very long in the body. Depending on the person, the amount of factor VIII — the protein missing in haemophilia A — in the bloodstream drops by half in a mere 8–12 hours. Factor IX — which people with haemophilia B lack — lasts longer, 18–24 hours. Those short half-lives mean that most people with haemophilia must transfuse themselves every two or three days. And inserting a needle directly into a vein can be difficult. "Adherence to therapy is not great, because you have to inject yourself, and it's a hassle," says David Lillicrap, a professor of pathology and molecular medicine at Queen's University in Kingston, Ontario, Canada.

One 2001 study suggested that up to 40% of

people with severe haemophilia do not follow the prophylactic schedule[1]. Those people are more likely to develop spontaneous bleeding that causes joints to fill with blood and results in progressive damage similar to arthritis. They can also develop intracranial bleeding, which can cause brain damage and even death.

Drug companies have responded with clotting factors that last longer, making the time between infusions greater. Biogen Idec, based in Cambridge, Massachusetts, has two such factors approved by the FDA this year. Eloctate, for haemophilia A, was approved in June and is recommended for an initial infusion once every four days, with a physician adjusting that up to five days or down to three as appropriate. Alprolix, the company's treatment for haemophilia B approved in March, promises infusions once a week, and perhaps every ten days or two weeks in some patients. Other versions of the clotting factors from other drug developers are showing similar extensions of lifetimes.

"It's a big improvement," says Timothy Nichols, a cardiologist and pathologist who studies haemophilia at the University of North Carolina at Chapel Hill. "It's not *no* treatment, but it is a lot easier than sticking a needle in your kid three times a week."

Steven Pipe, a paediatric haematologist at the University of Michigan's C. S. Mott Children's Hospital in Ann Arbor, agrees that the progress is significant. In particular, work that is stretching the lifetime of factor IX by three to five times is "really transformative", he says. And because half-lives can vary between patients, "at high doses, you could probably in some individual cases get a month's worth of factor IX," Pipe says.

BORROWED TIME

The trick to extending the half-lives of clotting factors is to interfere with the body's natural mechanisms for flushing them away. There are three very similar approaches, each of which extends half-life by about the same amount for the respective clotting factors. The only real difference is between factor IX, for which the techniques are offering extensions long enough to make a substantial difference in treatment, and factor VIII, for which the improvement has been more modest. Unfortunately, haemophilia A, which is caused by factor VIII deficiency, is about four times as common as haemophilia B.

Two of the techniques piggyback on the half-lives of other longer-lived proteins that occur naturally in the body. One such is immunoglobulin, a large Y-shaped protein with a half-life of about three weeks. The stem of the Y is known as the Fc region. When a clotting protein is fused to an Fc region, the body treats the clotting factor more like an immunoglobulin, and allows it to stick around for longer, although not for as long as a complete immunoglobulin molecule.

DRUGS TO HELP THE BLOOD

A number of treatments to aid blood clotting are in clinical trials or have been approved this year.

	Product	Approach	Company	Half-life (hours)	Status
Factor VIII infusions (for haemophilia A) Conventional infusion half-life: 8-12 hours	Eloctate	Fc fusion protein	Biogen Idec	20	FDA approved in June 2014
	BAX 855	PEGylation	Baxter International	19	Submission for approval planned for late 2014
	BAY94-9027	PEGylation	Bayer	19	Submission for approval planned for mid-2015
	N8-GP	PEGylation	Novo Nordisk	19	Submission for approval planned for 2018
Factor IX infusions (for haemophilia B) Conventional infusion half-life: 18–24 hours	rIX-FP	Albumin fusion	CSL Behring	92	In clinical trials
	N9-GP	PEGylation	Novo Nordisk	110	Submission for approval planned for 2015
	Alprolix	Fc fusion protein	Biogen Idec	87	FDA approved in March 2014

FDA, US Food and Drug Administration.

For factor VIII, Fc fusion extends the half-life from a maximum of about 12 hours to about 18 hours. Factor IX, which has a longer half-life to begin with, shows a more dramatic increase, from one day to five days.

Both the approved Biogen drugs are based on Fc fusion. Similar fusion drugs have been on the market to treat other diseases for many years, for example the rheumatoid arthritis drug Etanercept, which was approved by the FDA in 1998. Jerry Powell, the retired director of the Hemophilia Treatment Center at the University of California, Davis, says that the success of those drugs suggests that this is a safe approach to altering the clotting factors.

Coagulation factor IX, used to treat haemophilia B.

BIOGEN IDEC

A similar approach, which is being pursued by CSL Behring, based in King of Prussia, Pennsylvania, is to fuse the clotting factors with albumin. Albumin is a major protein of blood plasma and, like immunoglobulin, has a half-life of about 20 days. Phase I safety studies of factor IX fused to albumin showed a fivefold increase in half-life, up to about four days. Unfortunately, attempts to do the same with factor VIII have been unsuccessful. Powell says that the albumin seems somehow to interfere with the normal activity of that clotting factor.

"These are really big molecules," he says. The activity of factor VIII in action, he adds, is so complex that it resembles a dancing elephant — too easily thrown off its rhythm when something else is attached. "If you put the wrong kind of contraption on the elephant, it doesn't dance as well."

The third strategy takes a slightly different approach. Instead of marrying the clotting proteins to a natural substance in the body, they are attached to synthetic polyethylene glycol (PEG) molecules (see 'PEGylation protection'). The PEG forms a sort of 'watery cloud' around the protein, protecting it from various mechanisms that would break it down; for instance, PEG prevents the clotting factors from binding to protein-specific receptors that would normally clear them away. PEG is eventually flushed from the body through the kidneys and liver, but before then it gives the clotting factors a new lease of life. Three large drug companies — Bayer in Leverkusen, Germany, Baxter International in Deerfield, Illinois, and the Danish company Novo Nordisk in Bagsvaerd — have all developed PEGylated factor VIII with a half-life of roughly 19 hours. Baxter expects to submit its product for regulatory approval by the end of this year, Bayer next year, and Novo Nordisk by 2018.

Novo Nordisk is also testing a PEGylated factor IX that has shown a half-life of 110 hours in clinical studies. The company says that it hopes to submit that drug for approval next year.

Up to now, tests have not shown much difference, in safety or effectiveness, between the three approaches. There are concerns that PEG might accumulate in the liver or kidneys over years of use, but studies of PEG have found it to have very low toxicity, and Powell thinks that those fears are exaggerated[2]. "PEG's been around a long time, there's a lot of toxicology and all the toxicology indicates no concern," Powell says. And if, as he expects, gene therapy replaces these treatments in the next decade, patients will in any case not have lifetime exposure to PEG.

One barrier to haemophilia therapy is the tendency of factor VIII to prompt the body into producing anti-factor VIII antibodies,

known as inhibitors. For a person with haemophilia A, factor VIII is a foreign substance, and the immune system can see it as a threat. About 30% of people with haemophilia A develop inhibitors, and once they do, treating their bleeding becomes much more difficult. Only about 4% of people with haemophilia B develop inhibitors to factor IX.

There is a lot of worry, Pipe says, that altering factor VIII to extend its half-life could make the inhibitor problem worse. "Everyone treads lightly in the factor VIII field, because there is such a fear of immunogenicity with any change of the molecule," he says. "There's no question with the current strategies that all of them have sort of hit a ceiling. If we're really going to overcome that ceiling, you are going to have to accept more dramatic changes to the molecule."

PEG may prove helpful in that regard. Studies dating back to the 1970s have shown that PEGylation can reduce the chances of a foreign protein stimulating an immune reaction, although the effect has not yet been proved in people with haemophilia. "That'd be a huge breakthrough if that were true," Powell says.

CONSTANT CASCADE

One researcher might have worked out a way to avoid the inhibitor issue almost entirely, by developing a different molecule to take the place of factor VIII in the clotting cascade.

Normally, once activated by previous steps in the cascade, factor VIII grabs hold of both factor IX and factor X, bringing them together to perform the next steps in the cascade. Midori Shima, director of the Hemophilia Center at Nara Medical University in Japan, has created a 'bispecific' antibody to do the same job.

Antibodies are immunoglobulins, and the upper arms of these Y-shaped proteins are designed to bind specifically to another molecule. Shima has created an antibody with one arm that binds to factor IX and the other to factor X, pulling the two together so that the clotting cascade can continue. The bispecific antibody has a half-life of about 30 days, much longer than the 12-hour upper limit of factor VIII, Shima says. Chugai Pharmaceuticals, based in Tokyo, and Hoffman-La Roche, based in Basel, Switzerland, are working on developing his findings into a treatment.

The researchers have not yet released the results of their phase II initial clinical trials, but Shima says that in the patients with haemophilia they looked at, bleeding frequency decreased dramatically. Among six people receiving the lowest dose of the treatment, who had each had 20–60 episodes of bleeding in the 12 weeks before the trial, two had no bleeding episodes at all during the 12 weeks of the trial. And out of 64 patients, only one developed an inhibitor. The team is planning a larger, phase III trial.

One bonus of this treatment is that because of the nature of the antibody, it does not have to be delivered intravenously, but instead can be injected under the skin, like insulin. "We think we can change the whole concept of haemophilia treatment," Shima says.

Lillicrap agrees. "That bispecific antibody would be hugely disruptive if it works," he says. "We'll know within the next couple of years whether it delivers on the promise which so far it's shown."

Treatments with extended half-lives may provide benefits beyond the convenience of less-frequent infusions and the potential increase in the number of people who stick to their treatment regime. If people under treatment now keep to their current schedule with the extended-life products instead of taking fewer infusions, the increased concentration of clotting factors in their blood could improve their quality of life even further.

"It is a lot easier than sticking a needle in your kid three times a week."

When patients have an infusion of clotting factor every 48 hours, the concentration of clotting factor initially reaches 100% of normal levels and stays there for about 12 hours. For the next 36 hours, it is high enough to be useful, but below normal. For the last 6 to 8 hours, the level is very low, less than 5%, Pipe says. Physicians try to keep the lowest level, the trough, from falling below 1% of the amount a non-haemophiliac person has circulating in their blood, enough to prevent spontaneous bleeding.

But if the trough level can be higher, it might make life easier for the patients, allowing them to, for instance, take up athletics with less fear of injury. "Ideally, you'd like to have zero bleeding," Pipe says. "What is the threshold for that I don't think anybody knows." Still, there would be substantial benefit from a less-than-perfect level of clotting factor. "If you could maintain a level of 10% or 15%, you would probably eliminate all joint disease," he says.

Lillicrap hopes that the emergence of several therapies means that it will make economic sense for drug companies to provide treatments to poorer parts of the world that have not been able to afford them. "No longer are people thinking about these therapies being only Western European and North American therapies," he says. If pharmaceutical companies are pouring money into this research, he thinks that it is at least in part because they can see a worldwide profit benefit.

For all the advantages of these extended-life molecules, the researchers predict that they will be supplanted in perhaps a decade by advances in gene therapy, which will enable people with haemophilia to produce their own clotting factors. But in the meantime, trading current therapies for longer-lasting ones can improve patients' lives. "As a bridging therapy between the really good outcomes we have currently and maybe a cure down the line," says Pipe, "I think the extended-half-life molecules are a perfect transition." ■

PEGylation protection

A key advance in haemophilia treatment is to prolong the effectiveness of the injected coagulation-promoting proteins (clotting factors) by shielding them from destruction.

BEFORE

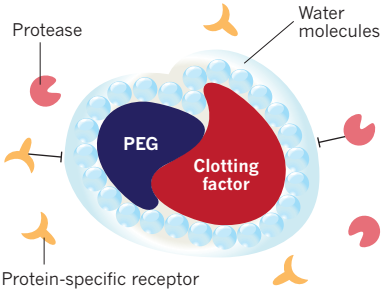
Unprotected molecule

Under normal circumstances, proteases and protein-specific receptors break up the clotting factor and rapidly clear it from the bloodstream.

AFTER

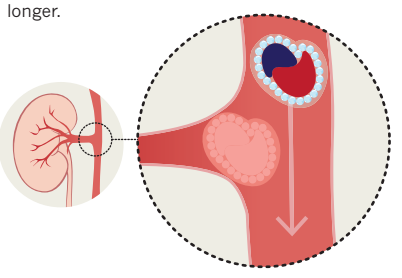
Microscopic shield

In PEGylation, molecules of polyethylene glycol (PEG) are attached to the clotting factor. The PEG molecules bring with them water molecules, which shield the clotting factor from attack.



Too big to discard

The watery cloud makes the factors too big for the kidneys' filtration mechanism, so the molecule circulates in the bloodstream for longer.



Neil Savage *is a freelance writer based in Lowell, Massachusetts.*

1. Hacker, M. R., Geraghty, S. & Manco-Johnson, M. *Haemophilia* **7,** 392–396 (2001).
2. Webster, R. *et al. Drug Metab. Dispos.* **35,** 9–16 (2007).

PERSPECTIVE


HEATHER VAN UXEM LEWIS

The fix is in

History explains why people with haemophilia, and their physicians, are cautious to believe that a cure is in sight, says **Stephen Pemberton**.

In 2011, a remarkable study[1] in the *New England Journal of Medicine* detailed the successful treatment of six adults with haemophilia B, which is caused by a deficiency in the coagulation protein known as factor IX. All of the participants were able to eliminate or reduce the frequency of clotting-factor-replacement injections — the current standard treatment for the disease — after their livers began producing functional levels of factor IX. The experimental therapy came in the form of an adeno-associated virus (AAV) carrying a gene that encodes instructions for production of normal levels of human factor IX. Three trials of AAV-mediated gene transfer in patients with haemophilia B are ongoing, with high expectations.

After more than 20 years of research on gene transfer, it is a promising time for haemophilia therapies. It now seems likely that a single-dose treatment for haemophilia B using an AAV or another gene-transfer technique will be a viable option for many people in the next decade or two.

Yet haemophilia researchers are not inclined to speak enthusiastically of a cure. Part of that caution comes from recognition that there are still problems to solve. For example, some 40% of people with haemophilia B would find no refuge in an AAV treatment because they produce antibodies that attack and neutralize this virus[2].

And even if that problem were solved, the treatment would apply only to those with haemophilia B. The more common form of the condition, haemophilia A, stems from a deficit in another protein — factor VIII — and the gene for that protein is a more difficult target. Regardless of the type of haemophilia, researchers remain hesitant about gene therapy owing to the unresolved ethical issues that arose decades ago.

RESEARCHERS ARE HESITANT ABOUT GENE THERAPY OWING TO THE UNRESOLVED ETHICAL ISSUES.

The unfettered optimism that characterized the early years of gene-therapy research came to a screeching halt in 1999, when 18-year-old Jesse Gelsinger died in a phase I clinical trial at the University of Pennsylvania in Philadelphia. Gelsinger had undergone an experimental gene transfer for his otherwise treatable metabolic disorder. His death, along with a series of other harmful events in early gene-therapy trials for a variety of diseases, threatened the whole field.

Haemophilia specialists who were engaged in gene-transfer studies were more guarded than most of that era's self-proclaimed gene doctors[3]. The source of their reserve goes beyond the cautious optimism that characterized such research after 1999; it is grounded instead in the long and troubled experience that the haemophilia community has had with technological fixes.

By the late 1970s, a therapeutic revolution had transformed haemophilia from an obscure hereditary malady into a manageable disease[4]. But the glory of this achievement was tragically short-lived. The same clotting-factor-replacement therapies that delivered a degree of normality to the lives of people with haemophilia brought unexpected and fatal results: tens of thousands of people with haemophilia were diagnosed with transfusion-related HIV/AIDS in the 1980s and with hepatitis C virus (HCV) in the 1990s.

The memory of tainted transfusions still haunts those who have, or work with, haemophilia. Add Gelsinger's death into the mix and it is clear why specialists are debating thorny ethical problems, such as when to try out AAV-mediated gene transfer on children. Gene therapy is not even the most promising treatment for haemophilia on the immediate horizon. The biotechnology industry is producing recombinant-clotting-factor products for both haemophilia A and B that can limit bleeding episodes with less-frequent injections (see page S8).

But the lure of a less-intrusive form of treatment raises a historical spectre of its own. It was this same desire for convenience that led many haemophilia physicians and patients in the United States in the 1980s to continue using clotting-factor concentrates that had a high risk of HIV contamination rather than switch back to older, more cumbersome but less risky forms of plasma-replacement therapy. Thousands of people with haemophilia contracted HIV and HCV because of this acculturated preference[4].

Finally, there is the difficulty of making costly treatments available to the vast majority of the world's haemophilia patients who live in low income countries. About 75% of people with haemophilia still receive inadequate treatment, particularly in less-developed nations where clotting-factor therapy is limited[5]. An effective gene therapy could well offer these underserved patients their first chance at effective intervention[6].

History suggests that the fix will not lie in just one solution, but will be contextual and messy. The wants and needs of people with haemophilia in the developed world might not be the same as for those in low income countries. Yet social justice demands that there be equity in access to treatment. The transfusion scandals of the past remind us of the importance of bringing together patients and treatment professionals with stakeholders from industry and public health to weigh the various technological fixes. If such discussions had taken place in the 1970s and 1980s about the known problem of transfusion-related hepatitis B, the haemophilia community would not have been blind-sided by the emergence of HIV and HCV. ■

Stephen Pemberton *is a medical historian at the New Jersey Institute of Technology in Newark, and author of* The Bleeding Disease: Hemophilia and the Unintended Consequences of Medical Progress.
e-mail: stephen.pemberton@njit.edu

1. Nathwani, A. C. *et al. N. Engl. J. Med.* **365,** 2357–2365 (2011).
2. High, K. H., Nathwani, A., Spencer, T. & Lillicrap, D. *Haemophilia* **20** (Suppl. 4), 43–49 (2014).
3. Wailoo, K. & Pemberton, S. *The Troubled Dream of Genetic Medicine: Ethnicity and Innovation in Tay-Sachs, Cystic Fibrosis, and Sickle Cell Disease* (Johns Hopkins Univ. Press, 2006).
4. Pemberton, S. *The Bleeding Disease: Hemophilia and the Unintended Consequences of Medical Progress* (Johns Hopkins Univ. Press, 2011).
5. Mannucci, P. M. *Haemophilia* **17** (Suppl. 3), 1–24 (2011).
6. High, K. A. & Skinner, M. W. *Mol. Ther.* **19,** 1749–1750 (2011).

KWANG-CHUL KWON, JIN SU & HENRY DANIELL, UNIV. PENNSYLVANIA

Blood-clotting factors produced by these lettuce plants could eliminate the problem of immune rejection.

IMMUNOLOGY

Oral solutions

Pills made from lettuce leaves could help to prevent one of the most serious complications of haemophilia treatment.

BY ELIE DOLGIN

The food in Anita's bowl is not your average dog chow. Although the dish contains pellets and wet food, there is also a sprinkling of green powder — the product of a trailblazing experiment to address a potentially lethal complication of haemophilia treatment. Anita, so named because her red coat reminded breeders of the character from the animated film *One Hundred and One Dalmatians*, is a keagle (a mix of a beagle and a Cairn terrier) with haemophilia B.

Like people with this rare genetic disorder, Anita is naturally deficient in factor IX, a protein that helps the blood to form clots. When treated with replacement coagulation proteins, the dog naturally develops antibodies, or inhibitors, against the therapy — a problem that is also seen in some 5% of humans with haemophilia B. In these people, the immune system identifies the therapeutic protein as dangerous, causing the body to stop accepting the protein as a normal part of the blood, and destroys it before it can stop the bleeding. Continuing to take factor-replacement therapies can result in life-threatening allergic reactions, such as anaphylaxis.

The problem is even worse with haemophilia A, a disease that is four times more common than haemophilia B and in which the missing link in the coagulation chain is a protein called factor VIII. Around 30% of people with haemophilia A develop antibodies against replacement factor VIII.

Therapies are available to eliminate these antibodies. Some people, for example, undergo an intensive treatment called immune tolerance induction therapy, which involves regular intravenous administration of coagulation factors. But this is time consuming and costly (around US$1 million for an average five-year-old patient), and the treatment works in only about three-quarters of patients. "The challenges of treating haemophilia with inhibitors are just staggering," says Timothy Nichols, director of the Francis Owen Blood Research Laboratory at the University of North Carolina at Chapel Hill, which maintains the colony of haemophiliac dogs to which Anita belongs (see page S18).

Inducing immune tolerance in people who have developed inhibitors is one approach. But avoiding the problem altogether would be even better. "If you can prevent antibody formation in the first place, by finding some way of producing immunological tolerance that gets around that type of protocol, that would be a major advantage," says David Lillicrap, a clinician and researcher who specializes in bleeding disorders at Queen's University in Kingston, Ontario, Canada.

The green powder in Anita's dish might do just that. The oral treatment is a concentrate of freeze-dried lettuce-leaf cells, each containing around 10,000 chloroplasts — the organelles responsible for photosynthesis — that have been genetically engineered to produce factor IX. These proteins cannot themselves be used to prevent bleeding episodes, because the cellular machinery found in plants cannot package the human clotting factors into the biologically active form. What they can do, however, is prevent the immune system from mounting an attack against subsequent therapy.

The researchers behind the bioengineered lettuce have shown that inhibitor formation and severe allergic reactions can be prevented in mice by feeding the animals with a product based on these plants[1,2]. If the strategy also works in Anita and her kennel mates — and ultimately in humans — it could form the basis of the first product to protect against the immune responses associated with haemophilia treatment.

Anita is one of only two dogs to have received the bioengineered lettuce. "So far, it's going very well," says lead researcher Henry Daniell, director of translational research at the University of Pennsylvania School of Dental Medicine in Philadelphia.

AN ACT OF TOLERANCE

In 2006, Lillicrap demonstrated that a simple oral treatment could train the immune system not to produce inhibitors. Working with a mouse model of haemophilia A, he and his colleagues gave the mice a purified fragment of the human factor VIII protein, through the nose or mouth. The researchers found that the treatment afforded some protection against antibody development after factor VIII replacement therapy[3]. But the approach did not deliver sufficient amounts of the factor to immune cells in the gut or nasal passage to fully quash inhibitor formation.

Daniell came up with an improved delivery system. He focused first on haemophilia B. Adapting a technique[4] that he had previously developed to delay the onset of type 1 diabetes, Daniell and his group genetically modified tobacco plants to express human factor IX in their chloroplasts. (Daniell has since switched to using lettuce.)

Chloroplast DNA is separate from the genome DNA in the plant nucleus, and the large numbers of these tiny organelles in the

cell allow huge volumes of the coagulation protein to accumulate in each tobacco leaf. Once ingested, the plant cell wall protects the coagulation protein from being destroyed by stomach acid. Gut microorganisms farther down the digestive tract then chew away at the cell wall, releasing the clotting-factor protein.

To target the proteins to the immune system, Daniell then attached a second protein that has high binding affinity for a receptor found on the inside of the human gut. With this fused construct tethered to the intestinal wall, the coagulation protein could be absorbed into the body and processed by the specialized cells in the immune system that induce tolerance.

Working with Roland Herzog, a molecular biologist at the University of Florida in Gainesville, Daniell then tested the plant-based product in animal models. In 2010, they showed that oral delivery of factor IX expressed in chloroplasts in this way led to almost undetectable inhibitor levels in mice, and no sign of anaphylactic shock[1]. "The mice are healthy, they show no allergic responses and they don't form the inhibitors," Herzog says. "That's pretty exciting."

Daniell then modified the tobacco leaves to express factor VIII and shipped powders of the leaves to Herzog. Earlier this year, the two researchers and their teams documented[2] suppression of inhibitor formation and even reversal of pre-existing inhibitors in mouse models of haemophilia A.

INHIBITORY CONTROL

Other strategies being pursued to prevent the formation of inhibitors of clotting-factor therapy include immunosuppressants and drugs that deplete specific immune cells. However, these therapies have many side effects, including increased susceptibility to infection.

A potentially safer option comes from Selecta Biosciences, a company in Watertown, Massachusetts. Selecta has developed a nanoparticle delivery system in which an immune-modifying compound is contained in biodegradable plastic particles just 150 nanometres across. When injected together with factor VIII into mouse models of haemophilia A, the nanoparticles deliver their payload to cells in the lymphoid tissue that are responsible for initiating immune responses. These cells, in turn, instruct factor-VIII–specific immune cells to become tolerant to the coagulation protein, resulting in suppression of misdirected antibody responses to the replacement therapy — all without affecting the rest of the immune system.

David Scott and his colleagues at the Uniformed Services University of the Health Sciences in Bethesda, Maryland, teamed up with Selecta to show that inhibitors remained undetectable for at least six months after treatment with the nanoparticle formulation[5]. "This underscores the point that we're actually teaching the immune system to become tolerant to factor VIII," says Selecta's chief scientific officer, Takashi Kei Kishimoto.

The nanotechnology approach that is being tested for inhibitor control could also improve the haemophilia treatment that is now at the cutting edge of clinical research: gene therapy. Using the standard gene-therapy approach, researchers have shown that they can achieve long-term expression of factor IX in adults with haemophilia B at sufficiently high levels to convert the bleeding disorder into a mild disease (see page S6). There has so far been no reported evidence of inhibitor formation in the small number of human participants in clinical trials for this viral therapy[6].

KWANG-CHUL KWON, JIN SU & HENRY DANIELL, UNIV. PENNSYLVANIA

Green power: from leaf to powder to capsule.

Still, the standard form of liver-targeted gene therapy carries a range of potential complications, including the risk of harmful mutations and of the body mounting an immune response against the viral vectors used to carry the correct forms of the defective genes responsible for haemophilia. That is why several research groups are attempting to replace viral vectors with nanoparticles that can deliver gene therapies as 'DNA pills'.

PILL PROTECTION

DNA pills combine DNA plasmids — circular pieces of bacterial DNA containing the gene encoding either factor VIII or factor IX — with nanoparticles made of chitosan, a tough polymeric carbohydrate found in the exoskeleton of crustaceans. Chitosan protects the therapeutic gene product and chaperones it through the gut. "The oral route has significant appeal," says Gonzalo Hortelano, a gene-therapy researcher at McMaster University in Hamilton, Canada. "The key is to achieve a system of delivery that's persistent, effective and completely safe."

Independent studies by Hortelano's group and other research teams in Germany and the United States have shown that this oral gene therapy does not activate the immune system. Indeed, exposure of the protein produced by the nanoparticle-based gene therapy to the gut mucosa prevents inhibitor development and restores clotting-factor activity in mouse models of both haemophilia A[7,8] and B[9]. "This approach really could hold big benefit for patients," says Jörg Schüttrumpf, a transfusion-medicine specialist who led one of the studies performed at the German Red Cross Blood Donor Service in Frankfurt.

Kam Leong, a biomedical engineer at Columbia University in New York City whose team was the first to demonstrate success with this approach in mice[7], has even tried feeding the chitosan–DNA nanoparticles to dogs with haemophilia A. Leong found some evidence of gene transfer and a reduction in inhibitors in the animals. But bleeding times were not reduced, which would be expected if sufficient levels of factor VIII were being produced. "It is still a very inefficient process," Leong says, "so it requires continued optimization."

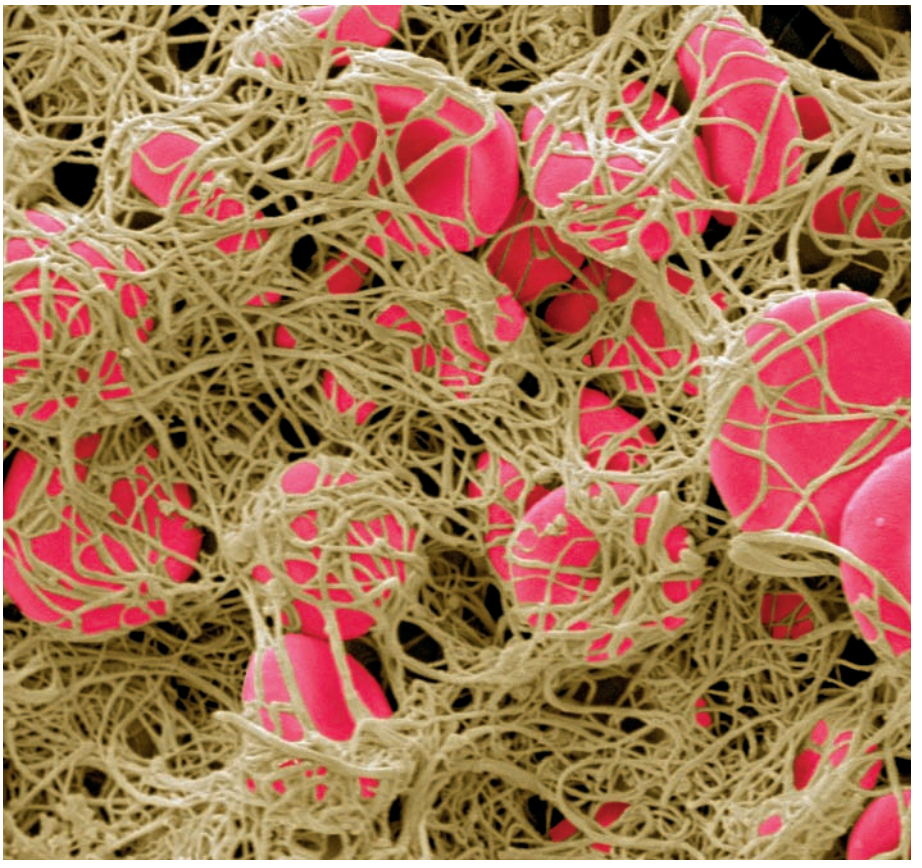
Although the ideal remains a gene therapy that both corrects the disease and offers immune tolerance, some scientists have focused on treating inhibitor formation, without worrying about fixing the disease. Under this strategy, people would still need to take factor-replacement therapies, but they could do so without fear of inhibitor development.

With this in mind, independent teams led by Scott and Herzog took the conventional viral-vector approach to inducing tolerance through gene therapy. But rather than delivering the entire gene for the clotting-factor proteins to cells, as most gene therapies do, the researchers used the viruses to engineer immune-regulating B cells to express a fragment of the clotting factor fused to an immune molecule called an immunoglobulin. This led to long-lived tolerance in mouse models of haemophilia A[10] and B[11].

Pursuing such gene-therapy approaches offers a degree of bet hedging, says Herzog. "Each strategy has potential advantages and disadvantages," he points out, "and we do not really know yet what will work or may work best in people." With so many therapeutic tactics moving through the preclinical pipeline, scientists and clinicians remain hopeful that at least one will ultimately succeed, eliminating the problem of inhibitor formation for people with haemophilia altogether. ■

Elie Dolgin *is a science writer in Somerville, Massachusetts.*

1. Verma, D. *et al. Proc. Natl Acad. Sci. USA* **107,** 7101–7106 (2010).
2. Sherman, A. *et al. Blood* **124,** 1659–1668 (2014).
3. Rawle, F. E. *et al. J. Thromb. Haemost.* **4,** 2172–2179 (2006).
4. Ruhlman, T., Ahangari, R., Devine, A., Samsam, M. & Daniell, H. *Plant Biotechnol. J.* **5,** 495–510 (2007).
5. Zhang, A.-H. A. *et al. Blood* **122,** 2337 (2013).
6. High, K. A. *Blood* **120,** 4482–4487 (2012).
7. Bowman, K., Sarkar, R., Raut, S. & Leong, K. W. *J. Control. Release* **132,** 252–259 (2008).
8. Dhadwar, S. S., Kiernan, J., Wen, J. & Hortelano, G. *J. Thromb. Haemost.* **8,** 2743–2750 (2010).
9. Quade-Lyssy, P. *et al. J. Thromb. Haemost.* **12,** 932–942 (2014).
10. Lei, T. C. & Scott, D. W. *Blood* **105,** 4865–4870 (2005).
11. Wang, X. *et al. Mol. Ther.* **22,** 1139–1150 (2014).



STEVE GSCHMEISSNER/SPL

The control of blood clotting treads a fine line between promotion and inhibition.

THROMBOSIS

Balancing act

A promising therapy curtails clotting inhibitors rather than replacing proteins that promote blood clotting.

BY CASSANDRA WILLYARD

Kanjaksha Ghosh has seen more than a thousand people with haemophilia since he became a physician. But he has always wondered why some patients bleed spontaneously and develop crippling joint damage whereas others barely seem to be affected.

Ghosh, who heads the National Institute of Immunohaematology in Mumbai, India, remembers a soldier who had been fighting insurgents in the northeast of the country. The man's brother was almost bedridden by haemophilia, but the soldier's symptoms were so mild that he did not even realize that he had the disease until he was shot on the battlefield.

In the 1990s, Ghosh began trying to work out why such discrepancies existed by studying families like the soldier's. When he delved into the genomes of those with a milder disease, he often saw not just a mutation in the affected clotting-factor gene, but also a mutation in another gene — the first causing haemophilia, the tendency to bleed, and the second causing thrombophilia, the tendency to clot. Ghosh's research leads to the conclusion that a patient with haemophilia who co-inherits a thrombophilic gene bleeds less than one without that mutation.

Blood coagulation is regulated by one set of proteins that causes clotting and another set that prevents it (see 'Perfect balance'). Too little clotting ability leads to bleeding disorders. Too much leads to vessel-blocking clots that can cause strokes and heart attacks. Existing haemophilia treatments tip the balance towards clotting by adding what the body lacks — the clotting factor that is missing or defective. But natural human experiments such as Ghosh's soldier suggest an alternative strategy to treat the disease. Rather than boosting the factors that promote clotting, researchers might instead disable the anticoagulation machinery that prevents clotting.

In the past few years, three drug companies have moved compounds aimed at inhibiting anticoagulation into clinical trials. The hope is that these therapies will be as effective as existing treatments and much more convenient. Rather than receiving multiple infusions of protein replacement each week, patients might be able to control their bleeding with long-lasting injections.

TARGET PRACTICE

The complex cascade that results in the formation of a clot begins when a blood vessel is injured. Several proteins hold the process in check to prevent clots from forming where they are not needed. One such protein, tissue factor pathway inhibitor (TFPI), impedes the initiation of coagulation. Studies published over the past two decades suggest that blocking this protein can promote clotting, which could curb bleeding in people with haemophilia.

The Danish pharmaceutical company Novo Nordisk in Bagsvaerd began working on an antibody designed to inhibit TFPI in the 1990s. Its researchers showed that this antibody could speed up clot formation in blood plasma from people with haemophilia[1]. They also found that it could shorten bleeding time and hasten clotting in rabbits with induced haemophilia. These results seemed promising, but Novo Nordisk began pursuing other strategies to treat haemophilia, and research to develop an anti-TFPI antibody was halted.

In 2006, Novo Nordisk decided to look for therapies that could be injected under the skin and revived the programme. By 2010, the company had launched a clinical trial in Europe and Asia to test the safety of an anti-TFPI monoclonal antibody called concizumab. The researchers administered the antibody either intravenously or subcutaneously to 28 healthy volunteers and 24 people with haemophilia. Preliminary results presented in 2013 at the International Society on Thrombosis and Haemostasis meeting in Amsterdam suggest that concizumab is safe, and that it can improve coagulation. Participants did not report any severe adverse events, although one of the healthy volunteers in the group receiving the highest dose of concizumab developed a small blood clot that disappeared on its own.

The company hopes to launch a second study in mid-2015 to determine the appropriate dose before moving on to test the efficacy of the treatment. "We have liked TFPI as a target for a long time," says Ida Hilden, scientific director of Novo Nordisk's concizumab project.

Drug company Baxter International, based in Deerfield, Illinois, sells recombinant clotting factors for treating haemophilia and also has its sights on TFPI. In the same year that Novo Nordisk launched its concizumab trial, Baxter struck a deal to purchase a suite of haemophilia-related assets from the former therapeutics company Archemix. Those assets included a therapy designed to inhibit TFPI that had already entered a safety study in the United Kingdom. This therapy was an aptamer, a small strand of nucleotides

designed to inhibit TFPI's activity by binding to it, much like an antibody.

The compound, known as BAX 499, performed well in animal studies but failed to deliver in humans[2]. In 2012, Baxter halted the trial due to an increased number of bleeding events. The failure came as a shock. "We did extensive safety studies in monkeys," says Fritz Scheiflinger, vice-president of research and innovation at Baxter BioScience in Vienna. "We gave huge amounts of aptamer over six months", yet there were no signs that the compound was unsafe, he says.

Scheiflinger and his colleagues think that they now have an explanation for this strange effect. TFPI lasts no more than a couple of hours in the bloodstream, but BAX 499 has a longer half-life. When BAX 499 binds to TFPI, it allows the protein to persist for longer and, over time, to accumulate. And although the drug binds to TFPI, it does not completely deactivate it. So, as partially active TFPI piles up, the balance eventually tips from a pro-clotting effect to an anti-clotting effect. The problem seems to be confined to this particular compound, but nonetheless, the company has shifted its focus away from aptamers.

Baxter is now concentrating on peptides — short strings of amino acids that can be tailored to block part of the TFPI protein — a strategy that Scheiflinger and his colleagues first considered in 2005. The company has identified several promising candidates, but has not yet decided whether it will move them into clinical trials.

TFPI is not the only target for companies hoping to hamper the anticoagulant system. Alnylam Pharmaceuticals in Cambridge, Massachusetts, has set its sights on antithrombin — a protein produced by the liver that hinders clotting. "Antithrombin is probably one of the most potent natural anticoagulants we have in the body," says Benny Sorensen, medical director of clinical research and development at Alnylam. But rather than inhibiting antithrombin's activity, the company plans to block its expression by using short strands of RNA to silence the messenger RNA that carries the code for antithrombin — an approach called RNA interference.

The company is testing its therapy, called ALN-AT3, in a safety study, and the initial results were presented at the World Federation of Haemophilia annual meeting in Melbourne, Australia, in May. After giving healthy volunteers a single low dose of the drug, expression of antithrombin was reduced by 28–32% — an outcome that Sorensen says left the researchers "very surprised". They had thought that it would take higher doses to achieve such a result.

But Sorensen believes that they can do even better. In that first phase, the researchers were not allowed to exceed a 40% reduction in antithrombin because of the safety risks to healthy volunteers. The next phase of the study will include people with haemophilia, and there will not be the same limitation. So the researchers plan to administer multiple doses of the drug. Sorensen thinks that if they can achieve a 50–80% reduction in antithrombin, ALN-AT3 may be able to control bleeding in people with haemophilia without infusions of clotting factor.

PERFECT BALANCE

The body must maintain a delicate equilibrium to ensure that blood flows freely most of the time but clots when necessary. Haemophilia tips the scale towards bleeding, but researchers are looking for new ways to restore the equilibrium.

HAEMOPHILIA

People with haemophilia do not produce enough factor VIII or factor IX, proteins that play a crucial part in clotting.

FACTOR REPLACEMENT TREATMENT

To prevent and staunch bleeding, physicians typically give patients with haemophilia infusions of the factors they lack. Adding these extra factors restores the balance between bleeding and clotting.

ANTICOAGULANT INHIBITION TREATMENT

An approach under development restores balance instead by inhibiting the proteins that prevent clotting – natural anticoagulants such as tissue factor pathway inhibitor (TFPI) and antithrombin.

CAUTIOUS OPTIMISM

All of these therapies have one major advantage over protein replacement: antibodies, peptides and RNA can be effective even when injected under the skin, in part because they are so much smaller than the proteins used for factor-replacement therapy. Novo Nordisk envisages putting its antibody into a 'pen' like the one that people with diabetes use to administer insulin. This would be much more convenient than the intravenous infusions required for existing therapies. "Haemophilia patients are pestered from when they are one or two years old for the rest of their lives with intravenous injections," Sorensen says. "If we can achieve a correction of this haemostatic imbalance that would prevent spontaneous bleeds, then we've really offered an unbelievable change in the lives of these haemophilia patients."

If compounds such as concizumab and ALN-AT3 prove effective, they will undoubtedly be a boon for at least one group of people with haemophilia: those who develop inhibitory antibodies against the blood-clotting factors VIII and IX, and who can no longer receive this standard therapy. Roughly 5% of those with haemophilia B fall into this category, and 30% of those with haemophilia A (see page S12). Baxter, Novo Nordisk and Alnylam think that their products will appeal to other people with haemophilia. But whether these therapies will be safe and effective enough to replace infusions of clotting factor "is the million-dollar question", Scheiflinger says. Sorensen is the most optimistic. He speculates that a once-a-month dose of ALN-AT3 might control bleeding without the need for prophylactic infusions of clotting factor. Even if patients cannot completely forgo factor replacement, he adds, ALN-AT3 might allow them to use less, which could reduce the risk of developing inhibitors.

But many of the physicians who treat patients with haemophilia are not convinced. "The common thinking among haemophilia treaters is that these new strategies can never replace treatment with factor VIII and IX in non-inhibitor patients," says Erik Berntorp, a haematologist at Lund University in Malmö, Sweden. David Ginsburg, a geneticist at the University of Michigan, Ann Arbor, is equally cautious. "In the case of a genetic deficiency, it's pretty hard to improve on replacing the missing factor," he says.

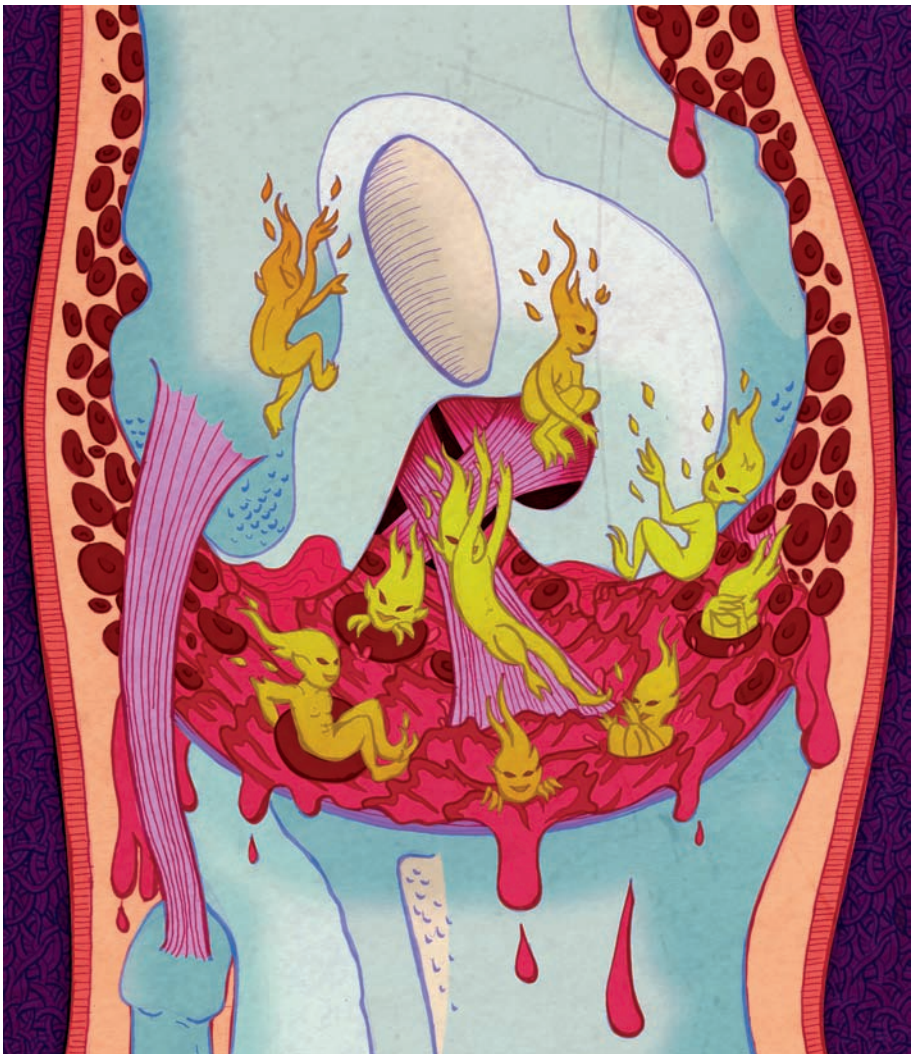
Kenneth Mann, a biochemist at the University of Vermont in Burlington, does not doubt that blocking these anticoagulant pathways will increase the production of thrombin, a key protein in clotting, but he does not think that these therapies will necessarily work for everyone. People with haemophilia "are more heterogeneous than we'd like to admit," he says. And companies will have to work out how to stratify patients on the basis of their real bleeding risk to determine who will benefit from these new approaches. "I don't mean to throw a wet blanket on this," he says, "but caution is required."

One risk is that these therapies will work too well, tipping the balance towards clotting. In a person without haemophilia, Ginsburg says, a total lack of antithrombin "seems to be disastrous". Mice that lack either antithrombin or TFPI die *in utero*. Although the antithrombin-based therapies for haemophilia are not designed to completely block their targets, "knocking them down is not without risk", he says. And as the failure of BAX 499 shows, the risks posed by any new medication can be hard to predict.

Jakob Back, vice-president of the concizumab project at Novo Nordisk, understands the scepticism. Protein replacement has been the go-to therapy for haemophilia for decades. Concizumab and similar therapies represent "a completely different way of approaching haemophilia compared to anything we've been doing for the last 50 years", he says. "We are moving into unknown territory." ■

Cassandra Willyard *is a freelance writer in Madison, Wisconsin.*

1. Nordfang, O., Valentin, S., Beck, T. C. & Hedner, U. *Thromb. Haemost.* **66,** 464–467 (1991).
2. https://ash.confex.com/ash/2012/webprogram/Paper51012.html



JESSICA FORTNER

ORTHOPAEDICS

Joint effort

The hunt is on for ways to diagnose and treat the joint problems that are now the main chronic problem in haemophilia.

BY KATHARINE GAMMON

As a physician who cares for adults with haemophilia, Annette von Drygalski sees patient after patient with bulging, painful knees and elbows caused by bleeding into the joint. The rise in cases of this crippling condition, which can lead to arthritis and disability, drives the work of von Drygalski and her team at the University of California's San Diego Medical Center — part of a growing body of researchers studying haemophilic joint disease and the pain that it causes.

Before clotting factor became widely available as a treatment (see page S8), people with haemophilia rarely reached adulthood, so haemophilic joint disease was not on the radar of most research programmes. But now that people with the disease have a life expectancy similar to that of the general population, arthritis caused by the disorder has emerged as a serious medical problem.

A bleed inside a joint leads quickly to stiffness and pain. The residual iron from pooled blood causes inflammation of the joint lining, a condition known as synovitis. Physicians can remove the inflamed tissue surgically (which, for people with haemophilia, comes with a high risk of bleeding) or by injecting radioisotopes into the joint. These emit radioactive particles that destroy the cells in the joint lining and prevent further bleeding. Such surgeries are delicate procedures, says Mauricio Silva, an orthopaedic surgeon at the University of California, Los Angeles, who specializes in haemophilic joint operations. "The deformities are much more severe than someone with arthritis," he says.

The basic remedy for bleeding into the joint has been for patients to self-administer more clotting factor when they believe they are having a bleeding episode. But this is expensive, and does not help everyone. "This field will require lots of new thoughts, beyond administering clotting factor for joint health, over the next decade to improve the life of those with haemophilia," says von Drygalski.

Researchers are tackling the problem from multiple directions: through better imaging, by using novel biomarkers that might be able to reveal even minor joint bleeds, and by applying knowledge from other types of arthritis. It will take research in all of these areas to work out new ways to diagnose and treat haemophilic joint disease and understand its causes.

JOINT INSPECTION

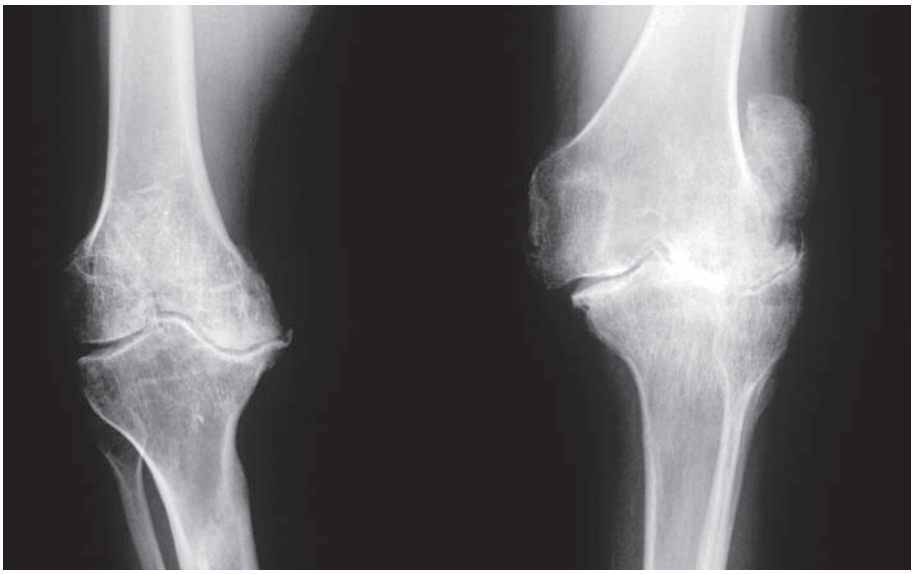
One problem is that there is no definitive way for physicians to distinguish between normal arthritic joint pain and that caused by a bleed. Von Drygalski's research shows that only one-third of painful episodes reported by people with haemophilia are associated with bleeding into the joint[1]. Similarly, physicians find it hard to determine the cause of joint pain: in one small study[1], von Drygalski and her colleagues found that physicians' assessments, based on patient interviews and physical examinations, were incorrect in 18 of 40 instances.

Imaging technologies can help. The highest-quality pictures come from magnetic resonance imaging (MRI), but these systems are slow, bulky and costly to run, and so are not commonly used in haemophilia clinics.

With an eye on those drawbacks, von Drygalski and her colleagues developed a clinical tool that uses ultrasound. The musculoskeletal ultrasound (MSKUS) system — featuring a hockey-stick-shaped ultrasound probe — can distinguish between bleeding and inflammation during painful episodes. As part of a large initiative in Europe sponsored by pharmaceutical giant Pfizer, staff at about 10–15 haemophilia treatment centres are currently being trained to use the technology. The same initiative is in the planning stages in the United States, where training will be given at 10 centres.

MSKUS checks the crevices of joints for inflammation or bleeding, and is less costly than MRI but just as accurate, says von Drygalski. In particular, she says, ultrasound provides greater detail on what is happening in acutely and chronically painful haemophilic joints, where bleeding has caused both synovitis and inflammatory changes to soft tissue.

MIKE DEVLIN/SPL



An X-ray of the knees of a person with haemophilia, both damaged from bleeding inside the joints.

MOLECULAR MARKERS

The molecular basis of how haemophilia results in joint pain is still not clear. One hypothesis is that the blood of patients with the disease is a poor activator of a key protein called thrombin activatable fibrinolysis inhibitor (TAFI), which controls clot stability and reduces inflammation. For example, administering additional TAFI relieves discomfort in non-haemophiliacs with inflammatory arthritis. Because the protein stops blood clots from breaking down, it helps people with haemophilia to form clots and maintain them. Von Drygalski, in collaboration with Laurent Mosnier, an assistant professor of molecular medicine at the Scripps Research Institute in La Jolla, California, is studying how treating patients with extra TAFI might help to relieve haemophilia joint problems.

Mosnier, for his part, is doing basic molecular studies to better understand the contribution of clot breakdown in bleeding, and to investigate whether TAFI can be genetically modified to make it more potent and diminish bleeding complications.

To tease out TAFI's clotting and anti-inflammatory roles — and to find out why TAFI may not be fully functional in people with haemophilia — both researchers are using haemophilic mouse models as well as mice that have been engineered to lack the gene that encodes TAFI. Von Drygalski hopes that this will lead to treatments beyond the standard infusions of clotting factor. If it is established that poor TAFI activation in haemophilia contributes to joint disease and inflammation, researchers could develop engineered versions of TAFI with high potency that persist for longer in the body. The researchers hope that such agents could eventually mitigate or even prevent haemophilic joint disease.

DRUG SEARCH

Ideally, physicians would like to have a test that determines which people with haemophilia have the highest risk of developing joint disease. At Rush University in Chicago, Illinois, molecular biologist Narine Hakobyan has found about half a dozen biomarkers in the blood of haemophilic mice[2] that could signal very minor bleeds before damage occurs in the joint.

She and her colleague Leonard Valentino (who now works at health-care company Baxter International in Deerfield, Illinois) set out to create animal models for haemophilic joint degradation in 2001. They made one mouse model that had joint bleeds after injury and another that bled into the joint even in the absence of trauma. They also created a scoring system to evaluate how well drugs stopped bleeding in the joints, which could be used to rank the effectiveness of new drugs.

Hakobyan's study[2] revealed biomarkers that could be detected after injecting just 25 microlitres of blood into the joints of mice that lack clotting factor — showing that even tiny bleeds have markers that could be used to predict joint deterioration. These could guide scientists' search for new drugs to treat haemophilic joint disease, and could point to the fundamental mechanisms underlying the illness. "It would be helpful to know at which point joint disease is reversible, and where we can act to use drugs as therapeutic agents," says Hakobyan. Other markers are likely to be found for different stages of the disease, Hakobyan says.

BEYOND CLOTTING FACTORS

To better understand the joint and its response to bleeding, researchers are studying changes to the bone around it. This may require creative thinking about mechanisms beyond clotting factors, says Paul Monahan, a haematologist at the University of North Carolina in Chapel Hill, who has studied whether rheumatoid arthritis drugs can improve mobility and reduce inflammation in haemophilic mice.

Monahan thinks that treatment with infusions of clotting factor, known as prophylaxis, is not a good way to treat all patients with haemophilia, especially those who have breakthrough bleeding — bleeds that happen in between their infusions of clotting factor. For instance, previous research[3] has shown that regularly giving extra doses of clotting agent beyond what is needed for primary prophylaxis adequately controls joint bleeding in less than 40% of people with haemophilia.

He likens this approach to giving only one therapy to patients with asthma. "You wouldn't treat an asthmatic with just a bronchodilator — you need to address both the acute spasm and the underlying inflammation," he says. Likewise, patients with haemophilia could potentially be treated with drugs that reduce inflammation as well as being given clotting factor.

Another potential therapy is the use of special radioisotopes to attack the inflamed joint lining. In July, Navidea Biopharmaceuticals of Dublin, Ohio, announced a partnership with the start-up firm Rheumco to develop a tin radioisotope technology that blasts out inflamed joint tissue. The idea is to inject a colloidal suspension of tin-117 particles into the joints of children with haemophilia. This radioisotope was selected because it has a small, focused area of radiative impact, so there is less chance of radiation damaging nearby tissue — an important consideration for children whose bones are still growing.

Navidea and Rheumco are completing animal testing for the tin-isotope project and are optimizing the technology for use in people. Being able to treat children with the method would be a boon because early treatment is key for these disorders, says Mark Pykett, formerly chief executive of Navidea and now chief executive of Agilis Biotherapeutics in New York. Physicians have identified joint microbleeds in patients as young as two years old. "If you can prevent that, 10 or 20 years down the road, they will be better off," he says.

The limited treatment options for haemophilic children and adults with joint pain strongly motivates researchers. Only a few decades ago, patients with haemophilia did not have the chance to grow old; now they are feeling the effects of living for longer with the disease. "Joints are so important," says von Drygalski, "because people are living to 60 or 70 years old — just trying to live normal lives." ■

Katharine Gammon *is a freelance science writer in Santa Monica, California.*

1. Ceponis, A., Wong-Sefidan, I., Glass, C. S. & von Drygalski, A. *Haemophilia* **19,** 790–798 (2013).
2. Hakobyan, N. *et al. J. Thromb. Haemost.* **12** (suppl. 1), 1 (2014).
3. Greene, W. B., McMillan, C. W. & Warren, M. W. *Clin. Orthop. Relat. Res.* **343,** 19–24 (1997).

T. C. NICHOLS, B. J. Q. NICHOLS & S. A. GALLAGHER

Haemophilic dogs at the University of North Carolina's blood-research laboratory are helping researchers to learn about the disease and develop treatments.

ANIMAL MODELS

Dogged pursuit

In the study of haemophilia, man really does have a best friend.

BY EMILY SOHN

Austin, a fluffy white-and-black Old English sheepdog, was still a puppy when his owners called the University of North Carolina's Francis Owen Blood Research Laboratory in Chapel Hill four years ago. After deciding that the children were finally old enough to get a dog, the family had quickly bonded with the rambunctious pup. But within six months of bringing Austin home, they had spent US$10,000 on veterinary bills to deal with extreme bleeding from small scrapes. Austin was also suffering from spontaneous bleeding into his joints and uncontrollable nosebleeds caused simply by overexcitement. The family loved him, but could not take care of him.

Timothy Nichols, director of the North Carolina lab, gets enquiries about haemophilic dogs from around the world four or five times a year. Sometimes he offers advice and information. Other times, he goes and gets the dog. After blood tests confirmed that Austin had haemophilia, two of Nichols' lab members flew to the family's home in New Orleans, Louisiana, where they rented a car, packed it with a cool box full of medication and drove Austin back to Chapel Hill. There, the dog joined a colony that for nearly seven decades has been quietly transforming understanding of haemophilia.

Unlike the rats favoured as animal models for many other diseases, dogs develop haemophilia naturally, have enough blood to contribute to research studies and live long enough to reveal long-term outcomes of treatments. "We have a 60-year track record now showing that if it works well in dogs, it's likely going to work well in humans," says Nichols.

LIKE HUMAN, LIKE DOG

The earliest recognized cases of haemophilia in dogs were documented in 1935 in three related Scottish terriers. About a decade later, a lawyer in New York contacted the North Carolina blood-research lab to discuss two Irish setters that were bleeding frequently, both inside and out. Already eager to acquire an animal model of haemophilia, the lab's then-director, Kenneth Brinkhous, adopted the aristocratic, long-haired dogs and began searching for breeding partners for them. Since then, colonies of haemophilic dogs have sprung up at Queen's University in Kingston, Canada; the University of Alabama at Birmingham; and Nara University in Japan. There are also a few dogs at Cornell University in Ithaca, New York. Today, these colonies breed both haemophilic and healthy dogs to maintain populations with specific variants of the disease.

It did not take long for dogs to become pivotal to scientists' understanding of the disorder in humans: the disease works in the same way in both species. Early breeding efforts in the 1940s, for example, made it clear that in dogs, the genes responsible for haemophilia lie on the X chromosome — which later proved to be true for people, too. Except in rare cases, only males get the disease; females are carriers. "The genetic and laboratory studies from breeding these dogs and testing their blood helped establish the classic parallel example of humans

and animals having the same genetic defects," says Jean Dodds, a veterinary surgeon in Santa Monica, California, who has been working with haemophilic dogs since 1959.

More recently, gene-sequencing studies have revealed that identical genes with parallel mutations account for many cases of the disease in both dogs and humans. Both species can have either haemophilia A or haemophilia B, versions of the condition caused by defects in the genes that produce the clotting proteins factor VIII and factor IX, respectively. Symptoms are remarkably similar across species: both people and dogs with the disease are unable to form clots, so cuts can bleed uncontrollably. Bleeding in the bowel can lead to diarrhoea. And lumps of blood can form in joints and muscles.

Dogs are also good models for practical reasons. Most of them are bigger than small children. They react to medicines much like humans do, allowing researchers to look to dogs first as they calculate doses. And the animals cooperate well. "The dogs here are around people all the time," says Nichols. "If you need to draw blood, they put their paws out."

DOGS FIRST

Dogs in haemophilia colonies often win researchers' hearts. Veterinary surgeon Clint Lothrop of the University of Alabama at Birmingham has adopted several from his colony, and he treats them at home when they bleed. The Queen's University dogs run, climb and play with balls and other toys every afternoon, says Queen's haematologist David Lillicrap. The North Carolina dogs have access to an outdoor play area. With severe haemophilia, animals can bleed simply from wearing collars, so handlers are careful to prevent fights or rough play.

Between play sessions, dogs give blood for research. Those donations have allowed scientists to make key discoveries about why the disease develops.

By the 1950s, researchers knew that normal blood could correct clotting defects, but they were not sure which components of blood mattered most. With the help of dog blood, Brinkhous and others deduced[1] that clotting factors were in the plasma rather than mixed in with platelets or blood cells. Giving healthy plasma to haemophilic dogs made them better. Once scientists had identified factors VIII and IX, and could distinguish between healthy and haemophilic dogs, Brinkhous and his colleagues were able to develop a test for measuring levels of the factors in plasma on the basis of how long it took for clots to form in test tubes.

In the 1940s, life expectancy for humans with haemophilia had been about 20 years, often plagued by painful bleeding into muscles and joints, says Nichols. Plasma-replacement therapy transformed the quality — and duration — of life, as did the ability to concentrate the factor in plasma, developed by the mid-1960s.

In the 1970s and early 1980s haemophilia treatment went through a dark period: contaminated plasma infected many recipients with hepatitis or HIV. Dogs helped people out of this tragic stage.

Scientists thought that they had found the light at the end of the tunnel in 1984, when the cloning of the gene for factor VIII allowed them to make artificial factor in the lab[2]. But after years of dealing with blood-borne infections and a cultural fear of such genetically modified products, it was hard to get people to try the synthetic factor. Then studies[3] in dogs showed that the treatment worked without complications, and a 43-year-old North Carolina state legislator agreed to be the first person to sign up. "He knew of Brinkhous's work and he knew of the dogs at Chapel Hill and it helped him to know that it had really helped the dogs and was safe," says Nichols.

To everyone's relief, the treatment worked. In fact, infusion of the factor was so uneventful that the recipient, known as GM, pretended to be a hamster during the procedure (the product had been produced in hamster cells). After the treatment was licensed, GM spoke at a celebration at the Genetics Institute in Cambridge, Massachusetts. "After slowly and painfully climbing to a balcony half way up the stairs, he delivered a powerful story about what it was like to grow up with hemophilia without adequate treatment, how as a child he had lost a beloved older brother from a bleed, and how important the development of safe recombinant factors was to him and all people with hemophilia," wrote Gilbert White, director of the Blood Research Institute at the BloodCenter of Wisconsin in Milwaukee, in a paper[4] describing 35 years of advances in haemophilia research. "His comments had the entire company in tears."

> ***"We have a 60-year track record showing that if it works well in dogs, it's likely going to work well in humans."***

POINTING THE WAY

Research in canines often foreshadows what is coming for humans. Over the years, more than 25 products that had been tested in dogs have been licensed for clinical use in people. One of the first studies to show the feasibility of gene therapy[5], published in 1993, involved three factor-IX-deficient dogs and an extremely invasive procedure, in which researchers removed two-thirds of each dog's liver. Over the course of three days, they injected the regenerating organs with a potentially dangerous HIV-like virus loaded with the healthy gene. The procedure boosted levels of factor IX from zero to 1% of normal — enough to fuel optimism that a more efficient procedure might one day be possible.

By 1999, dog studies[6] began to show that one injection with a much safer vector called an adeno-associated virus could deliver a healthy factor IX gene, boosting levels of the clotting factor to 2% — enough to reduce spontaneous bleeds. "We were able to move past that rapidly and have had levels of 10% for a long time," says Katherine High, a haematologist at the Perelman School of Medicine at the University of Pennsylvania in Philadelphia. Dogs can now get simple, 10- to 15-minute infusions of factor-bearing viral vectors. Similar work with factor VIII is close behind, says Nichols.

Some of the first dogs to receive factor IX gene therapy with just a single injection have lived full and happy lives. Brad and Semi were two basenjis — African hunting dogs — who lived in the Alabama colony. After receiving the treatment, one died at 13, the other at 14, neither from haemophilia-related causes. Several clinical trials are now assessing gene therapy with factor IX in humans (see page S160).

Other studies are testing the possibility of administering factors VIII and IX orally instead of with an injection — a technique that has been shown to work in mice and is now being tested in dogs. And ongoing work by Lothrop and his colleagues suggests that replacement factors might become available as longer-lasting, less-invasive subcutaneous shots instead of intravenous injections.

Dogs are also helping scientists to develop strategies for combating the inhibitor antibodies that many patients develop in response to factor-replacement therapy. One approach[7] gives dogs a gene to express another clotting factor, factor VIIa, completely bypassing the need for factors VIII and IX. The technique can reduce the number of bad bleeds each year from five or ten to one or even none.

In other lines of work, dogs have undergone bone-marrow transplants to express factor VIII in their platelets, shielding them from inhibitors. And Nichols' team has acquired a strain of dogs deficient in clotting factor VII, allowing it to test therapies for rare bleeding disorders that may not occur in enough humans to allow large clinical trials.

It is unlikely that any of these next-generation approaches would have been possible without canine models. "The role of haemophilic dogs in the preclinical development of novel therapies for haemophilia during the past three decades has been enormous," says Lillicrap. The disease once seemed insurmountable, but in the years ahead, he says, dogs will continue to provide insights that will make life better for humans. ■

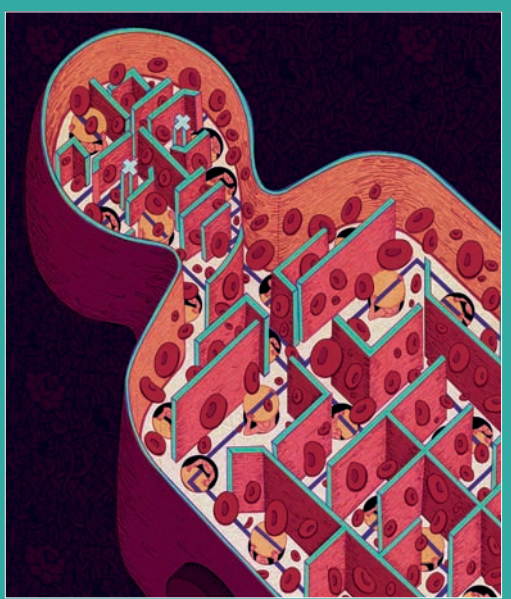
Emily Sohn *is a freelance journalist in Minneapolis, Minnesota.*

1. Brinkhous, K. M., Penick, G. D., Langdell, R. D., Wagner, R. H. & Graham, J. B. *AMA Arch. Pathol.* **61,** 6–10 (1956).
2. Wood, W. I. *et al. Nature* **312,** 330–337 (1984).
3. Giles, A. R. *et al. Blood* **72,** 335–339 (1988).
4. White, G. C. *Trans. Am. Clin. Climatol. Assoc.* **121,** 61–75 (2010).
5. Kay, M. A. *et al. Science* **262,** 117–119 (1993).
6. Herzog, R. W. *et al. Nature Med.* **5,** 56–63 (1999).
7. Margaritis, P. *et al. Blood* **113,** 3682–3689 (2009).

nature OUTLOOK

in association with

SCIENTIFIC AMERICAN™



nature

www.nature.com/nature/outlook/haemophilia

Get All-Access!

Subscribe to All-Access and read any issue, any year, on any device. All-Access subscriptions include:

PRINT
12 issues featuring the latest developments in science, medicine and technology.

DIGITAL
Instant access to current issues and the archive using any computer, tablet or smartphone.*

ARCHIVES
Search over 4,960 issues and 133,700 articles to find the information you need. 1845–present.

Go to: scientificamerican.com/all-access

SCIENTIFIC AMERICAN™

*Internet connection required.

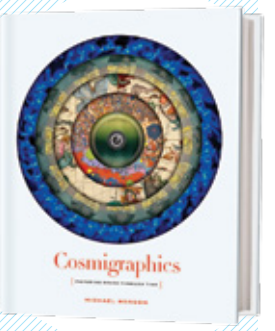
MORE TO EXPLORE For more recommendations and an interview with author Amir D. Aczel, go to ScientificAmerican.com/jan2015/recommended

PLEIADES BRONZE DISK

Cosmigraphics: Picturing Space through Time

by Michael Benson. Abrams, 2014 ($50)

Long before Hubble Space Telescope photographs wowed us with their beauty, other images of the cosmos awed us as well. This oversized art book samples humanity's attempts to depict the heavens throughout history. Some works are scientific; others are religious or purely artistic. Examples include modern supercomputer simulations of a sunspot, a 16th-century French painting of a solar eclipse and a bronze-and-gold image from Germany of the Pleiades star cluster dating to 2000–1600 B.C.—possibly the oldest known graphic depiction of celestial objects. Photographer and writer Benson gathers around 300 pictures in this collection, which illustrates both how much our knowledge of astronomy has progressed and how timeless the human fascination with celestial images is.



Finding Zero: A Mathematician's Odyssey to Uncover the Origins of Numbers

by Amir D. Aczel. Palgrave Macmillan,* 2015 ($26)

Our modern lives depend on mathematics, which in turn depends on the numerals 0 through 10. Yet the historical origins of these so-called Hindu-Arabic numerals, as well as the deeper concept of numbers themselves, are a mystery. "How did the idea of a number originate," asks mathematician and writer Aczel, "and how did it develop and mature through history?" In his quest to find out whence the numbers came, Aczel crosses the globe, visiting India, Thailand, Vietnam and elsewhere. In Cambodia he finds an ancient stone tablet that could be the earliest depiction of 0 yet found.

The full story of the numbers remains to be uncovered, but in weaving together mathematics and history with his personal explorations, Aczel enables readers to experience the joy of the chase.

Malformed: Forgotten Brains of the Texas State Mental Hospital

by Adam Voorhes and Alex Hannaford. powerHouse Books, 2014 ($39.95)

A collection of 100 human brains stored in jars of formaldehyde languished for decades in a closet at the University of Texas at Austin. Amassed between the 1950s and 1980s, the jars note the maladies of their brains' owners: Alzheimer's disease, Huntington's disease, Down syndrome, and many others. Photographer Voorhes first encountered the brains in 2011 and began carefully documenting them. He and journalist Hannaford proceeded to learn all they could about the cache and the people it represents.

The co-authors did not always uncover a great deal about the individuals, but the resulting presentation of images and stories is riveting. Some brains appear typical, whereas others display strange textures, unusual shapes and unexpected colors. The book is only one product of their efforts; the brain collection has sparked new interest in using the specimens for research.

The Man Who Couldn't Stop: OCD and the True Story of a Life Lost in Thought

by David Adam. Sarah Crichton Books,* 2015 ($26)

Intrusive thoughts, for most of us, are generally fleeting. We fixate for a moment on attractive strangers or on the perfect buttery cupcake. Such ruminations generally ebb and flow with the other thousands of thoughts we have in a day. For Adam, an editor at *Nature,* and several million others with obsessive-compulsive disorder (OCD), thoughts can circle in the mind repeatedly and become nearly impossible to banish. These unwanted preoccupations can drive people toward irrational actions. By recounting his and others' struggles with the disorder, Adam aims to make readers more aware of what living with the condition is like. He also lucidly describes the scientific research into OCD, which is scant and sometimes contradictory.

"This is not intended as a self-help book," Adam writes. "But if it does help … or if it can merely prise open the eyes of others, then I am glad." —*Julia Calderone*

COURTESY OF DBACHMANN *Wikimedia*

*SCIENTIFIC AMERICAN, PALGRAVE MACMILLAN AND SARAH CRICHTON BOOKS ARE AFFILIATES

Michael Shermer is publisher of *Skeptic* magazine (www.skeptic.com). His next book is *The Moral Arc*. Follow him on Twitter @michaelshermer

Here Be Zombies

What the living dead can teach us about ancient prejudices

The 2014 premier of *The Walking Dead*—AMC's postapocalyptic dystopian television series about zombies—was the most watched cable show in history. There have been a slew of popular zombie films such as *Dawn of the Dead, Day of the Dead, Night of the Living Dead, 28 Days Later, I Am Legend* and of course the perennial favorite *Frankenstein*. There is even a neuroscience text on the zombie brain, *Do Zombies Dream of Undead Sheep?* by Timothy Verstynen and Bradley Voytek (Princeton University Press, 2014), in which the authors consider real disorders that could turn the living into the living dead. Why are we so intrigued by zombies?

Zombies, for one thing, fit into the horror genre in which monstrous creatures—like dangerous predators in our ancestral environment—trigger physiological fight-or-flight reactions such as an increase in heart rate and blood pressure and the release of such stress hormones as cortisol and adrenaline that help us prepare for danger. New environments may contain an element of risk, but we must explore them to find new sources of food and mates. So danger contains an element of both fear and excitement.

We also have a fascination with liminal beings that fall in between categories, writes philosopher Stephen T. Asma in his 2009 book *On Monsters* (Oxford University Press). The fictional Frankenstein monster, like most zombies, is a being in between animate and inanimate, human and nonhuman. Hermaphrodites fall between male and female, and hybrid animals fall between species. Our innate templates for categorizing objects and beings are modified through experience, and when we encounter something or someone new, we check for category matches. Moderate deviation from the known category generates attention (friend or foe?), Asma says, but a "cognitive mismatch" elicits both dread and fascination. Add the emotion of disgust triggered by slime, drool, snot, blood, feces and rotting flesh, and we may find ourselves both repelled and drawn to such liminal creatures.

Distinguishing between zombies and nonzombies also hints at the deeper problem of xenophobia, which evolved as part of our nature to be suspicious of outsiders who, in our evolutionary past, were potentially dangerous. People from other groups, especially those perceived to be a threat, are moved into other cognitive categories and relabeled as mongrels, pests, vermin, rats, lice, maggots, cockroaches and parasites—all the easier to destroy them. Such labels are inevitably applied to new out-groups moving into the territory of an established in-group or conflicting economically or culturally with one—blacks moving into white neighborhoods, Jews establishing businesses in gentile-dominated markets, the Hutus resenting the dominant Tutsis in Rwanda. Fundamentalist Muslims do not "hate our freedoms" (as President George W. Bush conjectured). Instead, as Asma notes, they created a uniquely American monster in which "we are seen as godless, consumerist *zombies,* soulless hedonists without honor, family, or purpose."

On our cognitive maps are areas labeled "Here Be Monsters," where we put outsiders perceived to be dangerous. Fortunately, we have learned to curb such chauvinisms. As a result, the moral sphere has expanded to include all racial and ethnic groups as worthy of respect and equality, in principle if not always in practice. We have done so, in part, by overriding our instinctive impulses through reason, allowing us to take the perspective of another. Shakespeare worked out the logic in *The Merchant of Venice* when he has Shylock ask:

> Hath not a Jew eyes? Hath not a Jew hands, organs, dimensions, senses, affections, passions; fed with the same food, hurt with the same weapons, subject to the same diseases, heal'd by the same means, warm'd and cool'd by the same winter and summer, as a Christian is? If you prick us, do we not bleed? If you tickle us, do we not laugh? If you poison us, do we not die? And if you wrong us, do we not revenge? If we are like you in the rest, we will resemble you in that.

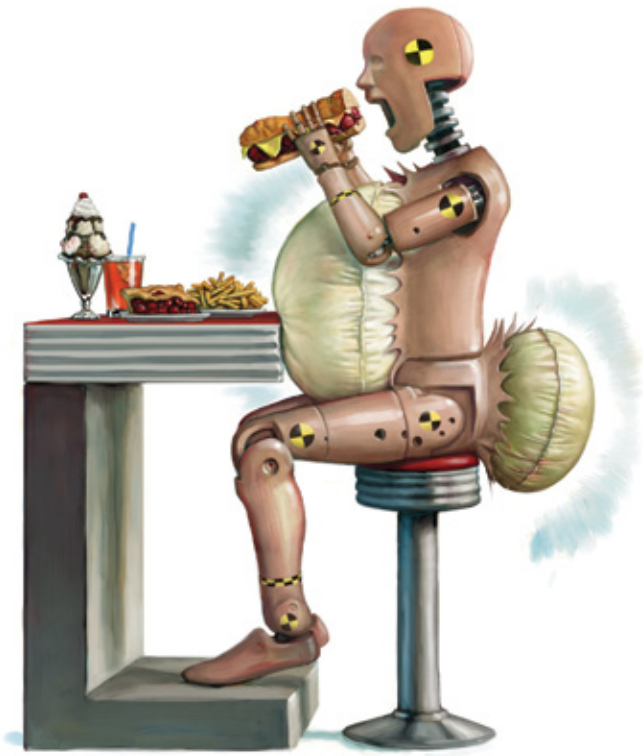
Perhaps zombies and other fictional beings stimulate those neural regions of our nonzombie brains that allow for a healthy and nonviolent outlet for such ancient callings. SA

SCIENTIFIC AMERICAN ONLINE
Comment on this article at ScientificAmerican.com/jan2015

Illustration by Izhar Cohen

The ongoing search for fundamental farces

Steve Mirsky has been writing the Anti Gravity column since a typical NFL offensive lineman weighed only 300 pounds. He also hosts the *Scientific American* podcast Science Talk.



From Big Men to Bronx Bison

A roundup with an emphasis on round

The fat is in the fire. According to the Cambridge Dictionaries Online, the expression refers to when "something has been said or done that will cause a lot of trouble." The saying goes way back: it's included in British writer John Heywood's collection of proverbs published in 1546. The adage's original, more literal meaning came from the kitchen danger resulting when globules of fat fell into the fire and accelerated the flame to a possibly out-of-control degree. Or degrees.

Those implications came to light, and heat, in October 2014, when a Virginia crematorium attempted to dispose of the mortal remains of a man who toppled the scales at some 500 pounds. A typical body can take two to three hours to cremate, according to the Web site of WTVR television in Richmond, itself quoting from the Web site of the Cremation Society of Virginia. A body of unusual size will take an unusually long time. (As the old joke goes, what's the difference between a violin and a viola? A viola burns longer. In this case, the 500-pound man is the viola.)

Fat is fuel. So the risk of an out-of-control fire over the extended course of the event is a weighty one. WTVR quoted a cremation expert thusly: "When the person is too heavy, the guy running the crematory needs to not have continuous heat coming down on the body. Otherwise it would get too hot." With the fat quite literally in the fire, the smokestack apparently became hot enough to ignite nearby rubber roofing, which in retrospect seems like a poor choice for the top of a crematorium. Fortunately, everyone got out of the burning building alive. Except for, well, you know.

The "burning man" case is still an outlier in our growing, and I mean that, population. But perhaps no other recent news story captures the obesity issue as well as an October 30 Canadian Broadcasting Company article that begins, "Crash test dummies are getting fatter so they better represent the expanding waistlines and bigger rear ends of American drivers."

Indeed, the entire purpose of a crash test dummy is to model the forces that a human body would experience in a vehicular accident. To perform that task correctly, you need the right dummy. (The previous sentence is basically my job description.)

The old dummies made by a leading manufacturer of dummies were the wrong dummies, according to the CBC article, because they were designed based on statistics gathered from the U.S. in the 1980s. One of those vintage dummies was a stand-in for a person weighing in at 169 pounds. The new dummies simulate a 270-pounder. Consider that in the 1980s, the average National Football League offensive lineman weighed 272 pounds. Of course, those behemoths have also gotten more gargantuan—in 2011, the last year for which I could find data, the figure had inflated to 310 pounds. To watch the NFL, you really do need a big-screen TV.

Speaking of large, ornery beasts that roam green fields: in a bipartisan resolution, the U.S. Senate established November 1 as National Bison Day to honor these lumbering bovines that stand around all day chewing their cud. Professional courtesy, I suppose.

As a resident of the Bronx, where the New York football Giants played when the linemen averaged between about 234 and 255 pounds, I always like to remind people about the pivotal role in the restoration of North America's bison population played by the Bronx Zoo, the flagship institution of the worldwide Wildlife Conservation Society.

Shortly after the turn of the last century, the plains that had once been covered by bison in the millions stood bereft of buffalo. The nation turned to the Bronx herd, which thrived in the bucolic mainland borough, for the salvation of the species. In 1907 the zoo shipped 15 bison to the Wichita Mountains Wildlife Refuge in Oklahoma. In 1913 another 14 Bronx buffalo arrived at Wind Cave National Park in South Dakota. Today many of the 20,000 free-roaming plains bison trace their lineage to those few plucky buffalo from the Bronx. To paraphrase Frank Sinatra singing about New York City as a whole, if you can make it here, you'll make it anywhere.

One last note: a big bull bison can weigh well over a ton. Exercise great care when interacting with these animals, whether they're pawing the earth or ready to be received by it. SA

SCIENTIFIC AMERICAN ONLINE
Comment on this article at ScientificAmerican.com/jan2015

Illustration by Matt Collins

January 1965

Synapse Transmission

"Since we do not know the specific transmitter substance for the vast majority of synapses in the nervous system we do not know if there are many different substances or only a few. The only one identified with reasonable certainty in the mammalian central nervous system is acetylcholine. We know practically nothing about the mechanism by which a presynaptic nerve impulse causes the transmitter substance to be injected into the synaptic cleft. Nor do we know how the synaptic vesicles not immediately adjacent to the synaptic cleft are moved up to the firing line to replace the emptied vesicles. It is conjectured that the vesicles contain the enzyme systems needed to recharge themselves. The entire process must be swift and efficient: the total amount of transmitter substance in synaptic terminals is enough for only a few minutes of synaptic activity at normal operating rates.—Sir John Eccles"

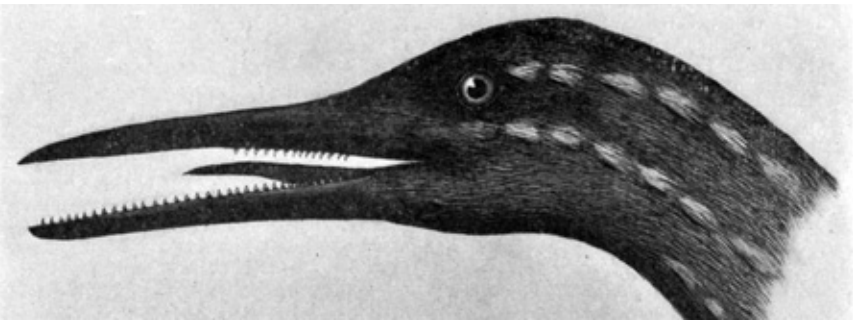
Eccles was a co-winner of the 1963 Nobel Prize in Physiology or Medicine.

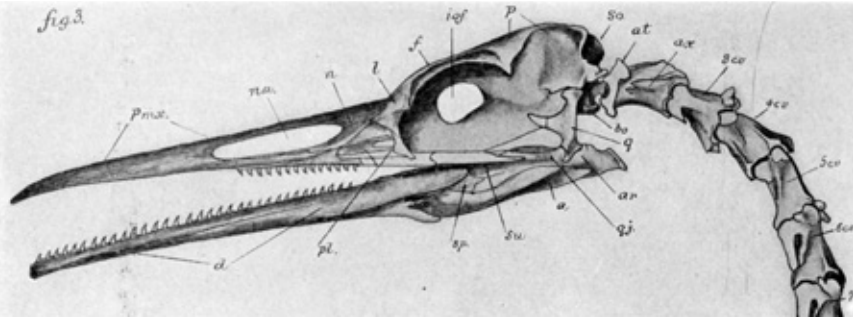
January 1915

Feeble-Minded?

"The tendency toward crime may exist in the presence of a brilliant intellect, as it very frequently does, and we are unable to detect it with any degree of accuracy; the measuring scales only determine the intellectual power, that is, the ability to think, to reason, to judge, to adjust one's self to the social requirements of the world around him and to exist harmoniously in it, in conformance to its laws and customs, exclusive of vicious tendencies, which last cannot be detected by the mere gauging of intelligence. The purpose of our mental measuring scale at Ellis Island is the sorting out of those immigrants who may, because of, their mental make-up, become a burden to the State or who may produce offspring that will require care in prisons, asylums, or other institutions."

Learn more about and see examples of the Ellis Island test at www.ScientificAmerican.com/jan2015/ellis-island





HESPERORNIS REGALIS: **A large, extinct bird with a toothed beak is depicted in a reconstruction and a drawing of a fossil, 1915**

A Bird with Teeth

"It has been shown, beyond all manner of doubt, that *Hesperornis* was an immense cretaceous diver or loon. In the United States National Museum there is a mounted restoration of the skeleton and its parts, which shows very correctly the swimming posture. The fossils were obtained back in 1870 near Smoky Hill River in western Kansas."

Piltdown Skull

"The most conspicuous feature of this skull, when seen from the side, is the low roof or dome and the slight development of the brow-ridges. The face must have presented an extremely ape-like appearance, owing to the enormous size of the jaws. The nasal bones, however, were negroid, not ape-like. The really ape-like characters are concentrated in the lower jaw. So much so is this the case that there are some who have gone to ridiculous lengths to show that this was really that of an ape, and had nothing to do with the skull. Needless to say such opinions were expressed only by those unfamiliar with the problems of comparative anatomy, and palaeontology.—Prof. W. P. Pycraft, British Museum, London"

The Piltdown fossils were conclusively proved as a hoax in 1953.

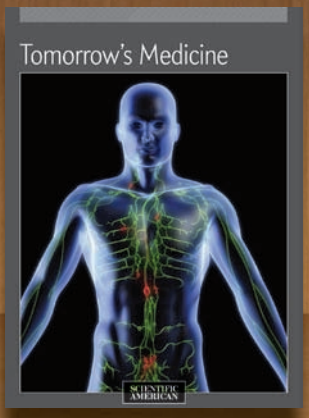
January 1865

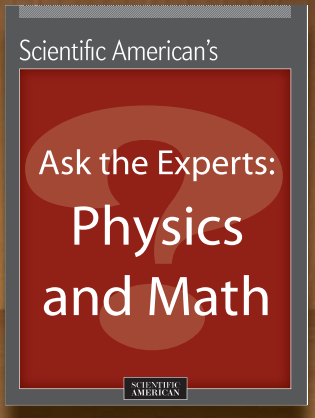
Safety Match

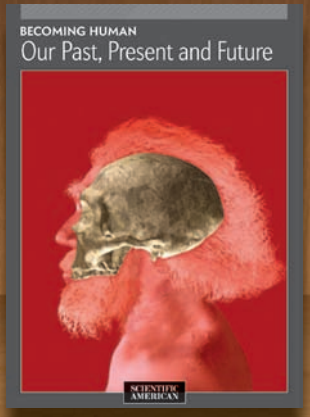
"A lucifer match is now in the market that differs from anything hitherto in existence. Upon the side of each box is a chemically prepared piece of friction-paper. When struck upon this, the match instantly ignites; when struck upon anything else whatever, it obstinately refuses to flame. You may lay it upon a red-hot stove, and the wood of the match will calcine before the end of it ignites. Friction upon anything else than this prepared pasteboard has no effect on it. The invention is an English one, and by special act of Parliament, the use of any other matches than these is not permitted in any public buildings. There is not a particle of sulphur in the composition of the lucifers in question."

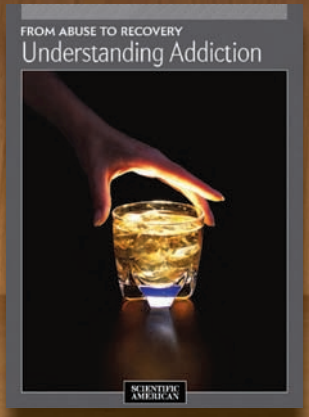
SCIENTIFIC AMERICAN SUPPLEMENT, VOL. 79, NO. 2038, JANUARY 23, 1915

eBooks From the Editors of SCIENTIFIC AMERICAN™









Start your SCIENTIFIC AMERICAN eLibrary today:

books.scientificamerican.com/sa-ebooks

Baxter

SPONSOR FEATURE

Pushing the frontiers of medicine: innovations in haemophilia care

Authors
Armin J. Reininger[1], Alessandro Gringeri[1], Leonard A. Valentino[2], Gerald Spotts[3], Vadim Romanov[3], Robert Numerof[3], Friedrich Scheiflinger[1] & Bruce M. Ewenstein[3]

[1] **Baxter Innovations GmbH, Industriestraße 67, 1220 Vienna, Austria.**

[2] **Baxter Healthcare Corporation, One Baxter Parkway, Deerfield, Illinois 60015, USA.**

[3] **Baxter Healthcare Corporation, One Baxter Way, Westlake Village, California 91362, USA.**

Congenital haemophilia is an X-linked bleeding disorder that is typically diagnosed in infancy or childhood and is caused by a deficiency or complete absence of coagulation factor VIII (FVIII) (haemophilia A) or FIX (haemophilia B). Acquired haemophilia A usually develops in adults and is triggered by the production of inhibitors that neutralize the clotting function of FVIII. Both congenital and acquired haemophilia can result in serious or fatal haemorrhage. The control or prevention of bleeding in patients with congenital haemophilia consists of replacing the deficient coagulation factor; haemostatic management associated with inhibitors may require treatment with bypassing agents that circumvent the need for FVIII or FIX. Since 1983, when Baxter introduced the first virus-inactivated (dry-heated at 60 °C for 72 hours), plasma-derived FVIII concentrate, the company has continued to innovate and advance haemophilia care with new products and treatment regimens, including the first genetically manufactured FVIII concentrate and the first third-generation human protein- and albumin-free recombinant FVIII (rAHF-PFM). Today, Baxter's vision for a functionally healthy life for all patients with haemophilia is closer to reality than ever before.

Prophylaxis: overcoming the burden of bleeding in congenital haemophilia

Congenital haemophilia occurs in approximately 1 in 10,000 births and affects an estimated 400,000 people worldwide, about 80% of whom have haemophilia A (deficiency of coagulation FVIII), whereas the remainder have haemophilia B (deficiency of FIX)[1]. Although life- and limb-threatening bleeding (for example, intracranial, iliopsoas and gastrointestinal haemorrhage) can occur in patients with congenital haemophilia, joint bleeding is its hallmark. Characterized by pain, swelling and stiffness (Fig. 1), haemarthroses account for more than 80% of all bleeding episodes in patients with severe haemophilia[1] (defined as baseline FVIII or FIX activity <1% of normal). Even a single serious joint haemorrhage can cause irreversible intra-articular changes that progress and culminate in joint destruction (Fig. 2) and impaired health-related quality of life (HRQoL)[2,3]. In other words, the importance of every bleeding episode cannot be overstated.

The development of factor concentrates, which first became commercially available in the 1970s (Fig. 3), allowed rapid intravenous infusions of the deficient clotting factor to be administered 'on demand' when a bleeding episode occurred. Moreover, patients could infuse at home, thereby shortening the delay between the onset of bleeding and the initiation of treatment. Although this strategy has proved effective in controlling acute haemorrhage, it cannot halt the progressive damage caused by haemarthroses. In the early 1990s, following publication of two articles describing long-term prophylaxis — the routine scheduled replacement of the missing clotting factor — the management of congenital haemophilia began to shift from reactive to proactive in an effort to prevent joint and other bleeding events[4,5]. These initial observations describing the benefits of prophylaxis were subsequently confirmed by five randomized clinical trials (RCTs) conducted over the next two decades[6–10]. In 1995, the World Health Organization[11] and World Federation of Hemophilia recommended prophylaxis as optimal therapy for patients with severe haemophilia A or B. These recommendations were later adopted by national haemophilia organizations.

FVIII prophylaxis. Response to FVIII prophylaxis is influenced by factors that are both patient-related (that is, haemophilia severity, FVIII genetics, bleeding phenotype, joint status, lifestyle and physical activity) and treatment-related (that is, dosing regimen, individual pharmacokinetics [PK] and adherence)[2]. Thus, a 'one size fits all' approach to bleeding prevention is not ideal and may lead to insufficient or inefficient dosing in some patients. Consequently, Baxter has focused on individualizing the prophylactic regimen by

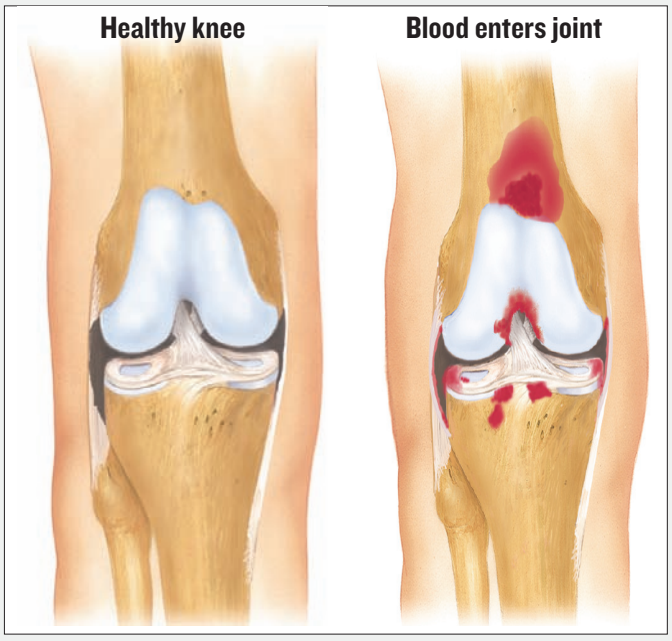


Figure 1 | Joint bleeding: short-term impact.

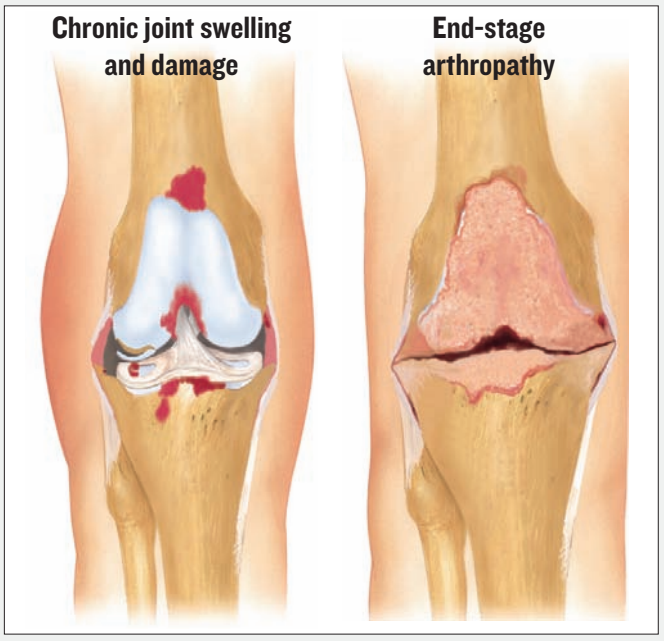


Figure 2 | Joint bleeding: long-term impact.

considering the patient's PK response to FVIII infusions as well as treatment outcome. In an RCT that enrolled 66 males aged 7 to 59 years with severe to moderately severe haemophilia A, PK-tailored rAHF-PFM prophylaxis administered every third day reduced joint and other bleeding from 44 events to 1 (median annualized bleed rate [ABR]), as compared with on-demand treatment. The treatment also had the advantage of decreasing the number of weekly prophylactic infusions by one-third compared with standard prophylaxis[8].

Taking the concept of individualized treatment further, Baxter developed a new medical software device that calculates a patient's PK and an appropriate prophylactic dose using as few as two blood samples taken after rAHF-PFM infusion. It also provides information about FVIII levels between infusions. The device has received the CE mark from the European Economic Area, and clearance by the US Food and Drug Administration is pending. Its use is expected to eliminate the need for multiple blood samples and cumbersome calculations, both major impediments to implementing PK-guided dosing in routine clinical practice.

FIX prophylaxis. Whereas prophylaxis is widely used in patients with haemophilia A, people with haemophilia B are less likely to receive such treatment, possibly owing to a relative paucity of data and/or the perception that bleeding episodes are not as severe in haemophilia B[12]. The availability of additional recombinant FIX (rFIX) products may encourage more physicians to consider this treatment option.

The pivotal clinical study that led to licensing of Baxter's rFIX concentrate in 2013 enrolled 73 males aged 12 to 65 years with severe or moderately severe haemophilia B[10]. A subsequent study in 23 children reinforced the safety and efficacy results demonstrated in the pivotal study. In both studies, the median ABR was 2.0 for patients on prophylaxis.

Prophylaxis for patients with inhibitors. Following exposure to clotting factor concentrate, up to 24% to 35% of patients with severe haemophilia A[13] and 3% with severe haemophilia B develop inhibitors: alloantibodies that neutralize the activity of clotting factor concentrate. The development of a high-titre (>5 Bethesda units) inhibitor complicates treatment and bleeding prevention because standard FVIII or FIX replacement is no longer effective. Consequently, patients with inhibitors are at increased risk for difficult-to-control haemorrhage and the development of complications.

People with haemophilia who develop inhibitors and have a high anamnestic response (that is, a marked increase in inhibitor titre on re-exposure to factor concentrate) have traditionally been managed with on-demand therapy using concentrates that bypass the need for FVIII or FIX. Two bypassing agents are currently available: activated prothrombin complex concentrate (aPCC) and recombinant activated FVII (rFVIIa). Over the past 3 years, however, two RCTs evaluating the prophylactic administration of aPCC have provided compelling evidence that the established benefits of FVIII and FIX prophylaxis can be extended to patients with inhibitors[14,15]. Consequently, the indication for aPCC was expanded to include routine prophylaxis.

The first of these RCTs enrolled 26 males (median age: 28.7 years) with haemophilia A and a history of high-responding inhibitors[14]. aPCC prophylaxis administered thrice-weekly for 6 months was associated with a 62% reduction in all bleeding episodes; a 61% reduction in joint bleeding; and a 72% reduction in bleeding into target joints, defined as ≥3 haemarthroses in a single joint during a 6-month treatment period), as compared with on-demand aPCC treatment ($P < 0.001$). Similarly, in the second RCT, which enrolled 36 males (median age: 23.5 years) with haemophilia A or B and inhibitors, the ABR in patients receiving aPCC prophylaxis given every other day for 12 months was 72.5% lower than with on-demand aPCC treatment ($P = 0.0003$)[15]. Both studies also showed that aPCC prophylaxis improved several dimensions of HRQoL.

Most of the patients enrolled in both studies had long-standing inhibitors and evidence of arthropathy[14,15]. Whether starting aPCC prophylaxis at a young age and before the development of repeated haemarthroses can provide joint-protective benefits similar to those provided by early FVIII or FIX prophylaxis is unclear. However, preliminary findings suggest that this may indeed be possible. After a median of 7 years of follow-up, seven children who began aPCC prophylaxis immediately after failing immune tolerance induction had a median ABR of 1.5, and none had major joint damage while receiving prophylactic aPCC infusions[16].

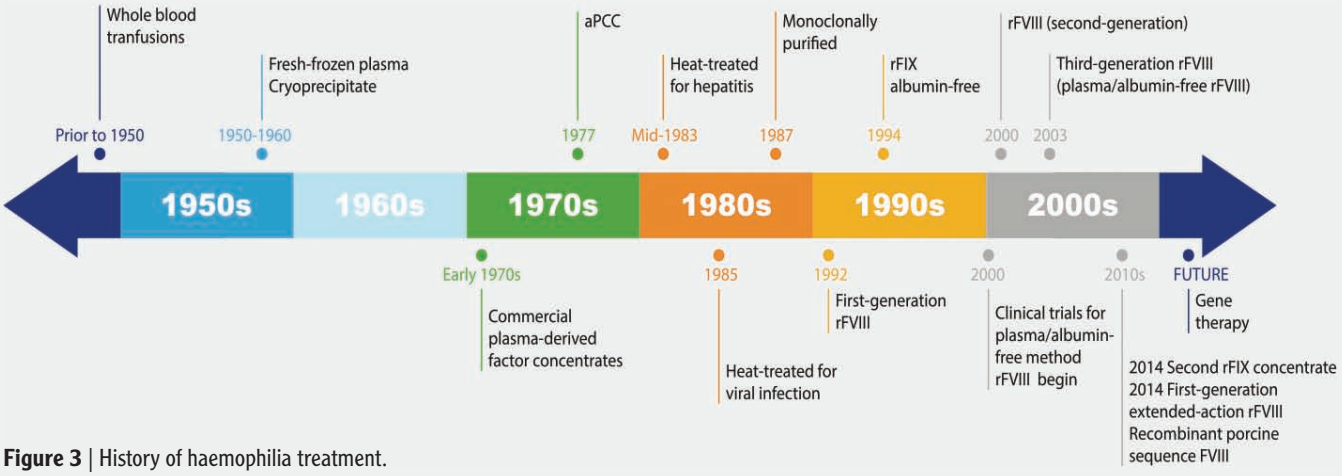


Figure 3 | History of haemophilia treatment.

A new option for treating acquired haemophilia

Acquired haemophilia A (AHA) is a rare bleeding disorder with an estimated incidence of 1.5 cases per million per year. As many as 85% of those affected are men and women aged 60 years and older, and approximately 10% are younger women diagnosed during the post-partum period. Some autoimmune diseases, especially rheumatoid arthritis and systemic lupus erythematosus, and cancers have been linked to the appearance of FVIII antibodies, yet nearly half of all AHA cases are not associated with an underlying disorder. The goals of management are twofold: stop the bleeding and eradicate the inhibitor. Haemostatic treatment currently consists of bypassing therapy because human FVIII usually cannot be given in sufficient quantities to overcome the inhibitor. Yet despite prompt initiation of treatment, fatal haemorrhage occurs in up to 16% of patients with AHA.

In the past, a highly purified plasma-derived (pd)-porcine FVIII (Hyate:C; Speywood Pharmaceuticals) provided an option to bypass therapy for the management of AHA-related bleeding. Porcine FVIII and human FVIII have a high degree of functional homology, but sequence variation between the two molecules results in reduced inhibitor cross-reactivity to porcine FVIII. Unless anti-porcine inhibitors developed, bleeding in AHA patients responded well to treatment with pd-porcine FVIII, and haemostatic efficacy rates of 90% were reported in clinical practice, although severe adverse events were common (for example, thrombocytopenia, allergic reaction and anaphylactic shock). Manufacture of the product was discontinued in 2004 because of concerns about possible residual viral contamination, chiefly by porcine parvovirus, and physicians lost a valuable tool in their AHA armamentarium.

Baxter has developed a recombinant (r)-porcine sequence FVIII that is produced in baby hamster kidney cells, formulated without animal-derived products and undergoes two viral reduction/inactivation steps. PK and safety studies found that a single dose of r-porcine sequence FVIII administered to patients with AHA and without measurable anti-porcine inhibitors had a higher bioavailability than Hyate:C[17]. In a pivotal phase 2/3 clinical trial (ClinicalTrials.gov identifier: NCT01178294), 28 patients with AHA aged 42 to 92 years achieved and maintained therapeutic FVIII activity levels with intermittent r-porcine sequence FVIII administration[18]. Importantly, r-porcine sequence FVIII — unlike bypassing therapy — can be monitored using standard assays for measuring FVIII levels (for example, one-stage FVIII assay or chromogenic assay).

Gene therapy

The ultimate goal of haemophilia research is to cure the disease, potentially through gene therapy to correct the underlying genetic defect. The most promising research to date has occurred in haemophilia B, which is particularly well-suited to gene therapy for several reasons. First, it results from a single defect in a relatively small gene. Second, tight regulation of FIX protein production is not necessary because a wide range of FIX levels are safe and haemostatic (in fact, an FIX level of only 3% of normal converts severe haemophilia B to a moderate bleeding phenotype). Third, increases in FIX concentration can be assessed using validated routine laboratory assays. In a small clinical study, a liver-directed adeno-associated viral vector (AAV serotype 8) was shown to sustain FIX levels for a period of 2 years and provide protection from spontaneous bleeding[19]. This research set the stage for the development of a vector with a natural gain-of-function transgene (FIX Padua) that provides five– to sevenfold higher FIX-specific activity than wild-type FIX[20]. This vector–transgene combination is currently being tested in a phase 1/2 safety trial in men with haemophilia B (ClinicalTrials.gov identifier: NCT01687608). Even if this AAV-based treatment approach does not prove to be fully curative, its ability to achieve long-term FIX expression is expected to lessen disease severity.

Gene therapy for haemophilia A is more challenging than for haemophilia B because of the larger size of the *F8* gene and the limited genome-packaging capacity of AAV vectors. Some promising results in animal models have been reported; however, no gene therapy trial has yet shown phenotypic or clinical improvement in haemophilia A in humans, and no such studies are currently active.

Baxter's research pipeline for bleeding and clotting disorders

Baxter's heritage is built on 80 years of healthcare innovations. Among the drugs being evaluated in clinical trials are a longer-acting rFVIII concentrate and a new rFVIIa for the treatment of haemophilia, a recombinant von Willebrand factor (rVWF) concentrate, and recombinant ADAMTS13 (rADAMTS13).

Extended half-life rFVIII. The scientific rationale for the development of rFVIII with an extended half-life is that it will reduce the number of infusions needed to treat acute bleeding episodes and extend the time between prophylactic infusions. Baxter is investigating an extended half-life rFVIII built on its full-length DNA rAHF-PFM platform. The product consists of rFVIII modified by a 20 kDa branched polyethylene glycol (PEGylated) moiety (PEGrFVIII). PEGylation is a well-established method for improving the PK and pharmacodynamic properties of therapeutic proteins. More than ten therapeutic

products marketed in the United States and European Union use PEGylation, and many more are in development.

Other products in clinical trials. The importance of having treatment options for patients with haemophilia who develop inhibitors cannot be overstated, as bleeding in these individuals is more difficult to control, and their response to bypassing therapy is variable. Baxter has developed an rFVIIa molecule as an alternative for haemostatic management in patients with high-titre FVIII or FIX inhibitors. The molecule is expressed in Chinese hamster ovary (CHO) cells and manufactured with a plasma/albumin-free process. A phase 3 trial of the investigational rFVIIa is currently underway in patients with haemophilia A or B and high-titre inhibitors (ClinicalTrials.gov identifier: NCT01757405).

Von Willebrand disease (VWD) is the most common bleeding disorder. It is caused by a quantitative deficiency of VWF or by abnormalities in the functioning of the VWF protein that impair the formation of a platelet plug necessary for clotting. Some forms of VWD are also characterized by haemostatically inadequate levels of FVIII, a combined defect that can lead to severe bleeding. Baxter is developing the first pure rVWF concentrate, representing the largest and most complex recombinant protein developed to date for use in humans. Produced using the same process as the company's full-length rAHF-PFM concentrate, the investigational drug has intact VWF subunits, a consistently high ratio of large-molecular-weight multimers, and the ultra-large-molecular-weight multimers present when VWF is released from its endothelial storage sites and that substantially enhance rVWF functional activity. rVWF is currently being evaluated in a phase 3 clinical trial in patients with severe VWD (ClinicalTrials.gov identifier: NCT01410227).

If ADAMTS13, the VWF-cleaving enzyme that controls multimer size, is lacking or impaired, thrombotic thrombocytopenic purpura (TTP) results. TTP presents in a congenital or acquired form and is characterized by thrombosis in microvessels, leading to life-threatening renal and neurologic abnormalities. A clinical study is underway of a rADAMTS13 protein developed by Baxter and produced in a CHO cell line for replacement therapy in patients with this clotting disorder. The investigational product is highly active under physiological conditions of blood flow and has been shown to be effective in an animal model that closely mimics hereditary TTP. When used prophylactically, all doses reduced the incidence and/or severity of TTP-related symptoms. When used therapeutically, the experimental drug mitigated the disease in a dose-dependent manner.

With these advances in haemophilia therapy, together with pipeline drugs for the treatment of other coagulopathies, Baxter has continued to strengthen its commitment to advancing care for the bleeding disorder community.

References

1. Srivastava, A. *et al.* Guidelines for the management of hemophilia. *Haemophilia* **19,** e1–47 (2013).
2. Gringeri, A., Ewenstein, B. & Reininger, A. The burden of bleeding in haemophilia: is one bleed too many? *Haemophilia* **20,** 459–463 (2014).
3. Valentino, L. A. Blood-induced joint disease: the pathophysiology of hemophilic arthropathy. *J. Thromb. Haemost.* **8,** 1895–1902 (2010).
4. Nilsson, I. M., Berntorp, E., Lofqvist, T. & Pettersson, H. Twenty-five years' experience of prophylactic treatment in severe haemophilia A and B. *J. Intern. Med.* **232,** 25–32 (1992).
5. Aledort, L. M., Haschmeyer, R. H. & Pettersson, H. A longitudinal study of orthopaedic outcomes for severe factor-VIII-deficient haemophiliacs. The Orthopaedic Outcome Study Group. *J. Intern. Med.* **236,** 391–399 (1994).
6. Manco-Johnson, M. J. *et al.* Prophylaxis versus episodic treatment to prevent joint disease in boys with severe hemophilia. *N. Engl. J. Med.* **357,** 535–544 (2007).
7. Gringeri, A., Lundin, B., von Mackensen, S., Mantovani, L. & Mannucci, P. M. A randomized clinical trial of prophylaxis in children with hemophilia A (the ESPRIT Study). *J. Thromb. Haemost.* **9,** 700–710 (2011).
8. Valentino, L. A. *et al.* A randomized comparison of two prophylaxis regimens and a paired comparison of on-demand and prophylaxis treatments in hemophilia A management. *J. Thromb. Haemost.* **10,** 359–367 (2012).
9. Manco-Johnson, M. J. *et al.* Randomized, controlled, parallel-group trial of routine prophylaxis vs. on-demand treatment with sucrose-formulated recombinant factor VIII in adults with severe hemophilia A (SPINART). *J. Thromb. Haemost.* **11,** 1119–1127 (2013).
10. Windyga, J. *et al.* Pharmacokinetics, efficacy and safety of BAX326, a novel recombinant factor IX: a prospective, controlled, multicentre phase I/III study in previously treated patients with severe (FIX level <1%) or moderately severe (FIX level </=2%) haemophilia B. *Haemophilia* **20,** 15–24 (2014).
11. Berntorp, E., Boulyjenkov, V. & Brettler, D. Modern treatment of haemophilia. Bull. *World Health Organ.* **73,** 691–701 (1995).
12. Biss, T. T., Chan, A. K., Blanchette, V. S., Iwenofu, L. N., McLimont, M., Carcao, M. D. The use of prophylaxis in 2663 children and adults with haemophilia: results of the 2006 Canadian national haemophilia prophylaxis survey. *Haemophilia* **14,** 923–930 (2008).
13. Collins, P. W., Palmer, B. P., Chalmers, E. A. *et al.* Factor VIII brand and the incidence of factor VIII inhibitors in previously untreated UK children with severe haemophilia A, 2000–2011. *Blood* published online October 22, 2014.
14. Leissinger, C. *et al.* Anti-inhibitor coagulant complex prophylaxis in hemophilia with inhibitors. *N. Engl. J. Med.* **365,** 1684–1692 (2011).
15. Antunes, S. V. *et al.* Randomized comparison of prophylaxis and on-demand regimens with FEIBA NF in the treatment of haemophilia A and B with inhibitors. *Haemophilia* **20,** 65–72 (2014).
16. Ettingshausen, C. E. & Kreuz, W. Early long-term FEIBA prophylaxis in haemophilia A patients with inhibitor after failing immune tolerance induction: a prospective clinical case series. *Haemophilia* **16,** 90–100 (2010).
17. Kempton, C. L. *et al.* Pharmacokinetics and safety of OBI-1, a recombinant B domain-deleted porcine factor VIII, in subjects with haemophilia A. *Haemophilia* **18,** 798–804 (2012).
18. Kruse-Jarres, R. *et al.* Recombinant porcine sequence factor VIII (OBI-1): results from a prospective clinical study investigating the treatment of serious bleeds in patients with acquired hemophilia A. *Haemophilia* **20 (Suppl. 3),** 1 (2014).
19. Nathwani, A. C. *et al.* Adenovirus-associated virus vector-mediated gene transfer in hemophilia B. *N. Engl. J. Med.* **365,** 2357–2365 (2011).
20. Simioni, P. *et al.* X-linked thrombophilia with a mutant factor IX (factor IX Padua). *N. Engl. J. Med.* **361,** 1671–1675 (2009).

Acknowledgements

The authors wish to thank H. Takedani of the Institute of Medical Science at the University of Tokyo for supervising the development of the joint images, E. Nakamura of Baxter Limited for leading the development of the joint images, and M. Grygotis, an independent consultant, who provided medical writing services that were funded by Baxter Healthcare Corporation.

Baxter's Hemophilia Vision

PURSUING A LIFE WITHOUT BLEEDS

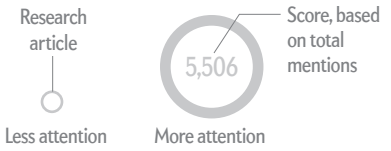
ONE PERSON AT A TIME

September 2014 GBL 2042 USBS/MG1/14-0834

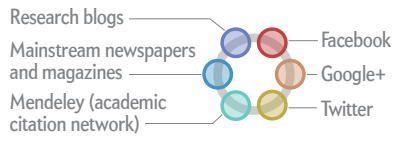
Baxter

Buzz about Top Research Papers

The 200 most talked about journal articles of 2014* are depicted here (*gray rings; many overlapping*). The top five are numbered. Bigger rings reflect more mentions:



Articles discussed most on digital academic and news channels carry bluish colors; those discussed most in social media have red, orange and yellow colors. Six notable channels among 14 are depicted:

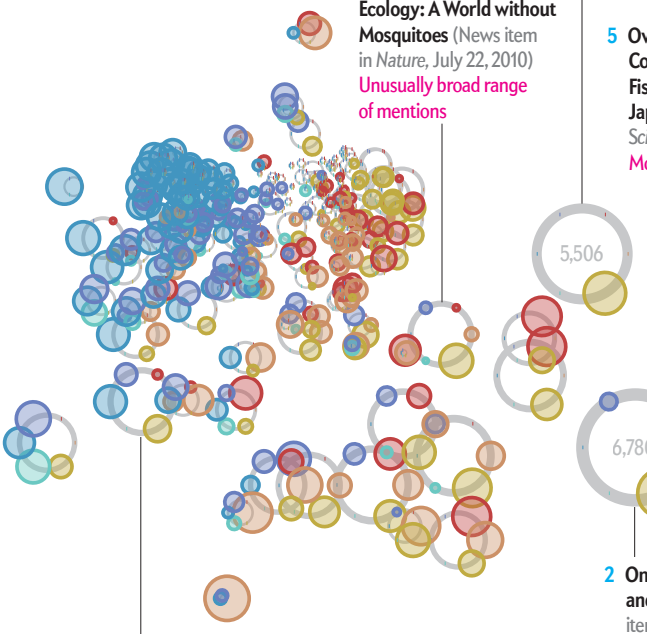


Articles with a similar mix of mentions cluster together and repel others that have a very different mix; outliers have an odd pattern of mentions, often extremely high on one channel and low on others.

Size of colored circles (channels) is a measure of the number of mentions above the mean for that channel.

**Late October 2013 to late October 2014*

4 Experimental Evidence of Massive-Scale Emotional Contagion through Social Networks (Research article in *Proceedings of the National Academy of Sciences USA*, June 17, 2014)
Most mainstream news mentions



3 Synthesis of Anthropomorphic Molecules: The NanoPutians (Research article in *Journal of Organic Chemistry*, November 14, 2003)
Social media buzz can make an old paper newly popular

Ecology: A World without Mosquitoes (News item in *Nature*, July 22, 2010)
Unusually broad range of mentions

5 Overview of Active Cesium Contamination of Freshwater Fish in Fukushima and Eastern Japan (Research article in *Scientific Reports*, April 29, 2013)
Most Twitter mentions

5,506

4,802

6,780

2 Online Collaboration: Scientists and the Social Network (News item in *Nature*, August 14, 2014)
Scientists' role on social networks garners much attention

Artificial Sweeteners Induce Glucose Intolerance by Altering the Gut Microbiota (Research article in *Nature*, October 9, 2014)
Unusually broad range of mentions

Natural Product Agonists of Peroxisome Proliferator-Activated Receptor Gamma: ($PPAR_\gamma$) (Review article in *Biochemical Pharmacology*, November 1, 2014)
Most Google+ mentions

1 Simulations Back Up Theory That Universe Is a Hologram (News item in *Nature*, December 10, 2013)
Most Facebook mentions

7,153

Sass vs. Substance

Twitter, mainstream media and academic blogs focus on surprisingly different scientific subjects

Hundreds of research papers are published every day worldwide. But which articles are most discussed and in which circles? To find out, Altmetric in London traced how often papers were noted in 14 digital channels, ranging from the serious (5,000 research blogs and Mendeley, an academic citation network) to the trendy (Twitter, Facebook) and everything in between (including 1,000 news outlets). Altmetric poured data for 2014 into an algorithm that created scores; the top 200 articles are mapped here. The results reveal a divide: the papers discussed most in serious channels (*bluish circles, which trend to the left of the page*) are different from those discussed most on social networks (*red, orange and yellow, which trend to the right*). (*Scientific American* is part of Macmillan, which is an investor in Altmetric.)

High-ranking subjects on academic sites included flaws in research, human cells, how the brain works and medical advances. Social media favored papers on scientific errors, the solar system and the universe, and health.

—Mark Fischetti

Why Most Published Research Findings Are False (Research article in *PLOS Medicine*, August 2005)
Most Mendeley and blog mentions

SCIENTIFIC AMERICAN ONLINE
Detailed rankings can be seen at ScientificAmerican.com/jan2015/graphic-science

SOURCE: ALTMETRIC

Graphic by Jan Willem Tulp

It's not a real movie, but it could be.

Quantum physics is crammed with intriguing characters, crazy ideas and ready-made plot twists. Our question is, can you put them in a story and bring it to the screen? Find your inspiration in the quantum world to enter our Quantum Shorts film competition.

- ***Films up to three minutes long***
- ***Win subscriptions to Scientific American and cash prizes***
- ***Enter by 23:59 EST 1 February 2015***

Quantum Shorts 2014

Short Film Competition

shorts.quantumlah.org

No purchase is necessary. Competition is void where prohibited. Subject to the official rules at shorts.quantumlah.org/rules

organisers:

CQT Centre for Quantum Technologies

NUS National University of Singapore

media partners:

SCIENTIFIC AMERICAN™

nature


WHEN THIS IS YOUR BACKYARD, YOU CAN'T HELP BUT EXPLORE.
When you've been in space long enough, you start to feel at home. We've been pushing the limits of what's possible out here since the dawn of the space age. For over 60 years, we at Northrop Grumman have been igniting the flame for space exploration—inspiring generations to stop and look up. From building the lunar module that led to one small step for man, to realizing the global dream that is the James Webb Space Telescope, the Great Pyramid of our generation. We've been here all along, and we aren't going anywhere but up.
WELCOME TO OUR NEIGHBORHOOD.
www.northropgrumman.com/space
© 2015 Northrop Grumman Corporation
THE VALUE OF PERFORMANCE.
NORTHROP GRUMMAN