ASTRONOMY
Cosmic Clues from Galactic Fossils

MEDICINE
How to Ease Chronic Pain

CLIMATE
Extreme Weather Becomes the Norm

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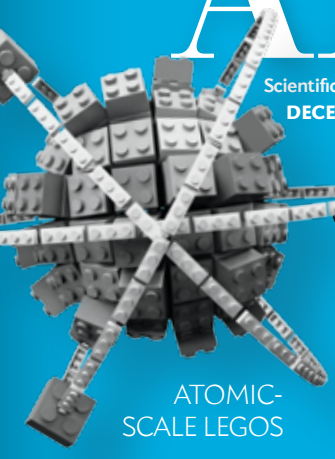

ATOMIC-SCALE LEGOS

NOVEL DNA EDITOR

REPROGRAMMABLE CELLS

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10 Transformative Technologies

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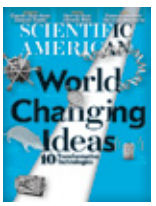
ON THE COVER

World Changing Ideas

PAGE 40



The Gene Genie A new DNA tool will revolutionize medicine. *By Margaret Knox*

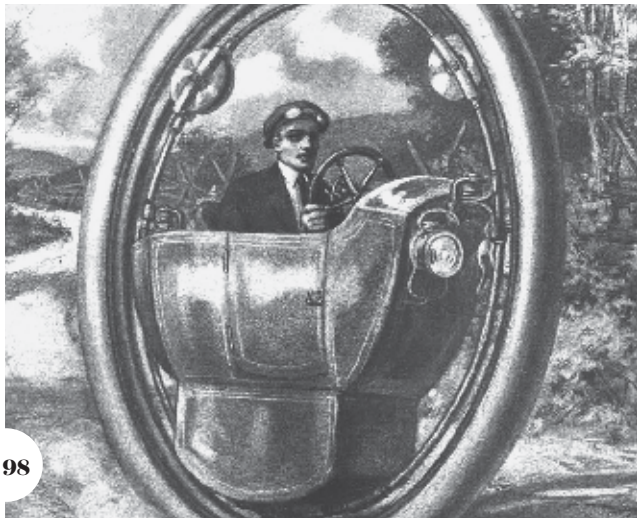
Atomic-Scale Legos *By Andre K. Geim*

Also: Reprogrammable cells. Transparent organisms. Saliva-powered fuel cells. Vision-correcting displays. Ultrahard recyclable plastics. Wireless charging with sound waves. Capturing low-temperature waste heat. Fast, affordable holographic microscopy. *By Ryan Bradley, Rachel Nuwer and Ben Fogelson*

Cover illustration by Ben Voldman

12

28



98

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DEPARTMENTS

ON THE WEB

Challenges in Nanotech
Hear what a panel of nanotechnology experts has to say about the challenges facing nanoscience in this *Scientific American* Science Talk podcast.
Go to www.ScientificAmerican.com/dec2014/nanotech

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

The Discovery Continuum

MR. THOMAS A. EDISON RECENTLY CAME INTO THIS office, placed a little machine on our desk, turned a crank, and the machine inquired as to our health, asked how we liked the phonograph, informed us that it was very well, and bid us a cordial good night."

So began an article in another December issue of *Scientific American*—one from 137 years ago, on December 22, 1877. As we welcome you to the latest edition of our annual "World Changing Ideas," this month's cover story, I am reflecting on just how many of this magazine's issues and 160,000 articles since its founding in 1845 have documented progress in a globe-changing innovation.

Although we highlight a selection of such innovations every year, in truth every issue of *Scientific American* contains news about discoveries and applications that shape our world in ways large and small—from expanding our knowledge base as a species to extending and improving human lives.

You can begin exploring this year's "World Changing Ideas" with the feature article "The Gene Genie," by Margaret Knox, starting on page 42. And if you're in the mood for a bit more history, turn to page 98 for the 50, 100 & 150 Years Ago column, compiled by Daniel C. Schlenoff, and to page 96 for Steve Mirsky's lively roundup of past authors in Anti Gravity.

While we are looking back in ways that inform our understanding of what is ahead, I would also like to point you to other feature articles: "Fossil Hunting in the Milky Way," by Kathryn V. Johnston (page 54)—which concerns discoveries that are helping to shape our knowledge of galactic evolution—and "The Storm God's Tale," by Zach Zorich (page 76), which describes a finding that is giving us new insights into the governance of the Maya people.

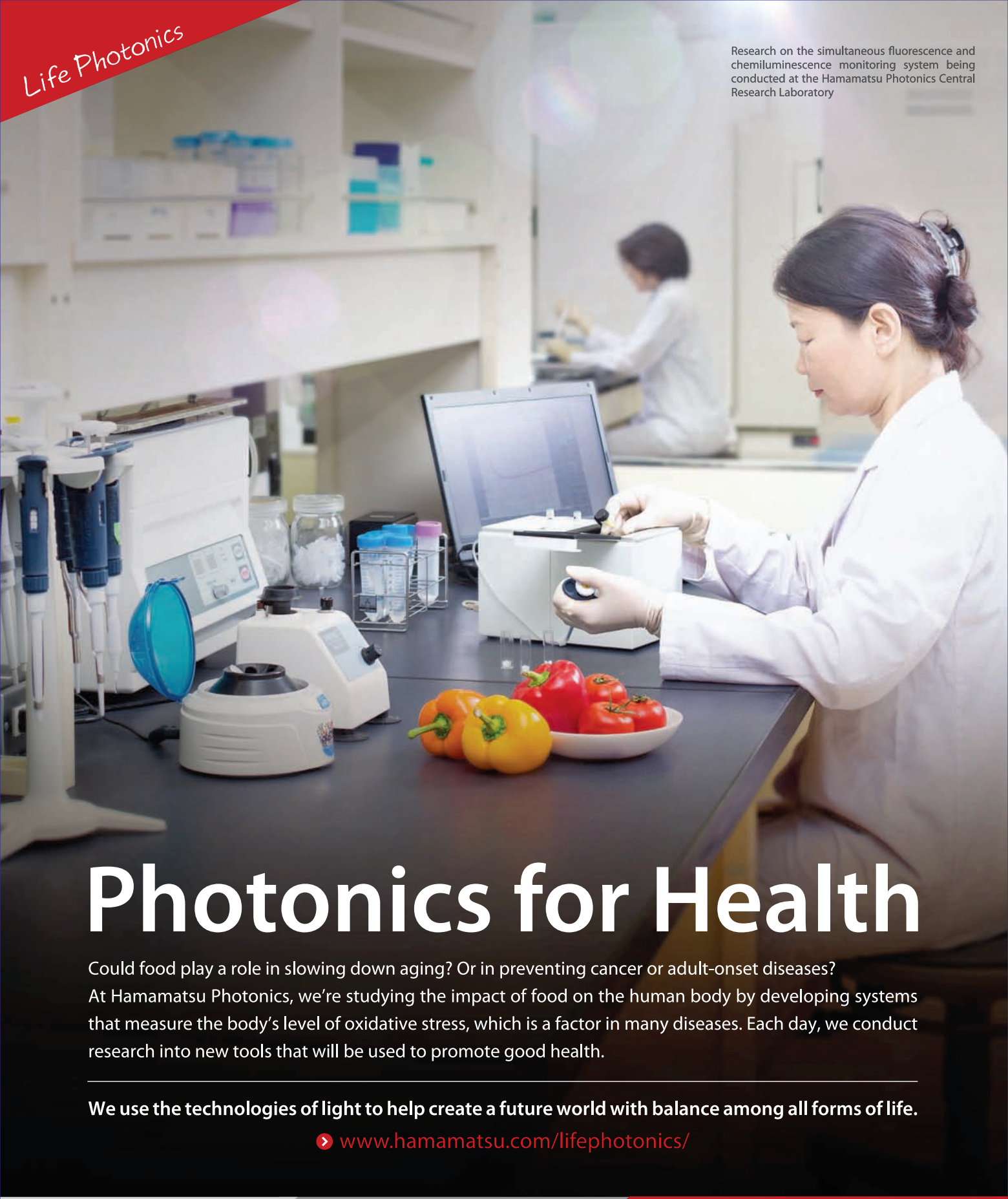
THOMAS EDISON demoed this "simple little contrivance," which talked to the editors in our New York City offices in 1877.

Indeed, after 169 years, *Scientific American* is still new every day, as it covers the rich ground of invention. As a 1911 issue explained: "The purpose of this journal is to record, accurately and in simple terms, the world's progress in scientific knowledge and industrial achievement. It seeks to present this information in a form so readable and easily understood, as to set forth and emphasize the inherent charm and fascination of science." Amen to that. SA

SCIENTIFIC AMERICAN, VOL. XXXVII, NO. 25, DECEMBER 22, 1877

Illustration by Nick Higgins

Life Photonics



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August 2014

CLIMATE CALCULATIONS

In "ClimeApocalypse!" [Skeptic], Michael Shermer draws on the widely criticized work of Danish political scientist Bjørn Lomborg to conclude that climate change is not a large concern when compared with poverty and global health.

This is a false dichotomy; few global issues we face are of greater consequence to the poor and to all living creatures on the planet than climate change. Without immediate, large-scale action, global water supplies, agriculture, disease rates and extreme weather will have profound negative consequences on all of us.

Rafael Reyes
San Mateo, Calif.

Shermer's analysis is very anthropomorphic. It takes into account only the damages and costs to humans. It also takes into account only the current population with no accounting for future ones.

Joe Vipond
Calgary, Alberta

SHERMER REPLIES: In response to Reyes: There appears to be a general consensus among scientists that global warming is real and human-caused, but I disagree that there is as much consensus about the consequences. Given the levels of uncertainty in climate models projecting out a century, wouldn't it be prudent to save lives now with the relatively less expensive measures we are already implementing?

As for the anthropomorphism of human suffering: Vipond is correct. We should care for the survival and flourishing of all sentient beings, starting with all primates and marine mammals and then working our way across the evolutionary branches to encompass any that can feel and suffer. Our children, and the offspring of all such sentient beings, deserve to be included in the moral sphere.

"Few global issues we face are of greater consequence to the poor and to all living creatures on the planet than climate change."

Rafael Reyes *San Mateo, Calif.*

PRODUCTIVITY'S PERILS

In "Will Work for Machines" [Science Agenda], the editors discuss the role technological innovations may have played in productivity and corporate profits having increased while incomes fell in the U.S. in recent decades, with job creation not keeping up with population growth.

We live in a culture that rewards corporations for cutting labor costs, which is done in ways that include replacing older workers with younger, less expensive ones; outsourcing jobs to lower-cost countries; eliminating pension plans; and, yes, displacing human jobs with machines.

We need to prioritize the well-being of people as more important than profits. We can partly do so by making profitable corporations carry a higher percentage of the national tax burden and rewarding those that employ a lot of well-paid domestic workers with a lower tax rate.

Robert Wise
Campbell, Calif.

The editors neglect the role that "financial engineering" has played in these trends. Over the past 35 years the idea that the only purpose of a corporation is to make money for its owners has become reentrenched in the U.S. and elsewhere. But through much of the 20th century, many corporations shared increases in productivity with their workers in the form of increased wages and benefits.

Tim Budell
via e-mail

EPIGENETIC INHERITANCE

In "A New Kind of Inheritance," Michael K. Skinner discusses the possibility that epimutations (persistent changes in certain molecules that affect gene activity without altering DNA sequences) may be a source of inherited human disease. The article details research into potential examples of multigenerational epigenetic inheritance but does not mention the caveats that currently apply to many studies in this field.

Whereas the described effects of chemical exposures on mice fit one definition of epigenetics, there is no convincing evidence that the inherited phenotypes, or traits, are caused by, rather than just correlated with, alterations in epigenetic marks such as DNA methylation.

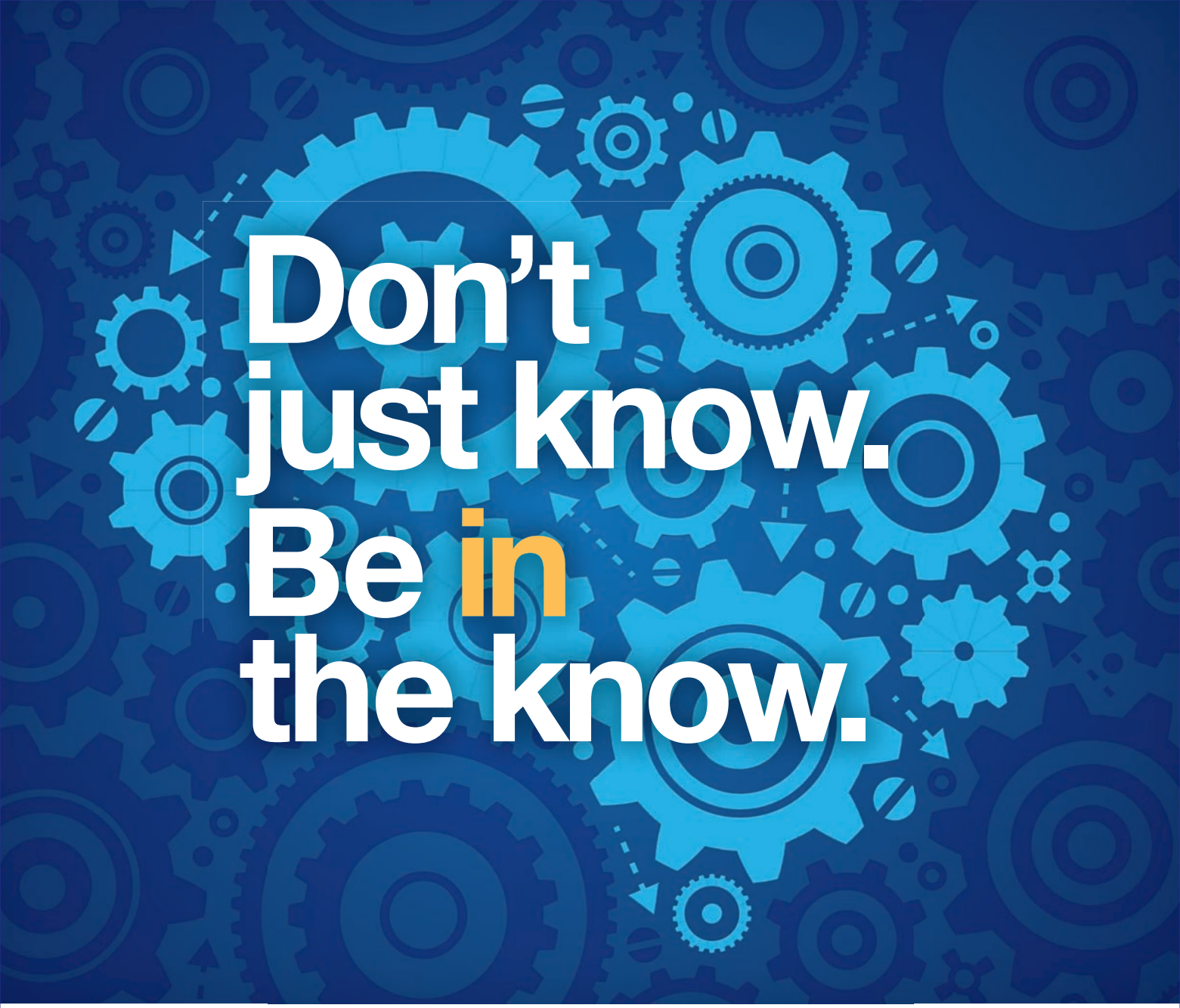
Duncan Sproul
MRC Human Genetics Unit
University of Edinburgh

How might the notion of epigenetic transmission of environmentally acquired traits relate to Soviet biologist Trofim Lysenko's ideas about the inheritability of acquired characteristics?

Mel Tremper
Berwyn Heights, Md.

SKINNER REPLIES: Regarding Sproul's comments: Epigenetic transgenerational inheritance has been shown to occur not only in rodents but also in plants, flies, worms, fishes, pigs and humans. The first step for both genetic and epigenetic mutation research is to identify the associations and reproducibility of the phenomena. That research will then move to the causal-link phase.

In response to Tremper: In the early 1800s Jean-Baptiste Lamarck proposed the theory that environmental factors promoted phenotypic changes that affect evolution, and Lysenko derived his theories from that earlier work. A number of different investigators agree that environmentally induced epigenetic transgenera-



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tional inheritance is a neo-Lamarckian concept. Clearly, neither Lamarck nor Lysenko had any concept for the molecular mechanisms involved. The new molecular (epigenetic) insights now provide a mechanism for these earlier observations.

HOW TO IMPROVE EDUCATION

As a retired educator, I was drawn to "The Science of Learning," Barbara Kantrowitz's article on experiments conducted in "an effort to bring more rigorous science to U.S. classrooms" and their results. But I cringed at the statement that this movement began with the No Child Left Behind Act.

In the late 1950s I went to a teacher's college, where "progressive education," then in its waning days, was propagandized, and I entered teaching in the days of the National Defense Education Act, with its science-teaching incentives. Then, over the years, came new models and curricula and related grants to education colleges.

Here's the bottom line: Place a student from a home that values education in a class with a teacher who loves his subject and enjoys teaching, and learning takes place. Everything else is window dressing.

ROBERT L. BALLANTYNE
Gilbertsville, Pa.

MATRYOSHKA MULTIVERSE?

In "The Black Hole at the Beginning of Time," Niayesh Afshordi, Robert B. Mann and Razieh Pourhasan posit that our three-dimensional universe may have arisen from the formation of a black hole in an earlier four-dimensional universe. Shouldn't we then expect to find two-dimensional universes created by our 3-D black holes and 1-D black holes from 2-D ones? And then what?

ANDY ROBERTSON
via e-mail

MANN REPLIES: In principle, this kind of dimensional "nesting" could exist. But there is currently no empirical evidence of such universes.

ERRATUM

Because of an editing error, "Cosmic (In) Significance," by Caleb Scharf, gave an incorrect measure for the smallest reproducing bacteria. They measure around 200 billionths of a meter.

LETTERS TO THE EDITOR

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Letters may be edited for length and clarity. We regret that we cannot answer each one. Post a comment on any article at ScientificAmerican.com/dec2014

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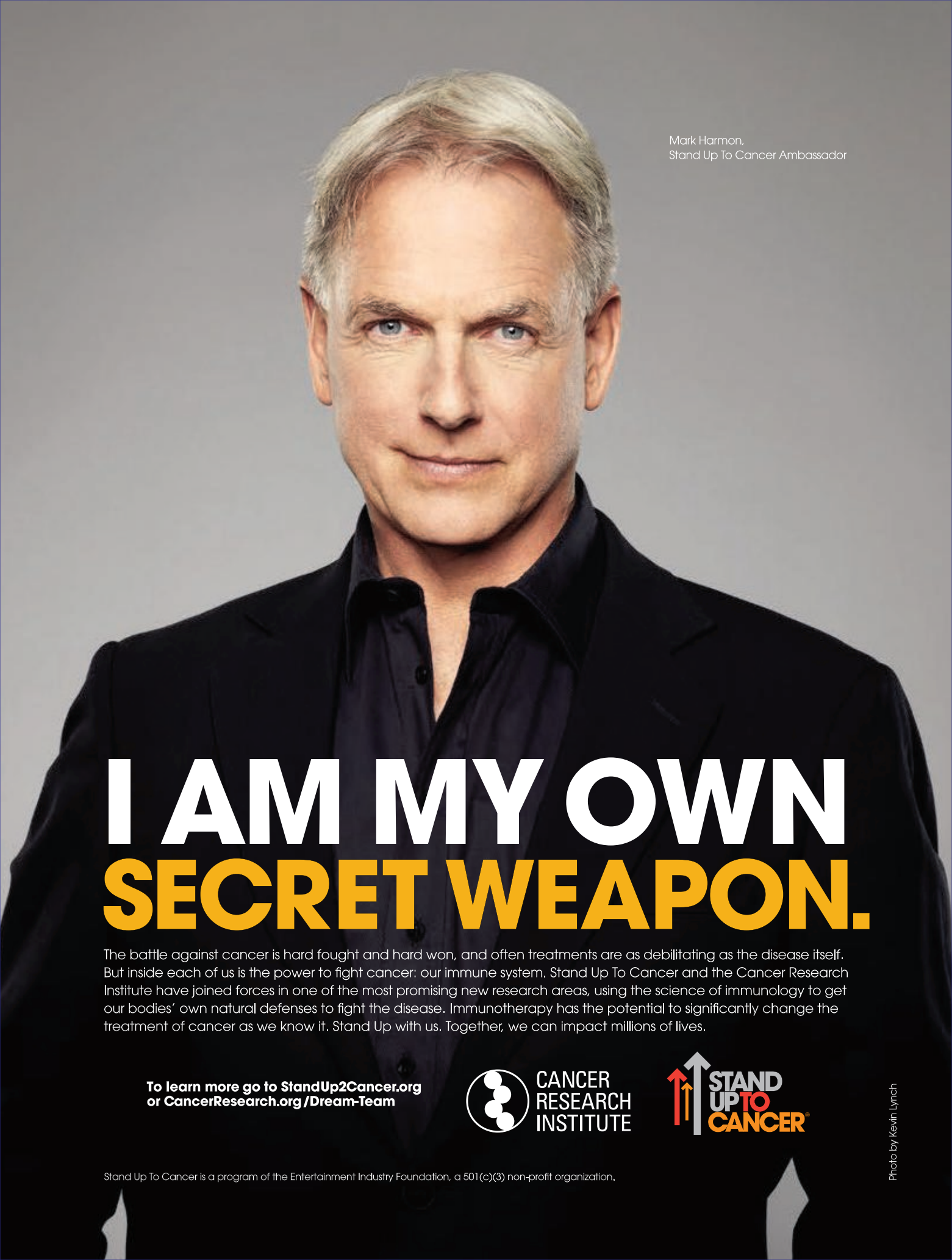
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Stand Up To Cancer Ambassador
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Photo by Kevin Lynch

Caution: Cops with Cameras

Wearing small recording devices could reduce violent confrontations, but without careful planning and better research, the attempt could backfire

Less than a month after Michael Brown was shot and killed by a law-enforcement officer in Ferguson, Mo., the municipal police department issued 50 wearable video cameras to its officers so they could record encounters with the public. Since then, at least a dozen other U.S. cities—including Miami Beach, Fla., and Flagstaff, Ariz.—have announced similar plans. The response is commendable, but police chiefs should proceed cautiously.

Proponents argue that the small, tamper-proof cameras will lead to fewer violent encounters between police officers and citizens because everyone knows that their speech and actions can be retrieved later. The evidence supporting such a conclusion is preliminary, however. Blindly adopting the technology without a carefully thought out policy and without training on how and when cameras should be used could make matters worse.

"What if video doesn't get recorded during a critical incident because officers are not trained, or they don't understand how to maintain the equipment?" asks Michael D. White, a professor of criminology at Arizona State University, who recently assessed body-worn cameras for the U.S. Department of Justice. A community that has learned not to trust civic authorities might suspect a cover-up. And the chances of this kind of mistake are fairly high: in one survey, nearly one third of public safety agencies using body-worn cameras did not have a written policy governing when or under what circumstances they should be activated.

Even when video images are available, they are not always conclusive. For instance, after watching surveillance recordings of a 2012 arrest in Denver, in which the head of a handcuffed woman was slammed into a wall, the police chief concluded the use of force had been appropriate. But the city's independent monitor found it excessive. Still, more evidence in most cases, even if it is not always conclusive, may turn out to be helpful.

Tantalizing hints that camera use could minimize clashes exist in the five small field trials that have been published so far. Although several of them were subject to biases because conditions were not well controlled, the tests nonetheless suggested that, overall, body-camera use decreased the number of times officers resorted to force, as well as the number of times citizens complained about police behavior.

More rigorous study is needed. Patrol areas chosen to pilot the devices should be carefully compared with similar neighborhoods where officers do not wear cameras. These comparisons should be done before and after deployment to establish a proper baseline against which to measure the results. And video recording should be compared with other efforts, such as community outreach programs or officer training to de-escalate tense situations, to see which tactics prove more effective at reducing clashes.

Research should also address important civil-liberty questions. Could the images be used to monitor or otherwise entrap law-abiding citizens? Within police ranks, some officers worry that an unsympathetic supervisor might troll videos for minor infractions to torpedo an officer's career. Who has access to the videos? Will eyewitnesses be less willing to speak forthrightly if their conversations are recorded?

The National Institute of Justice, the research and development arm of the DOJ, is funding two larger camera studies in Las Vegas and Los Angeles that should explore a few of these issues. Results are expected starting in late 2015.

Chances are that the movement to adopt body-worn cameras is unstoppable. The American Civil Liberties Union, a traditional opponent of surveillance, has cautiously embraced the technology. This momentum makes the urgent need for clear rules and training guidelines all the more apparent. Towns and cities that are planning to use the cameras should ensure that the community has an ongoing say in those plans, as well as a mechanism to resolve disputes when videos are subject to contradictory interpretations.

Finally, the DOJ, which will probably end up subsidizing the purchase of many of these cameras, should buy devices only for police forces that participate in larger research efforts and share the results with the wider public. This way we can all see what is going on. SA

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THE SMARTEST GIFTS IN SCIENCE

Commentary on science in the news from the experts

Ryan Calo is a law professor at the University of Washington and a leading scholar on robotics, law and policy.

Bring on the Robocrats

We need a federal agency to smooth the integration of robotics into society

The robots are no longer coming; they are here. And the law's response has been lacking. Many believe that the Federal Aviation Administration has overstepped its authority in regulating drones. Lawsuits imply that the Food and Drug Administration could have done more to vet robotic surgery. Nevada—the first state to pass a driverless car law—had to repeal its definition of autonomous driving and write a new one.

What is the best approach for integrating this transformative technology? We cannot know for sure. That is why we need a federal agency to help figure it out.

Important technologies have led to the formation of new agencies in the past. Trains did. Radio led to the Federal Radio Commission, which became the Federal Communications Commission. The Internet has no federal agency as such, but two governing bodies supervise its unique architecture. Why not robotics? It would go against precedent to *not* have a federal robotics agency.

The need for such an agency is already clear. I have mentioned the problems that the FAA, the FDA and the state of Nevada have had with robotics. Other examples abound. The FCC has been trying for more than 10 years to figure out whether it would be safe for people to use efficient, artificially intelligent radios that can change the frequency and power at which they broadcast. The Securities and Exchange Commission has been looking at high-speed trading algorithms—robots of the market, if you will—since they briefly crashed the stock exchange a few years ago. The agency still has no idea what to do about them. When Congress charged the Department of Transportation with determining whether a software glitch caused certain Toyotas to "suddenly accelerate," the agency had to call in NASA—which can take only so many breaks from putting robots on Mars to look at a sedan.

A big part of the problem is that the government lacks expertise in robotics, and because of its piecemeal approach to the subject, it is not accruing that expertise fast enough. Agencies, states, courts and others are not talking to one another about these issues. Government entities fail to see common themes in different technologies: drones, for instance, rarely come up in discussions of driverless cars even though they present similar issues of safety, privacy and psychological unease.

A "Federal Robotics Commission" could help. Such a body should not "regulate" robots in the sense of fashioning rules that roboticists or others must follow. That would be premature. Rather the commission would be organized to support and advise.

This past fall I wrote a Brookings Institution white paper, "The Case for a Federal Robotics Commission," explaining how this agency could operate. In broad strokes: it could coordinate basic robotics research in an attempt to solve the still considerable technical challenges this technology presents. It might advise other federal agencies on matters involving robotics, including the DOT on driverless cars, the SEC on high-speed trading, the FDA on robotic medical devices, the FCC on "cognitive radios," the FAA on drones and, eventually, the Federal Trade Commission on consumer products. A robotics agency could play a similar advisory role for lawmakers and even the courts. Finally, it could convene stakeholders from industry, government, academia and nongovernmental organizations to discuss the impact of robotics and artificial intelligence on society.

There would be other benefits. Today the government has a hard time hiring engineering talent away from academia or industry. A robotics agency would be well placed to attract technologists who might be reticent to work for the government otherwise. The U.S. has consciously cultivated a "best and brightest" approach to recruitment in the past—which is why, when faced with a tough technical challenge, the DOT found the people it needed at NASA.

Government agencies in Japan and Europe are already playing a central role in robotics. The European Union, for example, has commissioned a consortium of experts to develop comprehensive legal and policy guidelines. The U.S. should follow suit. If we fail to think about proper legal and policy infrastructure now, robotics could be the first transformative technology since steam in which America has not played a preeminent role. SA

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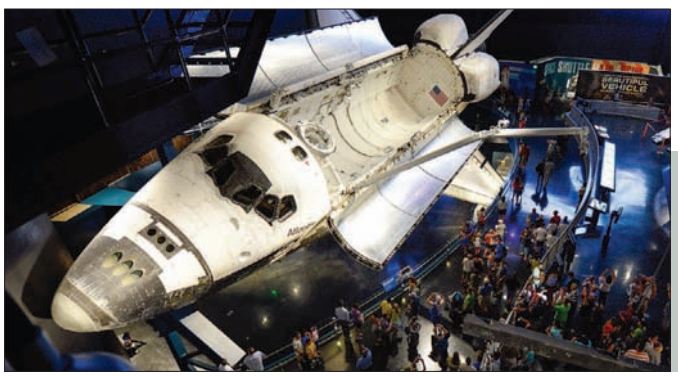

LIGHTNING

The Mysteries of Lightning

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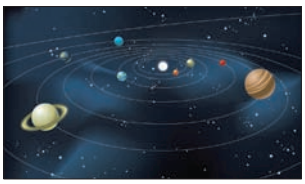

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Published in the 16 October issue of *Nature* and available free online for six months

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From the basic functions of the cell to cures for HIV and cancer, *Nature Outlook: Medical Research Masterclass* uses the 2014 Lindau Nobel Laureate Meeting as a basis to explore the latest research in medicine and physiology. Topics are viewed from the perspectives of Nobel laureates and the young researchers aiming to emulate their success.

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The People's Climate March in New York City brought thousands to the streets.

GETTY IMAGES

CLIMATE CHANGE

Cities to the Rescue

As nations dither on meaningful steps to combat climate change, localities are stepping in with their own measures to reduce emissions of greenhouse gases

In the city that never sleeps, the lights burn all night. And New York City needs energy for those lights, as well as for heating, air-conditioning and many other services. To meet these demands, the Big Apple belched nearly 60 million metric tons of greenhouse gases into the atmosphere in 2005.

Eight years later, despite a rise in population and new construction, emissions of greenhouse gas pollution had dropped by more than 11 million metric tons. How did Gotham manage to go so green? By banning the dirtiest oil used for heating and benefiting from a switch to natural gas for generating electricity.

New York is not alone in taking climate change seriously. Cities across the globe are stepping into the leadership vacuum left by nations, which have failed to take meaningful action on global warming for more than two decades. Coastal cities, which are particularly vulnerable to sea-level rise and other ill effects of rising temperatures, are leading the charge. Copenhagen, Melbourne and a handful of others have laid plans to go carbon-neutral. The "Compact of Mayors," a group of 228 cities representing

Continued on page 19

For people with a higher risk of stroke due to
Atrial Fibrillation (AFib) not caused by a heart valve problem

ELIQUIS® (apixaban) is a prescription medicine used to reduce the risk of stroke and blood clots in people who have atrial fibrillation, a type of irregular heartbeat, not caused by a heart valve problem.

IMPORTANT SAFETY INFORMATION:

- **Do not stop taking ELIQUIS for atrial fibrillation without talking to the doctor who prescribed it for you. Stopping ELIQUIS increases your risk of having a stroke.** ELIQUIS may need to be stopped, prior to surgery or a medical or dental procedure. Your doctor will tell you when you should stop taking ELIQUIS and when you may start taking it again. If you have to stop taking ELIQUIS, your doctor may prescribe another medicine to help prevent a blood clot from forming.
- **ELIQUIS can cause bleeding, which can be serious,** and rarely may lead to death.
- **You may have a higher risk of bleeding if you take ELIQUIS and** take other medicines that increase your risk of bleeding, such as aspirin, NSAIDs, warfarin (COUMADIN®), heparin, SSRIs or SNRIs, and other blood thinners. **Tell your doctor about all medicines, vitamins and supplements you take.** While taking ELIQUIS, you may bruise more easily and it may take longer than usual for any bleeding to stop.
- Get medical help right away if you have any of these signs or symptoms of bleeding:
  - unexpected bleeding, or bleeding that lasts a long time, such as unusual bleeding from the gums; nosebleeds that happen often, or menstrual or vaginal bleeding that is heavier than normal
  - bleeding that is severe or you cannot control
  - red, pink, or brown urine; red or black stools (looks like tar)
  - coughing up or vomiting blood or vomit that looks like coffee grounds
  - unexpected pain, swelling, or joint pain; headaches, feeling dizzy or weak
- **ELIQUIS is not for patients with artificial heart valves.**
- **Spinal or epidural blood clots (hematoma).** People who take ELIQUIS, and have medicine injected into their spinal and epidural area, or have a spinal puncture have a risk of forming a blood clot that can cause long-term or permanent loss of the ability to move (paralysis).

I was taking warfarin. But ELIQUIS was a better find.

I TAKE ELIQUIS® (apixaban) FOR 3 GOOD REASONS:

1. ELIQUIS reduced the risk of stroke better than warfarin.
2. ELIQUIS had less major bleeding than warfarin.
3. Unlike warfarin, there's no routine blood testing.

ELIQUIS and other blood thinners increase the risk of bleeding which can be serious, and rarely may lead to death.

Ask your doctor if ELIQUIS is right for you.

This risk is higher if, an epidural catheter is placed in your back to give you certain medicine, you take NSAIDs or blood thinners, you have a history of difficult or repeated epidural or spinal punctures. Tell your doctor right away if you have tingling, numbness, or muscle weakness, especially in your legs and feet.

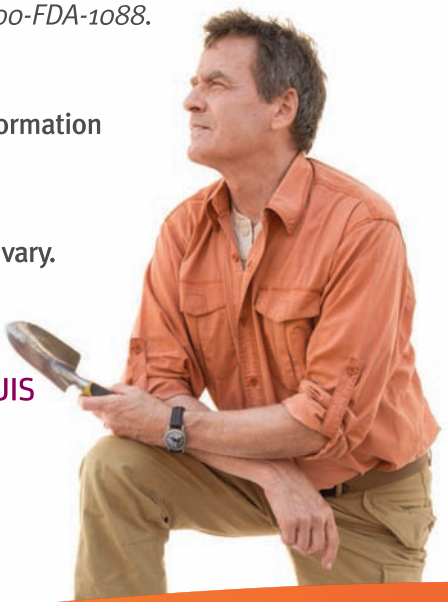
- **Before you take ELIQUIS,** tell your doctor if you have: kidney or liver problems, any other medical condition, or ever had bleeding problems. Tell your doctor if you are pregnant or breastfeeding, or plan to become pregnant or breastfeed.
- **Do not take ELIQUIS if you** currently have certain types of abnormal bleeding or have had a serious allergic reaction to ELIQUIS. A reaction to ELIQUIS can cause hives, rash, itching, and possibly trouble breathing. Get medical help right away if you have sudden chest pain or chest tightness, have sudden swelling of your face or tongue, have trouble breathing, wheezing, or feeling dizzy or faint.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

Please see additional Important Product Information on the adjacent page.

Individual results may vary.

Visit ELIQUIS.COM
or call 1-855-ELIQUIS



Eliquis®
(apixaban) tablets 5mg 2.5mg

IMPORTANT FACTS about ELIQUIS® (apixaban) tablets

℞ ONLY

The information below does not take the place of talking with your healthcare professional. Only your healthcare professional knows the specifics of your condition and how ELIQUIS may fit into your overall therapy. Talk to your healthcare professional if you have any questions about ELIQUIS (pronounced ELL eh kwiss).

What is the most important information I should know about ELIQUIS (apixaban)?

For people taking ELIQUIS for atrial fibrillation: Do not stop taking ELIQUIS without talking to the doctor who prescribed it for you. Stopping ELIQUIS increases your risk of having a stroke. ELIQUIS may need to be stopped, prior to surgery or a medical or dental procedure. Your doctor will tell you when you should stop taking ELIQUIS and when you may start taking it again. If you have to stop taking ELIQUIS, your doctor may prescribe another medicine to help prevent a blood clot from forming.

ELIQUIS can cause bleeding which can be serious, and rarely may lead to death. This is because ELIQUIS is a blood thinner medicine that reduces blood clotting.

You may have a higher risk of bleeding if you take ELIQUIS and take other medicines that increase your risk of bleeding, such as aspirin, nonsteroidal anti-inflammatory drugs (called NSAIDs), warfarin (COUMADIN®), heparin, selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs), and other medicines to help prevent or treat blood clots.

Tell your doctor if you take any of these medicines. Ask your doctor or pharmacist if you are not sure if your medicine is one listed above.

While taking ELIQUIS:

- you may bruise more easily
- it may take longer than usual for any bleeding to stop

Call your doctor or get medical help right away if you have any of these signs or symptoms of bleeding when taking ELIQUIS:

- unexpected bleeding, or bleeding that lasts a long time, such as:
  - unusual bleeding from the gums
  - nosebleeds that happen often
  - menstrual bleeding or vaginal bleeding that is heavier than normal
- bleeding that is severe or you cannot control
- red, pink, or brown urine
- red or black stools (looks like tar)
- cough up blood or blood clots
- vomit blood or your vomit looks like coffee grounds
- unexpected pain, swelling, or joint pain
- headaches, feeling dizzy or weak

ELIQUIS is not for patients with artificial heart valves.

Spinal or epidural blood clots (hematoma). People who take a blood thinner medicine (anticoagulant) like ELIQUIS, and have medicine injected into their spinal and epidural area, or have a spinal puncture have a risk of forming a blood clot that can cause long-term or permanent loss of the ability to move (paralysis). Your risk of developing a spinal or epidural blood clot is higher if:

- a thin tube called an epidural catheter is placed in your back to give you certain medicine
- you take NSAIDs or a medicine to prevent blood from clotting
- you have a history of difficult or repeated epidural or spinal punctures
- you have a history of problems with your spine or have had surgery on your spine

If you take ELIQUIS (apixaban) and receive spinal anesthesia or have a spinal puncture, your doctor should watch you closely for symptoms of spinal or epidural blood clots or bleeding. Tell your doctor right away if you have tingling, numbness, or muscle weakness, especially in your legs and feet.

What is ELIQUIS?

ELIQUIS is a prescription medicine used to:

- reduce the risk of stroke and blood clots in people who have atrial fibrillation.
- reduce the risk of forming a blood clot in the legs and lungs of people who have just had hip or knee replacement surgery.
- treat blood clots in the veins of your legs (deep vein thrombosis) or lungs (pulmonary embolism), and reduce the risk of them occurring again.

It is not known if ELIQUIS is safe and effective in children.

Who should not take ELIQUIS?

Do not take ELIQUIS if you:

- currently have certain types of abnormal bleeding
- have had a serious allergic reaction to ELIQUIS. Ask your doctor if you are not sure

What should I tell my doctor before taking ELIQUIS?

Before you take ELIQUIS, tell your doctor if you:

- have kidney or liver problems
- have any other medical condition
- have ever had bleeding problems
- are pregnant or plan to become pregnant. It is not known if ELIQUIS will harm your unborn baby
- are breastfeeding or plan to breastfeed. It is not known if ELIQUIS passes into your breast milk. You and your doctor should decide if you will take ELIQUIS or breastfeed. You should not do both

Tell all of your doctors and dentists that you are taking ELIQUIS. They should talk to the doctor who prescribed ELIQUIS for you, before you have **any** surgery, medical or dental procedure.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Some of your other medicines may affect the way ELIQUIS (apixaban) works. Certain medicines may increase your risk of bleeding or stroke when taken with ELIQUIS.

How should I take ELIQUIS?

Take ELIQUIS exactly as prescribed by your doctor. Take ELIQUIS twice every day with or without food, and do not change your dose or stop taking it unless your doctor tells you to. If you miss a dose of ELIQUIS, take it as soon as you remember, and do not take more than one dose at the same time. **Do not run out of ELIQUIS. Refill your prescription before you run out.** When leaving the hospital following hip or knee replacement, be sure that you will have ELIQUIS available to avoid missing any doses. **If you are taking ELIQUIS for atrial fibrillation, stopping ELIQUIS may increase your risk of having a stroke.**

What are the possible side effects of ELIQUIS?

- See **"What is the most important information I should know about ELIQUIS?"**
- ELIQUIS can cause a skin rash or severe allergic reaction. Call your doctor or get medical help right away if you have any of the following symptoms:
  - chest pain or tightness
  - swelling of your face or tongue
  - trouble breathing or wheezing
  - feeling dizzy or faint

Tell your doctor if you have any side effect that bothers you or that does not go away.

These are not all of the possible side effects of ELIQUIS. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

This is a brief summary of the most important information about ELIQUIS. For more information, talk with your doctor or pharmacist, call 1-855-ELIQUIS (1-855-354-7847), or go to www.ELIQUIS.com.

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August 2014
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Continued from page 15

436 million citizens around the world made commitments at the United Nations Climate Summit earlier this year to avoid two billion metric tons of greenhouse gas pollution per year. Even Chinese cities are in on the action: cap-and-trade markets for carbon pollution opened in 2013 in seven regions, including Shenzhen, which reduced carbon dioxide emissions by 2.5 million metric tons this past year, says Vice Mayor Tang Jie.

That forward motion is in contrast to China's failure as a nation to reduce carbon intensity—the pollution associated with economic activity—as it promised in the five-year plan that ends next year. China, the U.S. and the rest of the world spew more than 36 billion metric tons of greenhouse gases a year—and the number continues to rise.

In response to this lack of progress, at least 100,000 people took to the streets of New York this past September to demand action from leaders. Participants in the People's Climate March expressed hope that when country representatives meet in Paris in December 2015 for the 21st iteration of international talks, they will hash out a new, legally binding treaty to curb emissions. Many climate policy experts fear the meeting will not achieve nearly enough, however.

Regardless of how international talks go, the world's cities could cut eight billion metric tons of greenhouse gases by 2050, according to an analysis by the C40 group of cities. That is significant but delivers only slightly more than the Montreal Protocol of 1987, the single biggest step ever taken to restrain climate change. That one treaty accomplished what it would take hundreds of local laws to do. An international solution is important, but until one arrives, the cities will strive to keep the lights on and the pollution down. *—David Biello*

COURTESY OF CHRIS LARSEN *University of Alaska Fairbanks*

ATMOSPHERIC SCIENCE

Forecast: Cloudy

Climatologists often ponder clouds. Do they largely reflect sunlight away from Earth, helping it cool, or do they absorb and reradiate heat, accelerating rising temperatures? Their net effect in a changing climate remains an unknown. In September NASA deployed a team to the Arctic to gather more data on this question. Onboard a C-130 plane with solar, thermal and microwave radiometers, researchers recorded how sunlight and heat moved through the clouds; they also surveyed sea ice above 250,000 square nautical miles of Alaska. The work complements another NASA-supported team at the University of Alaska Fairbanks that is monitoring glacier size with planes such as the DHC-3 Otter (*above*). In both cases, planes collect sharper readings than satellites. "We'll be making the data set available to the scientific community within six months," says NASA mission leader William Smith. *—Amy Nordrum*

MATERIALS SCIENCE

Bend by Design

New progress in flexible displays

A handful of iPhone 6 owners were dismayed this past fall to find that their new gadgets bent ever so slightly. Apple responded by stating that the issue was extremely rare and that the products met high endurance standards. Still, some technology companies do want electronics that can bend—on purpose.

Materials scientists have been working on components that can flex and roll for years. In a paper published in September in the journal *APL Materials,* researchers at Seoul National University describe a recent success for displays: flexible LEDs that could help replace shatter-prone screens. The scientists first grew carpets of microscopic wires of gallium nitride, a light-emitting crystalline material, on an ultrathin mesh of graphene, which is a layer of carbon atoms that is flexible, conductive and tough. They then peeled the graphene-LED sheets off a copper backing and placed them on a pliable polymer—the beginnings of a bendy screen.

The blue LEDs found inside most of today's LCDs—and whose inventors were awarded the Nobel Prize in Physics this year—use gallium nitride because it is energy efficient and bright. It has been difficult to grow the material on a pliable surface, however. The Korean team's new LEDs, which can shine without interruption through more than 1,000 bending cycles, seem to balance the trade-off between quality and flexibility. If the researchers can integrate these individual sheets to make a full display, the LEDs might be found in future phones that bend—by design. *—Katherine Bourzac*

Illustrations by Thomas Fuchs

SPACE

Deep Space or Bust

NASA will soon launch its new capsule on a maiden flight

NASA retired its ride to space, the space shuttle, in 2011, but its next spaceship was in the works well before then. Conceived in 2005, the *Orion* capsule is now set to make its first test flight, which is scheduled for December.

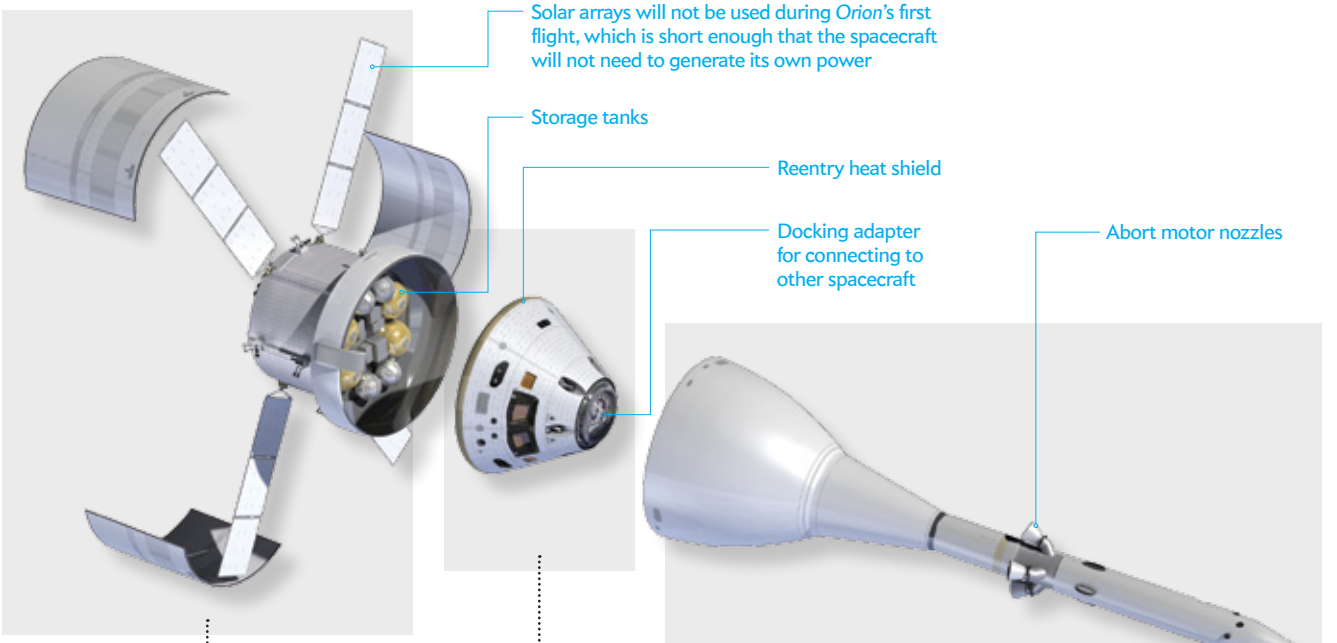
The cone-shaped vehicle, designed to carry humans farther into space than ever before, is reminiscent of the *Apollo* capsules that flew astronauts to the moon, but it is a third larger. These roomier dimensions can house between two and six crew members for missions of 21 days—longer than any previous vehicle except space stations.

The upcoming four-hour flight, when the capsule will launch from Cape Canaveral, Fla., and enter low-Earth orbit, will carry no human cargo. Rather the trial run will ensure that the spacecraft's rocket encasings safely jettison when they are supposed to, that its parachutes deploy correctly and that its heat shield can withstand the 4,000 degree Fahrenheit flames of reentry. The test should pave the way for a crewed flight in 2021 to visit a nearby asteroid. The ultimate goal is a journey to Mars, when *Orion* would dock with another traveling habitat for extra living space.

***Orion* assembly at the Kennedy Space Center**

Eventually *Orion* will fly atop NASA's Space Launch System (SLS), a rocket still in development that will be the most powerful ever built. For *Orion*'s test this month, the United Launch Alliance's Delta IV Heavy rocket will stand in. The Delta IV produces nearly two million pounds of thrust, much less than the 8.4 million pounds of thrust the SLS should generate (which is 10 percent more than the Saturn V rocket that launched astronauts to the moon). NASA estimates it will cost up to $22 billion to develop the first versions of *Orion* and the SLS.

A lot is riding on this maiden voyage besides money. Ever since the space shuttle was mothballed, the future of American spaceflight has been murky. This could be the energizer NASA has been hoping for. —*Clara Moskowitz*



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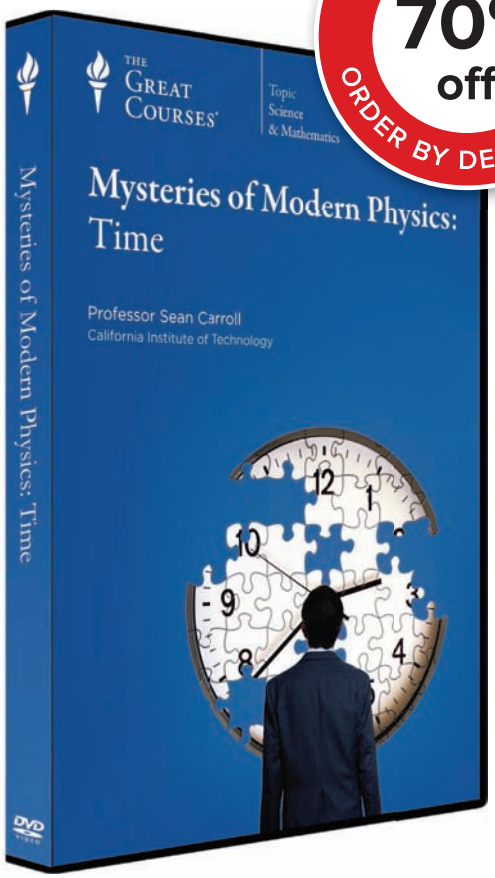

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SUSTAINABILITY

What Would John Muir Do Now?

December marks the centennial of the death of conservationist John Muir, who founded the Sierra Club and helped create the Yosemite and Sequoia national parks, among others. Scientific American asked four speakers from November's World Parks Congress—a meeting held every 10 years by the International Union for Conservation of Nature to discuss issues concerning protected areas—what would be at the top of their to-do lists for the next decade. *—Roger Drouin*

John Muir (1838–1914) advocated for the creation of today's national parks.

"Muir saw the decline of the passenger pigeon. Now we are facing an extinction wave. To stabilize and reverse the loss of biodiversity, we have to reduce our ecological footprint; we have to produce more wisely and consume more wisely, using less energy and less land and less water."
—MARCO LAMBERTINI, *director general, World Wide Fund for Nature International*

"We need to look at wetland restoration because we have lost so much: a 40 percent loss from 1970 to 2010. All of the water that is groundwater—the aquifers, the peat bogs, the salt marshes, the mangroves, coral reefs—all of these are classified as wetlands. That's why we have to tackle the issue from the global level."
—CHRISTOPHER BRIGGS, *secretary general, Convention on Wetlands of International Importance (Ramsar Convention)*

"People don't realize the value in the illegal trade in wildlife is nearly as high as the trade in drugs. We need governments to take this seriously. We need legislation in countries that makes killing rhinos a serious, serious crime."
—GREGORY CARR, *president, Gorongosa Restoration Project (the nonprofit manages the one-million-acre Gorongosa National Park in Mozambique)*

"Even where land is severely degraded, simple and cheap restoration methods can restore incredible biodiversity, replenish watersheds, attract migratory birds and shield the land from being ravaged by extreme weather. We may not recover everything, but the improvement is dramatic."
—MONIQUE BARBUT, *executive secretary, U.N. Convention to Combat Desertification*

GETTY IMAGES

COMMENT AT ScientificAmerican.com/dec2014

BY THE NUMBERS

A GALÁPAGOS ICON

Taxidermists give immortality to a beloved tortoise

Tucked in a corner of the American Museum of Natural History in New York City, next to fossils of long-gone gigantic sloths and knee-high horses, stands a newcomer to the extinction parade: Lonesome George, the last of his subspecies and a native of the Galápagos's Pinta Island. Until his death in 2012, the giant tortoise had stood as a global conservation icon for four decades. Now, preserved by a team of taxidermists and put on display at the museum until his January 4 return to his South American homeland, George still shares his message amid other vanished species—lonesome no more. *—Nicholas St. Fleur*

1971
Year George was found by József Vágvölgyi, a Hungarian scientist studying snails

165
Weight, in pounds

100
Estimated age at death

9
Months to dry his shell

1.5
Years to complete taxidermy

7
Height of the mount, in feet

100
Photographs consulted to get George's regal pose just right

Photograph by Liz Tormes

KNOW THE **JARGON**

Plantibody:

(*n.*) A human antibody produced by plants.

This past summer doctors treated two Americans infected with Ebola virus with an experimental drug created by Mapp Biopharmaceutical. Both patients lived, although experts are not certain whether the drug contributed to their survival. Named ZMapp, it is a mixture of different antibodies that bind to the virus—and is made by tobacco plants.

Plants do not have antibodies of their own, but they nonetheless have the cellular machinery to make these infection-fighting proteins. Researchers first recognized such potential in 1989 and went on to hijack a tobacco plant's biology to synthesize human antibodies. Since then, several biotech companies have been developing plantibodies that could treat diseases, such as Ebola and rabies.

Plantibody production is straightforward: scientists insert the gene for an antibody into a disarmed virus, which is taken up by a plant's leaves. Using the new DNA, the plant builds the human proteins. Scientists extract them about a week later. The process takes a little over a month—a faster and cheaper means of manufacturing than using hamster ovary cells, which is the standard. Growing the plants is inexpensive, says Julian Ma, an immunologist at St. George's, University of London. "It's basically just soil and water you're paying for."

Despite its ease, plantibody production is not widespread. Most large pharmaceutical companies are reluctant to make the switch because they have invested so much money in ovary cells, Ma says. Until plantibody drugs go through regulatory processes, smaller biotech companies most likely will be the ones producing them.

Plantibodies in development include those designed to target HIV, herpes, cancer and rabies. ZMapp itself is nearly ready to enter clinical trials: a recent study of Ebola-infected monkeys demonstrated its effectiveness. Experts estimate that plantibodies will not go on the market for at least five years, but that projection may change. In September the U.S. Department of Health and Human Services announced that it would like to accelerate ZMapp tests in an 18-month push.

—Annie Sneed

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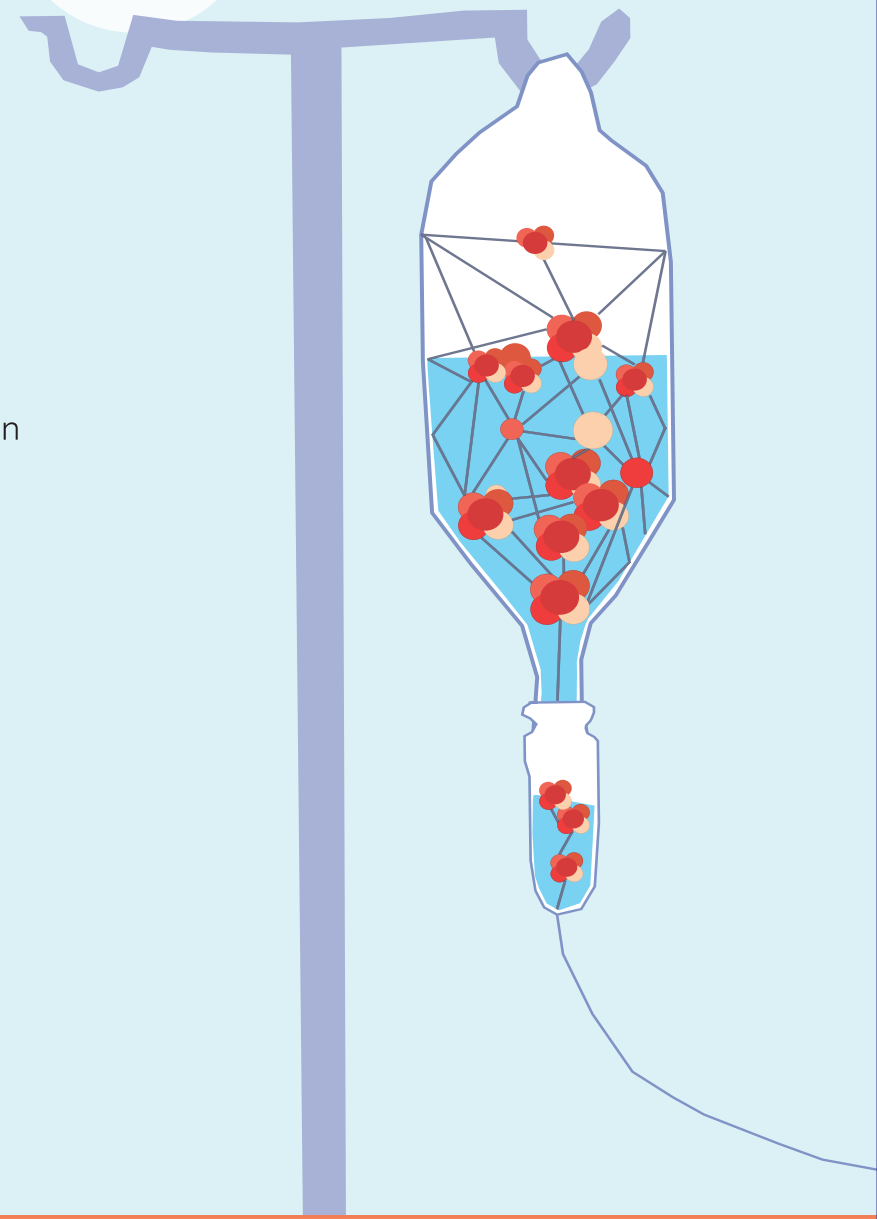

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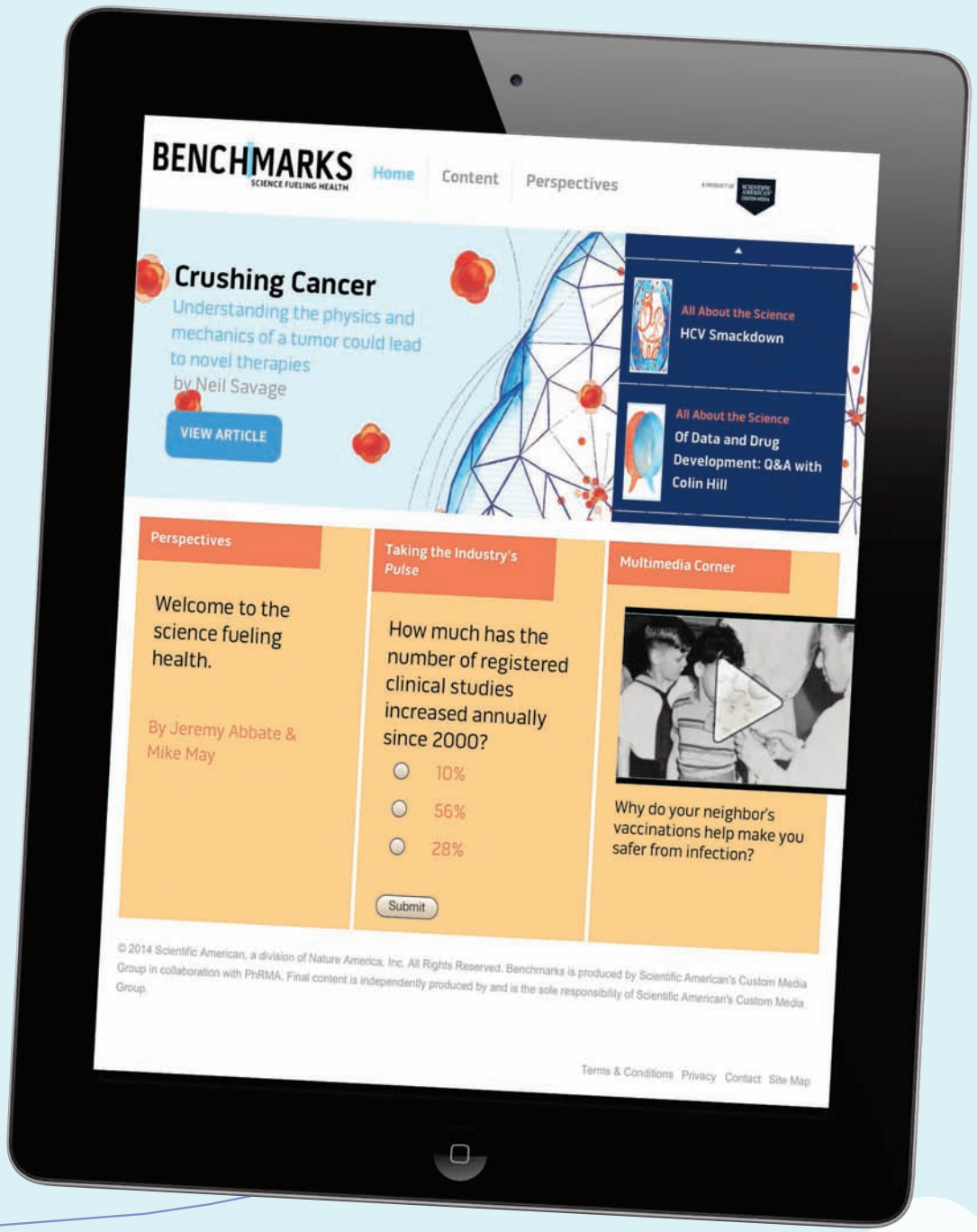

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MYCOLOGY

Mushroom Man

Collecting fungi is more than a hobby for Rodham Tulloss

One of the world's largest and most diverse collections of amanitas—the group of fungi that includes death caps, destroying angels and the polka-dotted mushrooms of Super Mario renown—is kept in a converted garage in Roosevelt, N.J. The stockpile is maintained by Rodham E. Tulloss, aged 70, who has documented species so rare they have been seen only once or twice in the past 50 years. His climate-controlled Herbarium Rooseveltensis Amanitarum may contain more distinct species than any university or museum. "I've never counted," he says. "I can tell you I have well over 6,000 collections of *Amanita* alone."

Tulloss, a retired electronics engineer and Bell Labs Fellow, is a passionate amateur who has collaborated with professionals. He has worked with evolutionary biologists at Harvard University and co-authored a paper with them in *PLOS ONE* that showed how amanitas lost genes associated with breaking

Photograph by Ethan Hill

“I don’t know how much time I have left so I want to give it my all.”

down cellulose as they evolved—in effect, moving from free-living organisms into a long-term, symbiotic relationship with trees. He is also an honorary research associate at the New York Botanical Garden in the Bronx and has worked with mycologists at the Chinese Academy of Sciences’s Kunming Institute of Botany and many others to reliably identify and describe new species.

Of the estimated 1.5 million fungi species worldwide, only a small percentage have been categorized. One hurdle is the biodiversity magnitude; another problem is that the fruiting bodies, the things we call mushrooms, can be inconspicuous and fleeting. Thomas Bruns, a microbiologist at the University of California, Berkeley, says, “If you had to identify all of the plants on earth by their fruit alone, it’d be a pretty tough job, and you’d probably make a lot of mistakes at it. That’s kind of what we’ve got here.” Two years ago, when Bruns convened a meeting of the North American Mycoflora Project, an ambitious attempt to catalogue and map the distribution of species, he looked to Tulloss’s garage. “He has a supervaluable collection,” Bruns says.

Genetic sequencing has revealed many misclassifications in the fungi world in recent years. Tulloss’s late mentor, Dutch mycologist Cornelis Bas, called him a bear because of his persistence in sorting out the conflicting labels. He took the description to heart and calls himself the Amanita Bear. Motto: “Only you can prevent taxonomic and nomenclatural confusion!”

Tulloss’s obsession does not extend to all mushrooms. In August he was walking in a cemetery near Steuben, Maine, when he ducked into the woods and spotted an edible fungus, *Hypomyces lactifluorum*, which resembles a cooked crustacean. “Lobsters!” He shouted. While his companions bent to collect them for dinner, Tulloss walked on in search of tall, white fungi with a ring around the stem: amanitas. “I don’t know how much time I have left,” he says, “so I want to give it my all.” —*Peter Andrey Smith*

TECHNOLOGY

Power to the Internet of Things

Four novel energy-gathering methods will keep gadgets abuzz

As many as 50 billion devices will be online by the end of the decade. Along with smart thermostats and appliances, this so-called Internet of Things (IoT) includes swaths of tiny sensors that track everything from steps and calories to humidity and light. A web of power cords would undercut its usability. Thus, universities and companies alike are refining energy-harvesting techniques to free the IoT from plugs—for good.

—*Corinne Iozzio*

PIEZOELECTRIC

This past summer Rochester, N.Y.–based MicroGen Systems rolled out the Bolt, a quarter-sized generator that converts ambient vibrations into usable power. A subtle rumble, perhaps produced by an air conditioner or microwave, causes a flap in the device to flutter, which in turn creates a current that goes into either a capacitor or a small rechargeable battery.

THE GOOD: Scalable. Vibration sources readily available.

THE BAD: Produces only enough energy for low-power devices, such as sensors.

SOLAR

SunPartner Technologies, a French company, has developed transparent solar panels that can cover screens and other surfaces. An array of microlenses on the photovoltaic material bends light around the strips to make them invisible. The company is already producing displays for smartphones and watches and is finalizing a prototype of an embedded sensor.

THE GOOD: Virtually invisible panels can be incorporated into a wide array of devices.

THE BAD: Will not work in inconsistent light or typically dark areas, such as basements and under sinks.

WI-FI BACKSCATTER

A prototype by University of Washington researchers harvests power from existing wireless transmissions, such as television and radio signals, to send messages over a local Wi-Fi network. The device selectively reflects Wi-Fi signals, encoding data that other devices on the network can then decode. The team's start-up aims to bring the first products to market within a year.

THE GOOD: Can both charge devices and transmit data.

THE BAD: Wi-Fi transmissions typically come in bursts, making connectivity unpredictable and power draw relatively low.

THERMOELECTRIC

By taking advantage of electrons' natural flow from the hot side of a conductive material to the cold side, a thermoelectric generator can convert body heat into power. A team at the Korea Advanced Institute of Science and Technology recently demonstrated a compact version encased in flexible glass; it is capable of producing 40 milliwatts of power at room temperature.

THE GOOD: Potential to continuously charge a battery as long as the device is in contact with a warm body.

THE BAD: Requires a large temperature differential (about 31 degrees Celsius) to work. Small power yield. Best suited for wearables, not ambient sensors.

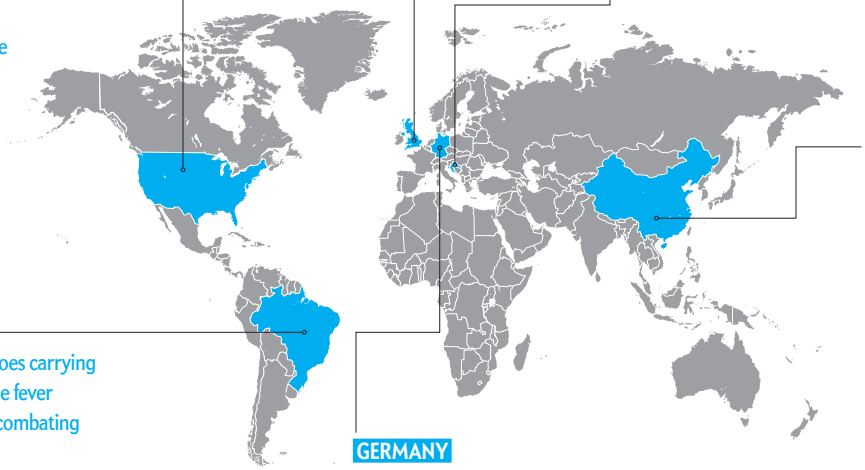
IN THE NEWS

Quick Hits

U.K.
Copyright law now permits citizens to transfer material on DVDs, CDs and MP3s to a backup device. Owners still cannot burn a DVD for friends—the copy must be for personal use.

CROATIA
A 70-year-old pilot completed the first underground descent in a hot-air balloon, navigating a shaft in Mamet Cave to nearly 700 feet below the surface.

U.S.
The federal government launched an open database to catalogue the financial ties among doctors and drug and medical device companies.



CHINA
Physicists plan to submit a blueprint for what would be the world's largest particle collider—twice the size of CERN near Geneva—to the government in December. The ring-shaped collider would be large enough to encompass Manhattan.

BRAZIL
Batches of 10,000 mosquitoes carrying bacteria that inhibit dengue fever were released in hopes of combating the disease's spread.

GERMANY
Attending any university is now free. Lower Saxony became the last state to abolish tuition fees.

ANIMAL BEHAVIOR

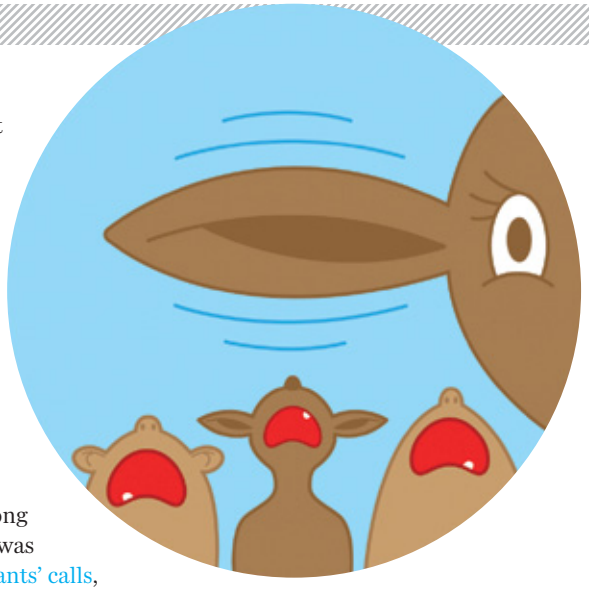
Call of the Crybaby

Distress calls of infant mammals are strikingly similar

A sharp cry pierces the air. Soon a worried mother deer approaches the source of the sound, expecting to find her fawn. But the sound is coming from a speaker system, and the call isn't that of a baby deer at all. It's an infant fur seal's.

Because deer and seals do not live in the same habitats, mother deer should not know how baby seal screams sound, reasoned biologists Susan Lingle of the University of Winnipeg and Tobias Riede of Midwestern University, who were running the acoustic experiment. So why did a mother deer react with concern?

Over two summers, the researchers treated herds of mule deer and white-tailed deer on a Canadian farm to modified recording of the cries of a wide variety of infant mammals—elands, marmots, bats, fur seals, sea lions, domestic cats, dogs and humans. By observing how mother deer responded, Lingle and Riede discovered that as long as the fundamental frequency was similar to that of their own infants' calls, those mothers approached the speaker as if they were looking for their offspring. Such a reaction suggests deep commonalities among the cries of most young mammals. (The mother deer did not show concern for white noise, birdcalls or coyote barks.) Lingle and Riede published their findings in October in the *American Naturalist*.



Mother deer should not know how baby seal screams sound.

Researchers had previously proposed that sounds made by different animals during similar experiences—when they were in pain, for example—would share acoustic traits. "As humans, we often 'feel' for the cry of young animals," Lingle says. That empathy may arise because emotions are expressed in vocally similar ways among mammals.

Psychologist David Reby of the University of Sussex in England, who studies the evolution of communication, is not surprised by these findings. From an infant's perspective, it is advantageous to attract any potential caregiver that could increase its chances of survival. And for parents, Reby says, "it is probably more advantageous to respond to anything that vaguely resembles a baby distress call." If a predator is involved, a parent cannot waste time deciding whether the baby in need of help is its own. The costs of ignoring the cry are too high.

These results might also explain some instances of cross-species adoption in the wild. If a mother has recently lost her own infant and still has maternal hormones circulating, Lingle says, she may be primed to care for a ward when she hears its call—no matter what it looks like. —*Jason G. Goldman*

Healy-Thow, Judge and Hickey (*left to right*) took home $50,000 worth of scholarships.

COURTESY OF SCOTT STUPPI

PLANT SCIENCE

Of Germs and Germination

Teens take top science prize for a plan to ease world hunger

A chance observation about warts on a pea plant led a group of teenagers on a three-year mission to ease the world food crisis using agricultural science. Their perseverance paid off when they won the Grand Prize at the annual Google Science Fair in Palo Alto, Calif., in September. (*Scientific American* co-sponsors the awards.)

The mission started after Émer Hickey, a now 17-year-old from Kinsale, Ireland, and her mother first embarked on gardening a few years ago. They pulled up a pea plant and saw that the roots were covered in nodules. Thinking the bumps might be a sign of poor health, Emer brought the plant to her science teacher. He explained that the growths held rhizobium, a beneficial bacterium that converts nitrogen in the atmosphere into ammonia and other compounds that help plants grow.

At the time, Hickey's geography class was studying the world food crisis, which inspired her and two friends, Ciara Judge and Sophie Healy-Thow, to try and apply rhizobia to barley and oats to see if the microbes might boost their yields. "We became really interested in what this bacterium can do," Healy-Thow says.

After some 120 tests on thousands of seeds in a bedroom-turned-laboratory, the team found that rhizobia sped up the rate at which barley seeds germinate by 50 percent and increased crop yield by as much as 74 percent.

They are now working with crop scientists to better understand how the bacteria interact with cereal crops and to confirm their results in broader field trials. Says Hickey: "We want to bring this into commercial use and change the world with our findings." —*Anna Kuchment*

Claudia Wallis is an award-winning science journalist whose work has appeared in numerous national publications.

Never Too Old for Chemo

As the number of elderly patients with cancer soars, researchers explore how best to treat them

For my hale and hearty father-in-law, the first sign that something was wrong occurred at 88 years of age, when his ever reliable tennis serve kept landing astray. A series of medical tests soon revealed the worst: advanced, metastatic pancreatic cancer. Treatment might buy him a little time, his doctors told him, but that prospect did not outweigh his dread of spending his final days in a toxic and debilitating haze of chemotherapy. He quickly opted for hospice care and died with dignity less than two months later, surrounded by loved ones.

My own father learned he had bladder cancer at 91 and made a very different choice. He underwent the full trifecta of treatment: surgery to pare down a tumor that had already penetrated the bladder wall, plus seven weeks of chemotherapy and 35 radiation treatments to destroy lingering cancer cells. There were times when he regretted it, complaining of weakness and torpor, but 20 months after completing the clinical gauntlet, he is alive and going relatively strong, considering he is 93. His sister made a similar decision when faced with lymphoma at 88; she, too, is a survivor—at 91.

Twenty years ago few oncologists would have attempted aggressive therapies with 90-year-olds. No one used the term "granny death panel," but people in their ninth and 10th decades of life were seen as too fragile for treatment. Their cancers were often believed to be so slow-growing that something else might kill them first; it made little sense to put them through the ordeal and cost of treatment.

Those ideas have since largely fallen by the wayside. Now, as my own family experience suggests, the elderly—especially the very old—are the fastest-growing group of cancer patients in the U.S., thanks mostly to the aging of the general population, better screening, improved therapies and other changes in medical practice. More than half of U.S. cancer patients are older than 65, and by 2030 that figure will rise to 70 percent, according to a 2012 analysis. Understanding differences in how cancer develops and behaves in the elderly and determining which older patients can benefit from treatment—and which ones lack the resilience to tolerate it—are therefore increasingly urgent issues. Fortunately, research is beginning to answer these questions and provide badly needed tools for doctors, patients and families facing complex decisions about treatment.

A DISEASE OF AGING

LIVE LONG ENOUGH, and chances are about 40 percent that you will develop a potentially life-threatening malignancy. Although cancer certainly can and does strike young people, it is, by and large, a disease of aging—and the leading cause of death in Americans between 60 and 79 years old.

Risks for most types of cancer increase as we grow older for at least three reasons. First, we experience more cumulative exposure to the things that mess with DNA in ways that can lead to malignant growth: sunlight, radiation, environmental toxins and noxious by-products of metabolism. Second, older cells are more vulnerable to this damage—or less able to repair themselves. "Most aging cells develop genomic changes that make them more susceptible to the carcinogens in the environment," says oncologist Lodovico Balducci, who studies and treats cancer in the elderly at the Moffitt Cancer Center in Tampa, Fla. Third, the various housekeeping systems—such as the immune defenses—that keep our tissues healthy begin to break down with age, the equivalent of watchdogs falling asleep.

The old idea that cancer is less aggressive in the elderly is not

Illustration by Richie Pope

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entirely without merit: breast and prostate cancers tend to grow more slowly in older patients. But other types—colon and bladder cancer and certain leukemias, for example—are usually more aggressive and harder to treat. This may in part be because of certain age-related genetic mutations.

An older body also provides a different internal environment for the growth of cancer cells than a younger body does. Whereas the drop in estrogen and other sex hormones that occurs with age can slow the development of some breast and prostate tumors, at least one other common endocrine change—rising levels of insulin—does the opposite, stimulating tumor growth. In addition, older tissues tend to exhibit more chronic inflammation—a low-level infiltration of immune cells and substances. "This hallmark of many old tissues," explains Judith Campisi of the Buck Institute for Research on Aging in Novato, Calif., "will generally promote the growth of cancer."

No wonder, then, that people who are 75 and older have the highest cancer rates of all age groups. According to 2010 figures from the U.S. Centers for Disease Control and Prevention, tumors with the potential to invade other tissues are nearly three times as common in people 75 and older as in individuals between ages 50 and 64—and that does not include common skin cancers (basal and squamous cell types) that tend not to spread deep within the body and that also become more pervasive with advancing age.

GETTING TREATMENT RIGHT

DESPITE THE PREVALENCE of cancer in the elderly, treatment studies rarely include people older than 70, leaving doctors without clear guidance on what works best for such patients. "In geriatrics, we are always having to extrapolate from treatment guidelines based on younger people, but the gap is most extreme in cancer care," says Holly Holmes, a geriatrician—or specialist in aging—at the University of Texas M.D. Anderson Cancer Center. That gap may finally begin to close in the years ahead. In September 2013 a report on the "crisis in cancer care" from the Institute of Medicine recommended offering drug companies a patent extension of six months on new drugs that have been tested in the elderly; a similar incentive has greatly increased the testing of drugs in children. Without such changes, Holmes notes, "we'll continue to test therapies only in the fittest people and get information that cannot be applied to older patients."

In the meantime, though, some researchers have designed tools that can help physicians and patients make informed decisions. Doctors such as Holmes and Balducci, who treat a lot of elderly patients, generally agree that chronological age alone is a poor indicator of how someone will respond to cancer treatment. What is more revealing, they say, is the patient's physiological age—a broad measure of health and well-being—and something called physiological reserve, which is essentially the ability to withstand stress, including the stress of surgery and chemotherapy. Doctors can best determine these attributes with a tool called a comprehensive geriatric assessment, a multifaceted inventory of the patient's strengths and weaknesses that looks at how well the body is operating. The assessment takes into account chronic diseases, medications, cognitive ability, nutritional status and social support. It also examines the patient's ability to function in the world: whether he or she needs help with what doctors call "activities of daily living" (getting out of bed, dressing, bathing, eating, toileting) and with such "instrumental activities" as managing money and medications, cooking, doing laundry and negotiating public transportation.

Much like the developmental milestones that pediatricians use to assess a toddler's health, activities of daily living involve multiple body systems working together and are therefore remarkably revealing of an older person's health—and predictive of the ability to tolerate treatment, says geriatric oncologist Arti Hurria of the City of Hope Comprehensive Cancer Center in Duarte, Calif. Unfortunately, such thorough assessment is rarely available outside of major medical centers. To address that problem, Hurria and her colleagues have developed a self-administered version that takes patients a median of just 22 minutes to complete. They have also devised and tested a tool for determining chemotherapy tolerance in older patients, published in 2011 in the *Journal of Clinical Oncology*. "It's 11 questions, and it's not hard to do," says Hurria, who just completed a two-year term as president of the International Society of Geriatric Oncology. She sees it as a tool to help oncologists refine their treatment plans for elderly patients. Balducci and his colleagues at Moffitt have developed a similar tool.

The idea is to give more guidance to doctors who are otherwise forced to improvise. In elderly cancer patients like my father and aunt, who suffer from a variety of chronic health problems, physicians often modify standard treatment regimens—perhaps using two chemotherapy drugs instead of three or lowering standard dosages—in the hope that the revised treatment will work well enough. The 11-question tool leads to a score that predicts—on a scale from 0 to 100 percent—the risk of severe side effects from chemotherapy. "If the risk score is very high, you might decide, after discussion with the patient, on a less aggressive approach," says oncologist William Tew of Memorial Sloan Kettering Cancer Center in New York City. Having a clearer idea of the patient's risk profile, he says, is especially critical when dealing with cancer that has spread from its original site in the body because such cases tend to require prolonged and arduous therapy.

Tools for predicting response also provide a framework for conversations with the patient and his or her loved ones about how much risk—and what kind of risk—they feel is appropriate. A young patient may be willing to tolerate extreme side effects and long hospitalizations for a chance to live longer. For an elderly patient, having to enter a nursing home because of side effects might seem like a fate worse than dying. Hurria and Holmes say they spend about equal amounts of time persuading octogenarian patients to consider treatment and warning them about taking on too much risk. "Sometimes we say, 'You're actually really fit,'" Holmes says. "'Maybe you'd like to treat the cancer as if you were a 55-year-old.'" As elderly survivors like my father can attest, having lived many years in no way disqualifies you from gunning for more time. SA

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Learn about Arti Hurria's 11-question scoring tool at ScientificAmerican.com/dec2014/soh

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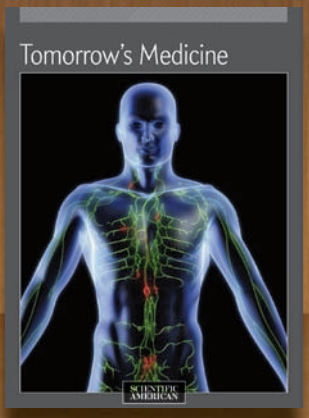

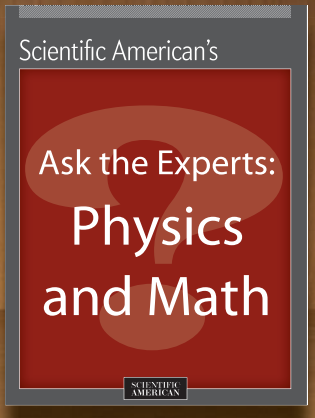

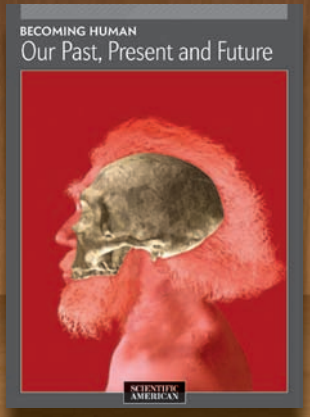

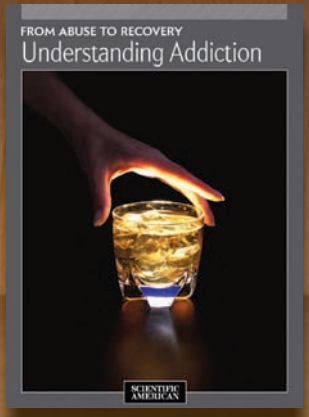

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David Pogue is the anchor columnist for Yahoo Tech and host of several *NOVA* miniseries on PBS.

Unpredictive Text

How Apple killed typing but still won the phone wars

Steve Jobs often swam against the tide of prevailing opinion. ("You can't make a mouse without two buttons!" "You can't make a computer without a floppy drive!" "You can't make a cell phone without a swappable battery!") He turned out to be right many times.

Occasionally, though, his decisions took the industry into awkward directions from which we've never really recovered. Jobs was fixed, for example, on the idea of a cell phone without any keys. The iPhone became a hit, it spawned imitators, and the rest is history (or the future, depending on how you look at it).

Eliminating the keyboard has its perks. It leaves more room on the phone for screen area—for photographs, movies, maps and reading material. Only one activity really suffers: entering text.

The first iPhone offered an on-screen keyboard. The advantage, as Jobs pointed out, was it could disappear when you didn't need it. It could also change languages or alphabets in a flash.

But at its core, typing on glass is slow and unsatisfying, especially compared with using a physical keyboard such as the BlackBerry's. The history of contemporary smartphones has been a seven-year quest to fix that problem.

The original iPhone tried to help in two minor ways, which are still at work today. First, the on-screen keys change size based on probability (not visually but behind the scenes).

Second, there is autocomplete: spawner of a billion curses, source of much hilarity but also often quite helpful.

The next big breakthrough was predictive text. That's where you see three words just above the keyboard—words that, statistically speaking, you're most likely to type next. When the phone predicts correctly, you feel a little surge of happiness. You type "the best," and the phone offers "thing," then "about." On the other hand, predictive text brings frustration of its own—such as when the software doesn't catch what you intend.

These predictive algorithms learn over time. And they save a lot of mistakes. But they're not the Ultimate Solution. They force you to split your focus between the keys and the suggestions as you type, which slows you down.

What about speech recognition? Isn't that the perfect solution?

Not really. As we all know, cell-phone dictation is far from perfect; you have to correct the mistranscriptions manually. It's a tough technology to perfect, of course—people have a million different accents and dialects, and you're transmitting their words over a connection to distant servers that convert the lo-fi audio into text.

Even if the accuracy were as good as it is on a desktop PC—when you're in a quiet room, wearing a headset microphone—you would still need a keyboard occasionally. "Bookmark it" sounds like "book market"; "the right or left" sounds like "the writer left." How can your phone algorithm know which you wanted?

So the world's engineers keep hammering away at the typing-on-phones problem. They have come up with alternative on-screen keyboards for popular phones. Swype and SwiftKey, for example, let you drag your finger sloppily and quickly across the keys, aiming for the letters you want.

The sheer quantity of attempts to solve the text-input problem hints at a larger truth: There is no obvious, perfect solution. There are only different sets of pros and cons.

We can take comfort from the fact that dictation, prediction and autocompletion solutions improve every year. (The word choices on iOS 8's predictive-text buttons, for example, attempt to reflect your style for different contexts—say, texting a friend versus e-mailing your boss—and predict what word you might prefer to use.) But text entry without a physical keyboard may be one of those receding-horizon deals: no matter how far we travel, we'll never quite reach the finish line.

Then again, we made the sacrifice for a good reason: to give ourselves a big, friendly screen for showcasing everything else our phones do. For most of us, it's been a trade-off worth making. SA

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INNOVATION

WORLD CHANGING IDEAS 2014

10 problem-solving, planet-improving, lifesaving advances set to drive progress in the years ahead

Predicting which scientific discoveries will change the world is, arguably, a fool's game. Who knows what the future will bring? Yet every year a handful of developments—say, the arrival of the quickest, cheapest genome-editing tool yet—get us so excited that we cannot help ourselves. This year those breakthroughs include tools for reprogramming living cells and rendering lab animals transparent; ways of powering electronics with sound waves and saliva; smartphone screens that correct for the flaws in your vision; Lego-like atomic structures that could produce major advances in superconductivity research; and others. Read about them now, then pay attention in the coming years to see what they do. *—Seth Fletcher, senior editor*

Illustrations by Ben Voldman

MEDICINE

THE GENE GENIE

A DNA-editing technique based on bacterial "memories" could revolutionize medicine. But some worry it could get out of control

By Margaret Knox

THE AGE OF GENETIC ENGINEERING began in the 1970s, when Paul Berg spliced DNA from a bacterial virus into a monkey virus and Herbert W. Boyer and Stanley N. Cohen created organisms in which introduced genes remained active for generations. By the late 1970s Boyer's company, Genentech, was churning out insulin for diabetics using *Escherichia coli* modified to contain a synthetic human gene. And in laboratories around the country, researchers were using transgenic mice to study disease.

These triumphs changed the course of medicine. But the early methods had two big limitations: they were imprecise and hard to scale. Researchers overcame the first limit in the 1990s by designing proteins that could snip specific locations of DNA, a big improvement over inserting DNA into cells at random and hoping for a useful mutation. Yet they still had to devise a new protein tailored to every sequence of DNA that they wanted to target—and that was slow, painstaking work.

Then, two years ago, a small group of researchers working in the labs of Emmanuelle Charpentier at Umeå University in Sweden and of Jennifer Doudna at the University of California, Berkeley, reported the discovery of a genetic mechanism in cells that allows scientists to edit genomes with unprecedented speed and ease. Shortly thereafter, a team of scientists at Harvard University and the Massachusetts Institute of Technology showed that the technique could be used to make multiple changes in a cell's genome, with great precision, all at once.

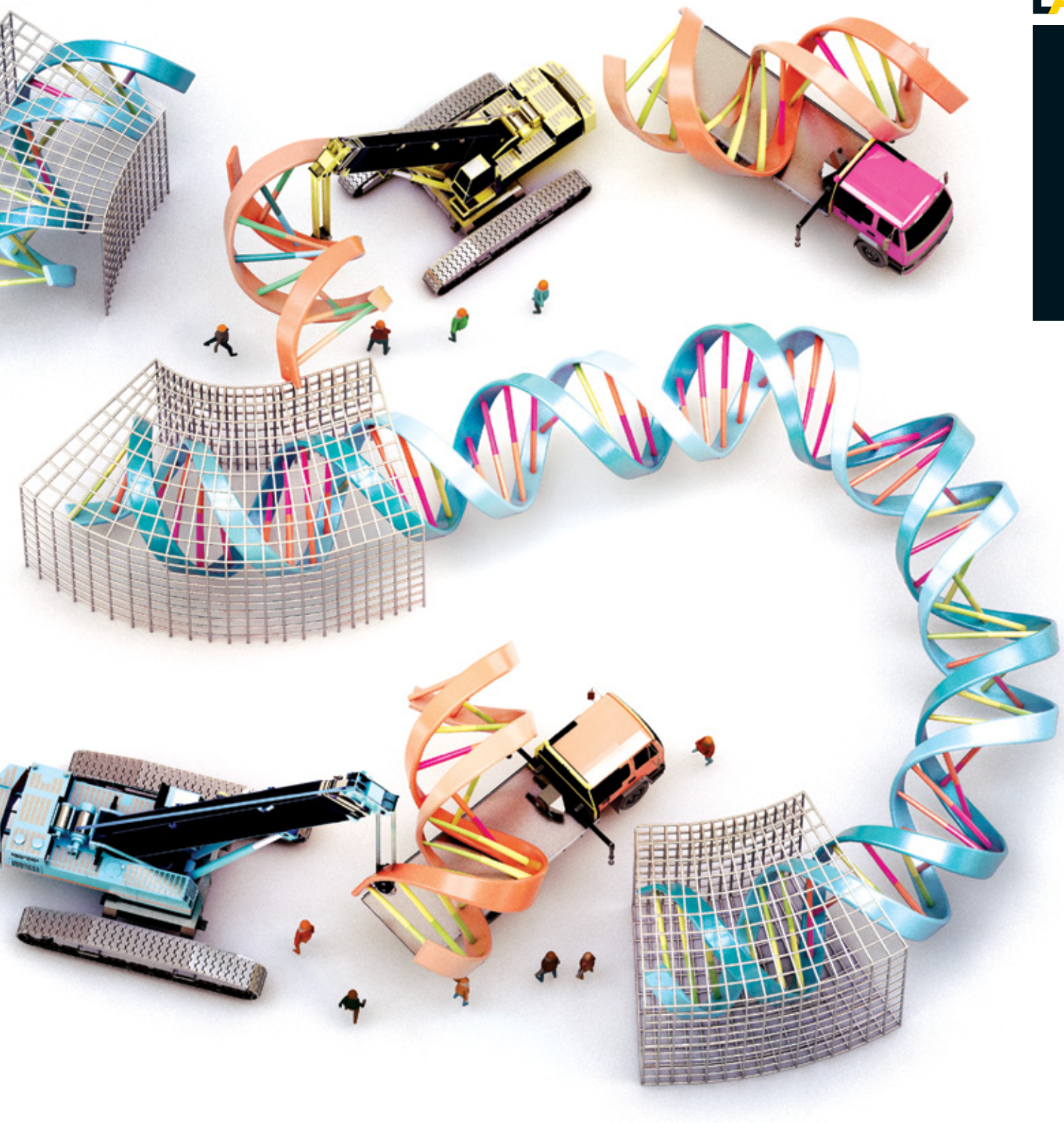
Already the advance has accelerated the genetic-modification industry in ways that are almost certain to have profound and beneficial effects on the field of genetics and medicine. Scientists can now engineer custom transgenic lab animals in a matter of weeks—saving about a year's worth of work. Researchers are using the technique to explore therapies for diseases as diverse as HIV, Alzheimer's disease and schizophrenia. Yet the technique makes genetic modification so easy and inexpensive that some ethicists are anticipating possible negative consequences.

IN BRIEF

Scientists have known how to alter the genomes of living organisms since the 1970s, but the tools available to them have long been imprecise and hard to scale. As a result, many experiments remained too difficult or costly to conduct.

Now a new method called CRISPR could foment the genome-editing revolution. Based on the immune defenses of bacteria, it is faster, cheaper and easier than older techniques. Money is pouring into companies seeking to commercialize CRISPR applications.

Researchers are already exploring CRISPR-based treatments for diseases, including HIV and schizophrenia. Yet CRISPR makes it so easy to alter the genomes of living organisms that ethicists worry about negative ramifications.



The technology is called CRISPR, after *c*lustered, *r*egularly *i*nterspaced, *s*hort *p*alindromic *r*epeats—the genetic mug shots that bacteria use to remember viruses that have attacked them. Scientists have been studying these odd genetic sequences since Japanese researchers discovered them in the late 1980s. But CRISPR's promise as a gene-editing tool did not become clear until Doudna's and Charpentier's teams figured out how to use a protein called Cas9.

THE POWER OF RNA

DOUDNA AND CHARPENTIER MET IN 2011, at a scientific conference in San Juan, Puerto Rico. They had a lot in common. Both man-

aged research groups that studied how bacteria defend themselves against viruses. Both had done work confirming that a bacterium identifies attacking viruses by using "memories" of past invaders' DNA to spot those enemies when they reappear.

Shortly after the meeting, Charpentier and Doudna decided to join forces. Charpentier's lab in Umeå was picking up clues that *Streptococcus* bacteria used a single protein, Cas9, as a kind of sword to chop up viruses that breached their cell walls. Doudna put her Berkeley lab on the job of figuring out how Cas9 worked.

By one of those quirks of fate that underpin many scientific discoveries, it turned out that Krzysztof Chylinski, a researcher in Charpentier's group, and Martin Jinek, then in Doudna's, had grown up in neighboring towns and spoke the same Polish dialect. "They started speaking by Skype, hit it off, and started to share data and discuss ideas for experiments," Doudna says. "The project really took off from there."

Scientists in both labs realized that Cas9 might be useful for genome editing, a type of genetic engineering that uses enzymes as molecular pruning shears. The enzymes, called nucleases, create breaks at specific sites in the double-stranded DNA helix; a cell then repairs the break, sometimes incorporating new genetic material that a scientist has placed in the nucleus. When Doudna and Charpentier began collaborating, the most advanced method available for disabling or altering a gene was to customize an enzyme that could find and cut the desired DNA target. In other words, for every genetic modification, scientists had to tailor a new protein targeted to the right DNA sequence.

But Doudna and Charpentier realized that Cas9, an enzyme that the strep bacterium used in its immunological defense, employed RNA to guide it to the DNA target. Probing for the target, the Cas9-RNA complex would bounce off the DNA, seemingly at random, until it found a promising site. The bouncing turned out to be the Cas9 enzyme searching, each time, for the same short "signal" sequence of DNA; Cas9 would attach to that sequence, pry open the double helix of the adjacent DNA and see if it matched the RNA guide. Cas9 would make the cut only when the RNA matched the DNA molecules. If that natural RNA-guided system could be harnessed, researchers would not have to construct a new enzyme to reach every target on the genome. Editing might become simpler, cheaper and more efficient.

After months of studying Cas9 together, the transatlantic team had a breakthrough. Doudna recalls the moment vividly: Jinek, then a postdoctoral researcher, had been running tests on Cas9 in the lab, which sits across from the Greek Theatre on a leafy hillside at the edge of the Berkeley campus. He showed up in Doudna's office one day to discuss results, and they mused about something that he had been discussing with Chylinski: in nature—in *Streptococcus* bacteria—Cas9 used not one but two RNA guides to target the right spot in the double helix of an invader's DNA. What if they could streamline those two guides into a single, artificially produced RNA strand without harming its effectiveness as a guide? With only one RNA sequence to modify, the engineering might be sped up tremendously. An RNA guide would be much easier to construct than the binding agents of the old customized enzymes, with their elaborate coding schemes.

"It was one of those moments when you see data, and something clicks," Doudna says. "We realized that we could design those RNA molecules into a single guide. A single protein and a single guide would be a powerful tool. I had chills running down my spine and realized, 'Oh, my gosh, run, don't walk, to the lab. If this works….'"

And work it did, with implications that Doudna, for all her excitement, could never have imagined. When Doudna and Charpentier published the results of their CRISPR-Cas9 research on August 17, 2012, scientists in the field immediately recognized its transformative potential—and a global race was on to test the applications.

Margaret Knox is a freelance writer and editor based in Boulder, Colo.

RUSH TO COMMERCIALIZATION

BY LAST YEAR RESEARCHERS were getting CRISPR-Cas9 to work in the cells of plants and animals much more complex than bacteria, and they were speculating about applications as fantastical as bringing back Neandertals and woolly mammoths. At Harvard, a team led by geneticist George Church used CRISPR to alter genes in human cells, opening up a whole new world of therapeutic possibilities.

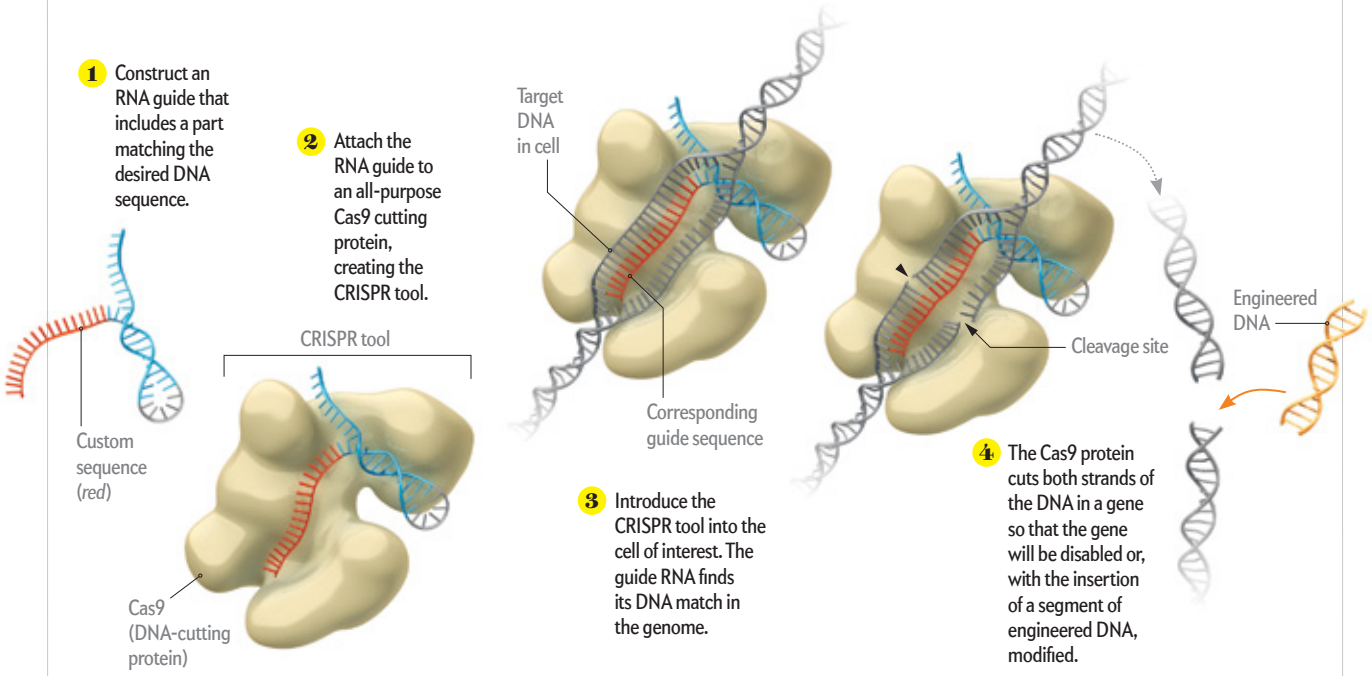
Not surprisingly, money soon began to pour into CRISPR-Cas9 work. A little more than a year ago Doudna teamed up with Church, Feng Zhang of M.I.T. and other researchers to launch Editas Medicine, with $43 million in venture capital and the goal of developing a new class of drugs based on CRISPR. (The company is not yet talking about which diseases it will target first.) In April, CRISPR Therapeutics launched in Basel and London, with investments of $25 million and a similar goal. Therapies from companies like CRISPR Therapeutics and Editas Medicine are still years away. But lab-supply firms are already shipping ready-to-inject CRISPR and made-to-order, CRISPR-altered mice, rats and rabbits to customers around the world.

On a steamy day this past summer I visited SAGE Labs in St. Louis, the first company to license Doudna's CRISPR technology for altering rodents, so I could see for myself how CRISPR works. SAGE ships to about 20 of the top pharmaceuticals companies, along with lots of universities, biotech institutes and foundations. (Horizon Discovery Group, a biotechnology company based in Cambridge, England, which was already barreling into CRISPR production of its own, bought SAGE for $48 million in September.) At SAGE, a set of low office buildings on a cul-de-sac in an industrial complex, scientists receive an online order from a lab in, say, Sacramento, Calif., for 20 *Pink1* knockout rats for research on Parkinson's disease. In a new, $2-million wing of the building, rats with this modification, as well as other CRISPR-modified rodents, live in superclean, climate-controlled cages that are neatly stacked from floor to ceiling. Filling the order is as easy as selecting 20 of the right rats, packing them gently into

BASICS

How CRISPR Works

Bacteria use a weapon called CRISPR to julienne invading viruses. Scientists can hijack this process to chop up sequences of DNA they would like to modify instead. Unlike previous genome-editing methods, the CRISPR system uses a single, all-purpose enzyme, called Cas9, to do the slicing. All the researcher has to do is create an RNA "guide" to steer it there; RNA is vastly easier to synthesize than enzymes.



boxes and airfreighting them to California. The same goes for animals ready-made for research on ills ranging from schizophrenia to pain control.

If a customer needs a rat or mouse that is not in stock, however, the process is different. A SAGE customer who wants to study a link between Parkinson's and a newly suspect gene—or even a specific mutation within a gene—has several options. SAGE scientists can use CRISPR to turn off the targeted gene, to introduce a mutation, or to turn off the gene and insert a human gene in its place. Many diseases, from Parkinson's to cystic fibrosis to AIDS, are affected by multiple genetic variants, and it used to take up to a year to create the complex, sequential mutations in animals that were needed to study such illnesses. Unlike previous genome-editing techniques, CRISPR allows researchers to make multiple genetic changes to a cell quickly and simultaneously, reducing the time it takes to produce a modified animal to a matter of weeks.

The SAGE employees start this process by making customized DNA from a chemical kit—and RNA to match the DNA. In a petri dish, they mix the RNA and Cas9, which combine into a chemical substance with gene-editing powers: the CRISPR tool. Then they spend about a week testing that tool on animal cells, using what looks like a desktop scanner to run electric currents that shock the CRISPR into the cells. The CRISPR goes to work, cutting the DNA and causing small insertions or deletions. Because CRISPR is not 100 percent efficient, it makes cuts and creates mutations in some cells but not in others. To see how well the CRISPR has performed, the scientists collect the DNA from the cells, pool it, and make copies of the region around the site of the supposed mutation. After processing and analyzing that pooled DNA, they look at the results on a computer monitor. Cut, mutated DNA shows up as a dim band—and the more DNA the CRISPR has cut, the brighter that dim band will be.

Next the process moves to the animal wing, where scientists use CRISPR to churn out genetically modified embryos and create mutant rodents. In one of those labs, I watched biologist Andrew Brown work the magic of CRISPR. Swaddled in surgical gloves and blue paper clothing—robe, overshoes and puffy bonnet—he hunched over a dissecting microscope, sucking at the end of a glass pipette to bring up a rat embryo. He then trundled the embryo across the room to a bigger microscope, flanked by robotic arms, released it into a drop of liquid on a slide and settled onto a stool. With his right hand, he commanded a joystick that moved a hollow glass needle into place against the wall of the embryo.

Through the eyepiece of the microscope, the embryo's two pronuclei, one from each rat parent, looked like little craters on the surface of the moon; Brown nudged the cell until a pronucleus spun close to the tip of the needle. He clicked the button of a computer mouse, and the needle squirted a tiny drop of liquid containing CRISPR through the plasma membrane of the cell. The pronucleus swelled like a flower blooming in fast motion.

Illustration by AXS Biomedical Animation Studio

With luck, Brown had created a mutant cell. SAGE's three technicians repeat the task as many as 300 times a day, four days a week.

When Brown finished injecting his rat embryo, he sucked it into a pipette, deposited it in a petri dish and stored it in a cupboard heated to body temperature. He would eventually inject the modified embryo—and some 30 to 40 others—into a surrogate rat mother. Twenty days later the rat would bear five to 20 pups, and when the pups were 10 days old, SAGE scientists would take tissue samples to see which ones had the modified gene.

In June, researchers at M.I.T. reported curing adult mice of tyrosinemia—a rare liver disorder caused by a mutation in an enzyme—by injecting CRISPR directly through their tails.

"That's the exciting part," Brown said. "It might be just one of 20 that have the modification. That's what we call our founder animal. When we get to that point, everybody celebrates." Watching the SAGE scientists making RNA or injecting embryos, it all looked easy—and the same processes are turning out genetically engineered animals at many labs. It is, as SAGE CEO David Smoller put it, gene editing "for the masses."

PROMISE AND MAYBE A LITTLE PERIL

AS CRISPR CHARGES AHEAD into commercial use, researchers and entrepreneurs keep imagining new applications for the technology, and some can come across as hubristic. It might be possible to tweak the chromosomal abnormality associated with Down syndrome early in a pregnancy, for example, or to reintroduce susceptibility to herbicides in resistant weeds, or to bring back animal species that have gone extinct. Not surprisingly, some people find it scary. Startled commentators have warned that in our rush to rid the world of malarial mosquitoes, cure Huntington's disease or design better babies, we could create a *Jurassic Park*–ful of harmful new genes.

Consider the idea of using CRISPR to eliminate malarial mosquitoes. It is one thing to vanquish the malarial parasite but quite another to annihilate its vector, says Todd Kuiken, a biosecurity analyst at the Woodrow Wilson International Center for Scholars in Washington, D.C. If the goal is eradicating malaria—which infects 200 million people a year and kills 600,000—Kuiken says that we have to be careful not to cause 10 other problems. "We've got to have an opportunity to ask, 'Do we really want to do this?' And if the answer is 'yes,' what kinds of systems do we have in place, what kinds of safeguards?"

To their credit, scientists are moving quickly to envision the most realistic dangers of CRISPR technology and to develop responses. In July, when a Harvard team published a paper on CRISPR-powered mosquito elimination, the scientists called for a public discussion and began to suggest technological and regulatory fixes for altered genes gone wild. "CRISPR is happening so incredibly fast," observes Jeantine Lunshof, a bioethicist on the team. "Many people have not heard of it, but people are using it. That is a new dynamic." Within Berkeley's Innovative Genomics Initiative, Doudna has been assembling a group designed specifically to discuss the ethical implications of CRISPR applications.

It is hard to imagine ethics concerns smothering the excitement over CRISPR. In June, for example, researchers at M.I.T. reported curing adult mice of tyrosinemia—a rare liver disorder caused by a mutation in an enzyme—by injecting CRISPR directly through their tails. Delivering three RNA guide strands, along with Cas9 and the correct DNA sequence for the mutated gene, they managed to insert the correct gene in about one of every 250 cells in the livers of mice. During the following month, the healthy liver cells thrived, eventually replacing a third of the bad cells, enough to rid the mice of the disease. And in August virologist Kamel Khalili of Temple University and his colleagues reported having used CRISPR to slice the HIV virus, which causes AIDS, out of several human cell lines.

For Khalili, who has labored in the trenches of HIV/AIDS since the dark days of the 1980s, CRISPR is nothing short of revolutionary. Despite huge strides in AIDS treatment, today's medications only control the virus—they do not eradicate it. But by using CRISPR, Khalili's team completely excised the integrated copy of HIV, converting infected cells to uninfected cells. Besides eliminating the virus from an infected cell, CRISPR can also protect an uninfected cell, Khalili says, immunizing it by incorporating a sequence from the attacking virus, just as Doudna and her team observed primitive bacteria doing. You could call it a genetic vaccine. "If you'd asked me two years ago, 'Can you precisely excise the HIV from a human cell?' I would have said that's a tall order. Now we've done it," Khalili says. "That is the ultimate cure." SA

MORE TO EXPLORE

RNA-Programmed Genome Editing in Human Cells. Martin Jinek et al. in *eLife,* Article No. 00471; January 29, 2013.

Cas9 as a Versatile Tool for Engineering Biology. Prashant Mali et al. in *Nature Methods,* Vol. 10, pages 957–963; October 2013.

Cas9 Targeting and the CRISPR Revolution. Rodolphe Barrangou in *Science,* Vol. 344, pages 707–708; May 16, 2014.

FROM OUR ARCHIVES

The RNA Revolution. Christine Gorman and Dina Fine Maron; April 2014.

scientificamerican.com/magazine/sa

INNOVATION

NINE MORE BIG IDEAS

REPROGRAMMABLE CELLS

Taking control of cells by squeezing them

If we could somehow make our own cells do our bidding, they might manufacture insulin, attack tumors and do other helpful things. But hijacking a cell is not easy. Current methods entail penetrating the cell walls with a virus, which tends to inflict permanent damage.

In 2009 researchers at the Massachusetts Institute of Technology solved this problem, by accident. The researchers were playing around with a method of implanting cells with large molecules and nanomaterials using a microscopic water gun. Mainly, they were trying to get things inside a cell—the sorts of things that might alter a cell's behavior while keeping it alive. Chemical engineer Armon Sharei noticed that some of the water-shot cells became momentarily misshapen, and while they were, the material was getting inside them. "It turns out if you deform a cell fast enough, you can temporarily break down its membrane," Sharei says. The water gun was too crude a tool, however. They needed a gentler way to squeeze cells.

Sharei, working under Klavs F. Jensen, a founder of the field of microfluidics, and biotech pioneer Robert S. Langer, developed a silicon-and-glass microchip that is etched with channels through which cells flow. The channels narrow gradually, until the gap tapers into a space slimmer than the cells themselves. The squeezed cells are supple, and they force their way through. In the process, temporary holes form in the cell membrane. The holes are tiny but wide enough to let in a variety of behavior-altering agents, including proteins, nucleic acids and carbon nanotubes. The technique works even on stem and immune cells, which were too sensitive to be manipulated using previous methods. "We were taken aback by how many cells this approach could apply to," Sharei says.

Since the initial discovery, the group has developed 16 different chips with channel arrays designed to squeeze different cells. More chips are coming, and the device, which can already process 500,000 cells a second, continues to get faster and more efficient. The group has started a company to commercialize the technology—called SQZ Biotech—and scientists in France, Germany, the Netherlands and the U.K. will soon be using its products. *—Ryan Bradley*

TRANSPARENT ORGANISMS

A Body Worlds–inspired method promises to speed up biomedical research

Five years ago Viviana Gradinaru was slicing thin pieces of mouse brain in a neurobiology lab, slowly compiling images of the two-dimensional slivers for a three-dimensional computer rendering. In her spare time, she would go to see the Body Worlds exhibit. She was especially fascinated by the "plasticized" remains of the human circulatory system on display. It struck her that much of what she was doing in the lab could be done more efficiently with a similar process.

"Tissue clearing" has been around for more than a century, but existing methods involve soaking tissue samples in solvents, which is slow and usually destroys the fluorescent proteins necessary for marking certain cells of interest. To create a better approach, Gradinaru, at the time a graduate student, and her colleagues in the late neuroimmunologist Paul Patterson's lab focused on replacing the tissue's lipid molecules, which makes it opaque. To keep the tissue from collapsing, however, the replacement would need to give it structure, as lipids do.

The first step was to euthanize a rodent and pump formaldehyde into its body, through its heart. Next they removed the skin and filled its blood vessels with acrylamide monomers, white, odorless, crystalline compounds. The monomers created a supportive hydrogel mesh, replacing the lipids and clearing the tissue. Before long, they could render an entire mouse body transparent in two weeks.

Soon they were using transparent mice to map complete mouse nervous systems. The transparency made it possible for them to identify peripheral nerves—tiny bundles of nerves that are poorly understood—and to map the spread of viruses across the mouse's blood-brain barrier, which they did by marking the virus with a fluorescent agent, injecting it into the mouse's tail and watching it spread into the brain. "It's like seeing the whole world versus individual slices of it," Gradinaru says. The process reduces opportunities for human error, makes lab work move faster, produces richer data and requires fewer lab animals. Gradinaru offers the recipe for her hydrogel solution to any lab that requests it. Her next step is to use the technique to find, map and learn more about cancers and stem cells. *—R.B.*

SPIT-FIRED FUEL CELLS

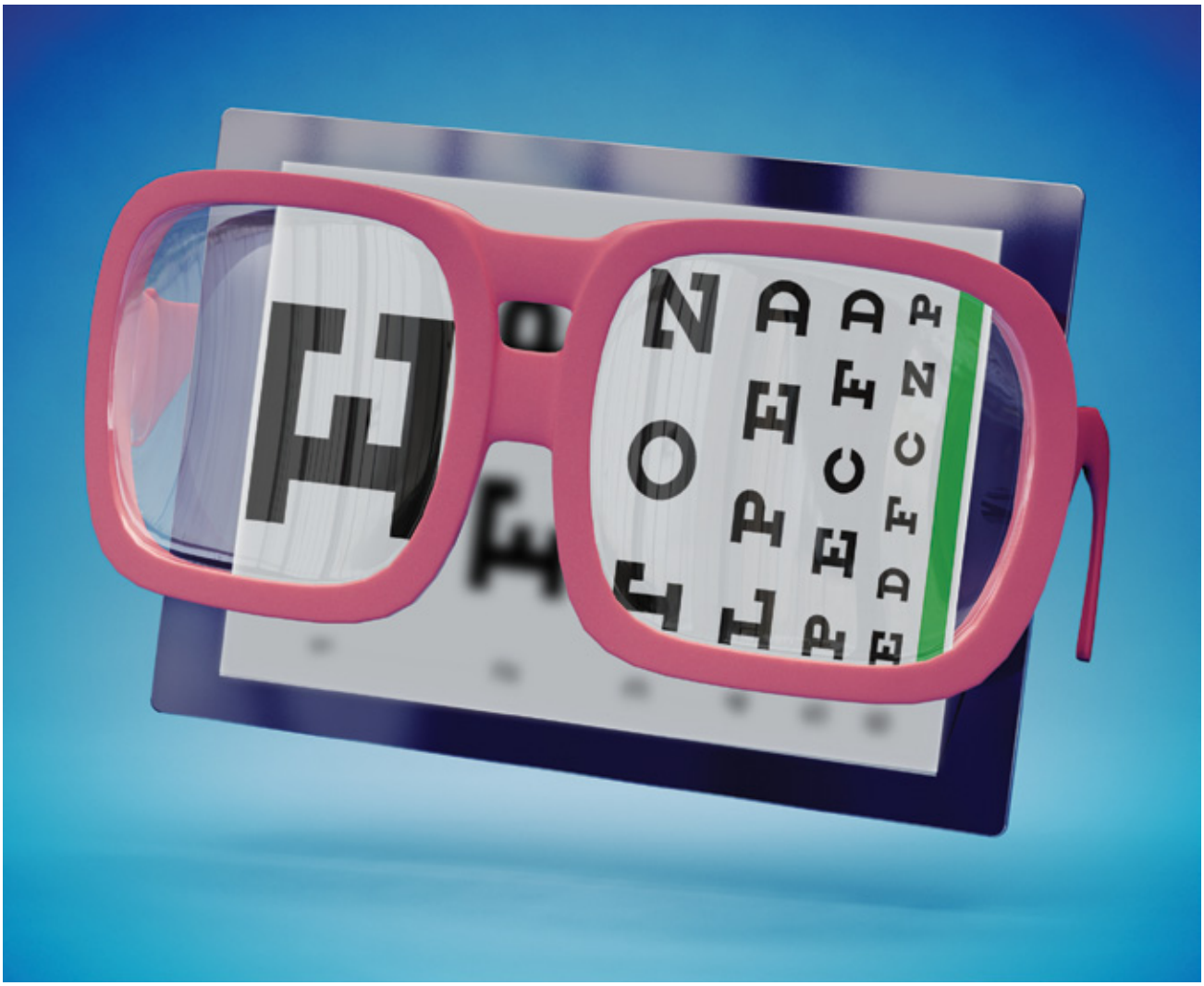
Saliva could be a new renewable energy source for medical devices

Muhammad Mustafa Hussain, a professor of electrical engineering at King Abdullah University of Science and Technology in Saudi Arabia, devotes nearly all of his time to building extremely tiny devices. "You make things very small, you get rapid results," he says. So in 2010, when he set out to develop an abundant, renewable power source that could be used in extremely remote places for machines that might purify water or diagnose disease, it was inevitable that he would start small. A tiny microbial fuel cell, for example, would be a natural starting point. It was not inevitable, however, that he would choose to power that fuel cell with saliva.

The idea of using spit came from Hussain's colleague Justine E. Mink, then a Ph.D. candidate in his lab (now a researcher at Dow Chemical). At the time, Mink was trying to build glucose-monitoring devices for diabetics with power sources small enough to fit inside the body, near the pancreas. A microbial fuel cell—which generates power by feeding organic matter (which saliva has lots of) to bacteria, which, in turn, produce electrons—was a natural candidate for their projects. So the two took a highly conductive graphene electrode, loaded it with saliva-eating bacteria, and within weeks they were producing nearly one microwatt, a millionth of a watt of power.

A microbial fuel cell generates power by feeding organic matter to bacteria.

A microwatt is a tiny amount of power, but it is enough for lab-on-a-chip devices, diagnostic tools and monitoring tools such as Mink's diabetes tracker. Hussain is working with companies that 3-D-print artificial organs to integrate his fuel cell into an artificial kidney, where a range of bodily fluids would provide fuel. He says this is simply the first step as he scales up: his long-term goal is to generate electricity from organic factory waste to power desalination plants in poor countries. *—R.B.*



VISION-CORRECTING DISPLAYS

Self-correcting screens on smartphones and iPads tailor themselves to a viewer's vision—no glasses necessary

In the U.S., more than 40 percent of 40-year-olds need eyeglasses for reading, and that figure jumps to nearly 70 percent for people aged 80 and older. "As we get older, refractive errors play more significant roles in our lives," says Gordon Wetzstein, an assistant professor of electrical engineering at Stanford University.

But glasses and contact lenses are not always ideal. If you are farsighted, for example, you do not need glasses to see traffic while driving, but you do need them to read your speedometer or GPS. The best solution in such cases, Wetzstein says, would be vision-correcting displays—screens that wear the glasses for you.

Wetzstein and his colleagues at M.I.T. (where he was formerly based) and the University of California, Berkeley, have developed just such a screen. The vision-correcting display makes two modifications to a standard high-resolution smartphone or tablet screen. The first is a low-cost, pinhole-covered printed transparency that covers the screen. The second: algorithms coded into the smartphone or tablet that determine the viewer's position relative to the screen and distort the image that is projected, according to his or her prescription. As the distorted image passes through the matrix of pinholes in the transparent screen cover, the hardware-software combination creates errors on the screen that cancel errors in the eye, thus delivering what appears to be a crisp image. The screen can correct for myopia, hyperopia, astigmatism and more complicated vision problems. The team presented the work at the SIGGRAPH conference in August in Vancouver.

Informal tests on a handful of users have shown that the technology works, Wetzstein says, but large-scale studies are needed to further refine it. In the process, the researchers also plan on developing a slider that can be used to manually adjust the focus of the screen. Wetzstein says that the technology could be a boon for people in developing countries who have easier access to mobile devices than prescription eyewear. —*Rachel Nuwer*

ATOMIC-SCALE LEGOS

Snapping together one-atom-thick sheets of material creates substances with completely new properties—and amazing possibilities

By Andre K. Geim

Andre K. Geim is a physicist at the University of Manchester in England. He shared the 2010 Nobel Prize in Physics for his work on graphene.

Generations of minds have been inspired by Legos, the small, snap-together plastic blocks. These blocks have become fantastic cars, elaborate castles and many other whole creations that are greater than the sum of their parts. Today a generation of materials scientists is being inspired by a new type of Legos: building blocks on the atomic scale.

These new construction elements are sheets of materials that can be as thin as just one atom and can be stacked, one on top of another, in a designed, precise sequence. This unprecedented fine construction control can produce substances with electrical and optical properties that have been impossible to create before. And they are allowing scientists to imagine devices made of materials that conduct electricity with very little resistance, faster and more powerful computers, and wearable electronic gadgets that could be bendable, foldable and incredibly lightweight.

This breakthrough followed the creation of graphene, a single sheet of carbon atoms that my colleagues and I at the University of Manchester in England isolated from a bulkier block of graphite in 2004. We made this sheet of repeating six-sided crystals—the atomic structure looks something like a chicken-wire fence—by pulling one-atom-deep layers from the top of the block with adhesive tape. In the past 10 years researchers have found several dozen other types of bulk crystals that can be pulled apart in this way, and their number continues growing rapidly. Mica is one example, and so are materials with exotic names such as hexagonal boron nitride and molybdenum disulfide.

These crystal layers are considered to be two-dimensional because a single atom is the smallest possible thickness for any material. (Slightly thicker crystals of three or so atoms can also be used.) Their other dimensions, width and length, can be a lot larger, depending on the maker's desires. In the past couple of years two-dimensional crystals have become a hot topic in materials science and solid-state physics because they exhibit many unique properties.

We can stack these layers in ways that are quite stable. They do not bond together in a conventional way—using covalent bonds that share electrons, for example. But the atoms are attracted to one another when they come into close proximity, through a weak pull known as the van der Waals force. This force is generally not strong enough to hold atoms and molecules together, but because these two-dimensional sheets are so dense with atoms and so close to one another, the cumulative force becomes formidable.

To understand the tantalizing possibilities offered by this kind of materials engineering, think about room-temperature superconductivity. The idea of transmitting electricity with no loss of energy and of doing so without the need to surround devices with almost unimaginable cold has been a goal of scientists for generations. If materials that can do it are found, consequences for our civilization will be far-reaching. There is a consensus that the goal is achievable in principle, but no one knows how. Today the highest temperature at which materials can be made superconducting is less than –100 degrees Celsius. There has been little progress in raising this limit during the past two decades.

Human progress has closely followed the discovery of new materials, and nanoscale Legos represent something that has never been created before.

We have recently learned that some superconductors made of oxides—compounds with at least one oxygen atom, along with another element—can be disassembled into individual layers in the manner that I have described. What if we reassemble them back in another sequence and insert additional crystal planes in between? We already know that superconductivity in oxides depends on interlayer separation and that adding extra layers between crystal planes can turn some poorly conducting and even insulating materials into superconductors.

This idea has not yet been fully tested, mainly because the technology of making atomic-scale Lego materials is still in its infancy. Indeed, it is difficult to assemble complex multilayer structures. For the moment, these structures rarely contain more than five different layers, and they usually use only two or three different Lego blocks—mostly graphene in combination with two-dimensional crystals of insulating boron nitride and semiconducting material such as molybdenum disulfide and tungsten diselenide. Because the stacks have a variety of materials, they are often referred to as heterostructures. They are currently small—typically only about 10 microns in width and length, which is less than the width of a cross section of a human hair.

Using these stacks, we can run experiments in search of novel electrical or optical properties and new applications. One intriguing aspect: as thin as these sheets are, they are also quite flexible and transparent. This presents opportunities to develop light-emitting devices that can be shaped in various ways, like display screens that can be folded and unfolded as a user needs a bigger size. Computer chips that use energy much more efficiently are also possible.

If researchers find something significant in their investigations of these structures, we believe it will be possible to scale up the technology for industrial use. It has already happened with graphene and some other two-dimensional crystals: Initially those came as tiny crystallites of a few microns across, but they can now be manufactured in sheets of hundreds of square meters.

No "killer app" has been reported yet. Nevertheless, progress in the field is causing a loud buzz of excitement in scientific communities. Human progress has always closely followed the discovery of new materials. Such discoveries were behind the transitions from the Stone to the Bronze to the Iron to the Silicon Ages. Nanoscale Legos represent something that has never been created before. Right now the possibilities seem endless.

ULTRAHARD RECYCLABLE PLASTICS

Eco-friendly polymers strong enough to use in cars and airplanes

When research chemist Jeannette García found a candy-size lump of white material in a flask she had recently used, she had no idea what she had created. The material stuck firmly to the glass, so she used a hammer to break it free. But when she turned the hammer on the material itself, it refused to crack. "When I realized just how high its strength was, I knew I needed to figure out what I'd made," García says.

García, a scientist at IBM Research–Almaden, enlisted the help of several colleagues to solve the puzzle. They found that she had stumbled on a new family of thermoset polymers, exceptionally strong plastics that are used in products ranging from smartphones to airplane wings. Thermosets account for about one third of the global polymers produced every year, but they are difficult to recycle. García's new material, nicknamed Titan, is the first recyclable, industrial-strength thermoset ever discovered.

Unlike conventional thermosets, which pretty much refuse to be remolded, the new polymer can be reprocessed through a chemical reaction. García and her colleagues reported their discovery in May in *Science*.

Global demand for durable, recyclable plastics is expected to soon increase. By 2015, for example, both Europe and Japan will require that 95 percent of car parts produced there be recyclable. "This is a perfect example of a material that would work for that," García says. But she believes that the new thermoset could also eventually extend into a range of applications—anticorrosive and antimicrobial coatings, drug delivery, adhesives, 3-D printing, water purification, among others.

Titan came with a bonus, too. García and her colleagues discovered a second form of the material—a self-healing, gel-like substance they call Hydro—that forms at lower temperatures. "If you cut it in half and then put it back together, it instantly forms bonds," García says. It could be used as an adhesive, she notes, or as a self-healing paint. Other, related compounds could follow. "It's not just this one new polymer but a new polymer-forming reaction." García says. —*R.N.*

WIRELESS CHARGING WITH SOUND WAVES

An efficient way to beam electricity through the air

In 2011 Meredith Perry, then a senior paleobiology student at the University of Pennsylvania, reached for her laptop charger and found herself wondering whether that cumbersome cord might someday become obsolete. She began researching ways to turn that idea into a reality. Perry learned that wireless power transmitters based on magnetic resonance and induction already existed but that they had limited range. Their curse was the inverse square law, which states that the intensity of electromagnetic radiation is inversely proportional to the distance from the emitting source.

Mechanical vibrations, however, would not have this problem. Harnessing vibrations from the air using piezoelectric transducers, which would convert that mechanical energy into electricity, seemed like a better idea. Because sound is nothing more than vibrating air particles, it should, in theory, be able to transmit energy. And ultrasound, which is safe, silent and highly energetic, would be perfect.

When Perry discussed this idea with professors at her university and beyond, many told her that it would never work—it would be impossible to extract enough power from ultrasound to charge electronic devices, and she would run into a slew of electrical engineering and acoustics problems if she tried. "But I knew the math was correct," she says. "And no one supplied me with enough evidence to show that it was actually impossible." So Perry founded a company, uBeam, to develop the technology. The uBeam transmitter, now in the prototype phase, acts as a directional speaker. It focuses ultrasound to create a hotspot of energy; a receiver attached to an electronic device picks up that energy and converts it into electricity. She is aiming to ship the first batch of products within two years.

A universal wireless charging system, Perry says, would eliminate the multitude of incompatible wires and chargers that we currently tote around and allow mobile devices to perform energy-intensive tasks without draining a battery. Doing away with wires could also create new options for interior design and reduce weight in airplanes, cars, spacecraft or any other vehicle that today is laden with heavy power cables. "Overall, wireless charging would free us up in terms of how we interact with the physical world," Perry says. "It untethers us from the wall." —*R.N.*

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BATTERIES THAT CAPTURE LOW-GRADE WASTE HEAT

A third of all the energy wasted in the U.S. could produce electricity instead

Banks of batteries could line the walls of factory smokestacks or power plants, converting low-grade excess heat into electricity.

Every year 10 gigawatts of potential power are squandered as waste heat from industrial processes—enough to light 10 million homes. The thermoelectric effect, in which charges are created by temperature differences, provides a way of transferring this heat into electricity—but only some of it. For decades the temperature differential had to be 500 degrees C or greater to capture any useful amount of energy, explains Yuan Yang, a postdoctoral scholar at M.I.T. That is unfortunate, because the Environmental Protection Agency estimates that a third of all wasted energy in the U.S. every year is lost at temperatures below about 100 degrees C.

Yang, his professor, Gang Chen, postdoc Seok Woo Lee and Yi Cui of Stanford have developed a way to harvest heat at temperatures 10 times lower—as little as 50 degrees C. The trick was to exploit the thermogalvanic effect, a cousin of the thermoelectric effect, in which the entire material's temperature changes, along with the voltage, rather than a gradient within the battery cell. The group took uncharged battery cells with copper-based electrodes, charged the cells while they were hot and then cooled them down. Presto: the batteries delivered a higher voltage than was used to charge them. In other words, the energy used to heat the battery was captured in the form of electricity.

Only in the past two years or so have battery electrodes become efficient enough to convert such low-temperature differentials into electricity, Yang says, and plenty of development remains before the process can be commercialized. But in time, banks of batteries could line the walls of factory smokestacks or power plants, converting low-grade excess heat into electricity. "This is something attractive," Yang says, "because low-grade heat is everywhere." —*R.B.*

VIDEO CAMERAS FOR NANOPARTICLES

Electron microscope resolution for quick-and-dirty industrial applications

Electron microscopes with nanometer resolution are widely used, but they cost millions of dollars, and preparing a sample for viewing is painstaking. This state of affairs is fine for the lab but impractical for industrial applications—say, for rapidly scanning product samples to look for embedded microscopic watermarks.

A new form of holographic microscopy developed by David Grier, a physicist at New York University, and his colleagues could provide a solution. They started with an off-the-shelf Zeiss microscope and replaced its incandescent light source with a laser. The laser shines on a sample of the material under study; light scatters off the sample and creates a two-dimensional pattern of interference between the laser beam and the scattered light—a hologram—which a video camera records.

Scientists have been making holograms of microscopic objects for decades, but it has always been hard to extract useful information from them. This is where Grier's invention adds value. His team wrote software capable of quickly solving the equations that describe how light scatters off a spherical object; by finding the values of certain terms buried in those equations, the software gathers information about the object that is causing that scattering. The microscope's nanometer resolution will allow researchers to track particles floating in colloidal solutions (for example, nanoscale beads floating in a sample of paint) using equipment that is at least a tenth of the cost of an electron microscope.

Grier hopes his device will provide the first rapid, affordable way to glimpse the individual particles at the heart of modern products. Imagine a paint bucket or shampoo bottle in which every drop contains particles that have been encoded with the product's manufacturing history—how it was made, in what factory and when, "sort of like a fingerprint," Grier says. He adds that the microscope could just as easily read a molecular message stamped into medicine, explosives or other goods. —*Ben Fogelson*

MORE TO EXPLORE

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FROM OUR ARCHIVES

World Changing Ideas. December 2013.

scientificamerican.com/magazine/sa

STARRY NIGHT: The Milky Way glows in the night sky over the Pacific Ocean off the coast of Chile's Atacama Desert.

ASTRONOMY

FOSSIL H

Early in its history the Milky Way gobbled up many tiny galaxies. The cosmic rubble it left behind is now yielding fresh clues into how our corner of the universe came to be ***By Kathryn V. Johnston***

UNTING

IN THE MILKY WAY

Kathryn V. Johnston is a professor and chair of the astronomy department at Columbia University. A native of Yorkshire, England, she studied at the University of Cambridge and the University of California, Santa Cruz. Johnston is interested in understanding how galaxies—the Milky Way in particular—form and grow.

GO OUTSIDE ON A DARK, CLEAR NIGHT, FAR AWAY FROM THE GLARE OF CITY LIGHTS, and look up. You will see the glowing band of the Milky Way arching dramatically overhead. It has now been four centuries since Galileo Galilei first turned a telescope toward this awesome sight and noted that the "milk" is actually countless individual stars, too faint to be separated by the naked eye. It took another three centuries for astronomers to convince themselves that the Milky Way is just one of billions of galaxies in the universe.

In fact, the Milky Way itself is not simply one galaxy: recent work has shown that it has lured in and engulfed many smaller galaxies over time, integrating their stars into itself. At least 20 dwarf galaxies—ranging in size from one millionth to one hundredth the size of the Milky Way—are known to orbit it now, with dozens more probably still undiscovered. And the current satellites are thought to be just a tiny fraction of those that ever existed, the rest having been drawn into our galaxy by gravity and absorbed long ago. This ingestion started when the Milky Way was younger and smaller than it is now and continues today—the satellite galaxies that still exist may eventually be swallowed up.

Long after their demise, these victims of the Milky Way's gravitational appetite leave traces in the form of faint streams of stars that stretch across the sky. Over the past 15 years a relatively new field, which came to be called galactic archaeology, has revealed many of these streams. By studying these fossils from our galaxy's past, galactic archaeologists are piecing together events from the Milky Way's history and gaining clues to the way other so-called spiral galaxies arise and evolve.

Ideally one would study galaxies from the outside as well as within. We cannot do that for our own galaxy. But by taking advantage of our close-up view from inside the Milky Way, we can obtain detailed information that cannot be gained by examining other galaxies from without.

Already this field has helped confirm one process by which the Milky Way and other young galaxies get bigger. The discovery of multiple star streams from long-gone satellites supports the widely held theory that our galaxy started small and swelled in part by adding mass in large gulps—a process called hierarchical structure formation. Although many particulars of this scenario still remain mysterious, we are slowly but surely writing the biography of the Milky Way.

HOW TO BUILD A GALAXY

THE HIERARCHICAL THEORY of galaxy formation says that the main driver of growth for large galaxies resembling the Milky Way is not the baryonic matter—the stars, gas and dust that we can see, made of the same particles composing you and me. Rather the motive force is vast "halos," or spheres, of unseen dark matter in which galaxies are embedded. Small dark matter halos are thought to form first and gradually agglomerate into larger ones and thus to drive bigger galaxies to swallow smaller ones.

Today each galaxy's dark matter halo is many times more massive and more extended than the normal visible matter. Strangely, although astronomers have yet to discover the nature of dark matter (we perceive it only through its gravitational pull on everything else), we have some confidence in this vision of how it clumps because observed clustering and interaction rates of galaxies match predictions of models that posit dark matter agglomeration. The mystery of galaxy formation actually lies not with the dark matter but with the ordinary baryonic matter made of particles that interact in known ways we can study here on Earth.

The basic view of how baryonic matter contributes to the evolution of galaxies starts with the dark matter halo. This body pulls ordinary matter, in the form of gas, toward itself

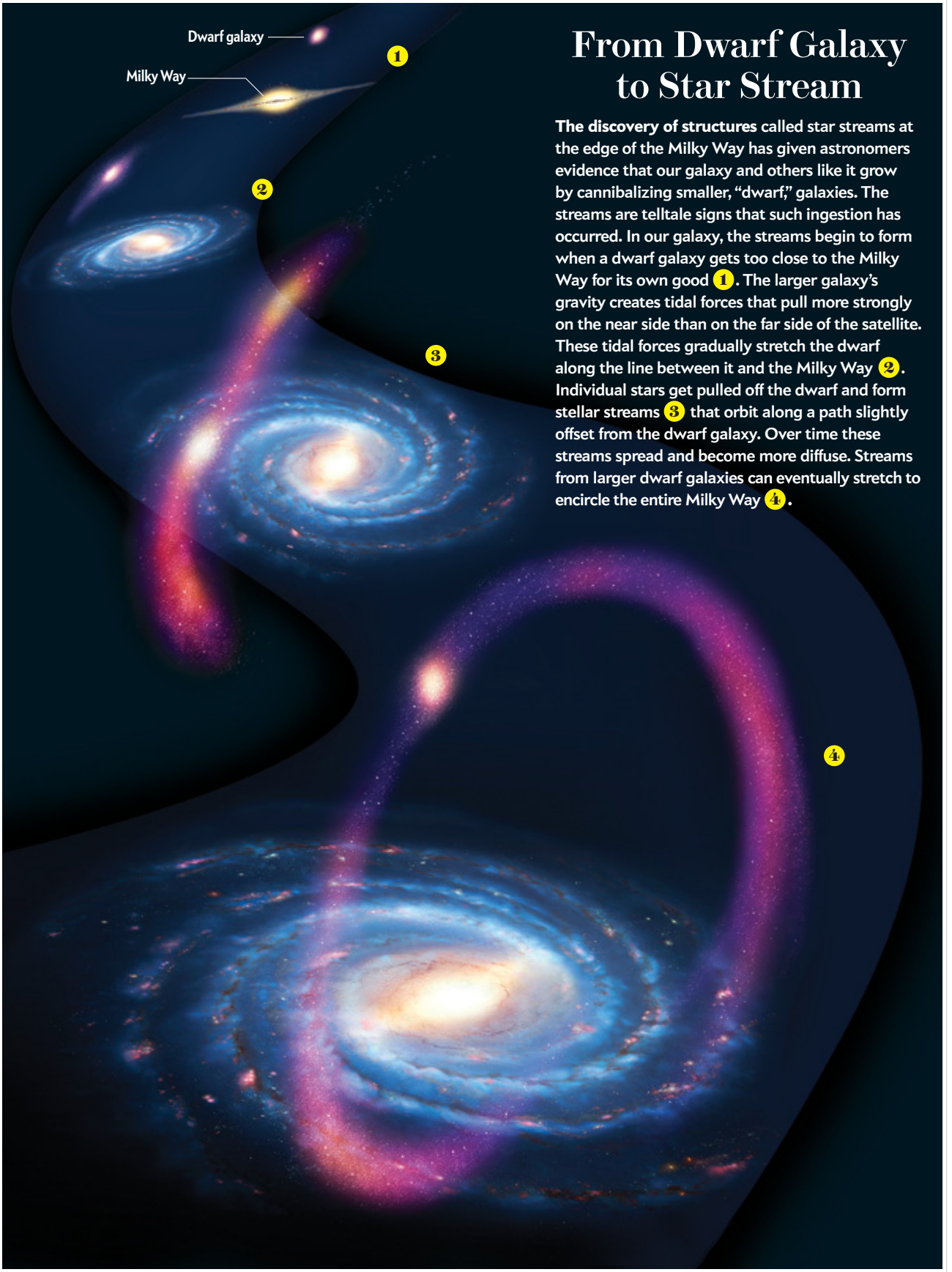
IN BRIEF

As dwarf galaxies orbit the Milky Way, our own galaxy's gravity slowly rips them apart into long tails called stellar streams. Astronomers who think of themselves as galactic archaeologists use these fossils of lost galaxies to study the Milky Way's past.

Astronomers discovered the first evidence of an extended stellar stream around our galaxy in 2003 and have found about a dozen more since then. Analysis of these streams supports the theory that the Milky Way grew in pieces by swallowing smaller galaxies.

Future studies of stars' orbital and chemical characteristics could reveal the constituents of stellar streams that have long since dissolved. Ultimately galactic archaeology could clarify not just the history of the Milky Way but also the way galaxies in general evolve over time.

PRECEDING PAGES: BABAK TAFRESHI *National Geographic*



From Dwarf Galaxy to Star Stream

The discovery of structures called star streams at the edge of the Milky Way has given astronomers evidence that our galaxy and others like it grow by cannibalizing smaller, "dwarf," galaxies. The streams are telltale signs that such ingestion has occurred. In our galaxy, the streams begin to form when a dwarf galaxy gets too close to the Milky Way for its own good 1. The larger galaxy's gravity creates tidal forces that pull more strongly on the near side than on the far side of the satellite. These tidal forces gradually stretch the dwarf along the line between it and the Milky Way 2. Individual stars get pulled off the dwarf and form stellar streams 3 that orbit along a path slightly offset from the dwarf galaxy. Over time these streams spread and become more diffuse. Streams from larger dwarf galaxies can eventually stretch to encircle the entire Milky Way 4.

SOURCE: DAVID HENDEL

Illustration by Mark Garlick

through the force of gravity. As the gas makes its way to the center of the halo, it can, given the right circumstances, form stars. When some of these stars reach the ends of their lifetimes, they explode, returning their atoms to the gas within and (possibly) beyond the galaxy and often triggering another generation of stars to form from any remaining gas and dust. In this way, the central heart (the "bulge") of the Milky Way and its spiral arms (the "disk") most likely formed.

But the Milky Way includes a vast sphere (also called a halo) of more diffuse stars surrounding the bulge and disk. Many of these stars are probably interlopers from long-destroyed dwarf galaxies. According to the hierarchical formation theory of how galaxies form, the stars join the halo in a sequence of events that goes something like this: As a dwarf galaxy orbits the Milky Way, it feels the gravitational pull of the big galaxy, which gets stronger as the satellite gets closer to the larger galaxy. The matter (stars, gas, dust and dark matter) located on the side of the satellite closest to the Milky Way experiences a slightly greater force of attraction than the matter at the far side.

As a result, the dwarf gets stretched along the line between it and the larger galaxy. The stretching stems from so-called tidal forces—the same physics that causes the moon to raise the tides in Earth's oceans. Unlike the moon-Earth interaction, the tidal forces of the Milky Way on its satellites can be strong enough to actually remove matter—in this case, stars get pulled off from the body of the dwarf. Once removed, the stars stay in the grip of the Milky Way's gravity and continue along a path slightly offset from the satellite's own orbit. Over time the slight offset causes the debris to steadily spread, becoming more diffuse and moving away from the satellite to form stellar streams.

This theoretical picture makes a lot of sense, but for a long time scientists lacked observational evidence. Now they have it. The discovery of many star streams has revealed that the Milky Way began eating its neighbors billions of years ago, when it was young, and continues to munch on dwarfs today. And although we have seen proof of streams from dwarf companions mainly around our own galaxy, such streams probably occur around all similar spiral galaxies, although those distant streams would generally be too faint to be detected from afar.

Many details of the process of hierarchical formation still remain elusive, however, such as when the Milky Way absorbed most of its satellite galaxies, how often it eats dwarfs and how long it takes to incorporate their stars. To answer these questions, astronomers must locate more star streams amenable to thorough study, as well as the remnants of defunct streams.

DIGGING FOR GALACTIC FOSSILS

ASTRONOMERS SEEK STAR STREAMS in the Milky Way in multiple ways. First and most straightforwardly, we can look for groups of stars at the same distances that cluster together in long filaments. For this, we need a good three-dimensional map of our galaxy's stars that shows the distances and positions of as many stars as possible in all directions.

Over the past 15 years galactic archaeologists have gotten just that in the form of data from the Sloan Digital Sky Survey (SDSS). The survey used a dedicated telescope at Apache Point Observatory in New Mexico to create a database of more than 80 million stars within the Milky Way, along with information on their distances, colors and other characteristics, spread over one quarter of the sky. The vast number of stars in this catalogue offered a perfect dig site to look for fossils from the Milky Way's past.

The fraction of stars that were initially born in other galaxies and subsequently subsumed into our own galaxy is thought to be small, roughly 1 percent or less of the Milky Way's hundreds of billions of stars. But Sloan's map gave astronomers potentially almost one million interloper stars to examine for evidence of long-dead galaxies. Galactic archaeologists looked in this map for stars likely to be at the right distance to lie in the galactic halo. Among these stars, they located star streams by homing in on areas that were denser with stars than their surroundings and took the shape of tails. Astronomers knew what the tails would look like in part from computer simulations I created and published in 2005 in collaboration with cosmologist James Bullock of the University of California, Irvine. We used our understanding of how dark matter halos form hierarchically, combined with the physics of tidal forces, to predict the sizes and spreads of the stellar streams that will result as many dwarf galaxies get swallowed during the formation of the Milky Way.

The known stellar streams are probably just a fraction of those that exist. Many more streams should be out there, too faint to see for now.

The first convincing evidence of an extended star stream came in 2003, when astronomers led by Steve Majewski of the University of Virginia uncovered giant tails emanating from the Milky Way's closest known satellite, the Sagittarius dwarf galaxy, in data from the Two Micron All Sky Survey (a similar project to Sloan, conducted in infrared light). The streams lie close to Sagittarius's projected orbit and contain almost as many stars as are still in the Sagittarius galaxy itself. The tails are so long that they entirely encircle our own galaxy. We had caught the Milky Way in the act of attacking its own nearest (but apparently not dearest) neighbor.

Since that discovery, galactic archaeologists have unearthed about a dozen more star streams around our galaxy in the Sloan catalogue. From the length of Sagittarius's tails, we can say it has been losing stars for two billion to three billion years. The other streams that we see also look to be a few billion years old. These discoveries indicate that the Milky Way was digesting galaxies more often during its early history and has ramped down lately as the number of dwarfs available to be eaten has diminished. So far these findings are in line with what hierarchical formation theory predicts. The known stellar streams, though, are probably just a fraction of those that exist. Many more streams should be out there, too faint to see for now but harboring further insights into the galaxy's past.

SCIENTIFIC AMERICAN ONLINE For a video animation of a dwarf galaxy ripping apart into stellar streams, visit ScientificAmerican.com/dec2014/johnston

NEW EXCAVATION TOOLS

RELYING ON STAR POSITIONS to find stellar streams will miss many older trails because over the course of a few billion years small differences in orbital properties between the stars can cause the streams to lengthen, diffuse and fade so much that they lose any obvious structure. Astronomers are now working on ways to exploit other stellar properties to find streams that are more dissolved, as well as remnants of streams that have come apart fully. These collections of stars will help scientists explore the most active epoch of galaxy formation, which occurred more than 10 billion years ago, within the first few billion years after the big bang, when most of the stars in the universe formed. That is the time during which not just a few but hundreds of small galaxies and star clusters were accreted to form the Milky Way.

One way to hunt for these leftovers from now defunct galaxies involves looking for stars with common orbits. Long after stars in streams have become too scattered to recognize from their positions, we can take advantage of their motion to identify stars that were once part of the same satellite galaxy and to learn how they joined the Milky Way. This goal is one of the many being pursued by the European Space Agency's Gaia satellite, launched in December 2013. Gaia will spend the next four years creating a game-changing data set for galactic archaeologists by measuring distances, positions and motions for more than a billion stars. This haul is exciting for our problem because of the sheer number of stars being catalogued and because the many dimensions of information being measured for each star will allow us to calculate their full orbits. Thus, we can pick out stars with similar orbital properties as likely to have come from the same original galaxy, even if their positions on the sky do not show us that they are related anymore.

Furthermore, there is one sense in which stars never forget where they were born: their chemical composition. This chemistry provides another potential way to discover stellar streams. Stars are constantly changing their overall composition via the nuclear fusion in their cores, which synthesizes light elements into heavier ones. Yet nuclear fusion can take place only in the densest and hottest central regions of the star, and it is thought that the star's atmosphere, which is what astronomers measure, is identical to the gas from which it was born. Astronomers Kenneth Freeman of the Australian National University and Joss Bland-Hawthorn of the University of Sydney aim to use this perfect memory not to find star streams but to group stars with identical chemical fingerprints into the clusters that birthed them, irrespective of where they sit in the sky now.

Freeman and Bland-Hawthorn's simple method of using a single chemical label will not work for identifying stars associated with a dwarf, because these galaxies themselves are likely to contain stars born in many different clusters having a range of chemical compositions. Nevertheless, the natures of cosmic history and of star formation conspire so that an analogous chemical approach might give us some information about the Milky Way's accretion history.

First, stars forming later within a given galaxy generally contain more heavy elements than those forming earlier because the material that constitutes them has already been enriched with the remains of previous generations of stars. Second, exactly how enrichment proceeds is informed by gas flows that are governed in part by the gravitational influence of the galaxy's dark matter halo. These two effects suggest that galaxies of roughly the same mass that are accreted and destroyed at roughly the same time should contribute stars with the same *distribution* of chemical compositions—meaning the same spread of abundances for many different elements. Conversely, differences in either a galaxy's mass or accretion time will lead to differences in the chemical distributions of the stars it contributes. Hence, the overall distribution of chemical compositions of stars around our Milky Way could allow us to discern what fraction come from similar mass galaxies at similar times, if not exactly the same galaxy.

Duane Lee investigated this idea while a graduate student in my group at Columbia University. His preliminary work suggests that chemical tags might be sensitive enough to recover contributions from even the smallest dwarf galaxies destroyed very early on in galactic history. By knowing which fractions of the Milky Way's stars arrived at different epochs, we can begin to sketch out a sequence of cannibalizations and to trace the accretion history of our galaxy, reaching back to the very earliest times. Two groups are now measuring chemical compositions for millions of stars, and their data could be used to tackle this problem. One is the GALactic Archaeology with HERMES (GALAH) survey led by Freeman and Bland-Hawthorn, which has a pilot survey currently under way. The other is called the APO Galactic Evolution Experiment (APOGEE); it started in 2011 as part of the ongoing Sloan survey.

Galactic archaeologists are just beginning to appreciate that studying the Milky Way is like studying 1,000 galaxies, because that many smaller objects have combined to build up the larger body. The fossils from those subsumed galaxies teach us not just about the Milky Way's history but also about the histories of all the smaller galaxies it includes. We should soon be able to study how galaxies of many different sizes were made at many different times, all in our own local laboratory. Such analyses in the next decade could potentially contribute as much to our understanding of galaxy formation as the stunning discoveries of stellar streams encircling the Milky Way have contributed in the past decade.

Ultimately we would like to know how the very first galaxies in the universe formed. The earliest progenitors of galaxies akin to our own are too small and distant to be directly detectable. Galactic archaeology, however, could reveal the remnants of these earliest seeds—the long-lived stars that still bear the imprints of their origins are scattered right here in the Milky Way. In a very real way, then, digging in our own backyard can give us a window on the early universe and the first steps of galaxy formation that is impossible to access by any other means. SA

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scientificamerican.com/magazine/sa

MEDICINE

PAIN THAT WON'T QUIT

Burning. Aching. Shooting. Whatever form it takes, chronic pain can defy treatment. New insights into the causes are leading to fresh ideas for combating it

By Stephani Sutherland

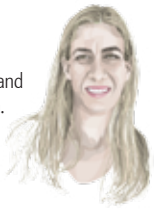
IN BRIEF

Chronic pain affects more people in the U.S. and incurs greater costs than cancer, heart disease and diabetes combined.

Opiates and other existing drugs do a poor job of relieving much chronic pain and can have serious risks. **Discovery of molecular pathways** specific to pain has revealed new targets for drug development. **Substances found** in animal venom are among those being tested as next-generation painkillers.

Photograph by Gerald Slota

Stephani Sutherland is a neuroscientist and science writer based in southern California.



MAKE SURE YOU

stop at the grocery store, not Burger King," Jama Bond instructed her husband on his cell phone as he made an ice-cube run one night in 2012. "Their ice cubes melt too fast." Bond, then 38 and nearly nine months pregnant, needed bags of ice to keep the water cold in the tub at her feet, which were red, swollen and painful. She had learned to cover them with trash bags so the ice water would not damage her skin. A few months before, Bond had been a healthy young woman with an office job at a company that installs solar panels, living a more or less normal life. Now she barely left the comfort of the water bath, except to shower, "which was torture."

Bond, who lives in Santa Rosa, Calif., was suffering from a condition called erythromelalgia (EM)—Greek for "red limb pain"—in which the hands or feet develop severe burning pain, becoming exquisitely sensitive to even mildly warm temperatures or light pressure. For most patients, like Bond, the condition arises without explanation (it has no known link to pregnancy). Although EM is rare, striking only about 13 in a million people, chronic pain in its myriad forms is astonishingly common and often has mystifying origins.

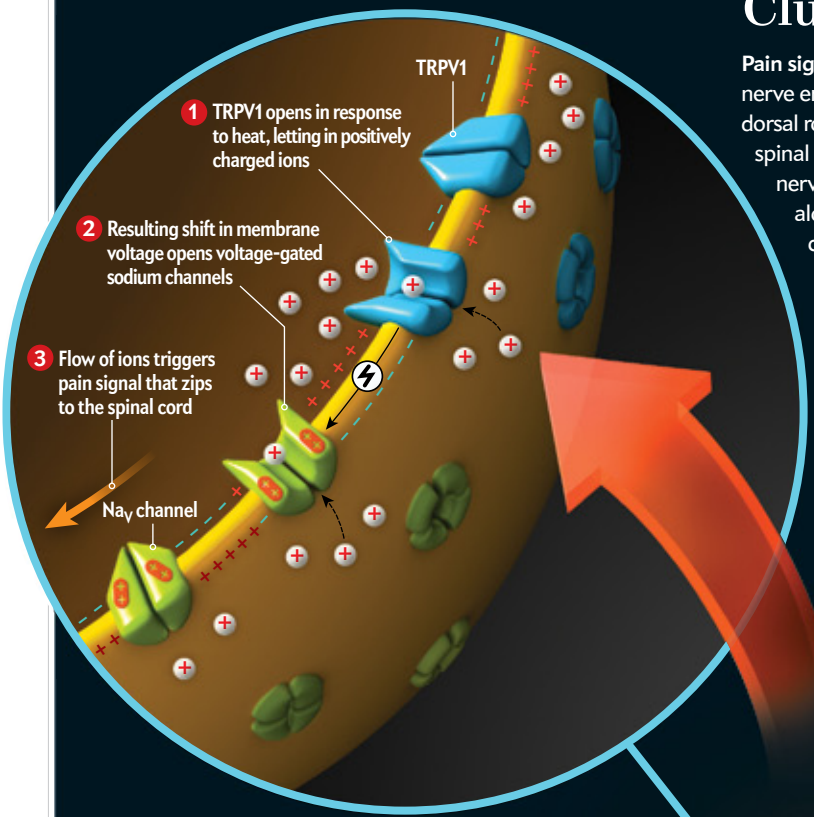
An estimated 100 million people in the U.S. struggle with it, most often in the form of back pain, headaches or arthritis. All told, chronic pain affects more Americans than diabetes, cancer and heart disease combined and costs more, too: as much as $635 billion a year in medical care and lost labor, according to a 2012 analysis. The toll in suffering is incalculable. People coping with the misery face an increased risk of disability, depression, mood and sleep disorders, drug and alcohol addiction, and suicide. Linda Porter, a pain policy adviser at the National Institute of Neurological Disorders and Stroke and director of the National Institutes of Health's Pain Policy Office in Bethesda, Md., calls chronic pain "a huge public health problem that is not adequately recognized nor addressed."

Pain exists for a reason: it provides us with a built-in warning against bodily damage, compelling us to yank a hand from a hot stove before it is badly burned or to stop walking on a leg that is broken. But sometimes it persists long after the threat is gone. Although chronic pain can arise inexplicably, in general it can be divided into two categories: inflammatory—such as that caused by osteoarthritis, for example—and neuropathic, which usually stems from nerve damage caused by injury, disease or another insult.

Chronic pain is notoriously hard to treat, and the neuropathic type is particularly challenging, in part because common anti-inflammatory medications such as ibuprofen and naproxen barely touch it. Morphine and other opiates are the gold standard for severe short-term pain. But they come with side effects that range from the mundane, such as constipation and drowsiness, to a life-threatening suppression of breathing. People who use them over long periods gradually develop tolerance to these drugs and need ever higher doses, raising the risks. Addiction and abuse are also serious issues with opiates: more Americans now die from an overdose of these prescription painkillers than from overdoses of cocaine and heroin combined. Other drugs currently used to treat chronic pain include some originally prescribed to treat seizures and depression, and these, too, have limitations. Despite the possible risks to her unborn baby, Bond received a cocktail of

Clues to Dampening Pain

Pain signals generated by heat or other stimuli travel from nerve endings in the skin or other sites to structures called dorsal root ganglia, near the spinal cord, and then on to the spinal cord and brain. Genetic mutations or damage to nerves can, however, alter the behavior of key molecules along the route, including ion channels, in ways that cause pain to become chronic. Hoping to ease the suffering, researchers are now targeting those critical molecules in a variety of ways.



Hyperactive Channels

Embedded in the membranes of nerve endings that detect painful stimuli are molecules called ion channels that open and close a central pore in response to the stimuli. A channel called TRPV1, for example, detects heat. When it opens, positively charged ions (mainly sodium) rush in, boosting the membrane voltage. In response, voltage-sensitive sodium channels (Na_Vs) open and trigger a pain signal to the spinal cord. Abnormalities in NA_Vs or TRPV1 can cause excessive signaling. Agents under study may decrease channel activity and thus halt the extra signaling.

Crossed Wires

Some nerves that detect sensory inputs specialize in transmitting pain; others convey touch. Cross talk between the two pathways is regulated by cells in the spinal cord called interneurons (*blue*). This regulation is often disrupted in people with chronic pain, who then experience allodynia—pain from an innocuous stimulus such as a gentle touch. Research shows that this condition can arise after a nerve is injured, when immune cells known as microglia release chemical signals that cause spinal cord neurons to lose a molecule essential to normal signaling. Drug developers are working on ways to fix this short circuit and relieve allodynia.

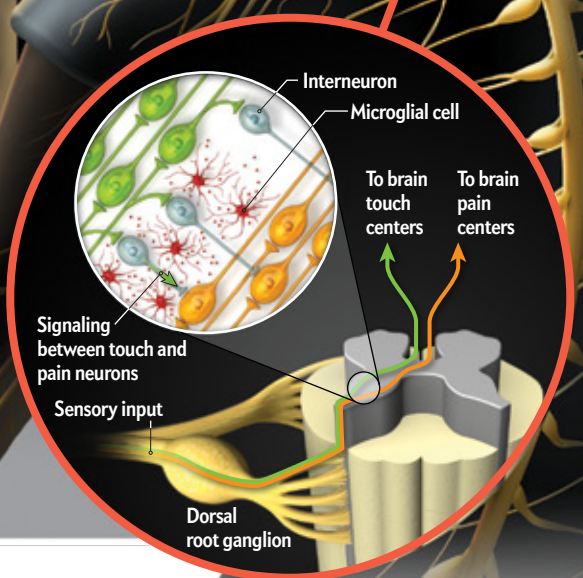


Illustration by Emily Cooper

opiates, anticonvulsants and antidepressants to help her sleep and to lower her dangerously high stress level.

Safer, more effective medications have eluded the best efforts of science, but that is beginning to change. Recent discoveries have opened several promising new avenues for drug development. "Researchers are making a lot of progress now by focusing in on pain's molecular signaling pathways," Porter says. "There is hope."

RELAY RACE

TO UNDERSTAND THESE NEW EFFORTS to control chronic pain, it is useful to know how pain arises. Pain begins as a stimulus detected by specialized nerve cells called nociceptors, which spread their feelers across the surfaces of the body, inside and out. Stimuli that could damage the body—very high or low temperature, mechanical force or a whole host of chemical threats—activate these nerve endings. Then the endings send signals zipping toward the nociceptors' cell bodies, which sit in structures known as dorsal root ganglia located just outside the spinal cord. From there the nociceptors relay the threat to neurons in the spinal cord. These, in turn, trigger the brain's extensive pain network, including areas involved in thought and emotion (which explains why placebos and distractions can sometimes ease pain).

Like all nerve signals, pain messages speed from one end of a neuron to the other via an electrical event called an action potential, created by the flow of ions—charged atoms of sodium and potassium—across a cell membrane. These ions move through tiny pores in the membrane called ion channels, made of proteins that change shape into an open or closed configuration. At nociceptors' endings, specialized ion channels detect possible threats, such as heat or chemicals spilling out from nearby damaged cells. When these channels open, positive ions flood the cell, subtly changing the balance of voltage across the membrane. This shift, in turn, triggers other ion channels that are sensitive to specific voltages. When enough of these voltage-gated ion channels open, the resulting ion flow sparks an action potential that races along the entire length of the neuron—much like a stadium crowd doing the wave. The action potential culminates in the release of a neurotransmitter in the spinal cord, a chemical message that relays information to a neighboring neuron.

Much of what has been learned about pain in the past 20 years centers on ion channels: how they detect signals such as heat and tissue damage; which of them are required for pain signaling, as opposed to playing supporting roles; and, perhaps the most pressing question, which channels could be targeted to safely silence unwanted pain signals.

Researchers and pharmaceutical companies have long understood that blocking sodium channels at nerve endings eases pain—the short-acting local anesthetics lidocaine and novocaine, for example, plug up sodium channels to numb not only pain but all sensation where they are applied. Nine voltage-gated sodium channels have been found in humans and other mammals, each opening in response to a slightly different voltage. Blocking all of them would have devastating effects because sodium channels occur in all nerve cells of the body and in other tissues, including in the brain and heart; indiscriminate blockade could interfere with the signals that give rise to heartbeat, breathing and movement. For years scientists have therefore sought a holy grail: sodium channels that are restricted to pain-sensing cells in the body.

In the late 1990s investigators got closer to this target with the discovery of three voltage-gated sodium channels that appear only in the peripheral nerve network (as opposed to in the spinal cord and brain), which is where pain signals generally begin. Designated $Na_V1.7$, $Na_V1.8$ and $Na_V1.9$, all three are mostly relegated to nociceptors and some other neurons involved in sensation. ("Na" stands for sodium, and "$_V$" stands for voltage, with the number indicating their position in the family of nine known channels.) Once the genes encoding the channels were identified, researchers were able to manipulate the channels' activity in laboratory animals. Over the next 10 years tests confirmed that, at least in mice, quieting sensory Na_Vs could alleviate neuropathic pain.

By 2000 Na_V channels were seen as promising targets for drug development, but pharmaceutical companies needed evidence beyond animal studies to justify a major investment. Those data came from four key papers tying $Na_V1.7$ to pain in people. In 2004 a group working in Beijing found mutations in the gene for $Na_V1.7$ in two Chinese families with an inherited form of erythromelalgia—the condition Bond developed spontaneously during pregnancy. In 2005 Stephen Waxman and Sulayman Dib-Hajj, both at the Yale School of Medicine and the Veterans Affairs Connecticut Healthcare System, confirmed that these mutations led to $Na_V1.7$ hyperactivity that could cause pain. Soon after, John Wood of University College London and his colleagues reported that another condition—paroxysmal extreme pain disorder, which causes pain in the rectum, eyes and jaw—also arose from an overactive mutant $Na_V1.7$ channel. Critically, Geoff Woods and James Cox, both then at the University of Cambridge, showed in 2006 that mutations in $Na_V1.7$ that wiped out its function also eliminated any sensation of pain, creating a rare and dangerous condition that often leads to death from unfelt injuries. Together these findings in unusual genetic conditions confirmed the importance of $Na_V1.7$ in human pain sensation.

"Researchers are making a lot of progress now by focusing in on pain's molecular signaling pathways," NIH's Linda Porter says. "There is hope."

Waxman explores rare genetic diseases because, he says, they can be useful as "pointers to pathological pathways that

Why Me?

A variety of factors explain why some people are more vulnerable to chronic pain than others

Take 10 people who suffer the same back injury in a car accident: three of them will have the misfortune to end up with chronic pain as a result. Or take 10 people with diabetes: about half will develop nerve damage, or neuropathy, but the injury will cause ongoing pain in only three of them. What factors make some people vulnerable and others resilient? The question has not yet been fully answered, but research points to three main influences that seem to work in concert:

Hardwiring: Genes help to determine an individual's pain sensitivity and tolerance, and some tip the scales toward unusual susceptibility to chronic pain. One of the biggest genetic factors is gender; women are far more likely than men to develop chronic pain over the course of a lifetime.

Experience: Stress, trauma and abuse—both physical and emotional—can raise the risk. Studies suggest that these experiences can cause long-term changes in gene activity, turning genes on or off in ways that affect pain pathways. In addition, the risk for chronic pain rises with age, not just because of wear and tear but probably also because the body's ability to repair injuries—including nerve damage—declines as we get older.

Personality: Certain personality traits skew risk. Pessimists, worrywarts and catastrophizers (such as *Saturday Night Live* character Debbie Downer) are more likely to suffer. Brain circuitry involved in motivation and reward also seems to influence pain vulnerability.

—*S.S.*

may be more common." In 2012, together with collaborators in the Netherlands, he made that leap to a more common condition. Small-fiber polyneuropathy is a broad label used to describe damage to pain-sensing nerves in the periphery, often the hands or feet. About half of patients diagnosed with the condition have an identifiable source of nerve damage, such as diabetes, but in the other half the cause of pain remains a mystery. Waxman and his Dutch collaborators examined DNA from patients with unexplained cases and found mutations in the genes for $Na_V1.7$ in close to 30 percent of them, mutations in $Na_V1.8$ in 9 percent and mutations in $Na_V1.9$ in another 3 percent. Waxman's group has also found that people with chronic pain from nerve injury have an increased number of $Na_V1.7$ channels in the nerves that are damaged.

Those findings were enough for drug companies to pursue the sensory-specific sodium channels in earnest. Pfizer has been developing drugs aimed at $Na_V1.7$ and $Na_V1.8$ for several years, and although it is too early to say when a new painkiller might be available, several are now being tested in patients, reports Neil Castle of Neusentis, Pfizer's pain and sensory disorders research unit in Durham, N.C. Unlike older drugs such as lidocaine, these newer molecules are not targeted to the main pore of the sodium channel, which is nearly identical from one channel subtype to the next. Instead they act on a region of the channel that senses voltage and differs from one channel to the next, giving them more specificity and, presumably, making them safer. In 2013 Castle's group reported discovery of a chemical that selectively hits the $Na_V1.7$ voltage sensor. Such molecules, Castle says, "have very high selectivity, so they do not affect heart or muscle function"—at least not in early testing.

Meanwhile a team at Duke University is also taking aim at the $Na_V1.7$ voltage sensor but is doing so with an antibody—a molecule that derives from the immune system. According to a study published in June, the antibody relieves both inflammatory and neuropathic pain in mice, and it alleviates itching, making the approach a possible three-fer in the realm of relief. Researchers exploring the ability of certain components in venoms to act on $Na_V1.7$ are having some luck as well [*see box on next page*].

HEATING UP

SODIUM CHANNELS are not the only targets painted with a bull's-eye. Another ion channel called the transient receptor potential channel V1 (TRPV1) is famously activated by hot temperatures and by capsaicin—the chemical that gives chili peppers their burn—and it is largely restricted to pain-sensing cells. Ever since David Julius and his colleagues at the University of California, San Francisco, discovered the gene for TRPV1 in 1997, scientists have been hot on the trail of molecules that could silence pain signals by closing this channel.

"TRPV1 has been such a promising and yet such an elusive target for so long," the NIH's Porter says. Early blockers that shut it down had unmanageable side effects, such as bodily overheating and insensitivity to heat that could cause burns. The channel, which also senses acid, spider toxins and substances that promote inflammation, has more recently emerged as a complex integrator of sensory signals. "The best drug would not perturb the channel's core heat-sensing ability," Julius says. It would merely calm an overactive channel.

Julius's team took a step forward in December 2013, when it published the first high-resolution pictures of the TRPV1 structure in various states. That information should help researchers to figure out a way to block the channel only when it takes on a shape that gives rise to pain.

PAIN, MISINTERPRETED

MOST PEOPLE WITH neuropathic pain experience its three hallmarks: hypersensitivity to painful stimuli; spontaneous pain that strikes out of nowhere; and allodynia, which makes a harmless touch feel painful. (Allodynia caused the pelting water of a shower to feel like torture to Bond.) Whereas research on ion channels has helped explain hypersensitivity, another line of investigation has clarified how allodynia arises. Normally pain signals and signals for nonpainful touch travel along separate pathways from nerves in the skin to the spinal cord and up to the brain, but in the case of allodynia, signals get crossed in the spinal cord: touch-sensing neurons activate the pain pathway.

How things go wrong has been worked out mainly by investigators in Japan and by two groups in Canada, one led by Yves De

Taking the Sting Out of Pain

Venom molecules could provide alternatives to addictive opiate drugs

By Mark Peplow

PAINKILLER: The Chinese red-headed centipede's toxic venom contains a component that can numb nerves without harming the rest of the body.

COURTESY OF YASUNORI KOIDE

When Glenn King milks centipedes, he is not going after nutrition. He is milking their poison, and it is no simple task. "We tie them down with elastic bands, bring a pair of electrical forceps up to their pincers, apply a voltage, and they expel the venom," says King, a biochemist at the University of Queensland in Australia.

The microliters of fluid could hold the keys to a new set of pain-relieving drugs. Venoms are natural storehouses of nerve-numbing molecules, and with 400 different types of venom in his laboratory, King is at the forefront of efforts to identify analgesics in the stings of centipedes, spiders, snails and other poisonous beasts.

Large pharmaceutical companies have been struggling to synthesize alternatives to addictive painkillers such as morphine but have had trouble making molecules that home in on the specific nerves they need to target. Venoms, however, have naturally evolved to contain molecules with this kind of specificity. In laboratory animals these molecules numb nerves without harming the rest of the body. The targets that many researchers are aiming at are called voltage-gated sodium ion channels, which are common in pain-sensing nerve cells. Plugging one particular type of channel, known as $Na_V1.7$, keeps the cell from passing a pain message to other parts of the body, as discussed in the accompanying article.

Certain venom components have just the right shape and chemical activity to latch onto a part of the channel called a voltage sensor, and that action shuts the channel. Last year King identified a venom molecule called m-SLPTX-Ssm6a that appeared to be one of the most selective inhibitors of $Na_V1.7$ ever seen. He found it in the venom of the Chinese red-headed centipede (*Scolopendra subspinipes mutilans*), which can grow up to 20 centimeters long and has a pair of vicious, pincerlike claws. "If they nail you, it'll hurt," King says. The molecule, however, had quite the opposite effect in injured mice: in experiments, it blocked pain better than morphine. But it had no unwanted effects on blood pressure, heart rate or motor function, indicating that it was not depressing the central nervous system, as an opiate such as morphine would.

King's team produced a synthetic version to see if the molecule could be manufactured as a drug. But to the researchers' dismay, this version did not work as well. King suspects that the original preparation they had made of m-SLPTX-Ssm6a actually contained traces of another active component. He is working on a further round of centipede milking to search for the mystery ingredient.

Snake venom is also a source of selective channel blockers. Anne Baron, a pharmacologist at the Institute of Molecular and Cellular Pharmacology in France, has isolated two painkilling molecules from the venom of the black mamba. "We are nearly ready for a clinical trial," Baron says. "We have done a lot of animal tests in rodents to assess toxicity." The mambalgins, as the molecules are called, plug a particular set of acid-sensing ion channels in peripheral nerve cells that, like sodium channels, help the cells send pain signals. Fortuitously, the mambalgins have no effect on most other ion channels, which may explain why mice injected with the substances had no apparent side effects.

Accurate nerve cell targeting is not the only goal of venom research, says David Craik, a biochemist at Queensland. If venom molecules are to be swallowed as pain pills, they need to resist degradation by the digestive system. In 2004 the U.S. Food and Drug Administration approved a painkilling drug called ziconotide that is based on a molecule isolated from the venomous cone snail *Conus victoriae.* But the drug could not withstand the rigors of the stomach, so it must be pump-injected slowly into patients, a cumbersome procedure. "Ziconotide hasn't been a big seller," Craik says.

Craik has started to reengineer painkillers derived from the cone snail toxins. His strategy is to turn the molecules, which are normally chains of amino acids, into rings. Circles are much more stable structures—enzymes in the body cannot snip off the ends. He spliced the ends together and gave oral doses of the rings to rats. The compound, dubbed cVc1.1, turned out to be 100 times more potent than gabapentin, a common treatment for nerve pain. And earlier this year at the American Chemical Society meeting in Dallas, Tex., he unveiled five more ring-shaped conotoxins that have also shown durability in early studies.

With tens of thousands of venomous species in the world, researchers think it is only a matter of time until they find a compound that hits the right target, is rugged and can be easily produced in quantity. "We perhaps know 1 percent of the products that are in these venoms," Baron says.

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SCIENTIFIC AMERICAN ONLINE See an animation of a promising drug target for pain at ScientificAmerican.com/dec2014/pain

Koninck of the Quebec Mental Health University Institute and the other by Michael Salter of the Hospital for Sick Children in Toronto. In animal studies, they found that in response to nerve injury, microglia, the nervous system's own Pac-Man–like immune cells, release a signal that causes spinal cord neurons to reduce their complement of an ion-transporting molecule called KCC2 ("KC" stands for potassium chloride). The transporter works to maintain the delicate balance of chloride ions inside and outside cells. Under normal conditions, small nerve cells in the spinal cord called interneurons regulate communication between the pathways for painful and nonpainful sensations. They prevent ordinary touch from causing pain but allow a soothing stroke to temporarily ease it. When spinal cord neurons lose KCC2, however, this communication goes awry, and a light touch can trigger pain. Researchers theorized that if KCC2 levels could be restored, the improper signaling would stop.

The future of medicine, most researchers believe, is personalized. For chronic pain, that future is only just coming into view. Treatment at even the best centers tends to rely largely on trial and error.

In November 2013 De Koninck and his colleagues reported discovery of a compound that bolsters chloride transport through KCC2. The drug restored the balance of chloride ions and electrical function in neurons of the spinal cord. Moreover, it alleviated signs of neuropathic pain in rats. The KCC2 enhancer was safe and free of side effects in the animals, even at high doses.

Although the work so far has been conducted only in animals, certain aspects of the KCC2 transporter make it an exceptionally good target for human therapies. Unlike other drugs that inhibit ion channels wholesale, this transport-enhancing agent would, for instance, affect only cells with the defect, De Koninck says. Cells with functional KCC2 would keep working as usual, and the drug would not overly boost their activity. Experiments indicate that rather than changing how KCC2 behaves, the drug shepherds more of the transporters to the cell's surface. A fuller understanding of how that traffic control works will be crucial to developing safe, effective painkillers.

PERSONALIZED PAIN TREATMENT

THE FUTURE OF MEDICINE, most researchers believe, is personalized, meaning that an individual's genes and specific drug sensitivities will determine the best course of treatment and the surest way to prevent disease. In the field of chronic pain management, that future is only just coming into view. "We would love to be able to tell what, specifically, has gone wrong in each patient. Then we could say, 'Oh, you get this drug, whereas you get that other drug,'" says David Bennett, a neurologist at the University of Oxford. But treatment at even the best comprehensive pain-management centers tends to rely largely on trial and error.

Now, however, patients with rare genetic mutations affecting the Na_V channels are helping to show the way to personalized pain therapy. For example, most people who suffer the burning limb pain of erythromelalgia because of an inherited $Na_V1.7$ mutation are not helped by carbamazepine, an antiseizure drug sometimes used to treat pain. One family with the condition, though, has a particular mutation (there are many types) that results in a good response to the drug. By studying the molecular structure and function of the family's mutated channel, Waxman and Dib-Hajj were able to see how carbamazepine calmed the channel's hyperactivity and then were able to accurately predict that it would also be effective with a somewhat different mutation. These findings are exciting, Waxman says, because they suggest that basing therapy on a person's genetic makeup "is not unrealistic" for patients with inherited erythromelalgia and those who are suffering from more common pain conditions.

As for Jama Bond, her symptoms abruptly halted just before she delivered a healthy baby boy a few weeks early. Unexpectedly, steroid injections meant to help the infant's lungs mature worked like a charm for his mother. "I woke up in the middle of the night," she recalls, "and my feet did not hurt—which had not happened in over six months." No one could explain why. The symptoms did return but never with the same severity she had endured during pregnancy. "If I am on my feet for a long time, it has a direct result: I will be in pain," Bond says. "I am managing it, and I am drug-free, so that's amazing. I would love to be cured." And pain researchers would love to bring relief to Bond and the many millions like her. SA

MORE TO EXPLORE

Black Mamba Venom Peptides Target Acid-Sensing Ion Channels to Abolish Pain. Sylvie Diochot et al. in *Nature*, Vol. 490, pages 552–555; October 25, 2012.

Discovery of a Selective $Na_V1.7$ Inhibitor from Centipede Venom with Analgesic Efficacy Exceeding Morphine in Rodent Pain Models. Shilong Yang in *Proceedings of the National Academy of Sciences USA*, Vol. 110, No. 43, pages 17,534–17,539; October 22, 2013.

Pain Vulnerability: A Neurobiological Perspective. Franziska Denk, Stephen B. McMahon and Irene Tracey in *Nature Neuroscience*, Vol. 17, pages 192–200; February 2014.

Regulating Excitability of Peripheral Afferents: Emerging Ion Channel Targets. Stephen G. Waxman and Gerald W. Zamponi in *Nature Neuroscience*, Vol. 17, pages 153–163; February 2014.

FROM OUR ARCHIVES

Toward Better Pain Control. Allan I. Basbaum and David Julius; June 2006.

scientificamerican.com/magazine/sa

WIND-WHIPPED lake waves froze this lighthouse in Michigan during a harsh winter storm.

CLIMATE

THE JET STREAM IS GETTING WEIRD

Extreme summers and winters of the past four years could become the norm

By Jeff Masters

THOMAS ZAKOWSKI *Landov*

Jeff Masters is director of meteorology at the Weather Underground, which he co-founded in 1995, and specializes in severe weather forecasting. He also writes WunderBlog, one of the most popular weather blogs on the Internet.

FROM NOVEMBER 2013 THROUGH JANUARY 2014, THE JET STREAM TOOK ON A REMARKABLY EXTREME AND PERSISTENT shape over North America and Europe. This global river of eastward-flowing winds high in the atmosphere dipped farther south than usual across the eastern U.S., allowing the notorious "polar vortex" of frigid air swirling over the Arctic to plunge southward, putting the eastern two thirds of the country into a deep freeze. Ice cover on the Great Lakes reached its second-greatest extent on record, and two crippling snow-and-ice storms shut down Atlanta for multiple days.

At the same time, a stubborn ridge of high pressure hunkered down over California, creating the warmest winter on record there. Although the balminess may sound nice, the resulting drought became the worst since record keeping began in the late 1800s, causing billions of dollars in agricultural losses.

The jet stream's contortions also pummeled Europe, where a succession of intense storms led to additional billions of dollars of damage. In England and Wales the winter was the wettest since at least 1766. Much of the rest of Europe basked in exceptional warmth: Norway suffered unprecedented January wildfires, and Winter Olympics officials in Sochi, Russia, struggled with melting ski slopes. In May nearly one third of the entire country of Bosnia was flooded by a massive, swirling rainstorm.

Ordinarily the jet stream resembles a band of air blowing across the middle latitudes. As we see on television weather forecasts, it often has mild bends from north to south and back to north again, looking somewhat like a sine wave on an oscilloscope. The bends are called planetary or Rossby waves and typically progress across the U.S. in three to five days. They deliver much of the day-to-day weather we experience.

During the 2013–2014 winter, however, the waves became amplified with gigantic, steep sides, resembling an erratic electrocardiogram printout. This configuration of winds also moved across the earth much more slowly than usual, at times stopping in place for weeks and bringing remarkably long periods of uncommon weather. A May study led by Shih-Yu (Simon) Wang of Utah State University found the jet stream pattern over North America during that time was the most extreme ever recorded.

Was the radical jet stream an anomaly? Apparently not, because it seems to be happening more and more. In 2010 Russia baked through its most oppressive heat wave in written history, one that killed more than 55,000 people. At the same time, intense rains deluged Pakistan, its most expensive natural disaster on record. In 2011 Oklahoma endured the hottest summer any American state has ever had. U.S. drought conditions in 2012 were the most extensive since the 1930s.

The bends in the jet stream during those particular events shared a common feature, according to an April 2013 paper by scientists at the Potsdam Institute for Climate Impact Research in Germany, led by Vladimir Petoukhov. The usually eastward-moving waves "ground to a halt and were greatly amplified," two of the authors wrote in a blog post about their research. In some cases, the bends remained stuck for days or even months at a time. The scientists also showed that the extreme configurations were twice as common during summers from 2001 to 2012 as they were during summers of the prior 22 years.

As Bob Dylan sang, "You don't need a weatherman to know which way the wind blows." Something is clearly up with the jet stream, and it is not hard to see the probable reason why. The base state of our climate has changed dramatically over the past 150 years, and that change is starting to alter the jet stream's behavior. Atmospheric levels of heat-trapping carbon dioxide, for example, have increased more than 40 percent, primarily because of the burning of coal, oil and natural gas. The extent of summer sea ice in the Arctic is down nearly 50 percent since 1900, affecting heat flow in the atmosphere and ocean. Solar energy reflecting off the earth's surface has changed significantly because we have modified more than half of the planet's landscape with crops, pastures and cities. Massive clouds of sunlight-reflecting and sunlight-absorbing soot and pollution belch forth

IN BRIEF

Severe weather outbreaks have occurred in the past four years when the jet stream has become contorted into extreme positions.

Extended bouts of outlandish weather have taken place when the jet stream has become stalled in these shapes for long periods.

Some scientists assert that the leading cause of a weird jet stream is the loss of Arctic sea ice, although other experts disagree.

Either way a more extreme jet stream will mean greater droughts, floods, heat waves and deep freezes in many parts of the world.

HIGH-ALTITUDE CLOUDS, as seen from the Space Shuttle, gather along the jet stream over eastern Canada. North is toward the bottom of the image, where Cape Breton Island is visible (*center*). The jet's speed can top 300 kilometers per hour.

from power plants, vehicles, buildings and industries. A huge ozone hole disrupts upper-level winds over the Antarctic.

Humans have kicked the climate system hard, and physics demands that the earth's fundamental weather patterns change as a result. Indeed, Wang and his colleagues concluded that the jet stream's configuration most likely could not have grown so strange without the influence of human-caused global warming.

The danger is that climate is not linear. A modest level of global warming can suddenly create a step change to a new regime with wildly different weather. Climate scientists are intensely debating whether climate as a whole and the jet stream in particular have crossed a tipping point into a new long-term state. They are also debating a controversial theory put forth by the Potsdam researchers and others that says that the changes in the jet stream stem largely from events occurring in the fastest-warming portion of the planet—the Arctic.

If indeed the jet stream is entering a new state, that bodes ill for civilization. An August paper published in *Nature Climate Change* by James Screen of the University of Exeter in England and Ian Simmonds of the University of Melbourne in Australia went so far as to pinpoint the potential effects. (*Scientific American* is part of Nature Publishing Group.) If jet stream waves "are amplified in response to anthropogenic [human-caused] climate change, as has been proposed," they wrote, "our results suggest that this would preferentially increase the probabilities of heat waves in western North America and central Asia, cold waves in eastern North America, droughts in central North America, Europe and central Asia, and wet extremes in western Asia."

This new normal would mean more terrible summer droughts for midwesterners. Winters featuring strings of snowstorms like the 2010 "snowmageddon" that closed Washington, D.C., would blast eastern U.S. residents more often. And people worldwide would see food prices go up, a consequence of intense and persistent droughts in central North America, Europe and Central Asia.

NATURAL VARIATIONS

CLIMATE CHANGE WOULD REVISE the jet stream indirectly by acting on big forces in the atmosphere that ultimately shape it. The ever present river of wind, nine to 14 kilometers high, circles the globe in both hemispheres and acts as a guide along which precipitation-bearing low-pressure systems ride. The jet stream typically has two branches: a polar jet that acts as the boundary between cold air near the poles and warm air closer to the equator and a less vigorous subtropical jet that lies closer to the equator. Henceforth, when I discuss the jet stream, I mean the dominant polar jet.

That jet's latitude rises and falls a bit with the seasons: it is typically over the central U.S. in winter and near the U.S.-Cana-

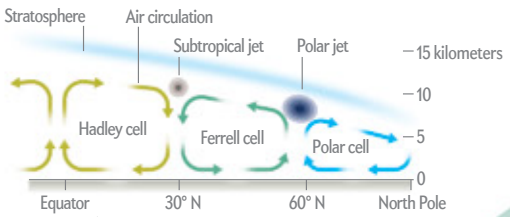
SCIENCE SOURCE

A Radical Jet Stream Delivers Extreme Weather

Two jets of high-altitude wind blow around the earth in each hemisphere. When bends in the polar jet become magnified (*left-hand page*), abnormally warm or cold air can wallop large regions of a continent. The bends can also get stuck that way for weeks, causing droughts, floods, heat waves and deep freezes. Two leading theories can explain the big bends (*right-hand page*), one driven by climate change and one linked to either climate change or natural variability.

Jet Streams Form

Because the equator gets more solar energy than the poles, hot air rises there, hits the stratosphere and spreads toward the poles. The earth's spin deflects the air into three major, interlocking atmospheric circulation cells in each hemisphere. Jet streams arise along the cell boundaries to equalize pressure differences.



Waviness Brings Heat Waves and Deep Freezes

When mild bends in the polar jet stream become amplified (*wavy blue arrow*), huge warm-air masses can surge much farther north than usual, and cold-air masses—such as the winter polar vortex—can plunge far to the south. The bends typically progress across the U.S. in three to five days, delivering our daily weather.

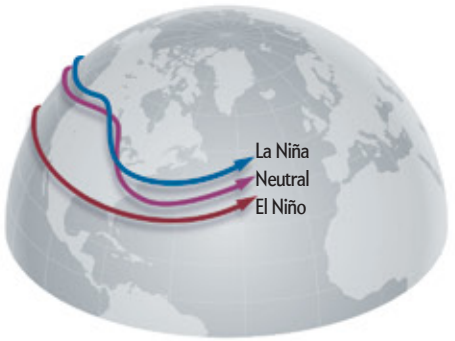
Long-Term Ramifications

If the polar jet stream has crossed a tipping point to a new state in which big bends become common, the U.S. may see more heat waves in the west, cold waves in the east and drought in the central states.

Why Waviness Changes: Two Possibilities

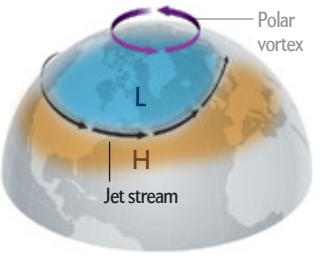
1 Atmospheric Oscillations

Natural phenomena in the atmosphere can alter the jet stream's path. Two prime suspects are the El Niño/Southern Oscillation and the Arctic Oscillation.

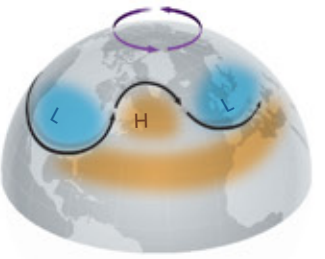


El Niño/Southern Oscillation

This cycle in tropical atmospheric pressure has two phases: El Niño brings warmer Pacific Ocean water eastward, moving the jet stream south; La Niña brings cooler water, moving the jet north. Recent, large differences in the phases, linked to a wavy jet, may be natural or driven by climate change.



Positive phase is linked to a large pressure difference, which helps the jet stream take a straighter path, and to a strong polar vortex, which keeps cold air north



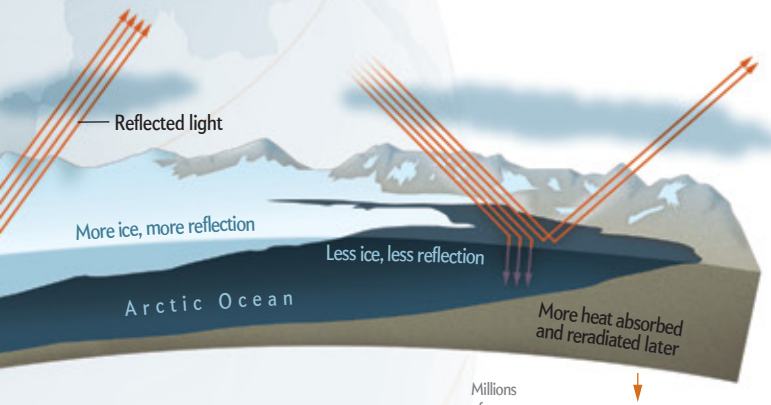
Negative phase is linked to a small pressure difference, which weakens the jet stream so big bends are more likely, and weakens the polar vortex, allowing cold air to drift south

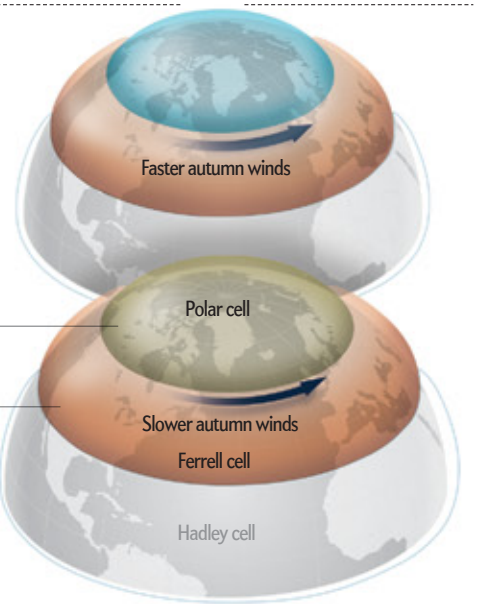
Arctic Oscillation

Week-to-week changes in sea-level pressure between the Arctic and midlatitudes cause this phenomenon; factors not fully understood shift it between positive and negative phases.

2 Arctic Amplification

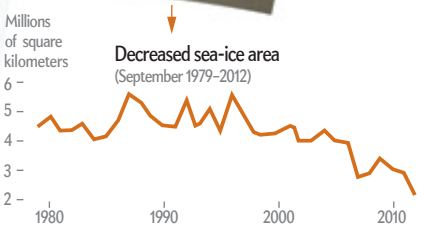
The Arctic is warming up two to three times as fast as the midlatitudes. Disappearing sea ice (*below*) is a major reason: more exposed water absorbs extra solar heat in summer and reradiates it in winter, raising air temperature in the polar cell faster than the rise in the Ferrell cell (*right*). The declining difference between cells makes a negative Arctic Oscillation and wavy jet stream (*above right*) more likely.

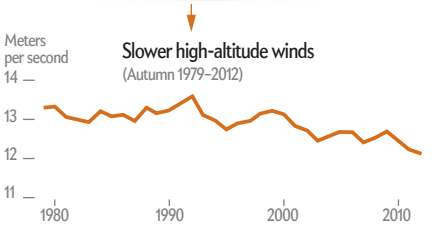




Less Ice, Weaker Winds

From 1979 to 2012 the minimum area of Arctic sea ice dropped 40 percent, and autumn winds high over North America slowed 10 percent (*graphs*). Slower winds are associated with big, problematic bends in the jet stream.





SOURCE: NATIONAL CENTERS FOR ENVIRONMENTAL PREDICTION AND EARTH SYSTEM RESEARCH LABORATORY (*bottom right charts, wind data*), NATIONAL SNOW AND ICE DATA CENTER (*bottom right charts, sea ice data*). COMPILED BY DR. JENNIFER FRANCIS (*bottom right charts*)

Illustration by Juan Velasco (5W Infographics), Research by Amanda Hobbs

dian border in summer. The flow, however, is chaotic, and large Rossby waves are always present. In the Northern Hemisphere, when the jet stream bulges northward as a ridge of high pressure, warm air flows up from south to north. Where the jet loops to the south as a trough of low pressure, cold air spills southward.

The jet stream is created by three major interlocking cells of circulating air over each hemisphere [*see box on two preceding pages*]. Although the cells help to shape the jet stream, other forces in the sky can contort it further. The atmosphere actually resonates because of energy from the sun, the shape and location of the continents and ocean currents, the presence of mountain ranges, and the amount of heat-trapping greenhouse gases and reflective dust in the air. Just as a guitar resonates differently when various strings are plucked, as these factors change, the atmosphere resonates with multiple tones, called teleconnection patterns. These natural resonances can reshape the jet stream, complicating the determination of whether its recent behavior is a sign of a permanent change.

In the Northern Hemisphere, the two most important teleconnection patterns are the El Niño/Southern Oscillation and the Arctic Oscillation. The El Niño/Southern Oscillation is a three- to eight-year cycle in tropical atmospheric pressures. It drives warmer than average ocean waters toward the eastern Pacific during an El Niño event and cooler than average waters during the opposite phase, La Niña. The jet stream typically dips farther to the south over the eastern Pacific during El Niño but bulges to the north there during La Niña. The Arctic Oscillation is caused by week-to-week fluctuations in sea-level pressure between the Arctic and the midlatitudes. If this pressure difference is small, the jet stream winds tend to weaken, allowing large-amplitude loops to form; in winter, a small pressure difference typically allows cold air to spill far to the south over the eastern U.S., western Europe and East Asia.

IF THE JET STREAM CONTINUES TO GET MORE WAVY, HARSH WEATHER CONDITIONS WILL GROW MORE INTENSE, CAUSING DEATH AND DESTRUCTION.

A REVELATION IN CALIFORNIA

THE ATMOSPHERE'S TELECONNECTION patterns are intertwined. They can cancel one another out or reinforce one another. Changing the base state of the atmosphere in which these patterns arise could alter them so that they cause jet stream weirdness. I thought about this possibility in 2011, when an extreme jet stream persisted with a weak to moderate La Niña in place for only part of the year, which was odd. At the time, there were no published theories detailing how this situation might arise. But in December of that year at the American Geophysical Union meeting in San Francisco, the world's largest gathering of climate scientists, Rutgers University atmospheric scientist Jennifer Francis presented intriguing new findings related to the event. At one point, she said, "The question is not whether [Arctic] sea-ice loss is affecting the large-scale atmospheric circulation…, it's, How can it not?" Francis pointed out that the Arctic is warming two to three times faster than the rest of the Northern Hemisphere—a phenomenon known as Arctic amplification—and that this phenomenon could significantly disrupt the flow of the Northern Hemisphere jet stream.

The assertion makes perfect sense. One of the main causes of Arctic amplification in fall and winter is sea-ice loss. The Arctic Ocean has lost a stunning amount of its ice in recent years because of melting and unfavorable winds. In September 2012, 49 percent of the ice cover went missing—an area 43 percent of the size of the contiguous U.S.—compared with the mean value from 1979 to 2000. When sea ice melts, it exposes dark water, which absorbs more solar energy than white ice. The ocean and atmosphere then heat up, driving additional warming and more sea-ice melt in a vicious cycle.

The exposed water releases its stored heat in fall and winter, resulting in a massive, months-long perturbation to the base state of the Arctic atmosphere. Unusual Arctic amplification in summertime has also been occurring as Arctic snow cover diminishes. Global warming has caused spring to arrive earlier by about three days per decade, melting the snow cover and exposing dark soil sooner. The soil absorbs heat and dries out, jump-starting an early continental heating season.

The Arctic amplification caused by sea-ice loss and reduced springtime snow cover, along with other factors, has significantly decreased the temperature difference between the Northern Hemisphere's midlatitudes and the North Pole. This reduction can make a big difference to the jet stream; if the temperature difference decreases, less energy is transferred between two of the large atmospheric circulation cells, and the jet stream winds slow down. Francis and Stephen Vavrus of the University of Wisconsin–Madison have documented a roughly 10 percent reduction in upper-level winds since 1979 in autumn over North America and the North Atlantic, in concert with a reduction in the temperature difference.

Slower flow allows the jet stream to make large, meandering loops, and Francis has documented a sizable increase in the amplitude of the troughs and ridges in the polar jet since 2000, in summer and winter. The bigger kinks tend to allow warm air to flow much farther poleward than usual on one side of the jet stream, with cold air pushing far to the south on the other side. Such a pattern occurred during this past January's cold air outbreak in the eastern U.S.—the much ballyhooed polar vortex invasion—and simultaneous record warmth and drought in California. Mathematical theory shows that a slower-flowing jet stream also causes the Rossby waves to progress eastward more slowly, allowing the abnormal weather in the high-amplitude loops to last longer in any particular location. These ridges and troughs might also be more prone to stalling in place completely and forming "blocks" that stop wave movement, the way that back eddies in a river create a dead spot with no flow.

DISAGREEMENT OVER THE ARCTIC'S ROLE

THE RESEARCH LINKING ARCTIC amplification to jet stream craziness has stirred up a blizzard of turmoil in the climate science

SCIENTIFIC AMERICAN ONLINE Video about links between climate and weather can be seen at ScientificAmerican.com/dec2014/masters

community. A September 2013 workshop on the subject at the University of Maryland, convened by the National Research Council, attracted more than 50 climate scientists who engaged in spirited debate. Although a large number of such experts agree that the jet stream seems to be changing, many of them question whether the relatively short period that Arctic amplification has been strong—about 15 years—is enough to link the two phenomena.

Some experts also question the hypothesis based on energy arguments. Because the high-volume flow of the jet stream contains a lot of energy, a lot of energy should be needed to change it. The amount of heat energy that has been added to the Arctic through Arctic amplification is an order of magnitude less than the energy in natural El Niño/Southern Oscillation–driven changes to the jet stream that have been studied, observes Kevin E. Trenberth of the National Center for Atmospheric Research. He co-authored a paper published online in August in *Nature Climate Change* showing that the large energy changes that have occurred naturally in the tropical Pacific Ocean in recent years because of a teleconnection pattern called the Pacific Decadal Oscillation could have caused the unusually wavy jet stream we have observed. Yet the paper also concluded that the nature of the changes to the oscillation during the past 10 years could mean that natural variability itself is being altered by climate change.

Trenberth was one of five leading climate scientists who published a critique of Francis's research in the journal *Science* this past February. The research linking Arctic warming to excessive jet stream waviness "deserves a fair hearing," they wrote. But they concluded that they did not "view the theoretical arguments underlying it as compelling."

Some scientists even question whether the amplitude of jet stream waves is increasing. In a 2013 paper, Screen and Simmonds measured jet stream bends using a different definition than Francis did and found few statistically significant changes in amplitude—although they did note a weak general tendency toward higher-amplitude waves. Yet critics have offered little else to explain the jet stream's extremes. One idea published in August in the *Proceedings of the National Academy of Sciences USA* by Dim Coumou of Potsdam and his colleagues noted that the dwindling difference in temperature between the midlatitudes and the poles, alone, could be enough to amplify the jet stream and cause it to get stuck, at least in summer.

TOO LATE TO WAIT

ALTHOUGH SCIENTISTS may not agree on an explanation yet, the weather data are eye-opening. Some of the most iconic and destructive weather events in U.S. history—the "supertornado" outbreak of 1974, the Dust Bowl heat and drought of 1936, and the great Mississippi River flood of 1927—were all matched or surpassed in 2011 and 2012 alone. Our recent jet stream behavior could well mark a crossing of a threshold into a new, more threatening, higher-energy climate.

As the planet continues to warm, hotter temperatures will drive more intense heat waves and droughts where high-pressure ridges ripple along the jet stream. Stronger storms with heavier downpours will occur where the jet bends toward the equator into troughs of low pressure, as increased evaporation from the oceans puts more moisture into the atmosphere. If the jet stream continues to exhibit slower-moving, higher-amplitude waves, these harsh weather conditions will grow even more intense and stay in place longer, multiplying their potential for death and destruction. If the theories presented by Francis and her colleagues are correct, there is no going back to our old climate unless we find a way of growing more Arctic sea ice. Given that the amount of heat-trapping carbon dioxide in the atmosphere continues to increase at about 0.5 percent a year, no scientists who study Arctic sea ice are expecting a long-term recovery.

Drought is the greatest threat because it affects the two things we need most to survive: water and food. If a high-amplitude jet stream pattern with eccentric ridges of high pressure were to stay stuck for an entire summer over the grain-producing areas of Russia and the U.S., the precipitation that these crops rely on would not arrive. The resulting droughts could cause huge spikes in food prices, widespread famine and violent unrest. During the great Russian drought and heat wave of 2010, a massive and impenetrable ridge of high pressure settled over the country. That shunted the low-pressure systems that usually bring rain to Russian crops over to Pakistan, causing catastrophic floods there. The drought and heat wave was Russia's deadliest and most expensive natural disaster in history. It forced the country to cut off wheat exports, which drove up global grain prices and helped to foment the "Arab Spring" unrest that toppled multiple governments in 2011.

Clearly, the world cannot safely wait to act until scientists fully understand how and why the climate is changing. According to the Intergovernmental Panel on Climate Change, we must act swiftly, forcefully and globally to keep warming below the dangerous two degree Celsius threshold. Energy sources such as solar, wind and nuclear that emit low or zero levels of carbon dioxide, along with technologies that can capture and store carbon, must at least triple by 2050, and greenhouse gas emissions must fall by 40 to 70 percent, compared with 2010 levels. The shift might be surprisingly affordable, cutting global economic growth by only 0.06 percent a year, the panel has said. But if we wait until 2030, the necessary actions will be much more expensive, and it may become impossible to avert the threshold.

That is also the year that summertime Arctic sea ice will essentially disappear, according to several leading climate scientists. If Arctic changes are truly to blame for wacky jet stream behavior, losing the remaining 50 percent of the Arctic sea-ice coverage between now and 2030 will bring even greater antics. If the Arctic is not involved, that is worrisome as well because it means jet stream changes are being triggered by an unknown mechanism, leaving us with no idea how the jet stream will respond as climate change progresses. Thus, my forecast for the next 15 years: expect the unprecedented. SA

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THE STORM GOD'S TALE

Newly discovered Maya artwork illuminates an ancient clash

By Zach Zorich

The king had been sitting in darkness for more than 1,400 years. Half of his finely carved face was missing when the archaeologists found him, but his elaborate headdress and badges of rank were still whole. He stared, one-eyed, into the dim tunnel the visitors had excavated inside one of the largest monuments in the ancient Maya city of Holmul, located in what is now northeastern Guatemala. Hieroglyphs near the figure spelled out his name: Och Chan Yopaat, or "Storm God Enters the Sky."

The king is the central figure in a recently discovered sculptural panel that is electrifying archaeologists who study the Maya civilization. Francisco Estrada-Belli of Boston University had been excavating the monument—a rectangular pyramid with a flat top where ceremonies were performed—to glean insights into the politics at play during a particularly tumultuous period of Maya history. Inside the pyramid are the remnants of all the buildings from centuries past that had previously stood on the same spot before bigger temples were constructed on top of them. Estrada-Belli and his team were tunneling through the nested structures, investigating what was left of those earlier monuments, when they

STUNNING FRIEZE uncovered in the ancient Maya city of Holmul in Guatemala is helping archaeologists piece together how Maya states functioned during a long-running war that defined this civilization's history for more than 1,000 years.

AP PHOTO

IN BRIEF

An excavation in the ancient Maya city of Holmul in Guatemala has revealed an elaborate frieze that is elucidating a critical chapter of Maya history.

The frieze is thought to show the founder of the dynasty that ruled Holmul, which lay at the center of a major conflict between two superpowers.

Rich in symbols and inscriptions, the artwork holds long-sought clues to Maya governance during this important period.

hit the base of a staircase. In the summer of 2013 they followed the stairs up the front of a 30-foot-tall temple that had somehow escaped demolition. The magnificent frieze—an expanse of intricately worked plaster 26 feet long by seven feet high—decorated the top of the temple.

The frieze is more than just an adornment, however. It is a historical document—one that is helping archaeologists understand how Maya states functioned in a time of upheaval. At the time the frieze was made, around A.D. 590, Holmul lay at the center of a conflict that many scholars believe defined Maya history for more than 1,000 years: the war between the kingdoms of Tikal and Kaanul. Experts think the king depicted on the frieze was the founder of the dynasty that ruled Holmul during this pivotal time. If they are right, the discovery could help answer long-standing questions about Maya governance.

WRITTEN IN STUCCO

THE REASON FOR THE LONG-RUNNING war has been lost to time, but many scholars think it had to do with access to wealth. The overlords of Tikal and Kaanul most likely fought to control the trade routes for goods such as obsidian for making tools and weapons, jade for making sacred objects, and cacao beans that were used both as currency and as the main ingredient in a chocolate beverage that was consumed during religious rituals. Holmul was probably just one city among dozens or hundreds that made up the web of trade partners that funneled the economic prosperity of the region toward the capital city of whichever kingdom it was allied to at a given time. It is becoming an especially important city to archaeologists, however, because of the rich stores of information preserved in its ruins—both about the site itself and about the politics of the time.

Analysis of the temple and its spectacular frieze is still under way. But already Estrada-Belli and his colleagues have begun to unravel the story it tells of Holmul at a crucial time in the city's history. One way Maya rulers used their vast accumulation of riches was to build monuments to please the gods and the spirits of important ancestors who made their prosperity possible and to ensure their continued benevolence. The Holmul temple appears to have served exactly this purpose: glyphs on the sides of the structure identify it as a "royal lineage house"—a temple for worshipping the ancestors of the ruling family.

To decode the symbol-rich frieze itself, Estrada-Belli enlisted the help of Karl Taube, an expert in Maya iconography at the University of California, Riverside. The king at the center is seated atop a mythological mountain deity called Witz, Taube observes. Caves on mountainsides were passages to the underworld and the source of wind and rain. On the frieze, the king sits above a cleft in the mountaintop, and two feathered serpents representing the wind emerge from the corners of Witz's mouth. "I think what they are labeling here is the king, juxtaposed with a sacred place, possibly a place of origin," Taube offers, noting that "the cleft is a place where ancestors emerge" from the underworld. The Maya believed that the part of the world that is underground and underwater was the home of the dead, as well as many sinister supernatural beings. Caves were passages between the underworld and the world of the living.

Figures representing death and the night flank the king. According to Taube, they are jaguar gods of the underworld. Because jaguars are nocturnal predators, different Maya groups attached a variety of meanings to them. Jaguars represent the sun at night, when it was believed that the sun traveled through the land of the dead. Interestingly, whereas kings in Maya artwork are usually shown making offerings to gods, this frieze depicts the jaguar gods making offerings to the king. Why this relationship is reversed is not apparent, except that it makes Och Chan Yopaat and, by extension, the ruling family seem important.

A band of glyphs at the bottom of the frieze adds an intriguing wrinkle to this tale of self-glorification, however. According to Harvard University epigraphist Alexandre Tokovinine, who translated the ancient writing, it states that the temple was commissioned by the king of a larger and more powerful neighboring city called Naranjo. The inscription identifies the king of Naranjo as the individual who restored the ruling dynasty of Holmul. But the inscription also states that the king of Naranjo was a vassal, or subordinate ruler, to the Kaanul overlord. Thus, as much as the images on the frieze glorify the Holmul king's place in the cosmos, the glyphs reveal that Holmul was actually at the bottom of a three-tiered hierarchy. The king of Holmul was a vassal of Naranjo's ruler, who was, in turn, a vassal of the Kaanul overlord. "It shows that Maya kingdoms were all linked," Estrada-Belli says. "We didn't know how Holmul fit into the grand scheme of Maya geopolitics until this inscription provided all that information."

WAR SPRINGS ETERNAL

THE DETAILS OF THE FRIEZE add to a growing body of evidence that contradicts the traditional view of the ancient Maya as peaceful people. Between 1995 and 2000 Simon Martin of the University of Pennsylvania and Nikolai Grube of the University of Bonn in Germany deciphered and mapped the power relationships recorded on monuments across the Maya realm—from southern Mexico to northern Honduras. Their work showed that warfare had been frequent and that each city had its place in a rigid hierarchy. Although the individual kings appeared to be independent, all were subordinate to either the Tikal or Kaanul dynasties. "These appear to be Maya superpowers that basically had a hegemonic rule over all of the other Maya kingdoms," Estrada-Belli explains.

"The question during [this time period] was, 'Who's going to be the major player?'" Martin remarks. Until the mid-500s, Tikal seemed to have the upper hand. A strong relationship with the powerful city-state of Teotihuacán in central Mexico seems to have helped Tikal expand its influence east across the Yucatán Peninsula and the Petén region of northern Guatemala. The city of Teotihuacán collapsed sometime around 550, and in 562 Tikal suffered a devastating military defeat, after which no major construction took place inside that city for more than 130 years. During that time the Kaanul rulers began to expand their influence across the region. One of the cities the Kaanul dynasty brought

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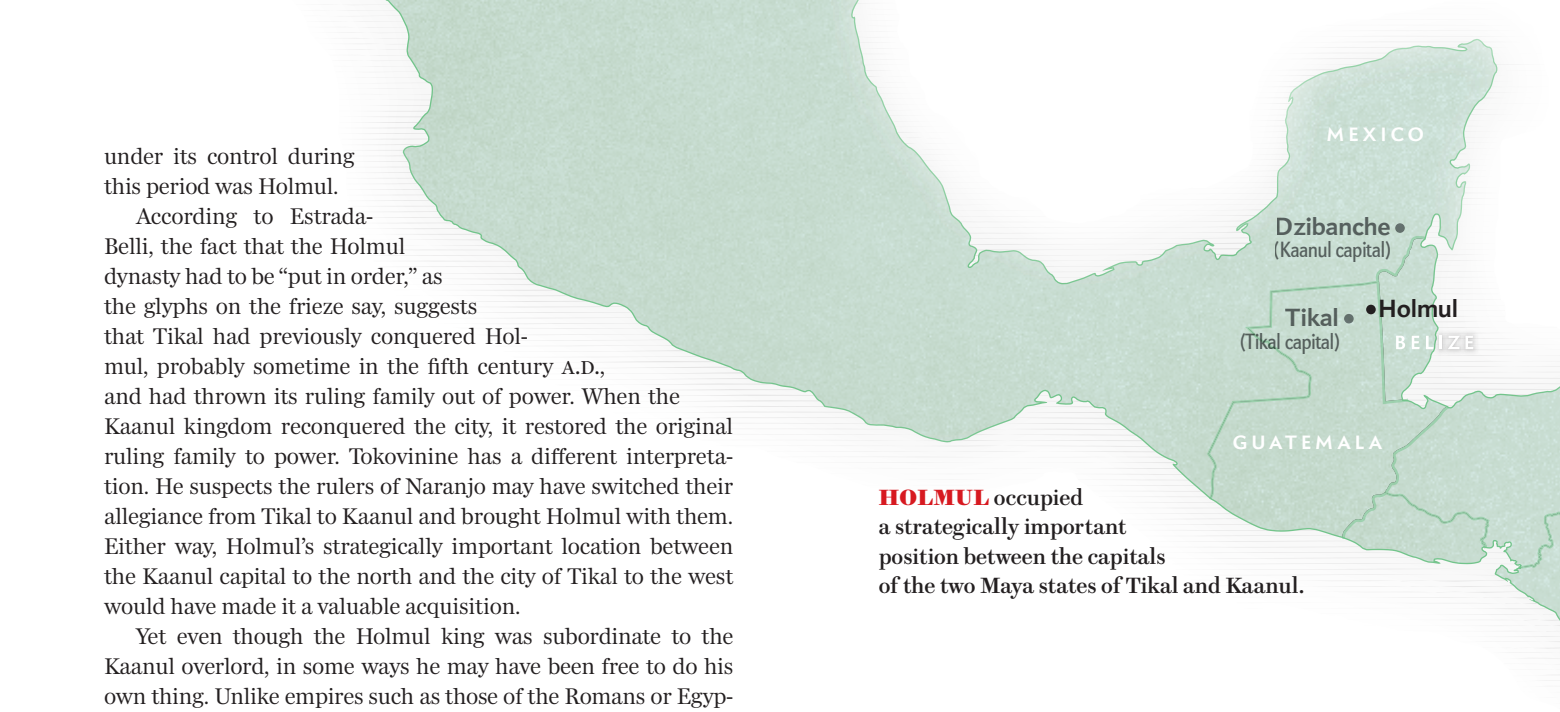

HOLMUL occupied a strategically important position between the capitals of the two Maya states of Tikal and Kaanul.

under its control during this period was Holmul.

According to Estrada-Belli, the fact that the Holmul dynasty had to be "put in order," as the glyphs on the frieze say, suggests that Tikal had previously conquered Holmul, probably sometime in the fifth century A.D., and had thrown its ruling family out of power. When the Kaanul kingdom reconquered the city, it restored the original ruling family to power. Tokovinine has a different interpretation. He suspects the rulers of Naranjo may have switched their allegiance from Tikal to Kaanul and brought Holmul with them. Either way, Holmul's strategically important location between the Kaanul capital to the north and the city of Tikal to the west would have made it a valuable acquisition.

Yet even though the Holmul king was subordinate to the Kaanul overlord, in some ways he may have been free to do his own thing. Unlike empires such as those of the Romans or Egyptians, which directly governed their conquered territories, the Maya superpowers preferred to let local authorities continue to rule while exacting payment from them. Says Martin: "They were interested in establishing dominance relationships. They were almost certainly interested in gaining tribute, but they were not very interested in [establishing] garrisons or in expanding their own territory. In that sense, it is a very decentralized picture."

SUPERPOWER OR EMPIRE?

THE DECENTRALIZED NATURE of Maya government lies at the center of a debate about whether the Tikal or Kaanul states were superpowers or empires. According to Martin, the geographical areas they controlled were too small—the entire Maya region was only about the size of New Mexico—and the control they exerted over subordinate kingdoms was too unstable to consider these Maya states to be on a par with the empires of Europe, Africa and Asia. Martin prefers to use the term "superpower" for the smaller and relatively unstable Maya states. Estrada-Belli disagrees. He believes that as monuments such as the Holmul frieze clarify the power relationships between cities, it is becoming easier to say that the Maya had empires. "It's time to shift the paradigm," he insists. "The Maya look more like this culture that was at one time ruled by one king—for example, the Kaanul in this period. So they are very much like some of the great civilizations of the old world."

Determining whether Kaanul and Tikal were superpowers or empires is an important part of understanding how these Maya states functioned, day to day—and why they so often went to war. Under both scenarios, Holmul would most likely have paid some kind of tribute to Naranjo, and, in turn, Naranjo would have paid tribute to the Kaanul lord. But what, if anything, Holmul might have received in exchange is not clear from the archaeological evidence.

"There's going to be some sweetness," Martin opines. He speculates that the elites of Holmul would have received exotic gifts and would have been invited to feast and perform ceremonies at the Kaanul capital as a way to induce them to cooperate with Kaanul ambitions.

David Freidel of Washington University in St. Louis takes a different view of the relationship. He thinks that the tribute the Kaanul rulers demanded from their subordinate kingdoms created a largely one-sided economic relationship. "The flow of resources, including trade goods and warriors to fight the unending wars, all went toward the capitals of the two superpowers," he argues. "There's no doubt that it was exploitative."

Freidel, who co-directs excavations at another Kaanul vassal city, believes that in many respects Maya states were similar to those in other parts of the world that made monuments to glorify their leaders—the pyramids of Egypt, for instance, or Rome's triumphal arches. "They loved the aesthetics of power," he notes. "All civilizations have this. This frieze is a prime example of it, and they buried it because it was beautiful, and they wanted to kind of have it alive and remembered." The Holmul frieze may have been buried to avoid angering the gods and ancestors it was meant to honor as a larger monument was built over the top of it. The rulers of Holmul could thus continue building grandiose new monuments while still, in a way, having the old ones.

Freidel says that he accepts most of Martin and Grube's interpretations of the new frieze, but as archaeologists learn more about the history of Maya states, they look increasingly like empires. Resolution of the debate may come from continued excavation of Holmul's buried temple, among other sites. Estrada-Belli plans to extend the tunnel around the rest of the building. He also intends to investigate two newly discovered rooms inside the temple and to continue uncovering the temple's exterior walls. As large as the frieze is, it covers only the top part of one side of the building. There could be far more artwork decorating the rest of the monument that may provide greater insight into how Holmul fared during the shifting fortunes of the centuries-long battle between these ancient states. SA

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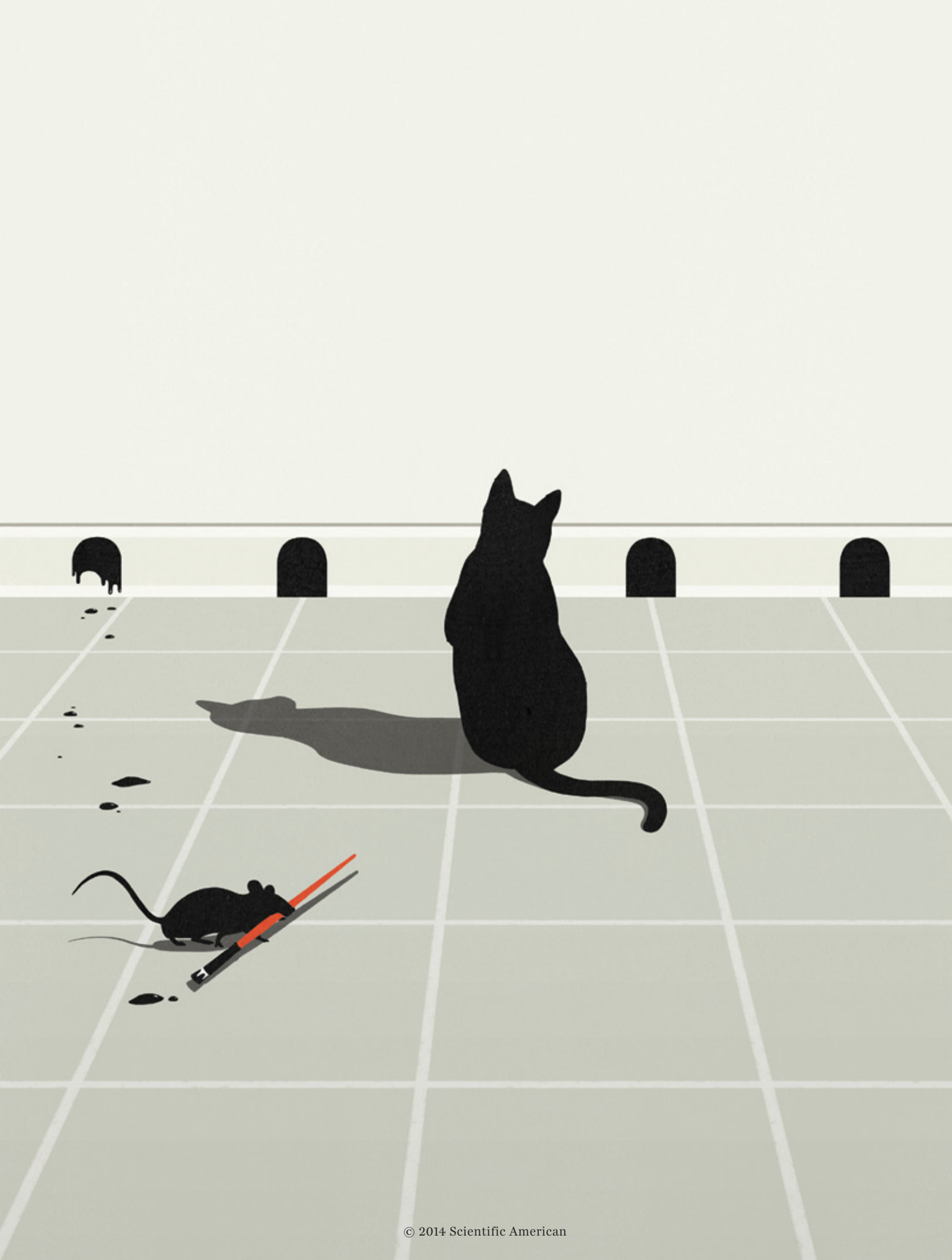


IMMUNOLOGY

IMMUNITY'S ILLUSION

Sophisticated mathematical tools suggest that the immune system has a blind spot when it comes to subtle mutations of the influenza virus

By Adam J. Kucharski

IN BRIEF

Infection with many kinds of disease-causing viruses, such as measles, gives people lifelong immunity against ever developing the illnesses again.

Flu viruses are different, however, because they tend to mutate, or change slightly from year to year, foiling the body's immune defenses.

A few studies have suggested that the first flu strains to which individuals are exposed as children can limit their ability to fight other flu strains later in their life.

Evidence to support this curious immune reaction, dubbed "original antigenic sin," has now been found in mathematical models as well.

Illustration by Anna Parini

Adam J. Kucharski is a research fellow in the department of infectious disease epidemiology at the London School of Hygiene and Tropical Medicine.

WHEN IT COMES TO INFECTIOUS DISEASES, CHILDREN GET A TOUGH deal. Not only do they spend all day in a school-shaped mixing pot of viruses and bacteria, they do not yet have the repertoire of immune defenses their parents have spent a lifetime building—which means that for most infections, from chickenpox to measles, it pays to be an adult.

Influenza is a different story, however. Studies of the 2009 flu pandemic have shown that immunity against regular seasonal flu viruses tends to peak in young children, drop in middle-aged people and then rise again in the elderly. Adults might have had more exposure to the disease in the course of their lives, but—aside from the eldest group—they somehow end up with a much weaker immune response.

This curious observation naturally leads biologists to wonder about the causes. Understanding influenza infection is far from straightforward, but we are starting to find some clues in mathematical models that simulate the immune system. These models allow us to explore how past exposure to flu viruses might influence later immunological responses to new infections and how the level of protection could change with age. By bringing together these mathematical techniques with observed data, we are beginning to unravel the processes that shape immunity against influenza. In the process, the work provides new support for a quirky hypothesis—first proposed more than half a century ago and known as original antigenic sin—about why the body's response to this illness is biased toward viruses seen in childhood. Taking these insights into account is already helping us to understand why some populations suffered so unexpectedly badly in past outbreaks and might eventually help us anticipate how different groups of people will react to future outbreaks, too.

A MODEL EPIDEMIC

TO DATE, MOST MATHEMATICAL MODELS of immunity have not looked at the body's reaction to the influenza virus, because the pathogen is so variable. Historically, models have instead focused on the response to viruses such as measles, which change so little over time that they trigger lifelong immunity. Once individuals recover from measles or are vaccinated against it, the immune system promptly recognizes the proteins on the surface of the virus, generates antibody molecules targeted against those proteins and homes in on them to neutralize any subsequent interlopers. (Scientists call these surface proteins "antigens," an abbreviation of *anti*body *gen*erator.)

If people have a certain probability of getting infected with measles every year, one might expect immunity (measured by testing the potency of an individual's antibodies in the blood) to gradually increase with advancing years—as has been observed in several laboratory studies across differing age groups. One way to test such an explanation is to use a mathematical model, which can show what patterns one might expect to see if a theory were true. Models are powerful tools because they allow us to examine the effects of biological processes that could be difficult or even unethical to reproduce in real experiments. For example, we can see how infection might influence immunity in a population without having to deliberately infect people.

In the simplest epidemic model, a population is divided into three compartments: people who are susceptible to an infection, those who have become sick and those who have recovered from—and are therefore immune to—the disease. During the 1980s epidemiologist Roy M. Anderson, zoologist Robert M. May and their colleagues used such models to examine the age distribution of immunity to a disease such as measles. Although a three-compartment model reproduced the general pattern, they found that real-world immunity increased at a faster rate in younger age groups than the model led them to expect. Perhaps the discrepancy occurred because children had more contacts with others and thus more exposures than did those in older age groups? By updating their model to include this variation, the researchers could test the prediction. Indeed, when they altered their calculations so that children were given a higher risk of infection, it was possible to re-create the observed changes in immunity with age.

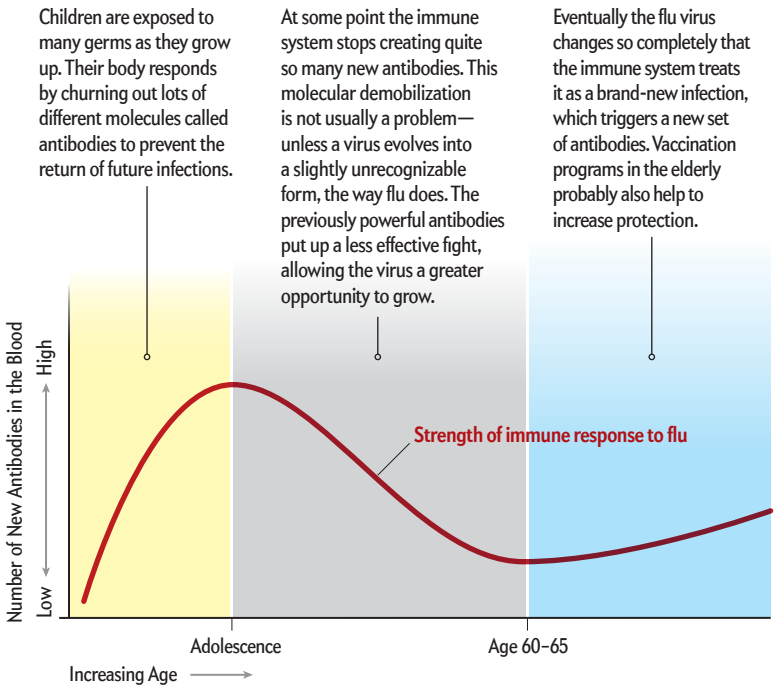
Unfortunately, immunity against influenza is not so straightforward. Flu viruses have a high rate of mutation, which means their antigens can change appearance from year to year. As a result, the body can struggle to recognize a new strain. This variability is why flu vaccines need to be updated every few years; unlike the measles virus, which looks the same every year, antigens from the flu virus change over time.

When I first became aware of the unusual age distribution of flu immunity in the 2009 data, I wondered whether the high rate of mutation for flu virus—along with intense social contact between children—could explain the rise-dip-rise pattern across age groups. Because people are exposed to lots of infections when they are young, they are likely to develop good, long-term

THE MECHANISM BEHIND A MYSTERY

First Impressions Last a Long Time

Most of the time when the human body conquers a virus, the immune system can provide lifelong protection against future infections with the same pathogen. Adults should therefore have stronger defenses than children and become sick less often. But that is not what happens with flu. Immunity grows throughout childhood, as expected, but then people become more vulnerable in middle age (*curve*). A possible explanation appears below: the immune system develops a kind of blind spot with flu, mistakenly expecting later infections of the highly changeable virus to resemble earlier ones. Because the body reserves its strongest responses for what are in fact outdated threats, it can fail to combat subsequent infections effectively.



immunity against the bulk of viruses that circulated during their childhood. In the case of flu, children do develop antibodies against the antigens of specific influenza viruses they meet, just as they do for measles.

After leaving high school or college, however, folks meet fewer people on average and so will generally catch the flu less frequently. This change in exposure means adults rely on the antibodies they built up as children to protect them against any new assaults. Yet because flu viruses change over time, their "old" antibodies would be less effective with advancing years at recognizing newer strains. Hence, one might expect levels of natural protection to drop in middle-aged adults—who, as a group, do not receive routine flu immunizations. And the subsequent rise in immunity seen in elderly individuals might occur because they often receive flu shots, which keep their antibodies up-to-date.

That was the theory, at least. The problem was how to test it. Because flu is so variable, it is much harder to build a mathematical model for it than for measles. Even if a person is immune to one strain, he or she might be only partially immune to another and completely susceptible to a third. To study immunity, we therefore need to keep precise track of the combination of influenza strains to which people have been exposed and in what order the exposures occurred.

This is where it gets tricky because of the vast number of combinations of strains that people could have seen. If 20 different strains have circulated in the past, for example, there would be 2^{20} (or more than one million) possible histories of infection for any particular individual. For 30 strains, there would be more than one billion combinations for each individual.

Along with Julia R. Gog, then my Ph.D. supervisor at the University of Cambridge, I set out to find a way around this mountain of complexity. We realized that if individuals had a certain probability of becoming exposed to flu every year, the probabilities of coming into contact with any two strains should be independent of each other. (In other words, exposure to strain A should not affect the chances of being exposed to strain B.) Thus, for fundamental mathematical reasons, we could reconstruct the probability that a random individual had been exposed to a certain combination of infections simply by multiplying the probabilities of exposure to each individual strain in the combination. This meant that instead of dealing with one million probabilities for 20 different strains, we would have to deal with only 20.

When we ran the equations for the model, however, the results were not what we expected. The model stubbornly suggested that if a person had previously been exposed to even a single strain, he or she was *more* likely to have seen another one. It was as if our model was saying that being hit by lightning made you more likely to have been exposed to flu—an obviously absurd conclusion.

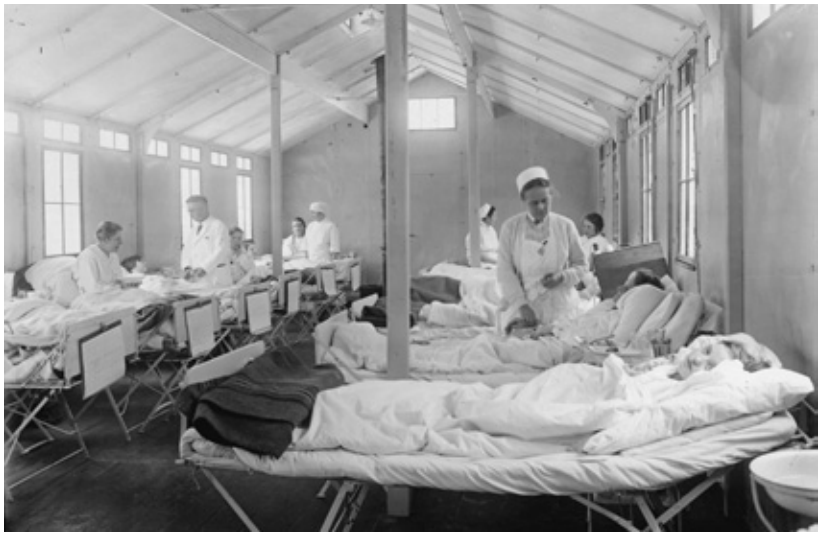
The reason for this seemingly nonsensical result turned out to be simple: we had not accounted for a person's age. Assuming infections occur at a fairly consistent rate, the longer a person is alive, the more likely it is that the individual will contract at least one infection. So if you pick a random individual—say, a female—and learn she was previously exposed to flu (or was struck by lightning), you immediately know she is more likely to be older than younger. And because she is older, you know that she is more likely to have experienced some other misfortune—such as exposure to a second flu strain.

As long as we dealt with each age group separately, however, the number of infections went back to being independent variables. Thus, for 20 strains, we no longer had one million things to

SOURCE: "THE ROLE OF SOCIAL CONTACTS AND ORIGINAL ANTIGENIC SIN IN SHAPING THE AGE PATTERN OF IMMUNITY TO SEASONAL INFLUENZA." BY ADAM J. KUCHARSKI AND JULIA R. GOG, IN *PLOS COMPUTATIONAL BIOLOGY*, VOL. 8, NO. 10, ARTICLE NO. E1002744; OCTOBER 25, 2012

keep track of: we were back to having only 20. With a viable model in place, we started to build simulations of how the body's immunity to influenza changed over time. The aim was to generate artificial data that we could test against real-life patterns. As well as having the virus mutate over the years, we assumed that each age group's risk of infection depended on the number of social contacts reported in population surveys within and between different age groups.

Alas, even with these changes, our model—which assumed that the middle-age dip in immunity arose from fewer exposures—could not reproduce the midlife drop seen in the real world. The model was not completely incorrect: it showed that children developed a stronger immunity than adults. But whereas the actual drop off in antibody levels appears to start between five and 10 years of age, in our model the decline occurred between 15 and 20 years of age—after individuals would have left school (where there are lots of people and germs).



NEVER UNDERESTIMATE FLU: Temporary barracks had to be erected in the 1930s to deal with an overabundance of flu patients.

ORIGINAL SIN

WHILE PUZZLING OVER THE FLU AGE PATTERN, I had talked to many people about the wider problem of modeling immunity. In particular, I spoke with Andrea Graham, an evolutionary biologist at Princeton University, who introduced me to the concept of original antigenic sin. Now that we had a model that could handle a large number of strains, I wondered if taking this hypothesis into account would help our model produce more realistic results. Because the idea was controversial, I also wondered if incorporating it might help indicate whether it was plausible or not.

Like the biblical concept, original antigenic sin is the story of the first encounter between a naive entity (the immune system) and a dangerous threat (a pathogen). In the immunological version, the body is so marked by its first successful counterattack against an influenza virus that each subsequent infection will trigger these original antibodies again. The body makes these antibodies even when it encounters a slightly different set of antigens on a pathogen, which would require a different set of antibodies for the host to combat the infection efficiently. At the same time, the body fails to make a good supply of antibodies against the pathogen with the altered set of antigens, instead relying on the immune response to viruses it has already seen.

Virologist Thomas Francis, Jr., first came across the problem in 1947. Despite a large vaccination program in the previous year, students at the University of Michigan had fallen ill with a new, albeit related, influenza strain. When Francis compared immunity against the vaccine strain with immunity against the new virus, he found that the students possessed antibodies that could target the vaccine strain effectively but not the virus with which they had been infected a year later.

Eventually Francis developed an explanation for his curious observation. He suggested that instead of developing antibodies to every new virus that it encountered, the immune system might reproduce the same reaction to similar viruses it had already seen. In other words, past strains and the order in which people get them could be very important in determining how well a person could fight off subsequent outbreaks of the ever variable flu virus. Francis called the phenomenon "original antigenic sin"—perhaps, as epidemiologist David Morens and his colleagues later suggested, "in religious reverence for the beauty of science or impish delight fueled by the martini breaks of which he was so fond."

During the 1960s and 1970s researchers found further evidence of original antigenic sin in humans and other animals. Since then, however, other studies have questioned its existence. In 2008 researchers at Emory University and their colleagues examined antibody levels in volunteers who had received flu shots and found that their immune system was effective at targeting the virus strain in the vaccine. The researchers' concluded that original antigenic sin "does not seem to be a common occurrence in normal, healthy adults receiving influenza vaccination." The following year, however, another Emory-based group, led by immunologist Joshy Jacob, found that full-scale infection in mice with a live flu virus—rather than an inactivated virus, as is typically present in a vaccine—could hamper subsequent immune responses to other strains, suggesting anew that original antigenic sin may play a more important role during natural infections with flu.

Jacob and his group proposed a biological explanation for original antigenic sin, hypothesizing that it could stem at root from how we generate so-called memory B cells. These cells form part of the immune response: during an infection they are programmed to recognize a specific threat and produce antibodies that finish it off. Some B cells persist in the body after a siege, ready to spew more antibodies should the same threat reappear. According to Jacob and his colleagues, infection with live influenza viruses could trigger existing memory cells to action rather than causing new B cells to be programmed. Suppose you were infected with flu last year and then catch a slightly different virus this year. Because memory B cells have already seen last year's similar virus, they can get rid of it before the body has time to develop new B cells that are specific to—and hence better at remembering—this year's strain. It is like the old military adage about generals always fighting the last war (especially if they won it). It seems the immune system depends more on shoring up past defenses rather than generating new ones, especially if the old strategy works reasonably well and more quickly.

GETTY IMAGES

SCIENTIFIC AMERICAN ONLINE See a video about what computers can teach us about biology at ScientificAmerican.com/dec2014/computers-biology

During the final stages of my Ph.D., we adapted our new model to simulate original antigenic sin. This time the distinctive decline in immunity showed up in our simulation right when it does in real life—after about age seven, when people are old enough to have seen at least one flu infection (instead of between ages 15 and 20). From that point onward, our model suggested, previous infections compromised the creation of effective antibodies. (Because younger individuals in the countries we studied are not typically vaccinated, this effect is likely to come from natural infection with flu.) It is still not completely clear what causes the increase in immunity in the eldest group. It could be partly the result of increased vaccination in that age range or partly the fact that individuals have been alive so long that the antigens of any new flu strains to which they are exposed are so different that they can no longer be mistaken by the immune system for the viruses from childhood. At any rate, our findings suggested that original antigenic sin, rather than the number of social contacts (and thus chances of exposure), was responsible for the curious age distribution of immunity in younger people.

BLIND SPOTS

HAVING BECOME CONVINCED that original antigenic sin can shape the immune profile of an entire population, we wanted to investigate whether misguided immune responses could also affect the size of an outbreak. In simulations, we found that every now and then, the model generated large epidemics even if the new virus was not particularly different from the previous year's strain. It seemed that original antigenic sin was leaving gaps in the immunity of certain age groups: although individuals had been exposed to strains that might have protected them, their immune systems had generated the "wrong" antibodies in response to the new infection.

The best historical evidence supporting this idea came from 1951, when influenza rippled across the English city of Liverpool in a wave that was quicker and deadlier there than the infamous "Spanish flu" pandemic of 1918. Even the two subsequent flu pandemics, in 1957 and 1968, would pale in comparison. Yet it is not clear what caused the outbreak to be so bad.

The most logical explanation was that the 1951 strain must have been very different from the strain circulating in 1950 and that, therefore, most people would not have had an effective immune response when the virus hit them. But there is not much evidence that the 1951 strain was significantly different from the one that circulated the year before. What is more, the size of the epidemic in the U.K. and elsewhere varied depending on location. Some places, such as England (particularly Liverpool) and Wales, were hit hard, whereas others, such as the U.S., saw little change in mortality from previous years. More recently, the U.K. experienced severe flu epidemics in 1990 and 2000, again without much evidence that the virus was particularly different in those years.

Yet our mathematical model could re-create conditions similar to the flu outbreaks of 1951, 1990 and 2000. When original antigenic sin was assumed to occur, the order in which different flu strains caused illness in a particular age group could shape how well its members fought off future flu infections. In other words, when it comes to flu, each geographical location may have its own unique immune profile, subtly different from its neighbors, with its own unique "blind spots" in immunity. Severe outbreaks such as the one in Liverpool may therefore have been the caused by such blind spots, which other regions simply did not have, because they experienced a different original antigenic sin.

REFINING ORIGINAL ANTIGENIC SIN

RESEARCH INTO INFLUENZA IMMUNITY has often focused on specific issues, namely the effectiveness of a particular vaccine or the size of an epidemic in a certain year. But these problems are actually just part of a much bigger question: How do we develop and maintain immunity to flu and other viruses that change their antigenic makeup over time—and can we use that information to understand how flu spreads and evolves?

Projects such as the FluScape study in southern China are now starting to tackle the problem. A preliminary analysis published in 2012 by Justin Lessler of the Johns Hopkins Bloomberg School of Public Health and his colleagues suggested that the concept of original antigenic sin might need to be refined. Rather than the immune response being dictated only by the first strain an individual encountered, the researchers found evidence that immunity follows a hierarchy. They suggested that the first strain someone was infected with gained the most "senior" position in the immune response, with the next strain generating a somewhat weaker response, followed by an even weaker response for the third strain. (Such a seniority hierarchy would apply only to highly variable viruses, such as flu viruses.)

Because the FluScape study looked at blood samples taken in the present day, Lessler and his colleagues could not examine how antibody levels changed over time. In August 2013, however, researchers at the Icahn School of Medicine at Mount Sinai looked at a series of blood samples taken from 40 people over a 20-year period. Their results support the idea of antigenic seniority: each new flu infection boosted antibody levels against previously seen strains. Individuals therefore had stronger immune responses against viruses they came across earlier in life than against those encountered later.

Over the past couple of years I have been collaborating with the FluScape team to investigate patterns in the new data coming out of China. One benefit of such work might be to help determine who is susceptible to particular strains and how this vulnerability could influence the evolution of the disease. With new models and better data, we are gradually starting to find ways to tease out how individuals and populations build immunity to influenza. If the past is anything to go by, we are sure to encounter more surprises along the way. SA

MORE TO EXPLORE

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STRANGER IN THEIR MIDST: Ant-mimicking spider lurks below a group of Asian weaver ants—the species that the spider has evolved to resemble.

LIFE SCIENCE

The Spider's Charade

Some arachnids go to extraordinary lengths to mimic the appearance and behavior of ants

By Ximena Nelson

IN BRIEF

Mimicry is a phenomenon in which one species evolves to resemble another. **Species that masquerade** as ants are the most common kind of mimic. Yet they have been the least understood. **But recent studies** have pulled back the curtain on ant impersonators—and in so doing have revealed that mimicry is far more complex than once was thought. **It turns out** that animals exploit mimicry for many reasons—and they pay a price for the advantages it affords.

Ximena Nelson is a lecturer in animal behavior at the University of Canterbury in Christchurch, New Zealand. Her research focuses on animal communication and cognition, particularly in jumping spiders and birds.

IMPOSTERS ABOUND IN THE ANIMAL KINGDOM. PERUSE ANY TEXTBOOK description of mimicry—in which one species evolves to resemble another—and you will encounter various classic examples, such as the king snake, which copies the coral snake, or the hoverfly, which masquerades as a bee. Less familiar, but in many ways even more fascinating, are the mimics in a genus of jumping spider known as *Myrmarachne,* which look for all the world like ants.

Unlike other jumping spiders, with their furry, round bodies, *Myrmarachne* species have smooth, elongate bodies that give the appearance of having the three distinct parts—head, thorax and abdomen—of ants, despite having just two. To complete the charade, the spiders walk on their three rear pairs of legs and raise the fourth pair overhead, waving them around to simulate ant antennae. They even adopt ants' characteristically fast, erratic, nonstop mode of locomotion in place of the stop-and-go movements other jumping spiders make. It is an Oscar-worthy performance and the secret of this group's success: more than 200 species of *Myrmarachne* thrive in the tropical forests of Africa, Asia, Australia and the Americas. This rich diversity makes ant mimicry the most common form of mimicry. Yet it is the least known.

New research is exposing the mind-boggling complexity of the ant mimics' charade, however. Like the king snake and hoverfly, *Myrmarachne* species gain a survival advantage by looking like other species—in this case, lethal ant species, because predators of spiders steer clear of both the ants and their look-alikes. But, it turns out, the spiders pay for that advantage: to give a convincing performance, they must expose themselves to considerable risk. The evolutionary forces that led to their fakery have left the ant-mimicking spiders living on the knife's edge, walking a fine line between avoiding one enemy and falling prey to another. In revealing the unexpected perils of mimicry, studies of these remarkable arachnids show the phenomenon of mimicry in a new light.

FAKING IT

MY FASCINATION WITH MIMICRY began one day in 1995 in the office of my then supervisor, Robert R. Jackson, while discussing potential research topics for my master's degree. Jackson, a spider expert at the University of Canterbury in New Zealand, had cemented his reputation as a leading arachnologist through his work on *Portia,* a genus of jumping spiders renowned for their mammalianlike levels of clever behavior. Accordingly, he suggested that I work on a species of *Portia*. As an afterthought, he mentioned the antlike jumping spiders found in the tropics. I was instantly intrigued. Now, 20 years down the track, Jackson and I are colleagues who share a laboratory and have traveled throughout Africa, Australia and Asia to research these remarkable creatures. Throughout our journeys we have discovered many unusual consequences of mimicry that underscore just how much more complicated the business of deception is than conventional wisdom would suggest.

The standard view originated with English naturalist Henry Walter Bates, who in 1861 provided the first scientific theory to explain mimicry in nature, based on his observations of Amazonian butterflies. Bates supposed that an edible species that resembled an unpalatable or downright toxic one would gain a survival advantage by tricking potential predators into leaving it alone. In Bates's scenario, predators would learn from experience that eating the nasty species was a bad idea. After that unpleasant encounter, the predators would avoid the toxic species and would then avoid the mimics, too—even though the mimics themselves were harmless. This "parasitic" charade, in which one species exploits another's defenses, is now known as Batesian mimicry.

But it turns out that mimicry does not work exclusively in the simple, straightforward manner Bates described—far from it. For one thing, some mimics use their resemblance to another animal not to avoid getting eaten but to deceive their own prey and thus obtain a meal through dishonest signals—so-called aggressive mimicry. And animals exploit mimicry for various other reasons. No group of organisms illustrates the complexities of the strategy, and the evolutionary forces that shaped them, better than ant-mimicking spiders do.

UPSIDES AND DOWNSIDES

TO THE UNINITIATED, ants might seem unworthy of imitation. But in the tropical rain forest, where their total biomass exceeds that of all vertebrate animals combined, ants are strong shapers of the environment and have great power over its inhabitants. As such, they are prime candidates for being imitated.

Myrmarachne spiders trade on the ants' fearsome reputations: ants avidly defend their nests by biting or stinging intruders, and an individual can recruit an entire colony to its cause—

PRECEDING PAGES: MARK MOFFETT *National Geographic*

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often with lethal consequences for the interloper. Predators are thus wise to avoid trying to eat any prey that look to be such ants. Yet for the spiders to trick predators into avoiding them, they must take some real risks. For instance, they need to live near the ants to avoid standing out to predators as being not antlike. Living in close quarters, which is unusual for spider species but common in ants, puts the spiders directly in harm's way; if they are found to be fraudsters, odds are they will become lunch.

Having to cohabit with their enemies is not the only price these ant-mimicking spiders pay. The dissemblers are so convincing that predators that specialize in eating ants—including some other species of jumping spiders—attack them as prey. And competition between males for access to females has raised this predation risk. The choosy females have driven *Myrmarachne* males to evolve enlarged mouthparts that can increase their body length by up to 50 percent. Exactly why the females prefer a big mouth is not known, although it may be an indicator of health. At first glance, one would be forgiven for thinking that this enlargement would hurt the spiders' chances of surviving by detracting from their antlike appearance. It does hurt them but not in that way. The trait makes them look like ants that are carrying something in their mouth. Because an ant's mouthparts are very dangerous, ant-eating jumping spiders tend to preferentially target ants that are carrying objects in their jaw and that are thus unable to bite their predators. So although having a big mouth may help male *Myrmarachne* spiders score with the ladies, it also has the unwelcome effect of making them more attractive to predators.

The cunning mimics can actively defend themselves against some of these threats, exhibiting a surprising degree of behavioral flexibility. For example, when an ant-eating jumping spider initiates stalking, the mimic makes a display toward the potential predator, raising its front legs from their normal antennae posture to a position vertically above the head and staring fixedly at the other spider without moving. The display seems to communicate that it is a spider or at least that it is not an ant after all. Whatever the message, it effectively deters the predator. Similarly, when a pesky scientist (and presumably other potential predators) comes along and tries to catch a *Myrmarachne* spider clinging to a plant, the mimic will abandon its antlike behavior, drop off the vegetation and hang out of sight on a thread of silk—the best of both worlds.

One particularly Machiavellian species of ant mimic, *Myrmarachne melanotarsa,* gets the best of both worlds in yet another way and upends the notion that parasitic and aggressive forms are separate phenomena that arise from distinct selective pressures. The spider's resemblance to ants is so terrifying to other, ordinary jumping spiders that in addition to avoiding predation, *M. melanotarsa* uses its antlike appearance to capture prey. It drives hapless jumping spider mothers out of their nests; then it penetrates the nest to raid the eggs or the brood of spiderlings. Ants have trouble raiding spider nests because their legs get caught in the spider silk, but spiders have adaptations that enable them to negotiate the sticky strands—and *M. melanotarsa* takes full advantage of them.

LEARNED OR INSTINCTIVE?

TO FULLY TEASE OUT the forces that have caused mimicry to evolve and take the forms it does, researchers need to know the factors that cause predators to avoid imposters. Back in the 1800s, Bates thought that the predator must experience, in some way, the danger posed by a creature that another organism is mimicking before it grasps that it ought to steer clear of the real McCoy and anything that looks like it. But here again the ant-mimicking spiders flout that conventional wisdom. The ordinary jumping spiders that abstain from eating both ants and *Myrmarachne* do so from instinct, not as a result of learning through bad experiences. In other words, the forces that shape evolution have baked that avoidance into the predators' hard wiring.

In hindsight, this avoidance instinct is not surprising: after all, if you die in an encounter with an ant, there is no room for learning. In some ways, it is easier to envision how hardwired avoidance could have evolved: predators that happen to dislike approaching ants are more likely to survive and reproduce, and their genes get passed on; ultimately instinctive ant aversion dominates the population, and those that lack the trait are quickly weeded out by the ants themselves.

A GLORIOUS MESS

THE COMPLEXITY my colleagues and I have discovered in the mimicry system of *Myrmarachne* serves as a cautionary tale: the tangled principles at work here almost certainly apply to other cases of mimicry. And we still have much to learn. Scientists have tended to view mimicry in terms of its being an adaptation to selective pressure from a single predator using a single sense: vision. (Because humans are so dependent on vision, this sense tends to be the one researchers focus on.) But we now know from *Myrmarachne* that multiple predators shape a mimic species: my own work has shown that ordinary jumping spiders and mantises are influential in this regard; birds, lizards and frogs probably are, too. And studies of other creatures hint that mimicry can involve smell and sound, among other senses. For example, a palatable species of tiger moth mimics the acoustic signals of a noxious one to avoid predation by echolocating bats. And some butterfly species copy the chemical signals emitted by ants to enter their well-defended nests, where the butterflies deposit their eggs for safekeeping.

Excitingly, scientists now have the technology to probe the sensory experiences of other species. High-frequency recording devices allow researchers to visualize noises above our own hearing threshold—including those emitted by tiger moths and bats; mass spectrometry lets them see the hydrocarbon profiles of ants and their mimics, providing a picture of their chemical interactions. Applying these techniques to the study of mimicry and other natural phenomena will no doubt expose more of the spectacular solutions and trade-offs that have evolved in the eternal arms race between predators and prey. SA

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scientificamerican.com/magazine/sa

STAYING STRONG

We associate growing old with slowing down and falling apart. But no one would have ever said that about Olga Kotelko. Right up until her death this past summer at age 95, she was an active track and field athlete, competing in 11 different events. Olga trained hard and flew across the globe to compete against athletes almost half her age.

She collected 750 gold medals and broke 26 world records. In *What Makes Olga Run?: The Mystery of the 90-Something Track Star and What She Can Teach Us About Living Longer, Happier Lives* (Henry Holt, 2014) author Bruce Grierson examines the "Kotelko phenomenon" in interviews with her and her doctors to try and uncover the factors behind her fine physical fettle. It was more than lifestyle alone. Her active longevity appears to have been a mix of smart habits and great genes. Russell Hepple, a researcher on aging at McGill University who has studied Kotelko extensively notes that she was "remarkable by every criteria that we measured" and that she had "the capability of somebody close to 30 years her junior."

Kotelko actually grew stronger after turning 90. Hepple has concluded that while she trained hard and was constantly moving, her activity level was only part of the explanation. In two years between tests, she lost virtually no wind and no strength, even though she had cut back her training. That seems to bear out Hepple's hunch that something else was going on in the muscles, irrespective of exercise effects.

Hepple and other exercise physiologists who worked with Kotelko note that she was free of sarcopenia, a decline in muscle mass and strength, and one of the most significant triggers for age-related disabilities.

Sarcopenia is, in fact, the most important cause of age-related frailty that you never heard about. There wasn't a term for the process until 30 years ago and doctors only recently came to an agreement about its clinical definition. For a long time muscle loss was virtually ignored by the medical community as public attention focused much more on osteoporosis.

Dr. Claudia Kawas a neurologist at University of California, Irvine and the director of what's known as the "90+" study, has been collecting data about the

© Clifford White/Corbis

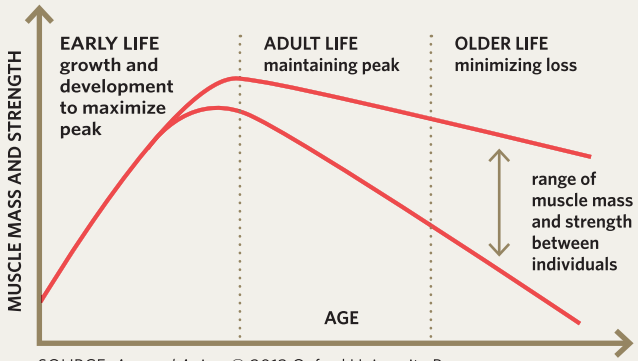
diet, exercise, vitamins and activities of thousands of seniors living at Leisure World (now known as Laguna Hills) for the past 20 years.

The study had originally asked "What kind of shape will we be in if we do live past 90?" In analyzing the research results it became clear that the real question was "what kind of shape do we have to be in if we want to increase our chances of living longer?"

Kawas recently told *60 Minutes,* "It turns out that the best thing to do as you age is to at least maintain or even gain weight." People who were overweight or of average weight outlived people who were underweight.

But there's a catch: It's not just how much you weigh, but how you maintain or gain weight. While the 90 + study hasn't studied the muscle health-longevity link, many scientists, curious about the role weight gain plays in living longer, have carried out such research.

Why is muscle important? Because loss of muscle mass and strength leads to frailty. People who are frail fatigue easily, are physically inactive, and have a slow—and often unsteady—gait, with an



SOURCE: *Age and Aging,* © 2013 Oxford University Press

increased risk (and fear) of falling. The consequences of frailty are serious: Frail individuals have many associated medical conditions, including depression, which ultimately lead to a reduced life expectancy.

Sarcopenia is an important biological process underlying frailty. We begin to lose lean muscle mass between 30 and 40 years of age. By age 50 the pace of muscle mass loss increases to 1 to 2 percent per year. After age 60 the decline accelerates to as much as 3 percent per year and after age 75 sarcopenia progress faster still.

Sarcopenia increases the risk of not just frailty, but physical disability, poor quality of life, and death. Scientists have not established exactly how and why, but they have shown that the amount of muscle plays a central role in whole-body metabolism, which is particularly important in the response to stress and the ability to fend off age-related diseases such as cancer, Alzheimer's and Parkinson's. In particular, researchers have found that muscle has an underappreciated ability to produce a number of immune responses and healthy growth factors that sustain the function of the heart, liver, lungs and the brain.

Research has also identified some of the biological sources of sarcopenia. One key factor promoting loss of muscle-related weight as we age is a protein called myostatin. Myostatin affects the cells and pathways responsible for muscle growth and regeneration. The older we get, the more myostatin we produce. As myostatin levels increase, it blocks the production of cells responsible for the lean muscle repair and growth. In turn, the reduction in lean muscle regeneration leads to increased fat deposits and fibrosis in muscle tissue.

The good news is that sarcopenia is preventable and reversible. Exercise is a key component in the fight against sarcopenia. Physical activity appears to reduce myostatin levels, which restores a healthy balance between muscle mass and fatty tissue. A healthy diet and a proper amount of protein are also essential for muscle development.

While exercise and better nutrition are important factors in combating sarcopenia, they may not be enough. A recent article in *The Wall Street Journal* noted that several pharmaceutical companies are now trying to develop drugs to regulate myostatin production and help us keep muscle-related weight. In addition, there do exist bio-nutritional products—foods that contain naturally biologically active molecules—that reduce the activity of myostatin.

The estimated direct healthcare cost attributable to sarcopenia in the United States in 2000 was $18.5 billion. The indirect costs of sarcopenia are likely ten times that because of the role it plays in the progression of costly illnesses. This doesn't count the loss in earnings and value of health from living without sarcopenia-related disabilities.

The potential benefit of preventing sarcopenia is hard to quantify. As University of Illinois demographer Jay Olshansky notes, "Slowing the aging process by an achievable three to seven years would simultaneously postpone all fatal and nonfatal disabling diseases, produce gains in health and longevity equivalent to cures for major fatal diseases, and create scientific, medical, and economic windfalls for future generations that would be roughly equivalent in impact to the discovery of antibiotics in the 20th century."

Staying strong could indeed be the penicillin of the 21st century.

THE GOOD NEWS IS THAT SARCOPENIA IS PREVENTABLE AND REVERSIBLE... EXERCISE AND NUTRITION MAY NOT BE ENOUGH

MYOS Corporation is an emerging bionutrition and biotherapeutics company focused on the discovery, development and commercialization of products that improve muscle health and function essential to the management of sarcopenia, cachexia and degenerative muscle diseases. **www.myoscorp.com**

Recommended by Clara Moskowitz

The Lost Elements: The Periodic Table's Shadow Side

by Marco Fontani, Mariagrazia Costa and Mary Virginia Orna. Oxford University Press, 2014 ($39.95)

The journey to the periodic table of elements we know today was not smooth. Chemists Fontani, Costa and Orna tell the story of the false starts and stray paths that led to the "discovery" of many elements that turned out not to be. Some, such as "didymium," were later revealed to be composites of multiple elements; others, such as "brevium," were isotopes, or variations, on other elements (in this case, protactinium). Many of these efforts, the authors show, were not wasted but rather helped to clarify the true nature of the elements we know now and the chemical laws they obey. "There are many more elemental 'discoveries' later shown to be false than there are entries in the present table," they write. "Some of these were good-faith errors, some were the result of personal wishful thinking, some were the fantasy children of pseudoscientists—and all have their fascinating stories."

Spare Parts: Four Undocumented Teenagers, One Ugly Robot, and the Battle for the American Dream

by Joshua Davis. FSG Originals,* 2014 ($25)

In 2004 an upstart band of undocumented Mexican-American teenagers beat well-funded college teams to take the top prize in the Marine Advanced Technology Education remotely operated vehicle competition. The high school students surprised the judges with their creative engineering solutions and an "ugly" robot named Stinky that was built from scraps and cheap materials but nonetheless bested fancier entries from the likes of the Massachusetts Institute of Technology. Yet as *Wired* contributing editor Davis shows, over the years that followed, the U.S. has by and large squandered the talent the students displayed. Laws prohibiting in-state tuition rates for undocumented students made college unattainable to three out of the four. Only the fourth has a happier story. He was initially denied U.S. residency even after graduating with special honors from Arizona State University. Ultimately, though, an Illinois senator intervened to allow him back in the country, where he has realized his lifelong dream of enrolling in the military.

Digging for Richard III: The Search for the Lost King

by Mike Pitts. Thames & Hudson, 2014 ($29.95)

One of the most surprising archaeological finds in recent history was the discovery of the skeleton of 15th-century English king Richard III buried underneath a parking lot in Leicester in 2012. For centuries archaeologists thought the king's remains had been lost, with his bones most likely having been scattered into the River Soar. Yet a small group of scholars pursued the hope of finding his grave, mounted an excavation, and uncovered the ruins of a friary church and the dead monarch, all within two weeks of breaking ground. Archaeologist and journalist Pitts recounts the exhilarating dig—in which the lead archaeologist had promised to eat his hat if the skeleton actually turned up—and the revelations about Richard III that followed from the discovery.

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Doctor ***Designed.*** Audiologist ***Tested.*** FDA ***Registered.***

Affordable *New* Digital Hearing Aid *Outperforms* Expensive Competitors Delivers *Crystal -Clear* Natural Sound

Reported by J. Page

Chicago: Board-certified physician Dr. S. Cherukuri has done it once again with his newest invention of a medical grade ALL DIGITAL affordable hearing aid.

This new digital hearing aid is packed with all the features of $3,000 competitors at a mere fraction of the cost. Now, most people with hearing loss are able to enjoy crystal-clear, natural sound—in a crowd, on the phone, in the wind—without suffering through "whistling" and annoying background noise.

After years of extensive research, Dr. Cherukuri has now created a ***state-of-the-art*** digital hearing aid that's packed with the features of those expensive $3,000 competitors – at a ***fraction of the price.***

New Digital Hearing Aid Outperforms Expensive Competitors

This sleek, lightweight, fully programmed hearing aid is the outgrowth of the digital revolution that is changing our world. While demand for "all things digital" caused most prices to plunge (consider DVD players and computers, which originally sold for thousands of dollars and today can be purchased at a fraction of that price), the cost of a digital medical hearing aid remained out of reach.

Dr. Cherukuri knew that many of his patients would benefit but couldn't afford the expense of these new digital hearing aids. Generally they are not covered by Medicare or most private health insurance.

The doctor evaluated all the high priced digital hearing aids on the market, broke them down to their base components, and then created his own affordable version—called the **MD**HearingAid® ***AIR*** for its virtually invisible, lightweight appearance.

100% MONEY BACK GUARANTEE 45 DAY RISK FREE TRIAL

Proudly assembled in the USA from Domestic & Imported Components.

BBB RATING A

- ✓ Nearly *invisible*
- ✓ *Crystal-clear* natural sound
- ✓ No suffering with *'whistling'* or background noise
- ✓ *Outperforms* $3,000 models
- ✓ Amazing *low price*

Affordable Digital Technology

Using advanced digital technology, the **MD**HearingAid® ***AIR*** automatically adjusts to your listening environment—prioritizing speech and de-emphasizing background noise. Experience all of the sounds you've been missing at a price you can afford. This doctor designed and approved hearing aid comes with a full year's supply of long-life batteries. It delivers crisp, clear sound all day long and the soft flexible ear buds are so comfortable you won't realize you're wearing them.

Try It Yourself At Home With Our 45 Day Risk-Free Trial

Of course, hearing is believing and we invite you to try it for yourself with our RISK-FREE 45-day home trial. If you are not completely satisfied, simply return it within that time period for a full refund of your purchase price.

MDHearingAid® AIR

Ecstatic Users Cheer

"I recently purchased an MDHearingAid AIR for both ears. They are as small and work as well as a $5,000 pair I had previously tried."

— Dennis

"I'm a physician, and this product is just as effective (if not more) than traditional overly-priced hearing aids. I will be recommending (it)."

— Dr. Chang

"As a retired advanced practice nurse, I purchased the MDHearingAid AIR after the Wall Street Journal *review. I am so pleased with the quality. You are providing a real service to our affordable health care."*

— Ned Rubin

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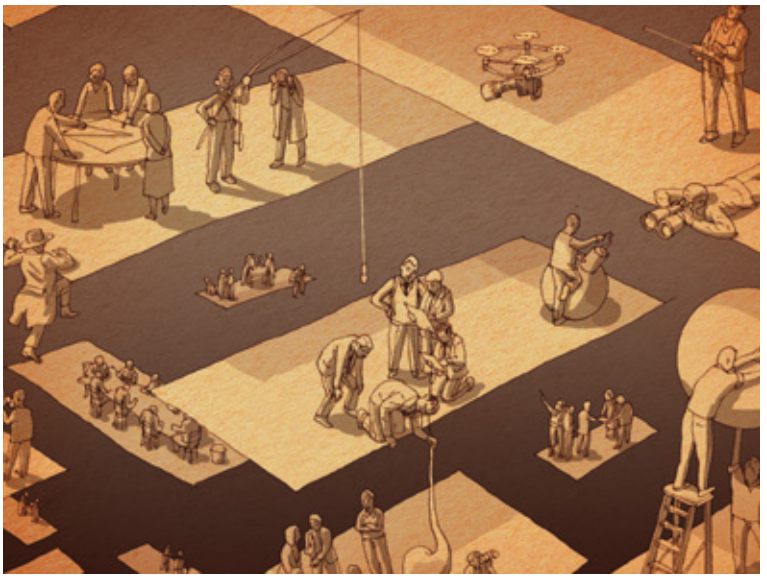

Conspiracy Central

Who believes in conspiracy theories—and why

President Barack Obama has been a busy man while in office: he concocted a fake birth certificate to hide his true identity as a foreigner, created "death panels" to determine who would live and who would die under his health care plan, conspired to destroy religious liberty by mandating contraceptives for religious institutions, blew up the Deepwater Horizon offshore drilling rig to garner support for his environmental agenda, masterminded Syrian gas attacks as a pretext to war, orchestrated the shooting of a TSA agent to strengthen that agency's powers, ordered the Sandy Hook school massacre to push through gun-control legislation, and built concentration camps in which to place Americans who resist.

Do people really believe such conspiracy theories? They do, and in disturbingly high numbers, according to recent empirical research collected by University of Miami political scientists Joseph E. Uscinski and Joseph M. Parent and presented in their 2014 book *American Conspiracy Theories* (Oxford University Press). About a third of Americans, for example, believe the "birther" conspiracy theory that Obama is a foreigner. About as many believe that 9/11 was an "inside job" by the Bush administration.

The idea that such beliefs are held only by a bunch of nerdy white guys living in their parents' basements is a myth. Surveys by Uscinski and Parent show that believers in conspiracies "cut across gender, age, race, income, political affiliation, educational level, and occupational status." People on both the political left and right, for example, believe in conspiracies roughly equally, although each finds different cabals. Liberals are more likely to suspect that media sources and political parties are pawns of rich capitalists and corporations, whereas conservatives tend to believe that academics and liberal elites control these same institutions. GMO conspiracy theories are embraced primarily by those on the left (who accuse, for example, Monsanto of conspiring to destroy small farmers), whereas climate change conspiracy theories are endorsed primarily by those on the right (who inculpate, for example, academic climate scientists for manipulating data to destroy the American economy).

Group identity is also a factor. African-Americans are more likely to believe that the CIA planted crack cocaine in inner-city neighborhoods. White Americans are more likely to believe that the government is conspiring to tax the rich to support welfare queens and turn the country into a socialist utopia.

Encouragingly, Uscinski and Parent found that education makes a difference in reducing conspiratorial thinking: 42 percent of those without a high school diploma are high in conspiratorial predispositions, compared with 23 percent with postgraduate degrees. Even so, that means more than one in five Americans with postgraduate degrees show a high predisposition for conspiratorial belief. As an educator, I find this disturbing.

Other factors are at work in creating a conspiratorial mind. Uscinski and Parent note that in laboratory experiments "researchers have found that inducing anxiety or loss of control triggers respondents to see nonexistent patterns and evoke conspiratorial explanations" and that in the real world "there is evidence that disasters (e.g., earthquakes) and other high-stress situations (e.g., job uncertainty) prompt people to concoct, embrace, and repeat conspiracy theories."

A conspiracy theory, Uscinski and Parent explain, is defined by four characteristics: "(1) a group (2) acting in secret (3) to alter institutions, usurp power, hide truth, or gain utility (4) at the expense of the common good." A content analysis of more than 100,000 letters to the *New York Times* in 121 years turned up three pages' worth of such conspirators, from Adolf Hitler and the African National Congress to the World Health Organization and Zionist villagers, catalogued into eight types: Left, Right, Communist, Capitalist, Government, Media, Foreign and Other (Freemasons, the AMA and even scientists). The common theme throughout is power—who has it and who wants it—and so the authors conclude their inquiry with an observation translated by Parent from Niccolò Machiavelli's *The Prince* (a conspiracy manual of sorts), for "the strong desire to rule, and the weak desire not to be ruled."

To those who so conspire, recall the motto of revolutionaries everywhere: *sic semper tyrannis*—thus always to tyrants. SA

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Illustration by Izhar Cohen

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The ongoing search for fundamental farces

Steve Mirsky has been writing the Anti Gravity column since a typical tectonic plate was about 34 inches from its current location. He also hosts the *Scientific American* podcast Science Talk.

Keeping Up with the Times

I came, I saw, Icons

On September 5 the Web site Mashable published an article entitled "9 Cultural Icons Who Have Written for 'The New York Times.'" The vanity piece was sponsored by and written by, you guessed it, the *New York Times*. The preamble to the list of nine iconic figures pointed out that "most people can name at least one *Times* writer." Nah, but I don't mean to be a pedant, so I'll move on. The intro then announced, "But you may not be aware that some of the biggest names in literature, pop culture and politics have earned a byline in the *Times,* too." Then came the starting nine of the paper of record's iconic byline earners.

I read the list, which was "pretty good, pretty good," as *Times* contributor Larry David, who did not make the cut, might have called it. I then compiled a competing register of cultural icons who have contributed to *Scientific American*. Frankly, I think the *Times* list could have been stronger—every U.S. president eventually writes something for the paper—but we can only go up against the lineup that's on the field. Play ball!

For the *Times,* batting first: John F. Kennedy. Undeniably a big name, but I counter with a man who in 1914 published a piece for us called "The Problem of Our Navy." He was assistant secretary of that branch of the military at the time, but Franklin D. Roosevelt was eventually sworn in as president—and again, and another time, and once more in those innocent days before term limits. He was also the last president I can think of to use a cigarette holder, which should make him a beacon of style for every Brooklyn hipster whose porkpie hat fails to complete the sought-after semiotic presentation.

Up next for the ink-stained wretches: Oprah Winfrey. Here the *Times* folks missed an opportunity to use only her first name to show just how iconic she is—nobody ever says, "Oprah? Which Oprah?" Oprah is part of our consciousness. Thus, Francis Crick, co-author of a 1992 *Scientific American* piece, "The Problem of Consciousness," seems to be a good choice. It has not escaped our notice that he was also a co-discoverer of the structure of DNA.

Batting third for the *Times:* Stephen King. This guy scares me. So I'll send up Al Gore, co-recipient of the 2007 Nobel Peace Prize, along with the Intergovernmental Panel on Climate Change. That combination makes global warming deniers experience mental meltdowns.

Cleanup *Times* hitter: Mary-Kate Olsen, now a fashion designer but once part of the popular TV sister duo the Olsen twins. I offer in response one of a set of brothers: Orville Wright, author of the 1914 *Scientific American* article "The Stability of Aeroplanes." He is also the most famous Orville not associated with popcorn, if you don't count the "popcorn chips" served on JetBlue flights.

Fifth for the *Times:* Oscar winner and humanitarian Angelina Jolie. For us: Nobel laureate and humanitarian Rita Levi-Montalcini, who worked in a home lab when driven out of academia by Mussolini. Jolie should play Levi-Montalcini in a biopic.

Sixth for them: Bono, world health advocate and rock star. For us: Bill Gates, world health advocate and nerd star.

Up seventh for the Gray Lady: Kurt Vonnegut, sometimes referred to as a modern Mark Twain. For us: Mark Twain. He penned a short satirical item in 1870 about the difficulties of installing stoves, which begins, "We do not remember the exact date of the invention of stoves, but it was some years ago," and who can argue?

Batting eighth for the *Times:* Martin Luther King, Jr. Now there's a cultural icon. My admittedly quirky counterpoint: Alexander Graham Bell's assistant, Thomas A. Watson, who wrote a 1913 article called "Pioneers in Telephone Engineering." He was mentioned by name in the world's first telephone call, when Bell famously said, "Mr. Watson, come here, I want you," because he had forgotten his two-step verification password.

And up ninth for the *Times:* William Howard Taft, the only man ever to be both president and chief justice. But we round out the *Scientific American* lineup with the author of the 1950 article "On the Generalized Theory of Gravitation." I'm talking, of course, about Albert Einstein, the only man ever to be Albert Einstein. I think we win. SA

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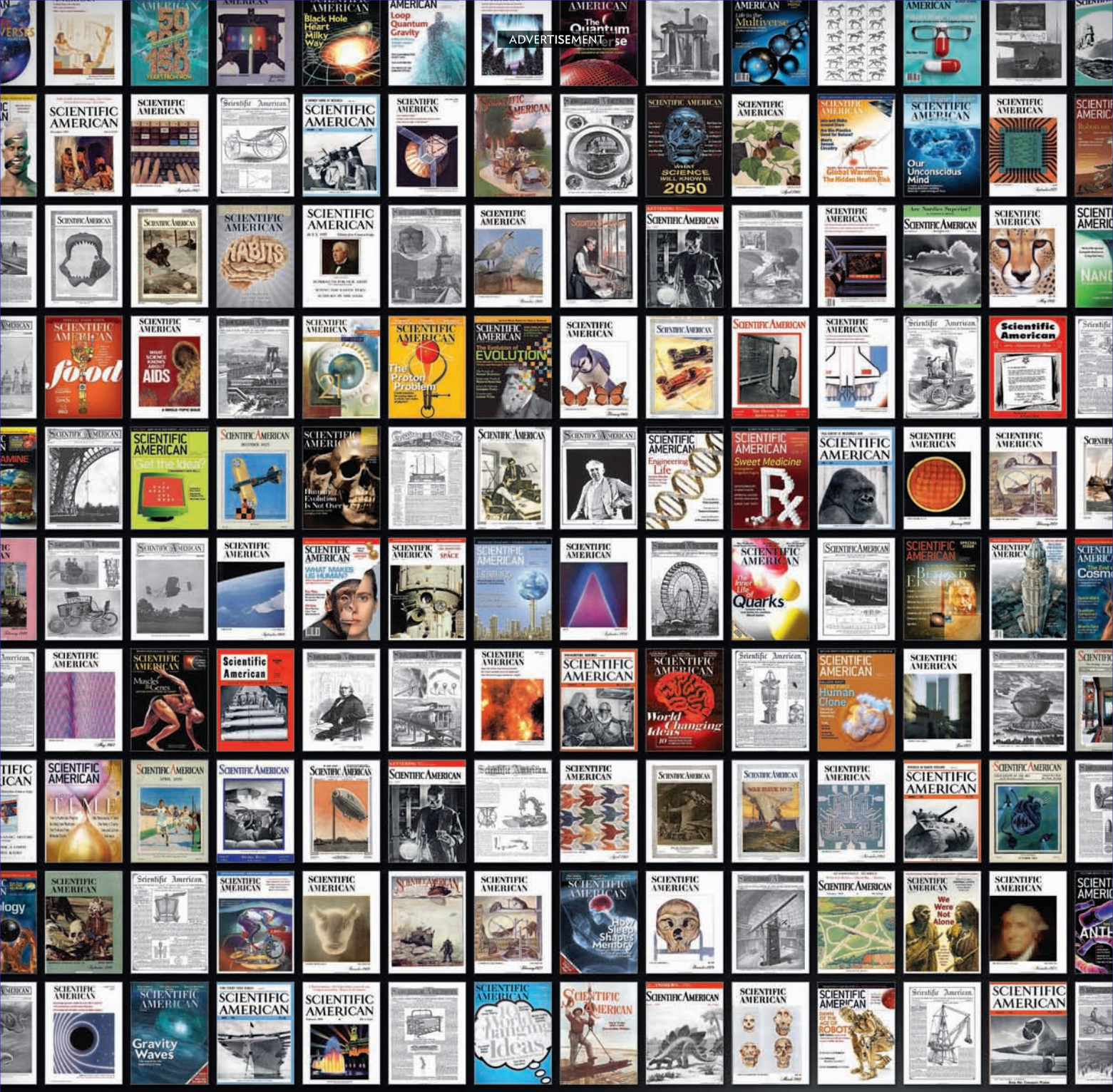
Illustration by Matt Collins



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December 1964

Moon Rocks

"We expect that the study of lunar geology will help to answer some longstanding questions about the early evolution of the earth. The moon and the earth are essentially a two-planet system, and the two bodies are probably closely related in origin. In this connection the moon is of special interest because its surface has not been subjected to the erosion by running water that has helped to shape the earth's surface.—Eugene M. Shoemaker"

Asbestos—Is It a Problem?

"Dust consisting of fine fibers of asbestos, which are insoluble and virtually indestructible, may become a public health problem in the near future. At a recent international conference on the biological effects of asbestos sponsored by the New York Academy of Sciences, participants pointed out on the one hand that workers exposed to asbestos dust are prone in later life to develop lung cancer, and on the other hand that the use of this family of fibrous silicate compounds has expanded enormously during the past few decades. A laboratory curiosity 100 years ago, asbestos today is a major component of building materials."

December 1914

Naval Blockade

"Germany can support herself on her home resources for fully a year, and this capacity for self-support in the face of a universal embargo [a blockade by the British navy] has a very high military value. It is probably true that long before next August, if the war were to last as long as that, the people of Germany would be put to many shifts from their usual mode of living. They might, for instance, have to learn to eat a greater part of their annual production of some two billion bushels of potatoes which are now mostly used in the production of industrial alcohol."

Espionage in Arabia

"A considerable amount of surveying and exploration has recently been done along the southern frontier of Palestine under the auspices of the Palestine Exploration Fund by parties headed by Capt. S. F. Newcombe, Royal Engineers, and including two archaeologists from the British Museum. Five parties surveyed and mapped the whole border region except a small area around Akaba [Aqaba], where the Turkish authorities refused the necessary permission."

The survey, ostensibly of biblical sites, was actually a clandestine military operation to map parts of the Ottoman Empire. One of the "two archaeologists" was T. E. Lawrence, later known by the sobriquet "Lawrence of Arabia."

Motor-Driven Unicycle

"The idea of a single-wheeled vehicle is by no means new. The novelty in the motor car shown [*see illustration*] lies not in the fact that it is a one-wheeled vehicle, but that it is stabilized by a gyroscope. The machine has not been built, but the design has been offered by one of the readers of the SCIENTIFIC AMERICAN as a suggestion to some enterprising inventor."

A slide show on the developments in motor-vehicle technology and industry from 1914 is at ScientificAmerican.com/dec2014/motor-vehicles

MOTORIZED UNICYCLE: A design proposed by a *Scientific American* reader, 1914

December 1864

Vice Abides

"Dr. Alfred Taylor, commissioned by the Privy Council in England, has sent in a Report. Laudanum (tincture of opium) appears to be sold wholesale, single shops often supplying three or four hundred customers every Saturday night. Retail druggists often dispense 200 lbs. in one year, and one man complained that his wife had consumed £100 in opium since he married. We are assured by a wholesale druggist that he could and did sell it in the eastern counties to the extent of some thousands of pounds weight in a year. This gentleman, an old and keen observer, declared that the demand had sprung up shortly after the introduction of teetotalism."

Thank the Gods

"The *Peking Gazette* contains a report from the Chinese government on the extinction of the [Taiping] rebellion, which ends with the following words: 'It is, therefore, most needful that thanks be offered to the gods for their assistance. Wherefore, the Board of Rites is directed to examine into the services rendered by the different gods, and to report to us.'"

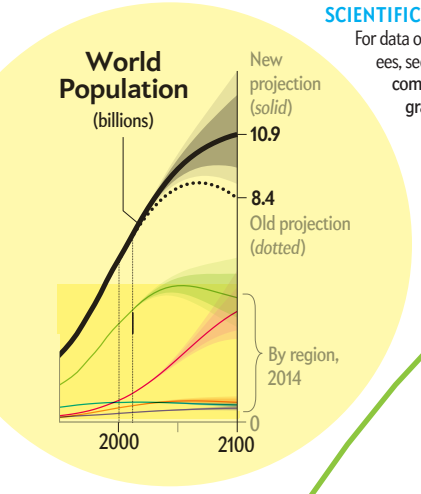
SCIENTIFIC AMERICAN, VOL. CXI, NO. 24, DECEMBER 12, 1914

Up, Up and Away

World population will hit nearly 11 billion by 2100

United Nations leaders have worried for decades about the pace of population growth. A few years ago leading calculations had global population peaking at nine billion by 2070 and then easing to 8.4 billion by 2100. Currently it stands at 7.2 billion. Recently the U.N. revised these numbers steeply upward: the population is now expected to rise to 9.6 billion by 2050 and continue to 10.9 billion by 2100 (*small graph at left*). What caused this drastic revision? Almost all the increase comes from Africa (*pink line at right*). Earlier models "had anticipated that fertility rates in Africa would drop quickly, but they haven't," says Adrian Raftery, a statistician at the University of Washington, who assessed the revised estimates. How the world will feed a few billion more people is the question of the day. —*Mark Fischetti*

SCIENTIFIC AMERICAN ONLINE
For data on ratios of workers to retirees, see ScientificAmerican.com/dec2014/graphic-science



Total Population (billions)

Light tints: 95% probability range

Dark tints: 80% probability range

Median

Solid lines: U.N. 2014 projections

Dotted lines: International Institute for Applied Systems Analysis 2001 projections

The Big Surprise: Africa
A large, unanticipated rise in Africa's future population accounts for almost the entire increase in the 2100 global projection. Data from 2010 censuses and subsequent surveys show that African fertility rates remain higher than predicted, and death rates from AIDS have eased, thanks to better treatment. The population of Asia (*above*) will be slightly higher; that of Latin America (*below*) will be lower.

Asia

Africa (new projection)

Africa (old projection)

Latin America and the Caribbean

Europe

North America

6
5
4
3
2
1
0

2000
2050
2100

SOURCES: "WORLD POPULATION STABILIZATION UNLIKELY THIS CENTURY," BY PATRICK GERLAND ET AL., IN *SCIENCE EXPRESS*, PUBLISHED ONLINE SEPTEMBER 18, 2014 (*2014 projections*); "THE END OF WORLD POPULATION GROWTH," BY WOLFGANG LUTZ ET AL., IN *NATURE*, VOL. 412, AUGUST 2, 2001 (*2001 projections*)

Graphic by Hana Ševčíková and Jen Christiansen

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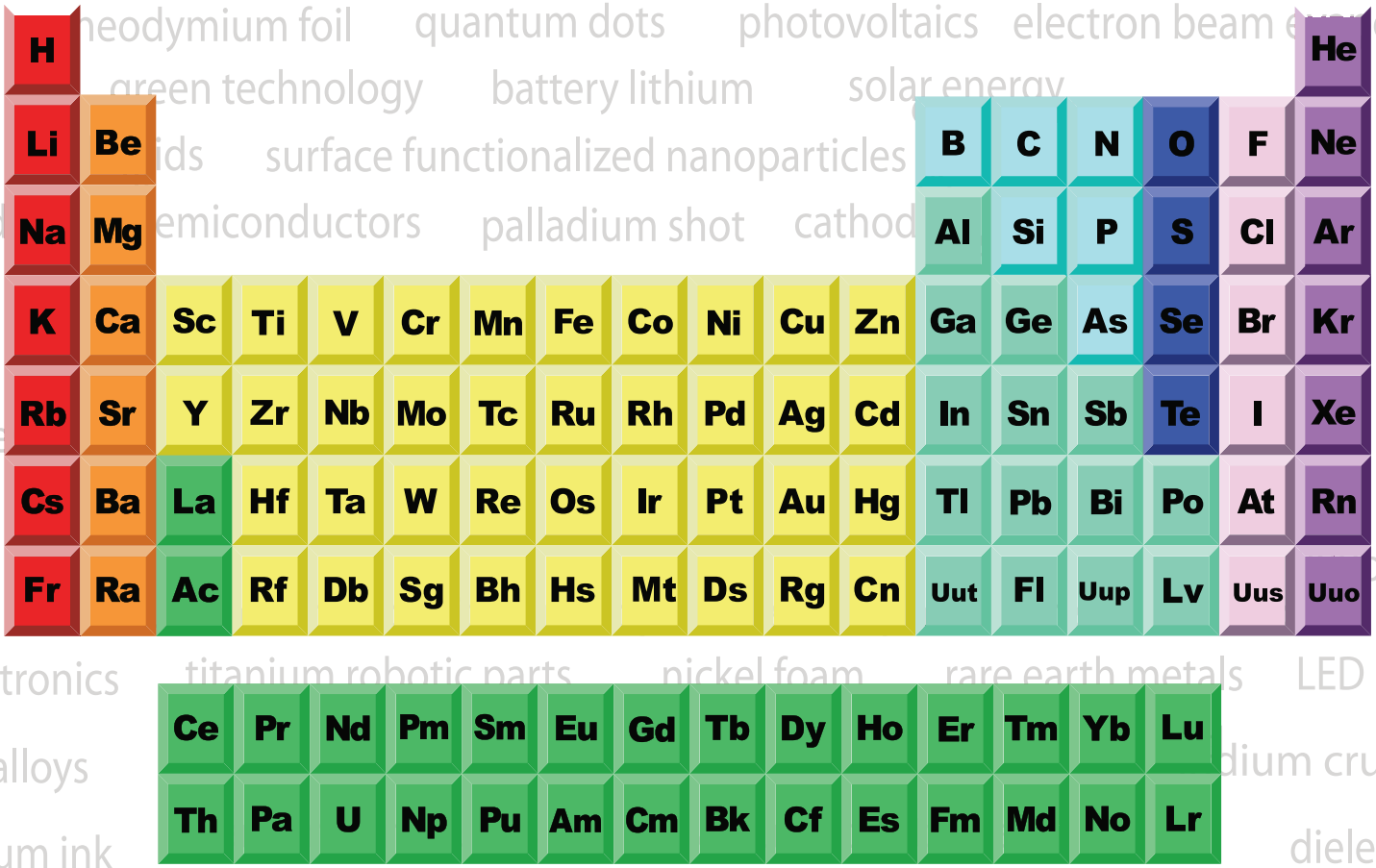

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