NEUROSCIENCE
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A New Way to Tame Cancer

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The Benefits of Video Games (Really)

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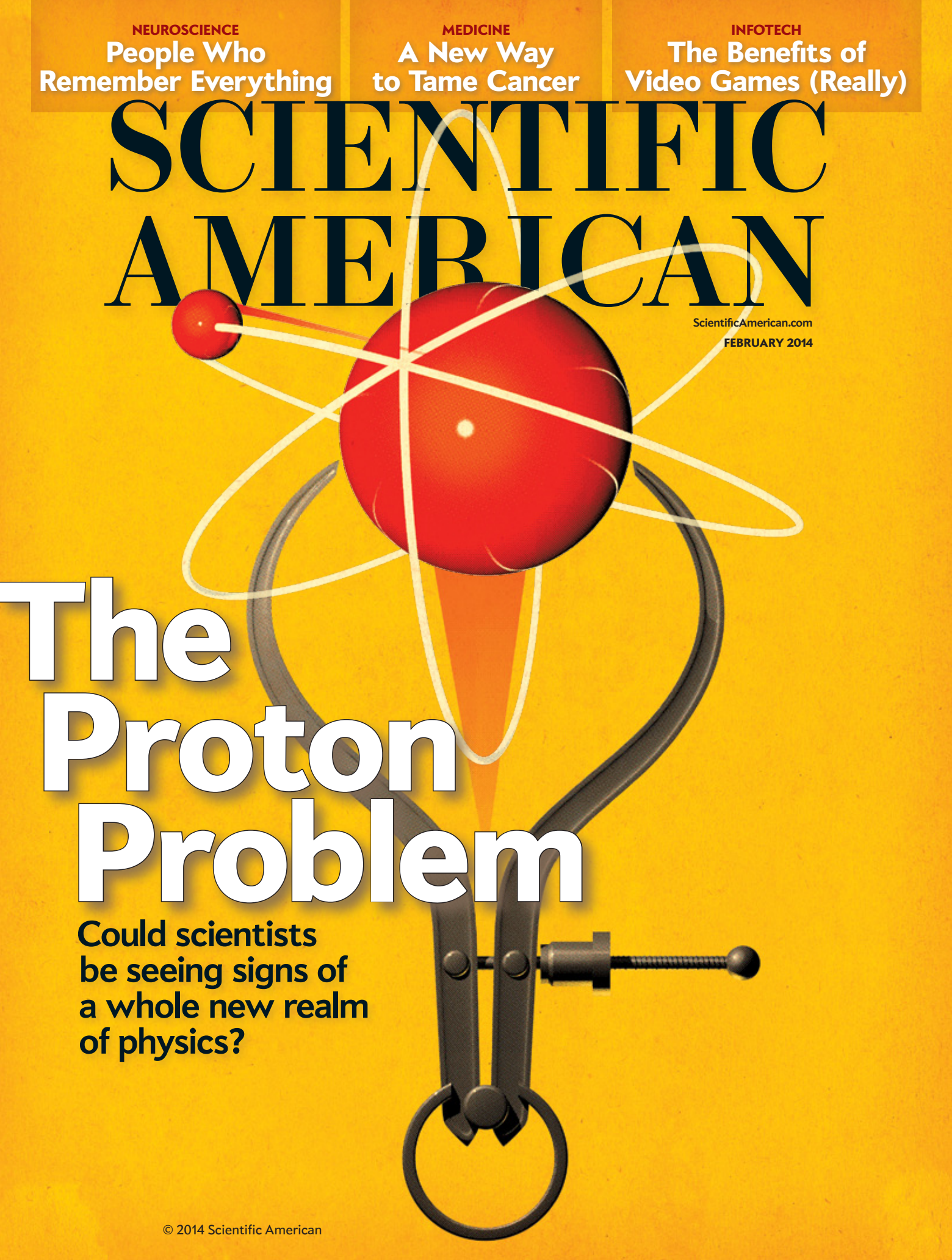

The Proton Problem

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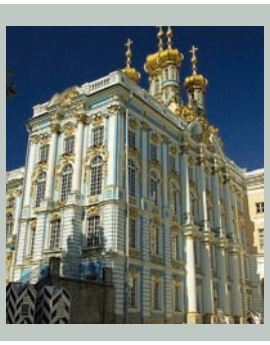

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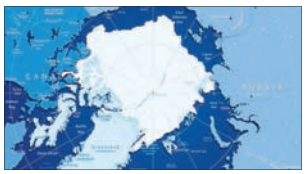

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- Scientific Exploration of the Arctic
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- The Evolution Controversy
- The Neo-Darwinian Synthesis

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- Antimatter: Facts and Fiction
- Nothing: Mysteries of the Vacuum
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- A Rational Look at GMO Food
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- The Thinking Robot

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Edward Larson, Ph.D.
Alan Winfield, Ph.D.

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ON THE COVER

The size of the proton was not thought to be in question. But a new experiment has determined that it is far smaller than expected. The results have puzzled physicists and called into question the exceedingly well verified theory of quantum electrodynamics. They have also raised hopes among researchers that the anomaly may point the way to a deeper understanding of nature. Image by Tavis Coburn.

SCIENTIFIC AMERICAN

February 2014 Volume 310, Number 2

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TODD McLELLAN *Gallery Stock*

FEATURES

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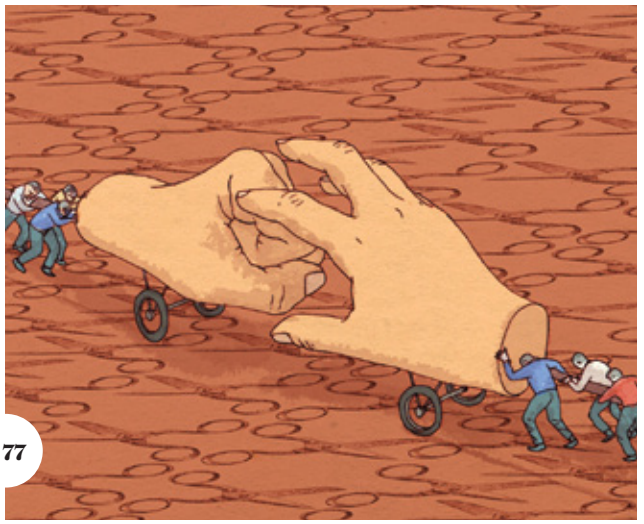

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SCIENTIFIC AMERICAN

DEPARTMENTS

ON THE WEB

What Is Information, Anyway?
At a conference hosted by the Foundational Questions Institute, physicists, neuroscientists and other researchers gathered to explore what role information plays in physics, in consciousness and in life itself.
Go to www.ScientificAmerican.com/feb2014/fqxi

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- Life on Mars: What Do We Know?
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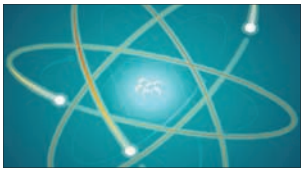

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- Life after Higgs: What's Next?
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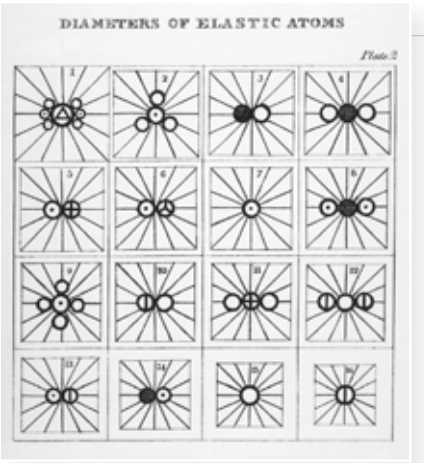
Knowledge Quest



ATOMS diagrammed by British chemist John Dalton, from an 1896 publication.

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

WE HAVE REACHED OUT INTO the universe and pulled back an anomaly," write Jan C. Bernauer and Randolf Pohl in our cover story, "The Proton Radius Problem," starting on page 32. "And so we have a great chance to learn something new."

Their task was a straightforward one: measure the radius of a proton. After using two complementary techniques to get precise measurements, however, the answers they got were not the same. And the values were not just slightly different; they were different by more than five times the uncertainty in either measurement. How could that happen? Could it be that we don't understand the physics of precise measurements or that we don't understand the seemingly familiar proton as well as we thought?

As I look over this feature and the rest of the pages we are preparing for the printer, I find myself again reflecting on how often the lesson that science teaches humanity is "what you thought just isn't so simple." And the scientists' response is not the frustration you might expect but a passion to get to the bottom of yet another delicious mystery. I find that quest very inspiring. The drive to learn and share that knowledge to improve the world not only powers science but underpins everything that we do at *Scientific American*.

We can support our ambition through some surprising tools, as you will learn in "Mind Games," beginning on page 54. Author Alan Gershenfeld explains that new research shows video games have great educational potential to exercise higher-order skills such as problem solving and evidence-based reasoning. Gershenfeld plans to bring further insights to the World Economic Forum Annual Meeting in Davos, Switzerland, in January and is a speaker in a discussion I am moderating on science literacy.

Last (literally), when you get to Graphic Science, on page 82, you will have a chance to engage in some of your own reflection about the progress of science as chronicled on our most recent nine decades of covers since *Scientific American*'s founding in 1845. As you will see in the images and the data about coverage topics, the magazine—the longest continuously published in the U.S.—not only has chronicled the arc of science over the years but has, like any creature on the planet, itself evolved and adapted over that time span.

Available for libraries and academic institutions for the past few years, our digital archives are now also ready for individual access for the first time. As any science-interested person would do, we invite you to explore the evidence for yourself—and we hope you, too, find it illuminating. SA

SCIENCE SOURCE

Illustration by Nick Higgins

Photonics rewrites our understanding of matter.

Have you ever admired the lovely, iridescent light that glows from an opal, or watched a jewel beetle from different angles and seen how the colors change? These mysterious colors are created by something called photonic crystals, which make use of the interaction between light and matter. Photonic crystals are nanostructures that can be made to strongly reflect or close out light at certain wavelengths, by tweaking their structure. The application of these crystals could lead to fascinating possibilities in new optical devices. Photonics technologies are rewriting the way we look at and understand matter, with each discovery adding another hue to the spectrum.

Akira Hiruma
President and CEO, Hamamatsu Photonics K.K.

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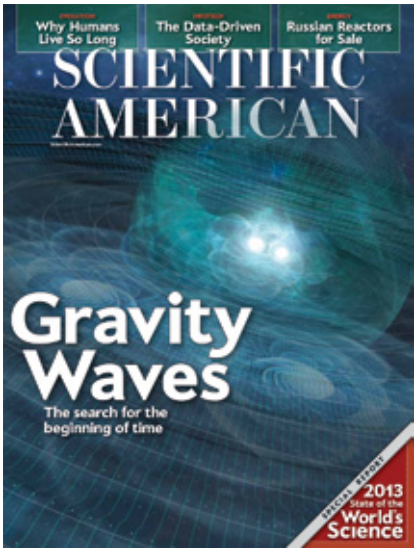

October 2013

"Even if a nuclear accident is a low-probability event, it is a high-consequence one."
NEAL FRIEDMAN *WOODINVILLE, WASH.*

GRAVITATIONAL WAVES

"An Ear to the Big Bang," by Ross D. Andersen, discusses various strategies being studied in the U.S. to develop space-based gravitational-wave observatories but fails to mention the eLISA mission concept, a strong candidate for the European Space Agency's next large mission. eLISA is a descendant of the Laser Interferometer Space Antenna (LISA) mission concept mentioned in the article. Europe has also made a particularly strong investment with the LISA Pathfinder mission, set to launch in 2015, which will demonstrate technological readiness and provide Europe with the opportunity to lead the first space-based gravitational-wave mission. No other competitive concept for such a mission currently exists.

The atom interferometry approach described in the article may be a candidate for future missions, but it is not nearly mature enough to be considered competitive with the eLISA concept.

JOHN MATHER
ROBIN STEBBINS
NASA Goddard Space Flight Center

While Andersen's article is entertaining, anyone reading it will come away with a distorted and misinformed view of gravitational-wave astronomy.

To say that LIGO has "limited" ambitions and is a "proof-of-concept mission" for space-based interferometers is simply inaccurate. LIGO and LISA operate in completely different frequency bands and are sensitive to very different classes of astrophysical sources. Each will teach us different things about the universe.

The most serious misrepresentation is the article's portrayal of atom interferometry as a true contender to LISA for a space-based mission. There is no sensible comparison to make between LISA and atom interferometers. LISA-like mission concepts have been studied and peer-reviewed for the past 20 years, with an active and successful program to develop the critical technologies in Europe and the U.S. Atom interferometry is at a much less mature level; conceptual designs are still being investigated and modified. While it is important to pursue these investigations, it is an enormous stretch to go from laboratory practice to a space-based atom-interferometer design with adequate sensitivity to observe even the strongest gravitational-wave sources.

DAVID REITZE
Executive director, LIGO Laboratory
California Institute of Technology
GABRIELA GONZALEZ
Spokesperson, LSC
Louisiana State University

RUSSIAN REACTORS

In "Russia's New Empire: Nuclear Power," by Eve Conant, a Westinghouse spokesperson dismisses the need for a core catcher in the company's AP1000 design, noting that aspects of the design preclude a meltdown. This and other quotes from nuclear experts demonstrate an attitude that could well doom nuclear power expansion in the U.S. Nuclear proponents need to understand they can never make a plant 100 percent immune from a catastrophe and must design both to prevent and to mitigate a disaster. Even if a nuclear accident is a low-probability event, it is a high-consequence one.

NEAL FRIEDMAN
Woodinville, Wash.

AUTISM EXPERIENCE

In "Help for the Child with Autism," Nicholas Lange and Christopher J. McDougle refer to autism as a "disorder" to be cured. But what if children with autism don't see it like this? Perhaps, for them, it is a way of going through the world, neither inferior nor superior to any other.

GIDEON FORMAN
Toronto

ILLUSORY OWNERSHIP

In "Edit Your Photos? Feed the Meter" [TechnoFiles], David Pogue laments that large software companies such as Adobe and Microsoft are switching to a subscription model for their programs. Let's not pretend that we have ever owned these applications. We merely pay for a license encumbered with restrictions on installations, inspection and manipulation.

ADAM WEBER
Pittsboro, N.C.

GUNS AND VIOLENCE

In "When Science Doesn't Support Beliefs" [Skeptic], Michael Shermer asserts that I have practiced "cherry picking and data mining of studies to suit ideological convictions" in my arguments that private gun ownership reduces violent crime. Like Shermer, my views on guns have changed over time. He ignores that, as I have shown in *More Guns, Less Crime* (third edition, 2010), the large majority of peer-reviewed studies demonstrate right-to-carry laws reduce crime and background checks do not.

JOHN R. LOTT, JR.
President
Crime Prevention Research Center

SHERMER REPLIES: The gun-control issue is one of the most complex I have ever encountered. So much data and so many variables affect the outcome of gun-control laws that one can easily make the data come out either in support of or against such measures. From the studies I have read (and cited in my debates with Lott), such proposed measures as background checks, assault weapon bans and maga-

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zine size restrictions could help reduce America's death rate from guns (more than 10 per 100,000), which is almost an order of magnitude higher than that of most European nations. I did read Lott's book. But I also read a scholarly analysis of it called "Shooting Down the More Guns, Less Crime Hypothesis," which is available for free at www.nber.org/papers/w9336.

CLARIFICATIONS

"Renewable Energy's Hidden Costs," by John Matson [Graphic Science], did not specify the low-end estimate for wind energy's greenhouse payback time, which is less than one year and is more reflective of modern wind turbines.

"An Ear to the Big Bang," by Ross D. Andersen, asserted that gravitational waves are "impervious to the astrophysical giants in their path"; they are nearly impervious. Gravitational waves are much more impervious than light waves are, but they can be affected by massive cosmic structures.

ERRATA

"Russia's New Empire," by Eve Conant, stated that TerraPower in Bellevue, Wash., is developing fast mini reactors and that it tests its prototypes in a Russian facility in Dimitrovgrad. TerraPower's fast reactors do not qualify as "mini," and it is testing nuclear materials, not prototypes, at the Russian facility. Also, the article referred to VVERs as being housed in a containment building. It should have specified recent VVERs. Furthermore, Finland was described as choosing Rosatom for its next reactor in July. Rather a private Finnish consortium had proposed using a Rosatom reactor for an already approved project.

In "The Liver Transplant Divide," by Dina Fine Maron [Advances], the key to maps indicating wait times for liver transplants had an error in it. The corrected graphic can be seen at ScientificAmerican.com/liver-transplants.

"Long Live the Humans," by Heather Pringle, incorrectly describes the causes and effects of the heat and swelling associated with inflammation. It should have said heat and redness come from an increase in the flow of warm blood to damaged tissue and swelling results when increased vascular permeability causes blood cells and plasma to leak into the affected area.

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/feb2014

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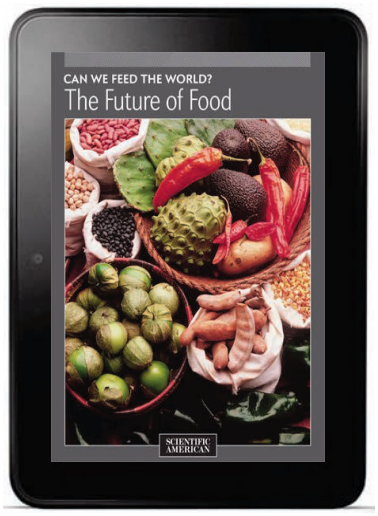
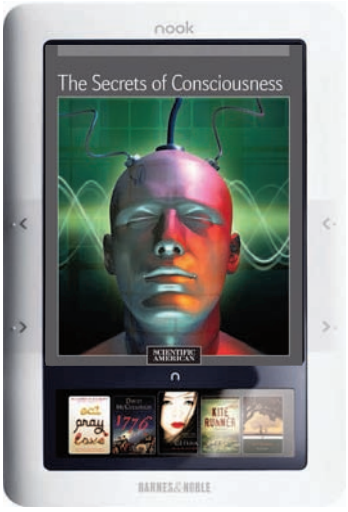


A companion to *Scientific American's* special September 2013 issue, this eBook looks at some of the complex factors involved in the coming "food crisis." With the global population projected to reach 9 billion by 2050, is it possible to increase food production and distribution both sustainably and safely?

The onset of cold weather brings out the boots, coats, gloves – and the block-lettered, stoplight-red "Flu Shots Available Here" signs in drugstore windows. And with good reason. For many scientists and public health specialists alike, flu season has become a little like Russian Roulette.



Consciousness is more than mere awareness. It's how our subjective experience relates to the objective universe around us. Once the province of philosophy, religion or perhaps fantasy, neuroscientists have added a scientific voice to the discussion, using available medical technology to explore just what separates so-called "mind" from brain.

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End the Drug War's Research Bans

It's time to let scientists study whether LSD, marijuana and ecstasy can ease psychiatric disorders

Discovery of new psychiatric medication, whether for the treatment of depression, autism or schizophrenia, is at a virtual standstill. As just one example, the antidepressants on the market today are no more effective at reversing the mood disorder than those that first became available in the 1950s.

New thinking is desperately needed to aid the estimated 14 million American adults who suffer from severe mental illness. Innovation would likely accelerate if pharmacologists did not have to confront an antiquated legal framework that, in effect, declares off-limits a set of familiar compounds that could potentially serve as the chemical basis for entire new classes of drugs.

LSD, ecstasy (MDMA), psilocybin and marijuana have, for decades, been designated as drugs of abuse. But they had their origins in the medical pharmacopeia. Through the mid-1960s, more than 1,000 scientific publications chronicled the ways that LSD could be used as an aid to make psychotherapy more effective. Similarly, MDMA began to be used as a complement to talk therapy in the 1970s. Marijuana has logged thousands of years as a medicament for diseases and conditions ranging from malaria to rheumatism.

National laws and international conventions put a stop to all that. The Controlled Substances Act of 1970 declared that these drugs have "no currently accepted medical use" and classified them in the most stringently regulated category of controlled substances: Schedule I. The resulting restrictions create a de facto ban on their use in both laboratories and clinical trials, setting up a catch-22: these drugs are banned because they have no accepted medical use, but researchers cannot explore their therapeutic potential because they are banned. Three United Nations treaties extend similar restrictions to much of the rest of the world.

The decades-long research hiatus has taken its toll. Psychologists would like to know whether MDMA can help with intractable post-traumatic stress disorder, whether LSD or psilocybin can provide relief for cluster headaches or obsessive-compulsive disorder, and whether the particular docking receptors on brain cells that many psychedelics latch onto are critical sites for regulating conscious states that go awry in schizophrenia and depression.

In many states, doctors can now recommend medical marijuana, but researchers cannot study its effects. The uneasy status quo leaves unanswered the question of whether the drug might help treat attention-deficit hyperactivity disorder, nausea, sleep apnea, multiple sclerosis and a host of other conditions.

A few privately funded studies of these compounds have yielded tantalizing hints that some of these ideas merit consideration. Yet doing this research through standard channels, as psychopharmacologist David J. Nutt of Imperial College London and his co-authors noted in a recent article in *Nature Reviews Neuroscience,* requires traversing a daunting bureaucratic labyrinth that can dissuade even the most committed investigator. (*Scientific American* is part of Nature Publishing Group.) It can take years to receive approval for a clinical trial from both regulators and hospital ethics committees, even while tallying thousands of dollars in licensing fees and tens of thousands to obtain drugs that are, of course, unavailable from a chemical supply catalogue.

The endless obstructions have resulted in an almost complete halt in research on Schedule I drugs. This is a shame. The U.S. government should move these drugs to the less strict Schedule II classification. Such a move would not lead to decriminalization of these potentially dangerous drugs—Schedule II also includes cocaine, opium and methamphetamine, after all—but it would make it much easier for clinical researchers to study their effects.

If some of the obstacles to research can be overcome, it may be possible to finally detach research on psychoactive chemicals from the hyperbolic rhetoric that is a legacy of the war on drugs. Only then will it be possible to judge whether LSD, ecstasy, marijuana and other highly regulated compounds—subjected to the gauntlet of clinical testing for safety and efficacy—can actually yield effective new treatments for devastating psychiatric illnesses. SA

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Illustration by Thomas Fuchs

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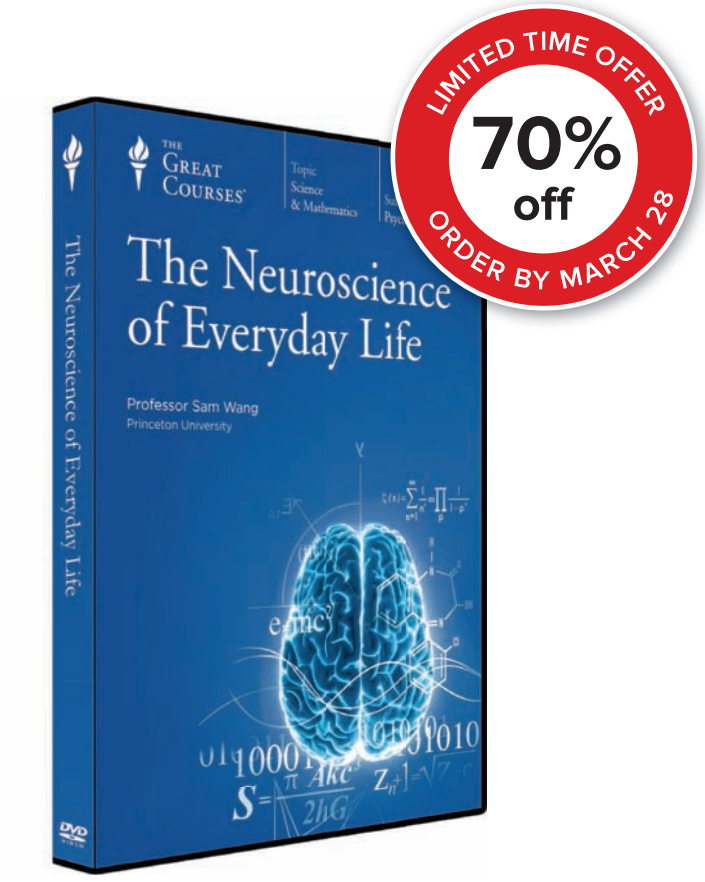

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Commentary on science in the news from the experts

Roy H. Hamilton is a faculty member at the Center for Cognitive Neuroscience at the University of Pennsylvania.

Jihad Zreik is a neuroscience graduate student at University College London, where he conducts cognitive experimentation in a brain-stimulation laboratory.

Wired for Thought

Should we use a device to become smarter, more attentive versions of ourselves?

It's hard to imagine anyone, no matter how brilliant, who doesn't yearn to be even smarter. Thanks to recent advances in neural science, that wish may come true. Researchers are finding ways to rev up the human brain like never before. There would be just one question: Do we really want to inhabit that world?

It may be too late to ask. Modern society has already embraced the basic idea of fine-tuning our intellects via artificial procedures—what might be termed "cosmetic" neurology. Schoolchildren take Adderall, Concerta and other attention-focusing medications. Parents and teachers rely on antidepressants and anti-anxiety drugs. And self-help books offer the latest advances in neuroscience to help ordinary people think faster and sharper.

Add to those advances another cognitive-enhancement method: transcranial direct-current stimulation (tDCS). With this technique, electrodes applied to the scalp deliver minuscule amperages of current to the brain. This trickle of electricity seems to cause incremental adjustments in the electrical potentials of membranes in the neurons closest to the electrodes, increasing or decreasing their likelihood of firing. And that, in turn, induces measurable changes in memory, language, mood, motor function, attention and other cognitive domains.

Investigators still aren't sure whether tDCS can cause long-term neural changes. Although most tests show only transient effects, there is limited evidence that repeated applications might have more persistent results. The procedure is not approved by the U.S. Food and Drug Administration, and the consensus among experts is that it should be performed only under qualified supervision. Nevertheless, if used properly, it is safe, portable, easy to implement and inexpensive.

The idea is so straightforward that some do-it-yourselfers have built their own devices for home use, ignoring cautionary disclaimers. Even though such a freewheeling approach won't appeal to everyone, electronic brain stimulation has a chance of catching on. In a recent online survey, 87 percent of respondents told us they would undergo tDCS if it could enhance their performance at school or work.

Should we welcome this opportunity to become smarter, faster, more attentive versions of ourselves? Although a few neuroscientists have unreservedly endorsed general use of this hot-wired thinking cap, others (including us) are not so sure. Safety is a paramount concern with any biomedical device. And what about distributive justice? If tDCS becomes widely available, will the wealthy use it to compound their privileged status?

Other issues are more perplexing. Brain-manipulating technologies such as tDCS might conceivably allow users to rewire the neural machinery that underlies critical aspects of an individual's cognitive experience and selfdom. Extending this thought to its logical conclusion, one could ask whether users might ultimately find ways to transform themselves. Beyond that, would it be acceptable to impose such changes on others—students, say, or workers, or soldiers—for the sake of strengthening certain skills? And what of society itself? If individuals build moral fiber by struggling against their own limitations, would something vital be lost if every challenging cognitive task or emotionally difficult moment could be eased with the press of a button?

We doubt that these extremes will come to pass. Still, they are worth examining when contemplating decisions that could have inadvertent outcomes. Any brain-enhancing techniques will have to be evaluated case by case, as society comes to a fuller understanding of their trade-offs. If such procedures become widely available, scientists and practitioners will bear the responsibility of teaching the public to use the technology safely and appropriately. Until then, we can only say that tDCS and similar tools are cause for excitement—and for caution. SA

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Illustration by Ryan Inzana

IAN HOOTON *Science Source*

HEALTH

Coughing Up Clues

The shortcomings of the whooping cough vaccine may help explain the disease's resurgence

Pertussis, better known as whooping cough, once sickened more than 100,000 Americans a year. The bacterial illness, which is particularly dangerous to infants, was brought under control in the 1940s with the introduction of pertussis vaccines. But in the past two decades pertussis has made an alarming comeback.

In 2012 the number of U.S. cases rose to 48,277—the most since 1955. The resurgence has led researchers to reexamine the workings of the current vaccine, which uses bits and pieces of the *Bordetella pertussis* bacterium to stimulate the production of antibodies. This so-called acellular pertussis (aP) vaccine is in the widely used DTaP and TdaP shots, which also protect against diphtheria and tetanus. An older formulation with whole, inactivated *B. pertussis* cells was phased out in the 1990s because of its side effects.

Recent studies have shown that immunity from the acellular vaccine wanes relatively quickly. In 2012, for instance, a *New England Journal of Medicine* study determined that children's odds of catching pertussis rose by 42 percent each year after receiving the final dose of DTaP, usually given between ages four and six, in the childhood vaccine series.

Tod Merkel and his colleagues at the U.S. Food and Drug Administration suspected another weakness lurked in the acellular vaccine—that it might not block the spread of the disease. To test their hypothesis, Merkel's team members infected baboons with pertussis. Some of the animals had been vaccinated, and some had acquired natural immunity from a past bout of the illness. None of the vaccinated or naturally immune baboons fell ill, but the bacterium lingered for 35 days in the throats of the baboons that had received the acellular vaccine. Animals that had received the whole-cell vaccine cleared the infection nearly twice as fast.

During their infections, acellular-vaccinated baboons were able to pass the bacterium to unprotected animals, Merkel's team recently reported in the *Proceedings of the National Academy of Sciences USA*. The study, says Eric Harvill, a professor of microbiology and infectious disease at Pennsylvania State University, "explains a lot of the observations about the circulation of pertussis in highly vaccinated populations."

Finding out exactly how the different vaccines convey immunity might lead to a better pertussis shot, which Harvill, Merkel and their colleagues hope to develop over the next several years. "Clearly, the natural infection and whole-cell vaccine are stimulating some response besides the antibody response, and we're trying to find out what," Merkel says. —*Tara Haelle*

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SPORT SCIENCE

Geologic Miracle on Ice

Why granite from a Scottish island makes the best curling stones

When the Winter Olympics commence this month in Sochi, Russia, there should be no shortage of heart-stopping action. Alpine skiers will carve downhill turns at 80 miles per hour. Hockey players will battle one another for the puck. Snowboarders will twist and flip multiple times in a single jump. And then there is curling, in which a more sedate bunch will push a 44-pound rock down a long sheet of ice and then sweep the ice with brooms to "curl" that stone toward a target.

Although curling is an Olympic newcomer, having been officially included only since 1998, the stones have a long, rich history of their own. "Every single Olympic curling stone comes from this little island off the coast of Scotland, called Ailsa Craig," says Erika Brown, skipper of the U.S. women's team. "And no other stone curls like an Ailsa Craig stone."

The 220-acre island, about 10 miles from mainland Scotland, is the source of two varieties of granite used in elite curling stones. Blue hone granite makes up the layer that glides down the ice, and common green granite makes up the middle layer, or striking band. "The layer of rock that runs along the ice doesn't chip or absorb water, but most important, it's very predictable on ice—you know what your shots are going to do," Brown says. "And the middle layer doesn't break when the stones collide."

The stones' performance traces back to the island's formation about 60 million years ago. Ailsa Craig is a volcanic intrusion—a mass of magma that forced its way up between existing formations—explains John Faithfull, a geologist at the University of Glasgow. The magma then cooled relatively quickly to form granite, and the surrounding rock eroded away, "leaving just the very resistant hard mass of Ailsa Craig poking up out of the water," Faithfull says.

As the volcanic rock crystallized, it developed a strong, uniform surface. "When magma cools quickly, it creates very small crystals. These ones interlocked, and chemical bonds developed between them," says Martin Gillespie, a geologist at the British Geological Survey. "It also doesn't seem to have any microcracks," he says of the granite.

The granite's unique qualities make Ailsa Craig stones the "gold standard," Brown says. "For us curlers, the island is a mystical place." —*Michael Easter*

BY THE NUMBERS

59%

Internet users who agree that "online dating is a good way to meet people," up from 44 percent in 2005.

RYAN McVAY *Getty Images (top)*; SOURCE: "ONLINE DATING & RELATIONSHIPS," BY AARON SMITH AND MAEVE DUGGAN. PEW INTERNET & AMERICAN LIFE PROJECT, OCTOBER 21, 2013 *www.pewinternet.org/Reports/2013/Online-Dating.aspx (bottom)*

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Do not take VIAGRA if you take nitrates, often prescribed for chest pain, as this may cause a sudden, unsafe drop in blood pressure.

Discuss your general health status with your doctor to ensure that you are healthy enough to engage in sexual activity. If you experience chest pain, nausea, or any other discomforts during sex, seek immediate medical help.

In the rare event of an erection lasting more than 4 hours, seek immediate medical help to avoid long-term injury.

If you are older than age 65, or have serious liver or kidney problems, your doctor may start you at the lowest dose (25 mg) of VIAGRA. If you are taking protease inhibitors, such as for the treatment of HIV, your doctor may recommend a 25-mg dose and may limit you to a maximum single dose of 25 mg of VIAGRA in a 48-hour period. If you have prostate problems or high blood pressure for which you take medicines called alpha blockers, your doctor may start you on a lower dose of VIAGRA.

In rare instances, men taking PDE5 inhibitors (oral erectile dysfunction medicines, including VIAGRA) reported a sudden decrease or loss of vision or hearing. If you experience sudden decrease or loss of vision or hearing, stop taking PDE5 inhibitors, including VIAGRA, and call a doctor right away.

VIAGRA should not be used with other ED treatments. VIAGRA should not be used with REVATIO or other products containing sildenafil.

VIAGRA does not protect against sexually transmitted diseases, including HIV.

The most common side effects of VIAGRA are headache, facial flushing, and upset stomach. Less commonly, bluish vision, blurred vision, or sensitivity to light may briefly occur.

Please see Important Facts for VIAGRA on the following page or visit viagra.com for full prescribing information.

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IMPORTANT FACTS

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Never take VIAGRA if you take any medicines with nitrates. This includes nitroglycerin. Your blood pressure could drop quickly. It could fall to an unsafe or life-threatening level.

ABOUT ERECTILE DYSFUNCTION (ED)

Erectile dysfunction means a man cannot get or keep an erection. Health problems, injury, or side effects of drugs may cause ED. The cause may not be known.

ABOUT VIAGRA

VIAGRA is used to treat ED in men. When you want to have sex, VIAGRA can help you get and keep an erection when you are sexually excited. You cannot get an erection just by taking the pill. Only your doctor can prescribe VIAGRA.

VIAGRA does not cure ED.

VIAGRA does not protect you or your partner from STDs (sexually transmitted diseases) or HIV. You will need to use a condom.

VIAGRA is not a hormone or an aphrodisiac.

WHO IS VIAGRA FOR?

Who should take VIAGRA?

Men who have ED and whose heart is healthy enough for sex.

Who should NOT take VIAGRA?

- If you ever take medicines with nitrates:
  - Medicines that treat chest pain (angina), such as nitroglycerin or isosorbide mononitrate or dinitrate
- If you use some street drugs, such as "poppers" (amyl nitrate or nitrite)
- If you are allergic to anything in the VIAGRA tablet

BEFORE YOU START VIAGRA

Tell your doctor if you have or ever had:

- Heart attack, abnormal heartbeats, or stroke
- Heart problems, such as heart failure, chest pain, angina, or aortic valve narrowing
- Low or high blood pressure
- Severe vision loss
- An eye condition called retinitis pigmentosa
- Kidney or liver problems
- Blood problems, such as sickle cell anemia or leukemia
- A deformed penis, Peyronie's disease, or an erection that lasted more than 4 hours
- Stomach ulcers or any kind of bleeding problems

Tell your doctor about all your medicines. Include over-the-counter medicines, vitamins, and herbal products. Tell your doctor if you take or use:

- Medicines called alpha-blockers to treat high blood pressure or prostate problems. Your blood pressure could suddenly get too low. You could get dizzy or faint. Your doctor may start you on a lower dose of VIAGRA.
- Medicines called protease inhibitors for HIV. Your doctor may prescribe a 25 mg dose. Your doctor may limit VIAGRA to 25 mg in a 48-hour period.
- Other methods to cause erections. These include pills, injections, implants, or pumps.
- A medicine called REVATIO. VIAGRA should not be used with REVATIO as REVATIO contains sildenafil, the same medicine found in VIAGRA.

POSSIBLE SIDE EFFECTS OF VIAGRA

Side effects are mostly mild to moderate. They usually go away after a few hours. Some of these are more likely to happen with higher doses.

The most common side effects are:

- Headache
- Feeling flushed
- Upset stomach

Less common side effects are:

- Trouble telling blue and green apart or seeing a blue tinge on things
- Eyes being more sensitive to light
- Blurred vision

Rarely, a small number of men taking VIAGRA have reported these serious events:

- Having an erection that lasts more than 4 hours. If the erection is not treated right away, long-term loss of potency could occur.
- Sudden decrease or loss of sight in one or both eyes. We do not know if these events are caused by VIAGRA and medicines like it or caused by other factors. They may be caused by conditions like high blood pressure or diabetes. If you have sudden vision changes, stop using VIAGRA and all medicines like it. Call your doctor right away.
- Sudden decrease or loss of hearing. We do not know if these events are caused by VIAGRA and medicines like it or caused by other factors. If you have sudden hearing changes, stop using VIAGRA and all medicines like it. Call your doctor right away.
- Heart attack, stroke, irregular heartbeats, and death. We do not know whether these events are caused by VIAGRA or caused by other factors. Most of these happened in men who already had heart problems.

If you have any of these problems, stop VIAGRA. Call your doctor right away.

HOW TO TAKE VIAGRA

Do:

- Take VIAGRA only the way your doctor tells you. VIAGRA comes in 25 mg, 50 mg, and 100 mg tablets. Your doctor will tell you how much to take.
- If you are over 65 or have serious liver or kidney problems, your doctor may start you at the lowest dose (25 mg).
- Take VIAGRA about 1 hour before you want to have sex. VIAGRA starts to work in about 30 minutes when you are sexually excited. VIAGRA lasts up to 4 hours.

Don't:

- Do not take VIAGRA more than once a day.
- Do not take more VIAGRA than your doctor tells you. If you think you need more VIAGRA, talk with your doctor.
- Do not start or stop any other medicines before checking with your doctor.

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WHAT IS IT?

COURTESY OF MELANIE MIKOSCH AND THOMAS HOLSTEIN *Center for Organismal Studies, Heidelberg University*

Some of us age more gracefully than others, but perhaps no animal group does it better than the tiny freshwater polyps known as hydras. In 1998 one biologist ventured that the tentacled creatures, by continually renewing their own cells, may stave off aging altogether to achieve a kind of biological immortality.

More recently, the species *Hydra magnipapillata* was one of a few dozen organisms included in a study of aging diversity. Whereas female fertility in humans spikes early, then tapers off, and mortality rises sharply as we age, plenty of organisms follow a different path. The water flea, for example, experiences fluctuations in fertility throughout its life span and a more gradual rise in mortality. But the hydra takes the prize for life-cycle oddity. The polyp's mortality appears to remain low for an indefinite period, the researchers reported in *Nature*. (*Scientific American* is part of Nature Publishing Group.) In a controlled laboratory setting, they estimated that 5 percent of a hydra population would still be alive after 1,400 years. —*Rachel Feltman*

MATHEMATICS

The Traffic Effect

A rule of urban expansion could guide smarter growth

Most of the world's cities started from an important marketplace or town square. Over time, they developed multiple centers where people could work, shop and play. But why? Some economists have suggested that cities fragment because of agglomeration—businesses that spring up in clusters increase their chances of success.

Yet physicists have arrived at a slightly different explanation: traffic jams. Marc Barthelemy and Rémi Louf, both at the Institute of Theoretical Physics in France, designed a mathematical model to explain how cities and their surrounding suburbs evolve. Their research suggests that as a city grows and congested roadways make it increasingly difficult to get to the center, subcenters emerge along the outskirts. "It's an interplay between how attractive the place is and how much time it takes to go there," Barthelemy says. Cities with accommodating transportation networks remain centralized longer, he adds.

The physicists validated their ideas using data from 9,000 U.S. cities and towns of different sizes.

A better understanding of how metropolitan areas evolve could prove useful, considering that two thirds of the world's population is expected to live in urban areas by 2050, notes David Levinson, a transportation engineer at the University of Minnesota. "There's a lot of urbanization left to happen," Levinson says. "If planners imagine a city to take a particular form, but that's not the way the city wants to behave, we'll be making unwise investments."

Barthelemy believes the model could also come in handy for estimating traffic delays, gas consumption and carbon dioxide emissions. "I think that this opens up the path to some really quantitative insights about cities," he says. "We can take simple mechanisms, simple ingredients, and in the end predict how important properties are scaling with population." —*Sarah Fecht*

CONSERVATION

Tusk to Dust

Why the U.S. destroyed a multimillion-dollar stockpile of illegal ivory

On a clear November day outside Denver, dust filled the air as an industrial rock crusher pulverized nearly six tons of confiscated elephant ivory. Loader trucks dumped batch after batch of whole tusks, carved figurines, bracelets and other baubles into the giant blue crusher, which spat out a stream of fragments that looked like bits of seashell.

The U.S. Fish and Wildlife Service destroyed the 25-year stash of ivory seizures—worth perhaps $12 million on the black market—to signal to the world that the U.S. will not tolerate elephant poaching or wildlife crime in general. Even though international commercial trade in ivory has been outlawed since 1989, poachers continue to kill African elephants for their tusks—one every 15 minutes. At that rate, the animals could be extinct in the wild within decades.

Authorities are concerned not just with the volume of the ivory trade but with whom is doing the killing. Today's poaching crisis is the work of transnational criminal syndicates that traffic in wildlife just as they traffic in humans, drugs and arms. Profits from the illegal sale of ivory, rhinoceros horn and other wildlife products—a $19-billion-a-year industry—are now known to fund terrorist and other extremist groups. The countries that harbor wild elephants rarely have the resources to counter such foes.

Whether the destruction of ivory stockpiles will actually help stamp out the trade is a matter of some debate. Critics contend that by reducing the ivory supply, such actions may drive up the price and thus stimulate even more poaching.

Yet past attempts to do the opposite by flooding the market with ivory have backfired and driven more poaching, says Peter Knights of WildAid, a nongovernmental organization based in San Francisco. "I think we have to look at history, and we have to learn this lesson," Knights asserts, likening criminal wildlife trafficking to the drug trade. "We don't put heroin back on the market when we seize it."

—*Kate Wong*

Travel expenses to attend the ivory crush were paid in part by the International Fund for Animal Welfare and the World Wildlife Fund.

ED ANDRIESKI AP Photo

COMMENT AT ScientificAmerican.com/feb2014

CHEMISTRY

Atomic Revelation

Extreme conditions yield exotic molecules

Many of us learned in high school chemistry that the electrons around an atomic nucleus occupy different energy levels. The low-energy levels are known as the inner electron shells, and the highest-energy level forms the outer shell. Chemical bonds, we were told, form only when atoms share or exchange electrons in their outermost shells.

But a chemist may have found a loophole in that familiar rule of bonding. Under very high pressures, it appears, electrons in the atom's inner shells can also take part in chemical bonds.

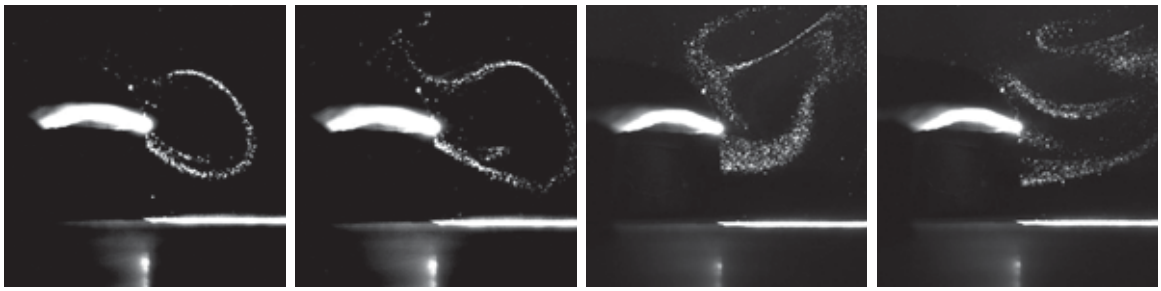
"It breaks our doctrine that the inner-shell electrons never react, never enter the chemistry domain," says Mao-sheng Miao, a chemist at the University of California, Santa Barbara, and the Beijing Computational Science Research Center in China. Miao's calculations show that under extreme pressures cesium and fluorine atoms can form exotic molecules with inner-shell bonds.

Ordinarily the atoms form relatively simple bonds. Cesium, an alkali metal, has a lone, so-called valence electron in its outer shell. The halogen gas fluorine, on the other hand, is one electron short of a full outer shell—a perfect match for an atom such as cesium that has an electron to give.

But Miao identified two molecules that, at high pressure, would involve cesium's inner electrons as well. To form cesium trifluoride (CsF_3), a cesium atom would share its single valence electron and two inner-shell electrons with three fluorine atoms. Four inner electrons would go into making cesium pentafluoride (CsF_5). "That forms a very beautiful molecule, like a starfish," Miao says. He reported his findings in *Nature Chemistry*. (*Scientific American* is part of Nature Publishing Group.) Both the shape of the resulting molecules and the possibility of their formation are "very surprising," says Nobel Prize–winning chemist Roald Hoffmann, a professor emeritus at Cornell University.

—Clara Moskowitz

Illustrations by Thomas Fuchs



COURTESY OF EMILIE DRESSAIRE *Trinity College* AND MARCUS ROPER *University of California, Los Angeles*

BIOLOGY

Mushroom Magic

Some fungi generate their own airflow to distribute spores

Within biology, mushrooms have sometimes been written off as uncomplicated organs that simply produce as many spores as possible. How far those spores traveled across a landscape, researchers assumed, depended on the whims of the wind. As scientists look closer, however, a more complex picture is emerging.

"Mushrooms are really the dark matter of biology," says Marcus Roper, a mathematician at the University of California, Los Angeles. "They're everywhere, but they're horribly understudied."

Roper and his colleagues used high-speed videography and mathematical analysis to investigate how spores dispersed, even in the absence of wind. In fact, as the researchers announced at a recent meeting of the American Physical Society's Division of Fluid Dynamics, the mushrooms themselves manufacture air currents.

The trick that mushrooms employ to stir things up is known as evaporative cooling. Small water droplets, which appear on mushrooms just before spore dispersal, evaporate and create enough vapor to lift and actively spread the spores.

The new finding "deepens our appreciation of the hidden complexities of the humble mushroom," says Nicholas Money, a biologist at Miami University in Ohio. "This is a beautiful example of ancient evolutionary engineering." —*Rachel Nuwer*

PHYSICS

Instant Weirdness—Just Add Water

Friction between tiny particles explains the bizarre properties of cornstarch in fluid

Cornstarch mixed with a little water is peculiar stuff. At first glance it seems like any other liquid—you can pour it from one bowl to another or dip your hands in it. But give it a squeeze or strike the surface of the fluid with a hard blow, and the cornstarch slurry suddenly firms up—you can roll it into balls, walk on it and even bounce on it.

Vigorously stirring the mixture will also turn it nearly to stone. Yale University physicist Eric Brown is fond of demonstrating the weirdness of cornstarch and water, sometimes called Oobleck, by mixing them together with a metal shaft. Stir forcefully enough, he says, and he can actually break the rod. Stranger still, the transition is reversible: ease up on the stirring, and what seemed solid turns right back to liquid.

Physicists long struggled to fully account for the rapid liquid-to-solid shift, known as shear thickening. Eventually, in 2003, a team of French experimenters saw the first hints that shear thickening is the by-product of friction between the particles.

More recently, researchers have confirmed that view with detailed simulations of particle interactions. At low starch concentrations, the liquid lubricates the particles, allowing them to move more or less freely, says co-author Jeffrey Morris, a professor of chemical engineering at the City University of New York who co-authored a new study on the phenomenon in *Physical Review Letters*. Even with more particles, water still "has that nearly perfect lubricating role," Morris says, until someone starts stirring a little too hard. The extra force slams suspended particles together, and their rough surfaces prevent particles from sliding past one another. Instead they form long, rigid chains held together by friction, which give shear-thickened fluids their near-solid feel, says lead study author Ryohei Seto, also at C.U.N.Y.

"Shear thickening is remarkable," Morris says, noting that it took countless experiments and theoretical studies to answer "a basic question" in physics. Many more questions remain, Brown says. It is not yet clear, for instance, whether the same microscopic interactions responsible for shear thickening also account for Oobleck's impact resistance. —*Nathan Collins*

Make Oobleck at home: ScientificAmerican.com/article.cfm?id=oobleck-bring-science-home

Q&A

The DNA Sketch Artist

A biologist aims to profile suspects from genetic material left at crime scenes

We have heard about DNA being used as evidence in court. What else can genetics do for forensics?
One of my main interests is in using DNA to predict appearance traits. I combine fundamental research on the genetics of human appearance with applied research such as forensic DNA phenotyping, which is using the prediction of appearance from DNA as a tool in police investigations.

Your latest study focused on stature. How well can you predict a suspect's height from DNA?
We were able to predict extreme height, which is those in the upper 3 percent, with an accuracy of 0.75, where 0.5 is random and 1 is a perfect indicator.

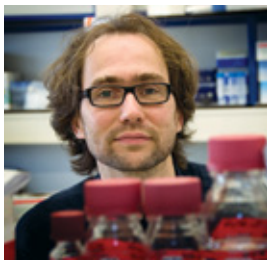
Are there physical traits you can recover more reliably?
The accuracy for human eye and hair color is much higher at 0.9, and chronological age—based on T cell receptors—is the same. But everything else we've looked at is actually much lower than our height accuracy.

PROFILE

NAME
Manfred Kayser

TITLE
Professor of forensic molecular biology

LOCATION
Erasmus University Rotterdam, the Netherlands



What other attributes might be predictable from genetic material?
Skin color is almost certainly next. You can do this now to some degree, mostly by working with ancestry markers, but there are of course variations. Face shape, which would be the holy grail, is in the distant future—we've only found the first five genes, and the effects of those genes are very small. There must be hundreds of genes that affect the face.

Artist Heather Dewey-Hagborg recently made 3-D portraits from DNA she found. Is it possible to make such portraits accurately?
I do believe it's possible in the long term. What I didn't like about her work is that it mixed things that are possible—hair and eye color—with things we can't predict yet, like facial shape, and things we can't predict for certain, like skin color. For these traits she used her artistic skills, and they had nothing to do with science or genetics. —*Rachel Feltman*

BY THE NUMBERS

23%

Online daters who have found a spouse or long-term partner through a dating site or app.

COURTESY OF MANFRED KAYSER (*top*); SOURCE: "ONLINE DATING & RELATIONSHIPS," BY AARON SMITH AND MAEVE DUGGAN. PEW INTERNET & AMERICAN LIFE PROJECT, OCTOBER 21, 2013 *www.pewinternet.org/Reports/2013/Online-Dating.aspx (bottom)*

ZOOLOGY

Living Claw to Mouth

A massive avian-tracking program reveals how songbirds survive winter

YOKU MISHIMA *Corbis*

They say that the early bird catches the worm. The truth, of course, is a bit more complicated.

Garden songbirds have one task during the winter, which is to survive long enough to breed during the spring and summer. Small birds can lose up to 10 percent of their body weight in a single night, so they need to eat well every day. But if they pack on too much weight, they might slow down, leaving them vulnerable to predators such as the sparrow hawk.

Researchers at the University of Oxford attached microchips to more than 2,000 songbirds to track the birds' movements. By outfitting an array of feeding stations with microchip detectors and moving some of the feeders every day, the researchers were able to infer how the birds found their meals.

Every morning the birds leave their nests and scout, assessing the quality and location of each food source without actually dining. By fasting in the morning, they remain nimble enough to dodge predators during the daylight hours. As the afternoon wears on, armed with knowledge about where to find food, the birds return to eat, the researchers recently reported in *Biology Letters*.

The new experiment represents one of the first attempts to investigate how wild songbirds negotiate the competing challenges of feeding enough without becoming a tasty morsel themselves. "Almost all previous studies are either theoretical models or work done in captivity," says Damien Farine, who led the experiment when he was a graduate student at Oxford.

Similar microchipping schemes will allow researchers to explore further questions about disease transmission among birds, as well as their social networks and cognitive abilities, says Ron Ydenberg, director of the Center for Wildlife Ecology at Simon Fraser University in British Columbia. "These kinds of analyses seemed impossibly complex when I was a graduate student 30 years ago," he adds.

—Jason G. Goldman

ENERGY

Solar on Demand

Cheap energy from sunlight could displace kerosene in African villages

In rural sub-Saharan Africa, only one in six people has access to electricity. Kerosene lamps provide a primary light source in many households—at a cost to both health and wealth. A villager in Kenya or Rwanda pays dozens of times more for kerosene than an American spends on grid electricity for a comparable amount of lighting. Charging a mobile phone at a kiosk is even more expensive. "The poorest people in the world are not just paying a bit more for their energy; they're paying a disproportionate amount," says Simon Bransfield-Garth, CEO of Azuri Technologies, a solar services firm based in Cambridge, England. Kerosene lamps also pollute the air, and the fuel poses a poisoning hazard, especially to children.

Solar kits for lighting and charging batteries are a promising alternative, but many rural families cannot afford the upfront cost of $50 or more. So Azuri and several other firms sell solar kits on a pay-as-you-go plan, which drives down the customer's initial investment to around $10. Families then pay for energy when they need it or when they can (say, after a successful harvest). After the solar kit is paid off, any subsequent electricity is free.

The idea is gaining steam. Azuri counts more than 21,000 solar customers. M-KOPA Solar, which builds on the widespread M-Pesa mobile payment network, serves 40,000 households. And U.S.-based Angaza Design is on track to reach 10,000 customers in the next year or so.

Scaling the technology to even more households could prove challenging. Some start-ups are running into limits of capital as they await reimbursement from new customers. The cash-flow constraints only intensify when customers default.

Still, the rollout may offer important lessons for the rest of the world. "There are all these debates about when solar will reach grid parity in the U.S. and elsewhere," says Bryan Silverthorn, chief technology officer for Angaza. "Africa is a place where, for a huge swath of the population, solar energy is now the cheapest option. No one knows what will happen next."

—David Wogan

BY THE NUMBERS

1 in 6

Number of recent daters who have received a breakup text, e-mail or online message, including nearly one in 10 daters over the age of 50.

GETTY IMAGES (*top*); SOURCE: "ONLINE DATING & RELATIONSHIPS," BY AARON SMITH AND MAEVE DUGGAN. PEW INTERNET & AMERICAN LIFE PROJECT, OCTOBER 21, 2013 *www.pewinternet.org/Reports/2013/Online-Dating.aspx (bottom)*

COMMENT AT ScientificAmerican.com/feb2014

FOOD SCIENCE

80 Proof, Zero Gluten

New labeling guidelines let liquor manufacturers in on the gluten-free trend

DMITRY KUDRYAVTSEV *Getty Images*

Here's a new twist on an old drink: gluten-free hard liquor. Vodkas marketed as "gluten-free" hit the market last year, after a 2012 interim ruling by the Alcohol and Tobacco Tax and Trade Bureau (TTB) opened the door to such labels.

The labeling allows liquor companies to join a burgeoning industry of gluten-free products. The gluten protein, which is found in wheat, barley and rye, causes severe gastrointestinal symptoms in the roughly three million Americans suffering from celiac disease. Gluten-free diets have also become popular with other consumers.

Vodka and other pure spirits have long been white-listed for sufferers of celiac disease, even in the absence of labels. The Academy of Nutrition and Dietetics has advised that distilled spirits are gluten-free unless a flavoring or other additive has been added to the liquor. During distillation, heat vaporizes the alcohol to remove it from the mixture, leaving proteins behind. "Distilled spirits, because of the distillation process, should contain no detectable gluten residues," says Steve Taylor, co-director of the University of Nebraska–Lincoln's Food Allergy Research and Resource Program.

Nevertheless, the makers of Blue Ice Vodka say that celiac sufferers frequently request gluten information for their products. The brand's potato vodka received gluten-free labeling in May 2013. "With the celiac and gluten-free products becoming more accessible, why not go through the process of proving we were gluten-free to TTB?" asks Thomas Gibson, chief operating officer for 21st Century Spirits, Blue Ice's parent company.

Vodka won't be the last product to don the "gluten-free" badge. Food-labeling guidelines released by the FDA last year allow even foods that never had gluten, such as vegetables, fruits, eggs and bottled water, to be labeled as gluten-free. —*Fred Minnick*

ENGINEERING

Mixology Micromachines

Inspired by nature, scientists and chefs team up to design culinary wonders

Finding a bug in your drink is no one's idea of a pleasant surprise. But a renowned chef and a team from the Massachusetts Institute of Technology hope that a fanciful cocktail accessory modeled after an aquatic insect will delight rather than repulse.

The tiny, boat-shaped gadget propels itself around the surface of a beverage for up to two minutes using a trick borrowed from nature. The boat contains a potent liquor, which it steadily dispenses into the cocktail through a notch at one end. The difference in alcohol content between the two liquids creates a gradient in surface tension, propelling the boat forward via a phenomenon called the Marangoni effect. Many aquatic insects rely on Marangoni propulsion—but instead of spewing Bacardi 151, they release chemicals that modify the surface tension underfoot.

The gizmo came into being after M.I.T. applied mathematics professor John Bush attended a talk by chef José Andrés, who lectures on the science of cooking at Harvard University. Bush suggested that they collaborate on novel culinary designs. "Much of my research concerns surface tension," Bush says, "which is responsible for a number of interesting effects that arise in the kitchen—or the bar."

The researchers also designed a flowerlike pipette that a diner can dip into a palate-cleansing cocktail to carry a droplet to his or her tongue. The pipettes fold their petals shut when pulled out of the liquid, trapping a droplet inside. The device inverts the design of floating flowers such as water lilies that close up to trap a pocket of air when water levels rise. Bush, Andrés and their colleagues described the designs in the journal *Bioinspiration & Biomimetics*.

Using a 3-D printer, the researchers prototyped the gadgets and then produced molds so that Andrés and his team could make boats and pipettes out of gelatin or candy. "The designs are to be not only functional and aesthetically pleasing but edible," Bush says. —*Rachel Feltman*

PHOTOGRAPH BY NICKE WILTSE; COURTESY OF JOHN BUSH *Massachusetts Institute of Technology*

COMMENT AT ScientificAmerican.com/feb2014

TECHNOLOGY

Gadgets for Gramps

Smart, networked devices around the home could help the elderly remain independent

Early adopters of technology are usually assumed to be the young and eager. But an increasing number of gadgets are designed not for the stereotypical technophile but for the elderly person. And why not? Between 2010 and 2050 the U.S. population of people aged 65 and up will more than double, the U.S. Census Bureau predicts.

Smart, networked sensors and monitors—part of what is known as the Internet of Things—could help make seniors more independent by letting doctors or relatives keep tabs from afar. "We have received significant interest from elder care providers who are seeking to keep the elderly in their homes rather than moving them to assisted-living centers," says technologist Jason Johnson, chair of the Internet of Things Consortium. The market for remote patient monitoring is expected to grow from $10.6 billion in 2012 to $21.2 billion in 2017, according to research firm Kalorama Information.

Among the new systems to enter the market is a set of sensors called Lively. The sensors can be placed on cabinets, drawers or appliances to track activity patterns and send data to loved ones.

Other technologies have a slightly different aim—to help those who live in senior communities remain in the most independent setting possible. The eNeighbor remote-monitoring system, marketed by Healthsense, uses sensors throughout the residence to detect motion (including falls) and to chart bed rest. eNeighbor can also provide reminders for medication or make distress calls in case of an emergency.

The fear of being put in a nursing home is "the number-one thing people cite about growing old," Lively CEO Iggy Fanlo says. But with assistive technology for the home taking off, seniors may be able to live on their own for longer than they thought.

—*Alison Bruzek*

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

The Curse of the Cloud

Online services are no longer optional. So who's in control of your data?

At one point, the phrase "in the cloud" probably meant something useful and specific. These days, though, it has just become a buzzy marketing term for "the Internet." "Your files are safely stored in the cloud!" "You can send video messages through the cloud!" "You can order books from the cloud!"

You mean the Internet? Oh.

Internet services such as these have become essential elements in the Apple, Google and Microsoft ecosystems. Have an iPhone? Then you have a big incentive to get a Mac and an iPad, too—because Apple's free iCloud service will make sure that your calendar, address book, e-mail, to-do list, notes and passwords are magically synced with all your Apple gadgets.

Have an Android phone? You'll want to stick with Google's Web browser, tablets and laptops for the same reason. Microsoft, too, has automatic syncing among Windows computers and phones and the Web.

If you take the bait and marry into one company's ecosystem, great! You enjoy astonishing convenience—free. And if this "in the cloud" stuff makes you a little nervous, no problem! You can opt out and confine your data's location to your own zip code.

At least that's the way it used to be.

Lately, the big tech companies have been quietly removing the option for you to keep your data to yourself.

Here's a startling example: Did you know that you can no longer sync your computer's calendar or address book with your Apple phone or tablet over a cable? Starting with this year's version of the Mac operating system, Mavericks, you can sync them only wirelessly—and only through an iCloud account.

Something similar is going on with Microsoft. In Windows 8 and 8.1, you can log on to your PC with either a local account (your name and password are stored on the PC) or a Microsoft account (they're online, like in iCloud). A Microsoft account automatically syncs your familiar settings, bookmarks, and Facebook and Twitter account information with any Windows 8 computer you use.

But Microsoft tries hard to make you feel like a loser if you choose the local account. ("Not recommended," the screen tells you ominously.) Many features aren't available or convenient without a Microsoft account: your SkyDrive, your photographs, the built-in Music app—in fact, you can't download any apps from the Windows store.

Online accounts are handy, but they're also imperfect. If you have an iPhone 3G, you can't connect to iCloud. If you're traveling out of Internet range, no syncing can take place.

There's an economic issue, too. The more data you're shuttling to and from the cloud, the faster you eat up your monthly Internet service allotment.

These cloud services keep your personal information perpetually backed up—another plus. Yet your hard drive isn't the only one that can die. From time to time, those big online services go down, too—Gmail has gone dark, Amazon services have crashed—and at that point, you can't get to your own stuff.

Above all, there's fear. You're no longer in possession of your own data. You're making them available, at least in theory, to Apple, or Google, or Microsoft. Or the National Security Agency. Or to a hacker. All it takes is one teenager, somewhere—anywhere—guessing your Hotmail password, and suddenly you're locked out of your own PC.

The big computer companies are quietly, slowly forcing us to entrust our life's data to them. That's a scary and dangerous development.

In fact, it may be that "in the cloud" really isn't the best term for the services these companies offer. What they really want is to have us "on the leash." SA

SCIENTIFIC AMERICAN ONLINE
When the cloud goes dark: ScientificAmerican.com/feb2014/pogue

Illustration by Brian Edward Miller

Roxanne Khamsi is chief news editor at *Nature Medicine*. She has written for *New Scientist*, the *Economist* and *Wired News*. Follow her on Twitter at @rkhamsi

The Trouble with Gluten

Gluten may not be the only wheat protein that can make people sick

Two years ago, at the recommendation of a nutritionist, I stopped eating wheat and a few other grains. Within a matter of days the disabling headaches and fatigue that I had been suffering for months vanished. Initially my gastroenterologist interpreted this resolution of my symptoms as a sign that I perhaps suffered from celiac disease, a peculiar disorder in which the immune system attacks a bundle of proteins found in wheat, barley and rye that are collectively referred to as gluten. The misdirected assault ravages and inflames the small intestine, interfering with the absorption of vital nutrients and thereby causing bloating, diarrhea, headaches, tiredness and, in rare cases, death. Yet several tests for celiac disease had come back negative. Rather my doctors concluded that I had nonceliac "gluten sensitivity," a relatively new diagnosis. The prevalence of gluten sensitivity is not yet clear, but some data suggest it may afflict as many as 6 percent of Americans, six times the number of people with celiac disease.

Although gluten sensitivity and celiac disease share many symptoms, the former is generally less severe. Compared with individuals with celiac disease, people with gluten sensitivity are more likely to report nondigestive symptoms such as headaches and do not usually suffer acute intestinal damage and inflammation. Lately, however, some researchers are wondering if they were too quick to pin all the blame for these problems on gluten. A handful of new studies suggest that in many cases gluten sensitivity might not be about gluten at all. Rather it may be a misnomer for a range of different illnesses triggered by distinct molecules in wheat and other grains.

"You know the story of the blind man and the elephant? Well, that's what gluten-sensitivity research is right now," says Sheila Crowe, head of research at the gastroenterology division at the School of Medicine at the University of California, San Diego. As doctors continue to tease apart the diverse ways that the human body reacts to all the proteins and other molecules besides gluten that are found in grains, they will be able to develop more accurate tests for various sensitivities to those compounds. Ultimately clinicians hope such tests will help people who have a genuine medical condition to avoid the specific constituents of grains that make them ill and will stop others from unnecessarily cutting out nutrient-dense whole grains.

SEEDS OF SICKNESS

AMONG THE MOST COMMONLY CONSUMED GRAINS, wheat is the chief troublemaker. Humans first domesticated the wheat plant about 10,000 years ago in the Fertile Crescent in the Middle East. Since then, the amount of wheat in our diet—along with all the molecules it contains—has dramatically increased. Of all these molecules, gluten is arguably the most important to the quality of bread because it gives baked goods their structure, texture and elasticity. When bakers add water to wheat flour and begin to knead it into dough, two smaller proteins—gliadin and glutenin—change shape and bind to each other, forming long, elastic loops of what we call gluten. The more gluten in the flour, the more the dough will stretch and the spongier it will be once baked.

Until the Middle Ages, the types of grain that people cultivated contained far smaller amounts of gluten than the crops we grow today. In the following centuries—even before people understood what gluten was—they selectively bred varieties of wheat that produced bread that was lighter and chewier, inexorably increasing consumption of the protein. As technology for breeding and farming wheat improved, Americans began to produce and eat more wheat overall. Today the average person in the U.S. eats around 132 pounds of wheat a year—often in the form of bread, cereal, crackers, pasta, cookies and cakes—which translates to about 0.8 ounce of gluten each day.

Although historical records dating from the first century A.D. mention a disorder that sounds a lot like celiac disease, it was not until the mid-1900s that doctors realized the gluten in wheat

Illustration by Daniel Zalkus

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was to blame. During World War II, Dutch physician Willem-Karel Dicke documented a sharp drop in the number of deaths among children with the severest forms of celiac disease in parallel with a bread shortage. In a follow-up study, researchers removed different components of wheat from the diet of 10 children with the intestinal illness. Adding back gluten caused symptoms such as diarrhea to resurface, but reintroducing a different complex molecule found in wheat, namely starch, did not. Thus, gluten was shown to be responsible for celiac disease.

Later experiments by other researchers revealed which component of gluten provokes the immune system. When digested, gluten splits back into gliadin and glutenin. For reasons that remain unclear, the immune system of people with celiac disease treats gliadin in particular as though it were a dangerous invader.

For years doctors used diet to diagnose the gut disorder: if someone's symptoms disappeared on a gluten-free diet, then that person had celiac disease. Over time, however, clinicians developed more sophisticated ways to identify celiac disease, such as tests that look for immune system molecules known as antibodies that recognize and cling to gliadin. With the advent of such tests, clinicians soon discovered that some people who became mildly ill after eating bread and pasta did not in fact have celiac disease: biopsies revealed little or no intestinal damage, and blood tests failed to find the same antibodies associated with the disorder. In the process, the new condition became known as nonceliac gluten sensitivity.

Now several studies hint that so-called gluten sensitivity might not always be caused by gluten. In some cases, the problem may be entirely different proteins—or even some carbohydrates. "We're so used to dealing with gluten as the enemy, but it might actually be something else," says David Sanders, who teaches gastroenterology at the University of Sheffield in England. Joseph Murray, a gastroenterologist at the Mayo Clinic in Rochester, Minn., agrees: "I'm starting to feel more uncomfortable calling it nonceliac gluten sensitivity. I think it might be better to call it nonceliac wheat sensitivity."

AGAINST THE GRAIN

IF THE CULPRITS BEHIND CERTAIN INSTANCES of gluten sensitivity are, in fact, wheat constituents other than gluten, finding the right ones will be difficult. Wheat has six sets of chromosomes and a whopping 95,000 or so genes. In comparison, we humans have just two sets of chromosomes and about 20,000 genes. Genes code the instructions to build proteins, so more genes mean more proteins to sift through. Some initial experiments have spotlighted a few potential offenders, however.

In laboratory tests, wheat proteins known as amylase-trypsin inhibitors have stimulated immune cells in plastic wells to release inflammatory molecules called cytokines that can overexcite the immune system. Further tests showed that these wheat proteins provoked the same inflammatory response in mice. Likewise, in an Italian study, small concentrations of wheat germ agglutinin, a protein distinct from gluten, roused cytokines from human intestinal cells growing in a plastic well.

Preliminary research suggests that, in other cases, by-products of gluten digestion may be the problem. Breaking down gliadin and glutenin produces even shorter chains of amino acids—the building blocks of proteins—some of which may behave like morphine and other soporific opiates. Perhaps these molecules explain some of the lethargy exhibited by people who do not have celiac disease but are nonetheless sensitive to wheat, suggests Aristo Vojdani, chief executive officer of Immunosciences Lab in Los Angeles. In a small study by Vojdani and his colleagues, the blood of people classified as gluten-sensitive had higher levels of antibodies that recognize these gluten by-products than blood taken from healthy volunteers.

A final group of potential culprits belongs to a diverse family of carbohydrates such as fructans that are notorious for being difficult to digest. A failure to absorb these compounds into the blood may draw excess water into the digestive tract and agitate its resident bacteria. Because these resilient carbohydrates occur in all kinds of food—not just grains—a gluten-free or wheat-free diet will not necessarily solve anything if these molecules truly are to blame.

NO PIECE OF CAKE

DESPITE THE RECENT EVIDENCE that wheat sensitivities are more numerous and varied than previously realized, research has also revealed that many people who think they have such reactions do not. In a 2010 study, only 12 of 32 individuals who said they felt better on a diet that excluded gluten or other wheat proteins actually had an adverse reaction to those molecules. "Thus, about 60 percent of the patients underwent an elimination diet without any real reason," notes study author Antonio Carroccio of the University of Palermo in Italy.

Nevertheless, uncovering nongluten agitators of illness will give doctors a more precise way to diagnose grain sensitivities and help people avoid certain foods. Researchers could, for example, design blood tests to look for antibodies that bind to various short chains of amino acids or proteins such as wheat germ agglutinin, explains Umberto Volta, a gastroenterologist at the University of Bologna in Italy. And some scientists think ongoing research will eventually yield new therapies. "If we know what triggers the immune system, we hope we can switch the system off and cure the disease," says Roberto Chignola of the University of Verona in Italy.

Personally, I suspect that something besides gluten might trigger my own symptoms. On occasion, I have tried gluten-free grain-based products such as beer made from barley from which the gluten has been extracted. Every time my headaches came roaring back with a vengeance (far sooner than any hangover might have struck), making me all the more suspicious that gluten is not the root of my troubles.

If that is true, and there is even the remote possibility of safely reinstating gluten in my diet, I would really like to know. As a New Yorker, it is hard for me to forgo pizza. If gluten was vindicated in my case, perhaps I could add it to nongrain flours or otherwise cook up experimental pizza at home and get those gooey, stretchy slices out of my dreams and onto my plate. SA

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HEALTH TRAVEL 2.0

MORE OPTIONS ACROSS A WIDENING HORIZON

The growing popularity of seeking surgery or other medical procedures overseas has been fueled as of late by a confluence of evolving factors. In the US, it is no secret that health care costs have been steadily on the rise for years. A flurry of recent media coverage in major outlets, such as the *New York Times*, has cast in stark relief the cost inequities between the US and elsewhere for both simple and complex medical interventions.

In addition to this expanded awareness of lower cost health options beyond borders, travel and hotel accommodations are becoming cheaper and easier to find (and also catering specifically to the needs of medical travelers). Moreover, information technology is now deftly linking prospective patients to a range of health service providers, near and far, and empowering this population to circumvent the legacy medical system and find alternative choices in many different regions.

Like everything else in the commodities world, healthcare is going global. And the regions that will become leadership hubs on the new map of medical innovation are those that offer the greatest value proposition in terms of quality, affordability, specific expertise and an environment in which global travelers feel welcome. Indeed, the nations that will excel in attracting international health travelers are the ones that can deliver excellence on both fronts: in HEALTH and in TRAVEL.

A VIBRANT DESTINATION:
Malaysia's famous Petronas Twin Towers glimmer against the night skyline.

SPOTLIGHT: MALAYSIA

There is perhaps no better example of this value proposition than Malaysia. A culturally and geographically diverse nation, it is a destination known both for its natural beauty (where rugged mountains reach dramatically for the sky while their rainforest-clad slopes sweep down to floodplains teeming with forest life) as well as its fast developing economy. It is a warm and welcoming culture where an English-speaking class of professionals are transforming the health and technology sectors rapidly.

Unlike many other countries, Malaysia's government actively promotes its medical sector to foreign patients, and works to ensure a uniform safety and regulatory code for all hospitals and centers of care. The country offers specialties in various medical disciplines and performs some of the most complicated treatments in the world. Today, the medical practices in Malaysia are on par with some of the most acclaimed in the world, marrying cutting-edge infrastructure and state-of-the-art technology with international expertise. Malaysia's renowned healthcare specialists have been trained in some of the world's most esteemed medical institutions, including those in Australia, the United Kingdom and the US.

FROM ACCIDENTAL HEALTH TOURISM TO ADVOCACY

Not long ago Dale Van Demark, an attorney from Washington, DC, was visiting Malaysia and decided to tour the Batu Caves, a unique ancient limestone hill with caverns and Hindu temples that also houses a significant population of macaque monkeys. Van Demark, a partner at McDermott Will & Emery, a firm representing international health systems and hospitals, unexpectedly became a health tourist: "This one monkey seemed to not like the cut of my jib…(he) jumped on my back, and started biting my shoulder." While not too severe a bite (and while he learned from a physician friend in the country that rabies was not indigenous to Malaysia), Van Demark did check himself into a private hospital, where his wound was treated and he was given a regimen of antibiotics. "I found the service to be excellent," he says. "They were attentive and spent a lot of time with me." His hospital bill was equivalent to about US$75 for both care and medicine.

Van Demark's story underscores the way a lot of people first experience healthcare in a foreign country: by accident and by chance. These experiences, however, help to create the powerful word-of-mouth, first-person testimonials that drive grassroots awareness of a country's health system and turn these accidental health tourists into vocal advocates for a country's overall medical capabilities.

Van Demark recently noted that after his trip to Malaysia, he went on to Bangkok and while there did, as a precaution, begin rabies treatment, a regimen of five separately timed shots. He returned to the US, and had to complete his treatment there. He notes that just one shot for rabies in the US costs more than all the medical care he received while on his extended travels through Southeast Asia.

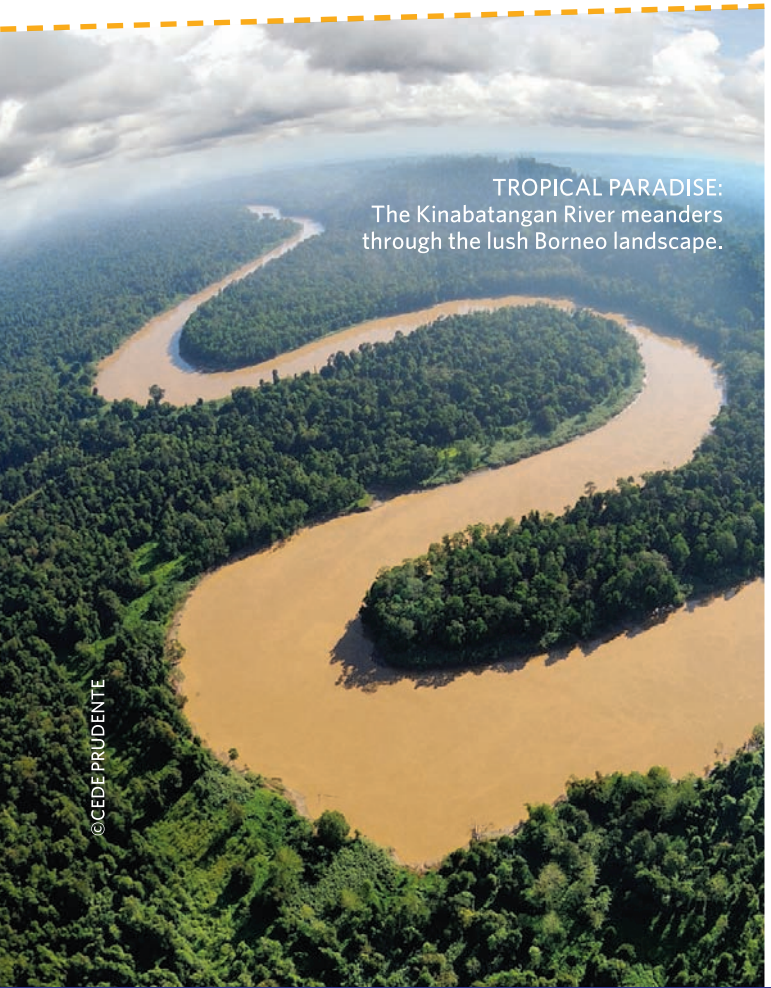
GOOD FOR INDIVIDUALS, GOOD FOR BUSINESS

It is not just the single prospective patient taking a closer look at health travel these days. Businesses and insurance companies in the West are eyeing the potential savings of sending employees across borders for medical treatment. In the mid-2000s, a *Washington Post* article on the topic quoted Arnold Milstein, then chief physician for New York–based Mercer Health & Benefits. He remarked that company-mandated medical travel is "just one of many ways in which our world is flattening…Many companies see it as a natural extension of the competition they've faced on other aspects of their business."

Until recently, the US market has been fairly immune to overseas competition, a significant reason why its health costs have been driven so high. Premiums for employer-sponsored coverage have surged approximately 80 percent from the year 2000 through 2010, and the total bill for family health coverage averages more than $12,000 annually.

The story of Kevin, an employer-sponsored patient from the US, is a prime example of how medical tourism can be cost effective. Companion Global Healthcare, a medical tourism facilitator, assisted Kevin in traveling to Kuala Lumpur to receive a total knee replacement. By choosing Ramsay Sime Darby over a typical US hospital, he saved his employer approximately $15,000 to $20,000, including travel costs. His company was able to cover the cost of business class airfare for Kevin and his wife, as well as their accommodations for the entire 12-day period, with his wife staying at the hotel the entire time and Kevin there for the first two days before being admitted to the hospital for surgery. After five days, Kevin was discharged and rejoined his wife at the hotel, where he continued his recovery while receiving daily physical therapy.

In 2012, there were 209 private hospitals in Malaysia, and that number is expected to increase to 239 by 2018.



TROPICAL PARADISE: The Kinabatangan River meanders through the lush Borneo landscape.

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THE MALAYSIAN ADVANTAGE: CULTURE, COMFORT & COMPETENCIES

Healthcare in Malaysia falls under the responsibility of the government's Ministry of Health. There exists a two-tier system consisting of both a government-run universal healthcare system and a co-existing private healthcare system. The Ministry has been very vocal in its efforts to assure that Malaysian citizens and foreign visitors have access to the best possible care the country can offer. More than most countries, Malaysia is very transparent in the data it collects on clinical outcomes, and has made it a stated goal to foster an environment where citizens and visitors can be assured of quality, safety and follow-up care.

A growing number of private hospitals offer expertise in medical fields such as cardiology, oncology, robotic surgery, fertility treatment, bariatric surgery, orthopedics, dental implants, ophthalmology, neurology and aesthetics procedures that include minimally invasive surgeries. Apart from being regulated by the Ministry of Health, in most cases these hospitals have internationally recognized accreditations from the Joint Commission International, which accredits healthcare organizations and programs in the US.

Because English is spoken everywhere in the country, and because the cultural "vibe" is one of warmth, friendliness and openness, foreign travelers immediately feel comfortable when stepping off the plane in Malaysia. These are critical components to maintaining and growing the Malaysian health travel market.

A HEALTH HUB ON THE GROW

Driven by rising affluence and increasing demand for quality healthcare, experts project that in the coming years medical tourism will be one of the top growth sectors in the Asia Pacific region. "The private hospital market size is forecast to grow close to US$5 million in 2016, at a compound annual growth rate of 18 percent during the period from 2011 to 2016," says Rhenu Bhuller, Asia Pacific vice president for healthcare at Frost & Sullivan, a business consulting firm. "[This is] due to the fact that new hospitals are expected to be completed within five years and investments that are being made in new areas like Iskandar."

During that same period, Malaysia's revenues from medical travel are predicted to triple. In 2011, the sector generated RM509.8 million (US$167 million), a number that Bhuller expects will soar to RM1.57 billion in 2016—registering a growth rate of 25.2 percent.

THE VISION OF MHTC

One of the many initiatives under the present government in boosting medical tourism is the establishment of the Malaysia Healthcare Travel Council (MHTC). this organization is a public-private sector corporation with the

New, minimally invasive surgical techniques are revolutionizing the patient experience.

objective of promoting Malaysia as the preferred healthcare and unique travel destination for world-class medical services in Asia.

MHTC has an important economic role to play. Malaysia is on track to reach its coveted developed nation status by 2020, and the economic value that healthcare brings to Malaysia is a major component of that success as well as one of the key performance indicators.

"Malaysia recorded more than 20 percent growth in health tourism over the past three years and it generated almost RM600 million in revenue alone last year," says Datuk Seri Najib Tun Razak, Malaysia's Prime Minister.

The positive growth, according to the Prime Minister, was due to MHTC's role in providing the technological platform for web-based medical and health-related information to a global audience.

Health tourism was identified as one of the country's National Key Economic Areas. In addition, it is seen to be a fueler of sustained economic growth and job creation and will attract more investment from outside Malaysia.

In October 2013, MHTC hosted its second **International Healthcare Travel Expo**, successfully bringing together the most influential global stakeholders in the field. This unique Expo, conducted in multiple languages, underscored the endless opportunities for collaboration in health travel, and served to enhance the reputation of the host region.

Malaysia will easily surpass its target of RM630 million earnings from medical tourism in 2013 from the rising number of patients.

MHTC cites an increase in medical tourists from 392,000 in 2010 to 671,000 in 2012. The council expects to receive 700,000 such patients in 2013.

CHANGING THE FACE OF SURGERY, MINIMALLY

Today, people are looking more and more to technology to satisfy their medical needs and experience faster care, while a decreasing number of patients choose conventional surgery. Demand for minimally invasive surgery, such as laser treatment and key-hole laparoscopic surgery, requiring only a one- or two-day stay, is on the rise. This is the way forward and Malaysia has an advantage in this field.

More than 80 percent of Malaysian surgeons are doing laparoscopic surgery already. "This is an area we need to highlight, as not that many people are aware of this," says Dr. Mary Wong Lai Lin, of the Malaysia Healthcare Travel Council. Less pain, less money, less scarring, is the best way to describe these relatively new procedures.

Obesity, the scourge of the 21st century, is an area that has been revolutionized by laparoscopic surgery. Dr. Cha Kar Huei, consultant bariatric and general surgeon at the Sime Darby Medical Centre, performs gastric banding using this minimally invasive technique.

Dr. Kan Choon Hong, consultant neurosurgeon at Pantai Hospital on the island of Penang, performs "neuronavigation," a type of minimally invasive brain surgery using technology similar to a global positioning system. And Dr. Selva Kumar, orthopedic surgeon at Global Doctors in Kuala Lumpur, feels that minimally invasive surgery has revolutionized the industry. "Keyhole to pinhole, performed with image intensifiers or x–ray guidance, affords the surgeon a clear all-round picture of the target location," Kumar says. These procedures employ cutting-edge surgical advances, and are better than open surgery."

Spine surgery is now safer, thanks to a new technique called XLIF, or Extreme Lateral Interbody Fusion, which is performed by Dr. Appasamy Velu, consultant orthopedic surgeon at the Sime Darby Medical Centre as well as the Sri Kota Medical Specialist Centre.

This innovative spinal surgery procedure is less invasive, has a quicker recovery period and requires less hospitalization. Normal activity is usually resumed within four to six weeks after surgery.

GETTING THERE

Without the right connections, many patients would not be able to benefit from the wealth of medical services available in Malaysia. Fortunately, a quick look at its airlines and airports reveals an expanding network on all fronts.

To better accommodate the influx of medical tourists, Kuala Lumpur International Airport will be inaugurating a new terminal (KLIA 2) in 2014, catering primarily to budget carriers. Its anchor tenant, Air Asia, has an expanding fleet well positioned to serve the cost-conscious market.

In addition the Sama Sama hotel (the only luxury hotel in the airport) is planning two hotels in the new KLIA 2 terminal, one of which will be in the transit zone. For medical tourists needing a stopover, the hotel will be forming special partnerships with some select hospitals in Kuala Lumpur.

Malaysia Airlines just recently joined the One World Alliance, which will facilitate connections from the US through its partnership with American Airlines. And for the latest in travel luxury, Qatar Airways provides excellent connectivity via its Doha hub, which offers flights to Kuala Lumpur from most world capitals three times a day. Its excellent US and European connecting times are the rival of other carriers. A quick online check found most American cities less than 24 hours hour away. As an example, one could leave New York at 11pm, arrive in Doha the following day at 6pm and have less than a two-hour connecting time before reboarding the Kuala Lumpur flight.

Other major hubs in Malaysia are Penang and Kota Kinabalu in Sabah, Borneo.

No matter where today's medical tourists may be traveling from—with so many quality options available—Malaysia is sure to provide them with a convenient and welcoming arrival.

FEELING GOOD, FLYING HIGH:

Healthy Travel from Soup to Nuts

Qatar Airways offers unique travel luxury.

There are many different reasons we travel. In fact, in the last few years, several distinct category terms have been introduced into the popular wanderlust lexicon: ecotourism, adventure travel, food travel, volunteer travel, and the list goes on and on. More than any other sub category, health travel (which includes journeys to seek either elective or critical medical procedures as well as other "softer" healthy pursuits, such as spas and relaxation centers) requires a very holistic "feel good" experience for the consumer. "Anxiety can run high in those that are pursuing medical care in other countries...thus, the total experience—from flight, to hotel stay, to recovery accommodations—needs to put the person at ease and make him or her feel comfortable," says Josef Woodman, CEO of Patients Beyond Borders.

The travel experience itself is many times just as important as the wellness or medical intervention that awaits upon landing. Peter Greenberg, travel editor for CBS, has said that the whole enterprise of medical health travel should be renamed "Hospitality Travel" because all of the factors in the journey are so inextricably linked. Airlines have taken notice, and many are addressing both the physical and mental wellness of their passengers.

Consider the unique approach that Qatar Airways takes to creating a truly remarkable passenger experience. The airline, one of the fastest growing carriers in the world and twice the recipient of the Skytrax Airline of the Year award, puts a heavy emphasis on hospitality and comfort. Its Business Class features signature 180-degree flatbed seats with a 78-inch pitch, a length of six feet four inches, a foot rest with eight in-seat massage settings and an in-seat power supply.

Hungry? Qatar's illustrious in-flight menu is created by a quartet of renowned chefs: Tom Aikens of London, Ramzi Choueiri, who specializes in Middle Eastern cuisine, Nobu Matsuhisa, a renowned master of Japanese fare, and Vineet Bhatia, the first Indian chef to receive a Michelin star. Simultaneously healthy, haute and delicious, it is 5-star dining close to the stars. Thirsty? Need a little of the grape to relax and better enjoy your food? Qatar's sommelier, James Cluer, a wine celebrity in his own right, has selected not only some of the finest vintages to pair with the menu, but actually performed a wine tasting atop Mt. Everest to see which varieties work well at high altitudes.

Well aware that the complete passenger experience must be addressed in every detail (from ease of check-in, to customer service needs and all of the in-flight options), Qatar Airways is poised to be a leader in health travel and every other category. The airline has developed a network of over 130 destinations, covering Europe, the Middle East, Africa, South Asia, Asia Pacific, North America and South America with a modern fleet of over 125 passenger and cargo aircraft.

From a global vantage point, it serves every region a wellness seeker might want to visit; for a traveler's experience, it is comfort soup to nuts.

PHYSICS

The Proton Radius Problem

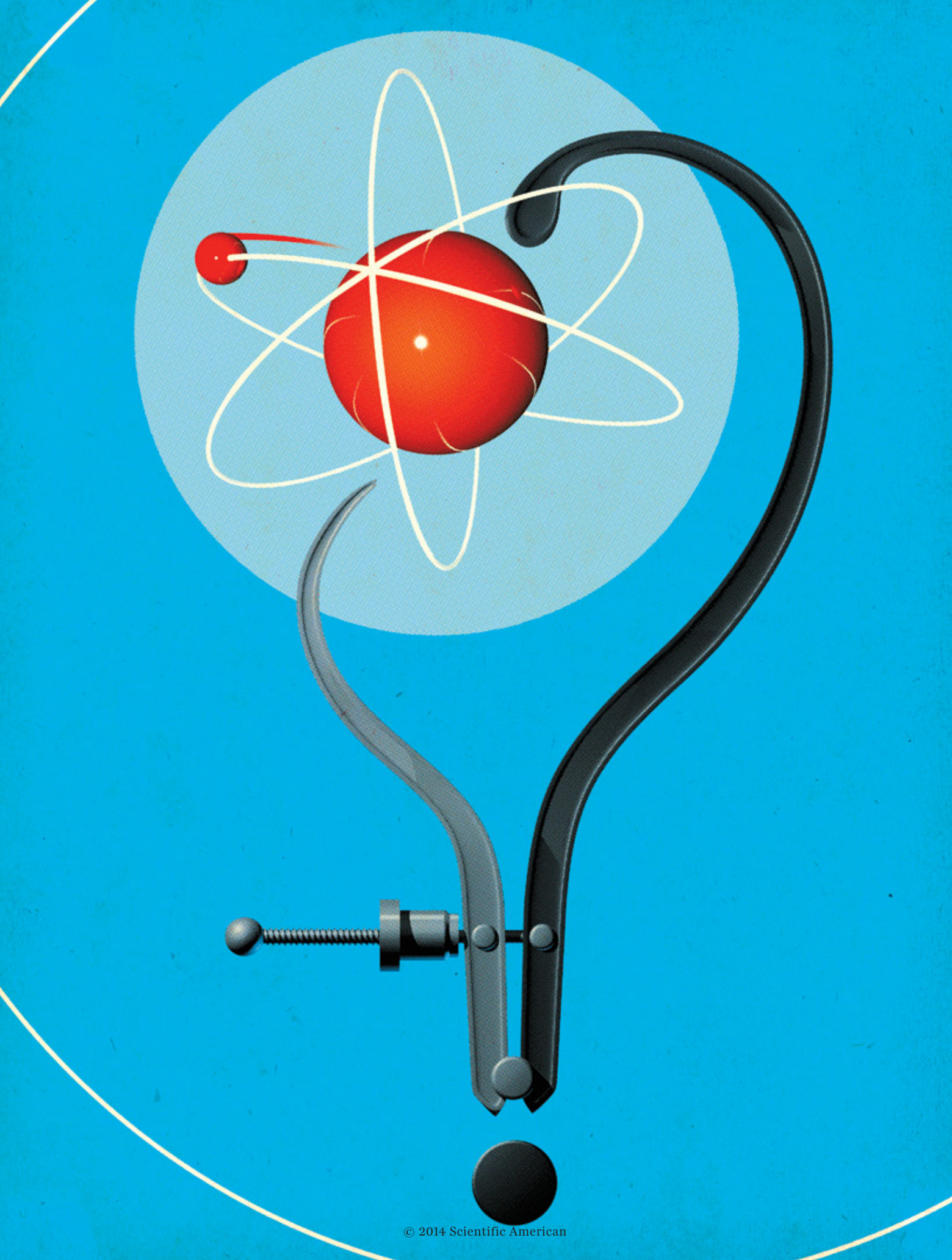
Two experiments have come up with two wildly different values for the proton's radius. What's going on?

By Jan C. Bernauer and Randolf Pohl

IN BRIEF

A new experiment to measure the proton radius has found it to be much smaller than expected.
The difference suggests that physicists do not understand something important about either the proton itself or the theory of quantum electrodynamics—until now the best-tested and best-understood theory in all of science.
With any luck, the anomaly could lead to a fundamental revision of the laws of physics.

Illustration by Tavis Coburn



Jan C. Bernauer is a postdoctoral researcher in nuclear physics in the Laboratory for Nuclear Science at the Massachusetts Institute of Technology.

Randolf Pohl works on laser spectroscopy of hydrogen and hydrogenlike exotic atoms at the Max Planck Institute of Quantum Optics in Garching, Germany.

YOU WOULD BE FORGIVEN FOR ASSUMING THAT WE UNDERSTAND THE PROTON.

It is, after all, the main constituent of matter in the observable universe, the fuel of stellar furnaces. Studies of the proton—its positive charge suitably bound up with a negatively charged electron to make a hydrogen atom—initiated the quantum-mechanical revolution a century ago. Today researchers trigger torrents of ultrahigh-energy proton collisions to conjure particle exotica such as the Higgs boson.

Yet recent studies of the proton have surprised us. The two of us (Bernauer and Pohl), along with our colleagues, have made the most precise measurements of the radius of the proton to date, using two complementary experiments. When we began the exercise, we suspected that our results would help add levels of precision to the known size of the proton. We were wrong. Our measurements of the proton's radius differ by a huge gulf. The difference is more than five times the uncertainty in either measurement, implying that the probability that this is all due to chance is less than one in a million.

Clearly, something is amiss. Either we don't fully understand the proton, or we don't understand the physics that goes into the precision measurements of the proton. We have reached out into the universe and pulled back an anomaly. And so we have a great chance to learn something new.

THE MISSING SHIFT

OUR STORY BEGINS on the Italian island of San Servolo, 10 minutes by fast boat from the Piazza San Marco in Venice. The island hosted a hospital for the mentally ill until the late 1970s. Three decades after it closed, a few dozen physicists began to meet on the island to discuss ever more stringent tests of the best-understood theory in all of physics, if not all of science: quantum electrodynamics, or QED.

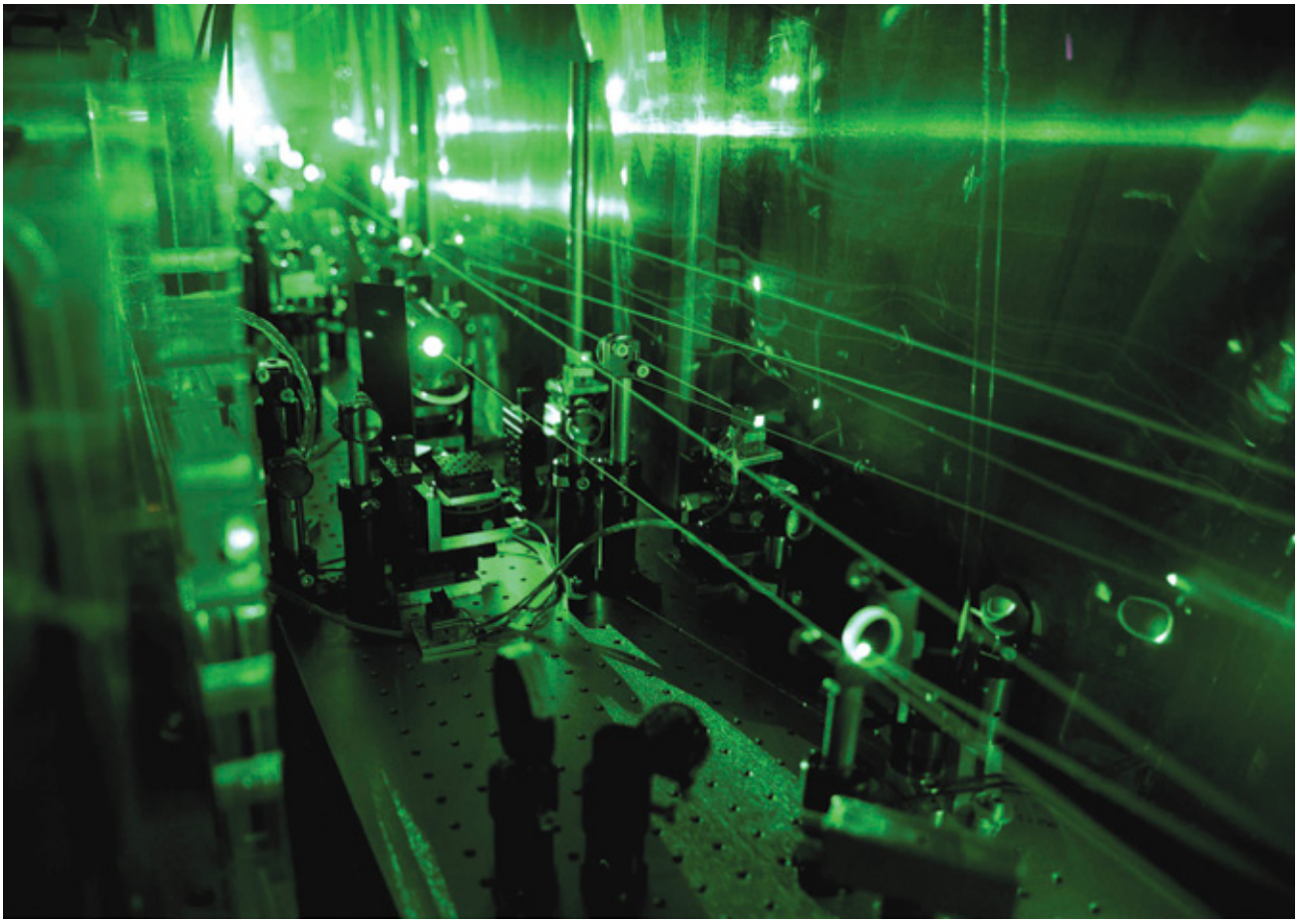
QED traces its history back to 1928, when P.A.M. Dirac combined quantum mechanics and special relativity into what is now known as the Dirac equation. It is our best theory of electricity and magnetism because it fully describes how light interacts with matter. To take just one example, QED explains the structure of atoms using nothing more than the laws of physics and the values of fundamental constants such as the mass of the electron. Because of this, physicists use simple atoms such as hydrogen to test QED. They can predict the outcomes of experiments with an uncertainty of 0.0000000001 percent. Experiments match this precision.

The two of us met on San Servolo for the first time. We were both embarking on measurements of the proton that would help refine our knowledge of QED. Bernauer's experiment was poised to investigate the proton's internal structure using an improved version of a technique that had already resulted in the most accurate measurements to date.

Pohl's group was using a new approach. The group was examining subtle shifts in the energy levels of an exotic, electron-free form of hydrogen—shifts that depend critically on the size of the proton. These shifts were first detected in regular hydrogen back in 1947 by the late Willis E. Lamb, Jr. Even though physicists refer to the phenomena by the singular name "Lamb shift," they have come to understand that two distinct causes are at play.

The first contributor to the Lamb shift comes from so-called virtual particles, phantoms that pop up inside the atom before quickly vanishing again. Scientists can use QED to calculate how these virtual particles affect atomic energy levels to an astonishing precision. Yet in recent years uncertainties in the second contributor to the Lamb shift have begun to limit scientists' predictive powers. This second cause has to do with the proton radius and the bizarre quantum-mechanical nature of the electron.

In quantum mechanics, the electron takes the form of a cloud-like wave function that is spread out over the size of the atom. The wave function (more accurately, the square of it) describes the probability of finding the electron at a given location and



PROTON PROBE: One way to measure the proton's radius is to shoot this precisely tuned laser beam at an experimental sample of so-called muonic hydrogen—atoms made up of one proton and one muon, the heavy cousin to the electron.

COURTESY OF A. ANTOGNINI AND F. REISER *Paul Scherrer Institute*

can only take certain discrete forms, which we call atomic states.

Some of the atomic states, labeled "S states" for historical reasons, have a wave function that is *maximal* at the atomic nucleus. That is, there is a nonzero probability of finding the electron *inside* the proton itself—a probability that grows along with the radius of the proton. When the electron is inside the proton, the electron doesn't "feel" the proton's electrical charge quite as much, which reduces the overall binding strength between the proton and electron.

This reduction in binding strength changes the Lamb shift of the lowest-energy state—the 1S state—by 0.02 percent. This fraction may seem insignificant. But the energy difference between the 1S ground state and the first excited state—the 2S state—has been measured to an incredible precision of a few parts in 10^{15}. Therefore, even the tiny effect of the proton radius must be included if one wants to confront QED theory with precision experiments.

Pohl's group had been trying for eight years to nail down the proton size. Yet at the time of that first conference on San Servolo, its experiment did not appear to be working—much to everyone's puzzlement.

Meanwhile Bernauer's team was about to begin a complementary investigation into the radius of the proton. His approach would not rely on the energy levels of hydrogen. Instead it would use the scattering of electrons off a hydrogen target to infer just how big protons are.

TARGET PRACTICE

HYDROGEN GAS is mostly a swarm of protons. If you shoot a beam of electrons at it, some of the negatively charged electrons will get deflected by a positively charged proton and "scatter" away from the initial direction of the beam. Moreover, this scattering depends strongly on the internal structure of a proton. (Protons, unlike electrons, are made of more elementary components.)

Let's look more closely at how a proton and electron interact when one scatters off the other. When the electron scatters, it transfers some of its momentum to the proton. In QED, physicists describe this interaction as the exchange of a virtual photon between the electron and the proton. If the electron scatters by only a small amount—a glancing blow—it transfers only a small fraction of its momentum. If it scatters close to 180 degrees, we imagine that the electron has hit the proton dead center, transferring a good deal of momentum. In QED, higher momenta mean that the virtual photons have a shorter wavelength.

Similar to a light microscope, if we want to see the smallest structures, we use the shortest wavelengths possible. Part of

Bernauer's work was to use small wavelengths to investigate the distribution of charge inside the proton.

Yet when Bernauer traveled to the conference on San Servolo, the scientists there asked him to extend his experiment. Short wavelengths are good for looking at the structures inside the proton, but if you want to examine the proton as a whole, you must use long wavelengths. In fact, if you want to measure the full extent of the proton (and thus its radius), you need to use an infinite wavelength, which allows the photon to "see" the complete proton. This is the limit at which no scattering happens at all.

Technically, of course, this is not possible—the electrons need to deflect by at least a small amount for anyone to make a measurement. So Bernauer's group measured the lowest momentum transfer his setup allowed and then extrapolated down to zero.

Compared with old experiments, his efforts managed to almost halve the gap between the smallest momentum transfer previously measured and zero, making the extrapolation much more reliable. In the end, the experiment had about twice the number of measurements of all previous measurements combined. After doing the experiment in 2006 and 2007, Bernauer required three years to analyze all the data—work for which he would earn his Ph.D. The radius of a proton, he found, was about 0.879 femtometer—about one ten-billionth the size of a droplet of mist and square in line with previous measurements.

We were scheduled for just one more week of observations. If those failed, the decade-long experiment would be permanently shut down as a failure.

STRANGE HYDROGEN

IN THE MEANTIME, Pohl and his team members continued to struggle. Their experiment replaced the electron in a hydrogen atom with the electron's fat cousin—the muon. Muons are nearly identical to electrons, except for the fact that they are about 200 times more massive. This difference causes the muon in muonic hydrogen to get about 200 times closer to the proton than an electron does.

If the muon is 200 times closer to the proton, it should also be spending considerably more time *inside* the proton. (Indeed, the probability is increased by a factor of 200^3, or eight million.) This, in turn, changes the Lamb shift of the atom by 2 percent—a relatively huge amount that should be easy to spot.

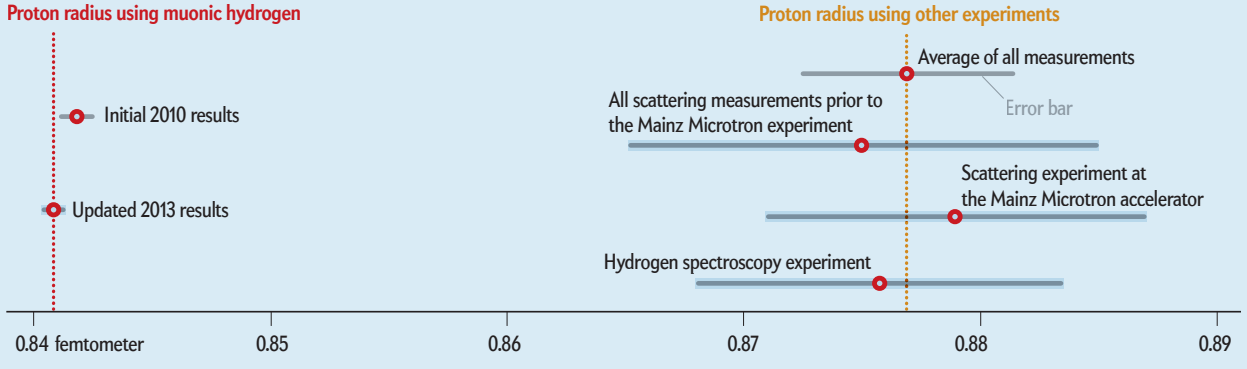
Pohl's experiment shot muons from an accelerator at the Paul Scherrer Institute (PSI) in Switzerland into a vessel containing hydrogen gas. Occasionally a muon would displace an electron, breaking up the hydrogen molecule and forming a muonic hydrogen atom in a highly excited state. Within a few nanoseconds the muonic hydrogen would tumble into lower and lower energy states. The experiment used only the hydrogen atoms that ended up in the first excited energy state (the 2S state).

As each muon entered the hydrogen vessel, it triggered a start signal for the laser system, which delivered a laser pulse about one microsecond later. If the laser had exactly the right amount of energy, as measured by its wavelength, the laser

RESULTS

The Incompatible Measurements

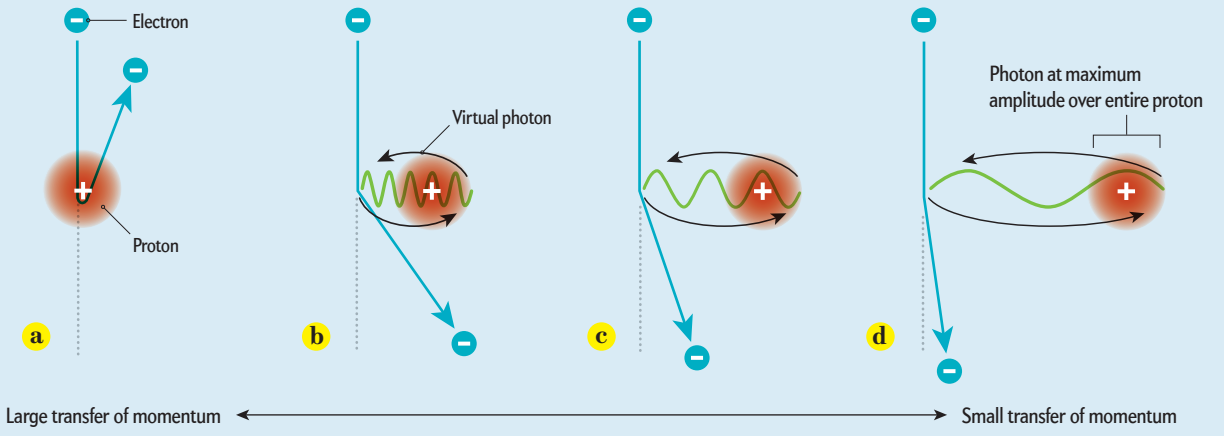
The size of the proton should stay the same no matter how one measures it. Laboratories have deduced the proton radius from scattering experiments [*see box on opposite page*] and by measuring the energy levels of hydrogen atoms in spectroscopy experiments. These results were all consistent to within the experimental error. But in 2010 a measurement of the energy levels of so-called muonic hydrogen [*see box on page 38*] found a significantly lower proton radius. Attempts to explain the anomaly have so far failed.



SOURCE: RANDOLF POHL

Scattershot Proton Measurement

Electron-scattering experiments fire a beam of electrons at hydrogen gas (which is mostly protons) and measure how the electrons scatter. Quantum electrodynamics (QED) describes these interactions using the exchange of "virtual" photons. An electron that hits a proton exchanges an extremely short-wavelength photon **a**. Short wavelengths imply higher energies that vigorously alter the electron's course. Electrons that pass farther from the proton produce progressively longer-wavelength photons (**b** *through* **d**) and smaller deflections. Information about the proton radius is encoded in the longest wavelengths. Imagine that the interaction between the photon and the proton is dependent on the photon's amplitude. To register the whole proton, the wavelength must be so long that the amplitude does not change over the entire extent of the proton's width **d**.



would push the 2S state up in to the higher 2P state. The shape of the 2P state is such that a muon will never be found inside the proton [*see box on next page*], so by measuring the energy difference between the 2S and 2P state, we could infer how much time the muon spent inside the proton—and thus the proton radius.

Here's the key caveat: we had to tune the laser so that it came in with exactly the right amount of energy. The atom would make the jump to the higher state only if the energy of the laser perfectly equaled the energy difference between the 2S and the 2P state. If the wavelength were a bit off, nothing would happen. How did we know if the atoms were making the jump? Any atom bumped up to the 2P state would quickly release a low-energy x-ray photon. If we found these photons, we knew we had the right energy.

Sounds simple enough in theory, but these experiments are notoriously difficult to execute. Similar experiments were first proposed back in the 1960s, when QED was still rather new, as a precision test of the theory. But the experiment was more difficult than complementary experiments on hydrogen and other electronic atoms, so interest faded until the 1990s, when those other tests became limited by the uncertainty of the proton radius.

Pohl's group proposed the muonic hydrogen Lamb shift measurement to administrators at PSI in 1997. The institute approved the project in early 1999, and we spent three years building a laser system, a beam of low-energy muons and detectors for the low-energy x-rays.

After we assembled the experiment at PSI in 2002, we had to deal with several technical issues. By the time we got them straightened out, we had only a few hours to really shoot lasers at muonic hydrogen atoms before our assigned time at the accelerator expired. Some of us were very disappointed because we had really believed that we would find the 2S–2P shift in the first shot. The senior physicists, however, were more realistic about the prospects of the first "machine development" run. They were happy that everything was working and that only a few minor technical issues had cropped up. These could be fixed before the beginning of the "real run," scheduled for 2003, where we would surely see the Lamb shift signal.

Then, after many months of preparation, three weeks of successful data taking revealed … nothing. Not the slightest indication of a signal. Even though the laser had scanned over the entire wavelength region that corresponded to the known experimental values of the proton radius. Nothing.

We assumed the obvious: something in our setup must have been in error. The conclusion at the time was that we needed to improve the laser system. We embarked on a major redesign, which was completed in late 2006. We took data for another three weeks in 2007 and again saw nothing. Luckily, we were given one final chance in the first half of 2009. It took a few months to get the complex apparatus to run. Once more, after a week of collecting excellent data, we found no sign of a signal.

We were scheduled for just one more week of observations. If those failed, we were afraid that some administrators would conclude that we were not up to the task. The decade-long experiment would be permanently shut down as a failure.

We finally started to wonder if something more profound was going on. What if we were searching for the proton radius in the wrong place? We decided to extend the search region. The

Graphics by Jen Christiansen

group made a collective decision to look for a larger proton radius. Late one evening, however, Pohl's colleague Aldo Antognini came into the control room to say that he had a good feeling about looking for a *smaller* proton. With time tight, Pohl and Antognini redirected the search to look for a proton radius smaller than anyone had any right to assume. Very quickly, we found a hint of a signal. But the very next day the accelerator was shut down for a four-day-long scheduled maintenance. We would have to wait.

Then, in the evening hours of July 4, 2009, 12 years after the beginning of the endeavor, an unambiguous signal showed up, telling us that the proton measured in muonic hydrogen was significantly smaller than everybody had believed so far. The group spent a few more weeks doing additional measurements and calibrations and a few months on data analysis. The final result, which we have since confirmed with additional measurements, is a proton charge radius of 0.8409 femtometer, plus or minus 0.0004. That figure is 10 times more accurate than any previous measurement but differs by 4 percent from them—a huge discrepancy!

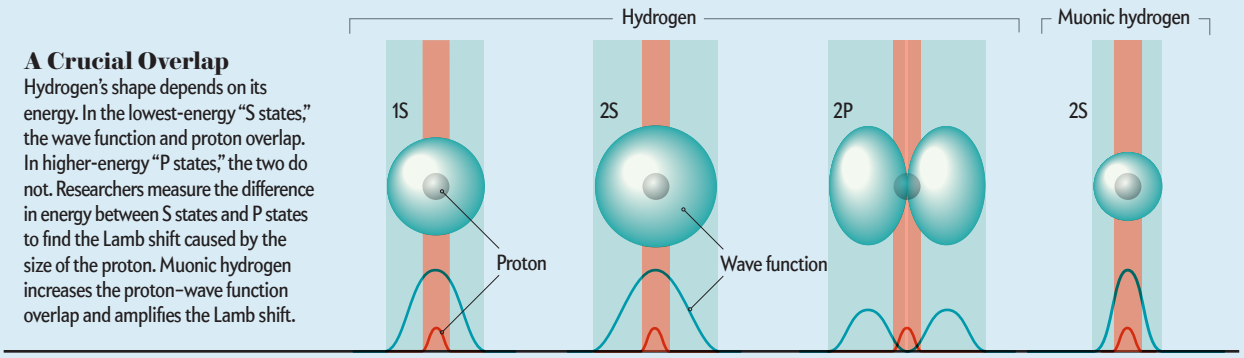
SECOND EXPERIMENT

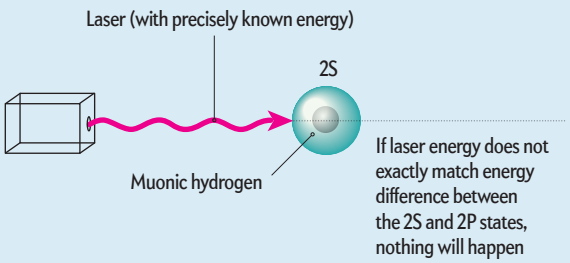
Strange Hydrogen Technique

The electron in a hydrogen atom takes the form of a probability cloud called a wave function. Sometimes the wave function overlaps the proton, implying that the electron may be inside it. This overlap changes the atom's energy. Researchers can measure this "Lamb shift" in energy to deduce the size of the proton, as larger protons will cause a larger shift. They also replace electrons with muons, which have a smaller wave function and so spend more time inside the proton, to enhance the signal.

A Crucial Overlap

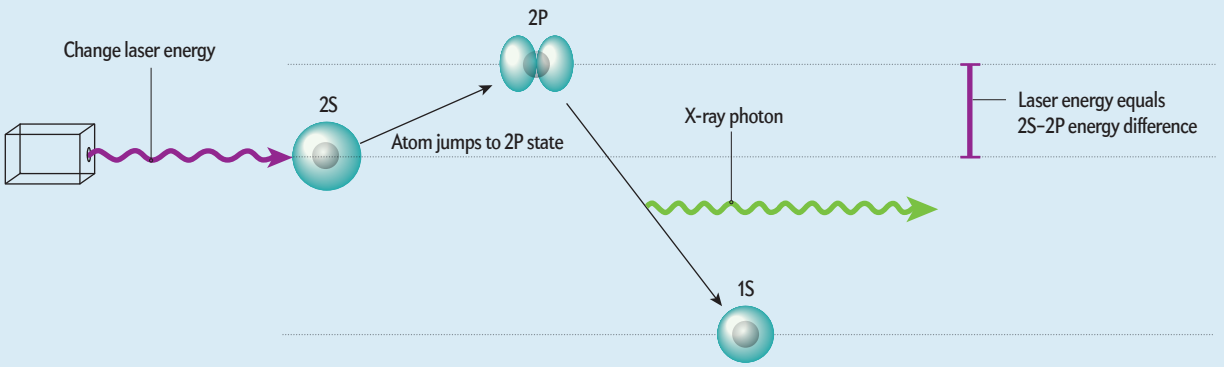
Hydrogen's shape depends on its energy. In the lowest-energy "S states," the wave function and proton overlap. In higher-energy "P states," the two do not. Researchers measure the difference in energy between S states and P states to find the Lamb shift caused by the size of the proton. Muonic hydrogen increases the proton–wave function overlap and amplifies the Lamb shift.





The Experiment

Muonic hydrogen is created by shooting a beam of muons into hydrogen gas (*not shown*). Around 1 percent of the resulting atoms will be in the 2S state. Next a laser beam is sent in with a very precise wavelength (*left*). For most wavelengths, nothing happens. But if the laser wavelength corresponds exactly to the energy difference between the 2S and 2P states (*below*), the atom will jump up in energy, then fall down to the 1S state, releasing an x-ray photon in the process. Because the difference in energy between the 2S and 2P states depends on the Lamb shift, researchers use this measurement to find the proton radius.



SCIENTIFIC AMERICAN ONLINE Watch a video showing how this experiment works at ScientificAmerican.com/feb2014/proton

In 2010 both of our groups shared their results at the same Precision Physics of Simple Atoms conference in Les Houches in the French Alps. Pohl presented the results of the muonic hydrogen measurement to the scientific community for the first time. In the afternoon of the same day, data from Bernauer's experiment were delivered. Pohl and his colleagues expected that Bernauer's analysis would back up the new, smaller result. Yet to their surprise, the results were nearly identical to the old radius: 0.877 femtometer.

NEW IDEAS

THIS DISCREPANCY created great excitement in the community. Discrepancies are useful because they stimulate new thinking, which leads to new ideas and a better understanding of nature.

At first, most people believed there must be a simple mistake. Perhaps something was off in the experiments, or perhaps the theoretical calculations needed to extract the radius went awry. Shortly after the conference, independent researchers came up with a flurry of possible candidates for straightforward mistakes.

Four years after the puzzle came to life, physicists have exhausted the straightforward explanations. We have begun to dream of more exciting possibilities.

For example, prior to Pohl's experiment, only three individuals had done the complex calculations needed to translate the experimental measurement of the laser wavelength into the proton radius. Many people speculated about errors or omissions in these calculations. Consequently, a large number of theorists repeated and extended the calculations but found no mistakes.

Others reconsidered how Bernauer extrapolated the radius from his scattering data. Could it be possible to reconcile the raw data with the smaller radius from muonic hydrogen? It seems that this fix has also been ruled out.

With every failed suggestion, the impact of the discrepancy has become more severe. Four years after the proton radius puzzle came to life, physicists have exhausted the straightforward explanations such as errors in measurements or in calculations. We have now started to dream about more exciting possibilities.

For example, do we really understand how the proton reacts when the muon pulls on it? The electrostatic force of the muon deforms the proton, in a way similar to how the moon's gravity causes tides on Earth. The crooked proton slightly alters the 2S state in muonic hydrogen. Most people think that we understand this effect, but the proton is such a complicated system that we may have missed something.

The most exciting possibility is that these measurements might be a sign of new physics that go beyond the so-called Standard Model of particle physics. Perhaps the universe contains a heretofore undetected particle that somehow makes muons behave differently from electrons. Scientists have been exploring this option but have found it difficult to model a new particle that does not also produce observable consequences that violate the results of other experiments.

On the other hand, physicists already have another muon puzzle to solve. Fundamental particles such as muons and electrons have a "magnetic moment"—a magnetic field that is much like a bar magnet. Tellingly, the muon's magnetic moment does not match the QED calculations. Perhaps new physical phenomena will explain both the proton radius measurement and the muon's anomalous magnetic moment.

To end these speculations, several new experiments have been proposed. At least two scattering experiments—one at Thomas Jefferson National Accelerator Facility in Newport News, Va., and another at the Mainz Microtron accelerator at the Johannes Gutenberg University Mainz in Germany, where Bernauer did his original experiment—aim to improve the accuracy of the earlier scattering experiments. These measurements will give independent verification and test some of the proposed explanations.

Both Pohl's group and the Mainz team are looking to measure the radius of deuterium—the nucleus formed from a single proton and a single neutron—to see if the difference shows up here, too. Pohl is also going to remeasure standard electronic hydrogen with better precision.

In addition, many physicists have noted that researchers have performed atomic measurements using both muons and electrons but have performed scattering experiments with only electrons. Missing is the combination of muons and scattering. Bernauer is involved in a project that aims to fill this gap. Using one of the muon beams at PSI, the same institute where Pohl's group performed its experiment, the Muon-Proton Scattering Experiment (MUSE) will scatter both electrons and muons off protons to make a direct comparison. The experiment will be able to check for some of the most viable proposed explanations.

Time will tell if the radius puzzle gets resolved as a freak mistake or as the gateway to a deeper understanding of the universe. It just might be the thread we have to pull to unravel the next chapter in the book of nature. Pull we will. SA

MORE TO EXPLORE

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FROM OUR ARCHIVES

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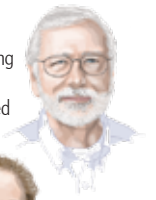
James L. McGaugh is a research professor specializing in the neurobiology of learning and memory at the University of California, Irvine. His studies have focused on the relation between memory and emotion.



Aurora LePort is a graduate student in neuroscience at the University of California, Irvine, who has performed psychological and physiological studies on individuals with superior memory.

BRAIN SCIENCE

Remembrance of All Things Past

Neuroscientists have discovered that some people can remember the details of events from 20 years ago almost as well as those experienced yesterday

By James L. McGaugh and Aurora LePort

IN BRIEF

Some 14 years ago an individual claiming to possess extraordinary recall of the distant past came forward.

Publicity about the case brought out hundreds of others who made similar assertions about their ability to remember.

Testing confirmed that a few dozen among this group can recite details of a specific date decades later.

Neuroscientists are now exploring the biological underpinnings of "highly superior autobiographical memory."

Illustration by Kyle Bean

IN THE LATE SPRING of 2000 one of us (McGaugh) received an e-mail message from a woman named Jill Price who was trying to cope with the burdens inflicted by her own memory. It read, in part:

As I sit here trying to figure out where to begin explaining why I am writing you … I just hope somehow you can help me. I am 34 years old, and since I was 11 I have had this unbelievable ability to recall my past … I can take a date, between 1974 and today, and tell you what day it falls on, what I was doing that day, and if anything of great importance … occurred on that day I can describe that to you as well. I do not look at calendars beforehand, and I do not read 24 years of my journals either.

We were skeptical of Price's assertions but intrigued enough to invite her to our research center at the University of California, Irvine, where we study the neurobiological bases of learning and memory. On June 24, a few months later, Price came for an appointment. It was a Saturday. We are certain about the date because her visit was recorded on a laboratory calendar. Price, we quickly discovered, remembers such facts without any need for a calendar.

We were cautious in that first interview and looked for some objective means of evaluating her claims. There was no way to immediately check what she told us about her own past. Yet we could query her about public events that occurred during her lifetime. We had a copy of a then just published book, *20th Century Day by Day,* by Sharon Lucas, that contained articles of daily news events going back 100 years.

We started with the mid-1970s, when Price first recognized that her memory might be unusual. When we asked what happened on August 16, 1977, she quickly replied that it was the day Elvis Presley died. When we queried June 6, 1978, she told us it was the day that California's Proposition 13, limiting the state's property tax rates, passed. May 25, 1979, was the day a plane crashed in Chicago. May 3, 1991, was the last episode of *Dallas.* And so on. Price answered correctly every time.

Then we reversed the process and asked Price to name the date for a particular event: When was J.R. shot? When did police beat Rodney King? Again, each time Price came up immediately with the right answer. During our testing, she identified an error in the book of milestones for the date of the start of the Iran hostage crisis at the U.S. embassy in 1979.

Although many of the dates we tested for were public events that had received considerable media attention, Price also excelled in remembering less significant occurrences. She correctly recalled that Bing Crosby died at a golf course in Spain on October 14, 1977. When asked how she knew, she replied that when she was 11 years old, she heard the announcement of Crosby's death over the car radio when her mother was driving her to a soccer game. In one interview, she described remembering dates visually: "When I hear a date, I see it, the day, the month, the year."

In a subsequent interview in March 2003, she recalled, with one error, the dates of the previous 23 Easters and told us what she did on each of those dates—and she is Jewish. We were able to verify many of her claims by checking a diary that she kept for many years. For some of her personal memories, we consulted our own records documenting the testing of her memory. At a subsequent interview, she correctly remembered the dates for all of our previous interviews and the details about the questions we had asked about her recall of past events.

After we were convinced that Price's mental diarylike abilities were real, we wanted to know whether this skill extended to other aspects of remembering. We determined that she does not have a "photographic memory"—that is, she does not recall the minutest details of daily experience. She has trouble remembering which of her keys go into which lock. She makes lists of things she needs to do. She also does not excel in memorizing facts by rote.

Price does have immediate recall of the day of the week for any date in her life after she was about 11 years old. Her recall is distinguished by highly organized, readily accessible and accurate memories of most of the days of her life from preadolescence onward. Until Price walked into our lab, this particular type of memory, which we call highly superior autobiographical memory (HSAM), had never been studied. We are now delving further into the psychological and biological roots of HSAM in the hope that an understanding of these processes may provide more general insight into the processes underlying memory.

IS SUPERIOR MEMORY COMMON?

FOR SEVERAL YEARS, we referred to Jill Price with the fictitious initials "A.J." because she did not wish to be identified. After publishing a paper on her extraordinary memory in 2006, our work gained national attention. We then appeared on National Public Radio on April 19 and 20, 2006. Price, who had decided to come out of the shadows, subsequently published a memoir, *The Woman Who Can't Forget,* in 2008.

Following that publicity, other individuals who thought that they have, or might have, similar memory abilities contacted us. After putting them through the rigors of testing, we identified five additional HSAM subjects. On December 19, 2010, these five individuals appeared on *60 Minutes.* Within hours of the episode's air-

PAGE 40: MITCH PAYNE (*photograph*)

QUERY from Jill Price to researchers at the University of California, Irvine, set off a series of events that led to identification of individuals with superior memory.

BRYCE DUFFY

ing, we received dozens of e-mails from potential subjects, and within days, many hundreds had reached our in-boxes. We contacted many of these people by telephone and tested them by asking them about sporting and political events, famous people, holidays, airplane crashes and other notable incidents.

We also began a more formal testing procedure at our center, recruiting several dozen control subjects of similar ages to that of the superior memory group—and both groups contained the same proportion of males and females. During the testing, a few of those who claimed to have exceptional memories performed more poorly than the controls. Clearly, believing that you have HSAM does not make it so.

The 40 or so subjects who did perform well then received, along with the control group, an additional test in which they had to identify the day of the week for each of 10 randomly selected dates, along with a newsworthy event that occurred on or near these dates, as well as something that had happened to them on that date. As a group, the prospective HSAM subjects very significantly outperformed the controls on all components of this test.

Eleven of the highest-performing subjects then came to our lab at U.C. Irvine for further testing. They were first asked to answer questions about five personal experiences that we were able to verify—events such as their first day at university and elementary school, their 18th-birthday celebration, the address and description of their first residence after leaving home, and the date of their last final exam in college. The 11 potential HSAM subjects outperformed the controls by a wide margin—registering an overall score of 85 percent in responding to these queries compared with only 8 percent for controls. We concluded that these 11 subjects, who ranged in age from 27 to 60, very clearly had HSAM.

We also tried to distinguish the HSAM group from others by administering a battery of lab memory tests. HSAM subjects performed better than the controls in only two of eight tests: one associating names with faces and another checking recall of visual objects. For both tests, however, the scores for the two groups overlapped considerably. A few other qualities distinguished the HSAM group. A higher than average number—five of 11—were left-handed, and they scored significantly higher on a test of obsessive personality traits. One-on-one interviews also revealed some compulsive behaviors such as hoarding of possessions and excessive efforts to avoid touching potentially germ-laden objects.

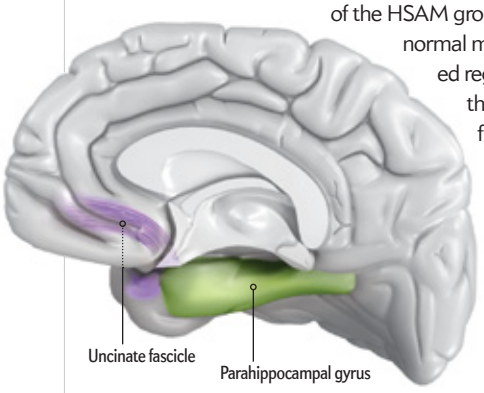
A further question in trying to understand superior memory was whether these differences in memory are related to differences in the brains of our group. Magnetic resonance imaging (MRI) scans revealed that several brain regions of HSAM subjects differed from those of control subjects. A few areas of gray matter (tissue made up of the cell bodies of neurons) and white matter (the wirelike extensions from the neurons covered with a whitish insulating material called myelin) varied from controls in size and shape. The structure of the white matter's fibers also hinted at greater efficiency in transferring information between brain regions.

Findings of other labs investigating the effects of brain lesions, as well as those using functional MRI and positron-emission tomography, have suggested that brain regions and fiber pathways that stand out in HSAM subjects are involved in remembering life events (autobiographical memory). In our group, the structure of one fiber tract, the uncinate fascicle, which transmits information between the temporal and frontal cortex, appeared to have better connections than in control subjects. This finding is intriguing because of evidence that injury to this pathway impairs autobiographical memory.

Our imaging results are, of course, merely suggestive. We do not know whether these anatomical differences in the brains of HSAM and control subjects contribute in some way to superlative memory ability or whether they might be a consequence of extensive use of that ability. To find out, we need to determine whether HSAM ability appears in early childhood. If the skill has some genetic basis, we should eventually be able to detect the genes involved. Yet we have no evidence so far of a higher incidence of this ability in relatives of those in the HSAM group.

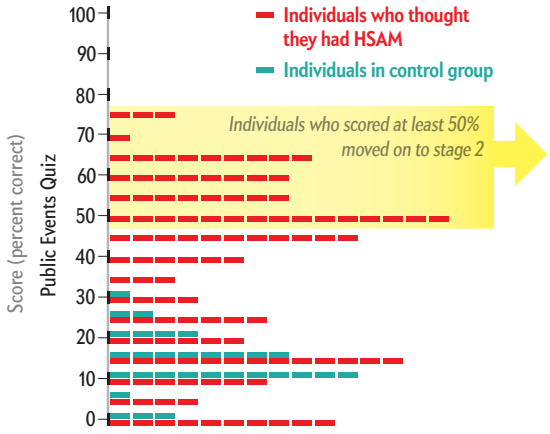
Super Memories in the Lab

The first challenge researchers faced when they encountered people claiming to have astute recall of events from decades earlier was to verify these assertions. The team at the University of California, Irvine, developed a multipart evaluation process (*graphs at right*) that led to several dozen individuals being classified as exhibiting highly superior autobiographical memory, or HSAM. A later step focused on whether the brains of the HSAM group differed from those with normal memories. Two memory-related regions stood out in brain scans: the uncinate fascicle, a nerve fiber tract that links the temporal and frontal cortices, and the parahippocampal gyrus are better connected to other brain areas.



Stage 1: Public Events Quiz

More than a third of the self-identified HSAM group recalled at least 50 percent of newsworthy items, a level unmatched by control subjects.



AN EMERGING PROFILE

OUR FINDINGS have enabled us to make a few tentative conclusions about these extraordinary people. First, HSAM subjects do not develop superior memory because they somehow learn things more readily than others who lack this talent. The members of this group distinguish themselves by their ability to retain what they do learn. Someone with an average memory can remember, for a few days afterward, many details of what happened, say, last Tuesday, but the information fades in a week or so. Not so for members of the HSAM group: their memories are considerably longer lasting.

Second, we know that the memory systems of individuals with HSAM are not precise video and audio recorders of every millisecond of their existence. Additionally, HSAM is not like the memory of "S," the subject in Alexander Luria's *The Mind of a Mnemonist: A Little Book about a Vast Memory,* a much cited 1968 account about one of Luria's patients who could readily learn and retain vast amounts of relatively meaningless material—rows and columns of numbers, for instance. Nor is HSAM like that of memory experts who train themselves by extensive rehearsal and the use of mnemonic tricks to learn material such as pi to many thousands of digits.

The HSAM group's memories are less detailed than those of Luria's subject but are highly organized in that they are associated with a particular day and date. We also know that this skill seems to occur naturally and without studied exertion. Many of the questions we have used in testing HSAM individuals have to do with subject matter, such as the weather on a particular day, recollections that they were highly unlikely to have spent time and effort rehearsing. When asked how they gained their knowledge, HSAM subjects typically responded, "I just know that." And although they enjoy mentally tying a date to an event, they generally have little, if any, interest in knowing what happened on calendar dates that arrived before they were born.

HSAM subjects typically appreciate their special skill. In this way, they are not at all like the eponymous character from Jorge Luis Borges's 1962 short story "Funes the Memorious." After being thrown from a horse, Funes acquired the ability to retain detailed memories of all his subsequent experiences; he could call up the image of every leaf on every tree he had seen. He was tortured by his recollections, which made him conclude that his life was no more than a garbage heap. Although Price told us that her memories were a burden, most HSAM subjects relish having such vivid access to their past. For the most part, they lead active professional and social lives. Several are in the entertainment industry: actress Marilu Henner and television producer and stand-up comedian Robert Petrella have HSAM. So do Louise Owen, a violinist, and Brad Williams, a radio news announcer and actor.

The extraordinary abilities of people with HSAM do not give them superhuman powers to outpace their colleagues in their chosen professions. Petrella has had occasion to use his skill when he wrote, for his own amusement, "The Book of Bob," in which he noted, for each day of the year, the best experience on that date during his adult life. But this project was merely a pastime—it had nothing to do with producing a TV show.

The work on HSAM joins a rich history of research on people with unusual psychological deficits and strengths. In 1881 French psychologist Théodule Ribot reported that brain damage impaired new memories but allowed older ones to persist—studies echoed in recent decades by the investigations of Brenda Milner of McGill University. Milner examined the famous patient Henry Molaison, for years known simply as "H.M.," helping to provide insight into what happens when a person is unable to form new autobiographical memories. After the surgical removal of a portion of the brain—the anterior medial

SOURCE: "BEHAVIORAL AND NEUROANATOMICAL INVESTIGATION OF HIGHLY SUPERIOR AUTOBIOGRAPHICAL MEMORY (HSAM)," BY AURORA K. R. LEPORT ET AL., IN *NEUROBIOLOGY OF LEARNING AND MEMORY*, VOL. 98, NO. 1; JULY 2012

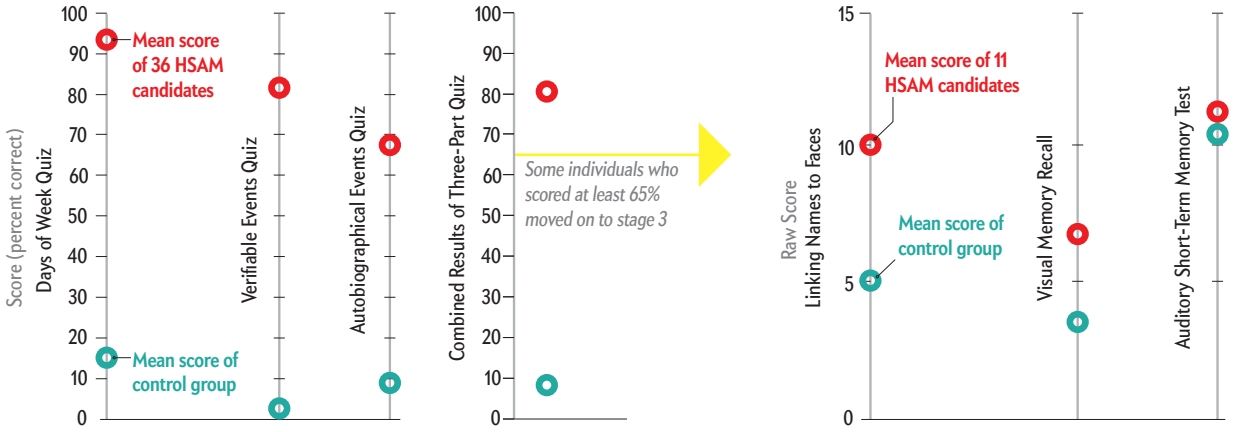
SCIENTIFIC AMERICAN ONLINE Watch interviews of people with superior recall at ScientificAmerican.com/feb2014/remember

Stage 2: Dates Test

The HSAM group excelled on a test in which they had to identify the days of the week and verifiable public and personal events that occurred on a random set of 10 dates.

Stage 3: Cognitive Testing

A subset of the HSAM group performed well on only some cognitive measures of memory—ones linking names to faces and recall of images—but not on several others, such as a short-term memory test.



temporal lobes in both hemispheres to treat epilepsy—Molaison almost completely lost the ability to learn new autobiographical information even though his memory for prior experiences remained mostly intact and motor learning of movement—known as procedural memory—remained unimpaired.

These findings forced the then novel conclusion that different brain systems are responsible for distinctive types of memory, and, as a consequence, memory research underwent dramatic change. The new discovery that some human subjects have very strong and lasting memories of both ordinary personal experiences and important public events has stimulated research that may, over time, provide new insights into the way the brain stores and retrieves recollections of past events.

LIKE A MUSCLE

EXTENSIVE EVIDENCE, beginning with psychologist Hermann Ebbinghaus's studies of human memory in 1885, has shown that repetition of material we wish to learn strengthens memory. More recent studies by Henry L. Roediger III of Washington University in St. Louis and Jeffrey D. Karpicke of Purdue University have found that memory retrieval—bringing to mind a memory for a few moments—can make recall stronger.

Even with practice, however, an individual with ordinary memory is unlikely to achieve the capabilities of our HSAM subjects, who did not rehearse for any of our tests. McGaugh has spent many years on studies that have found that we all make stronger memories of emotionally important experiences. The novel and intriguing finding is that HSAM subjects readily make strong memories of even relatively trivial events.

Despite considerable media coverage, we have so far identified only about 50 HSAM subjects out of several hundred potential candidates who have contacted us. That is a very tiny proportion of the total number of viewers and readers who learned about our research. If this ability aids in successful adaptation to the challenges of living, why is it so rare? Perhaps HSAM is a lingering trace of a once important and now almost lost skill. Before the printing press, much of human culture was preserved by stories and knowledge passed down orally from one generation to the next. In the preliterate world, a prodigious memory would have accorded the holder an elevated status among peers. The need for this type of highly organized mental capacity is waning and, with the introduction of computers and smartphones, may have already passed.

It is possible—perhaps likely—that many of the subjects whom we dismissed in our early testing as not having HSAM possess some other memory ability that we have yet to identify. Some of these people may have lucid memories of their past and simply neglect to mentally date them, as do the HSAM subjects, opening the prospects for new avenues of research. Instead of contemplating mental deficits, we and other investigators may now have an opportunity, sparked by an impromptu, 14-year-old e-mail message, to better understand the way the brain works by studying Olympians of human recall. SA

MORE TO EXPLORE

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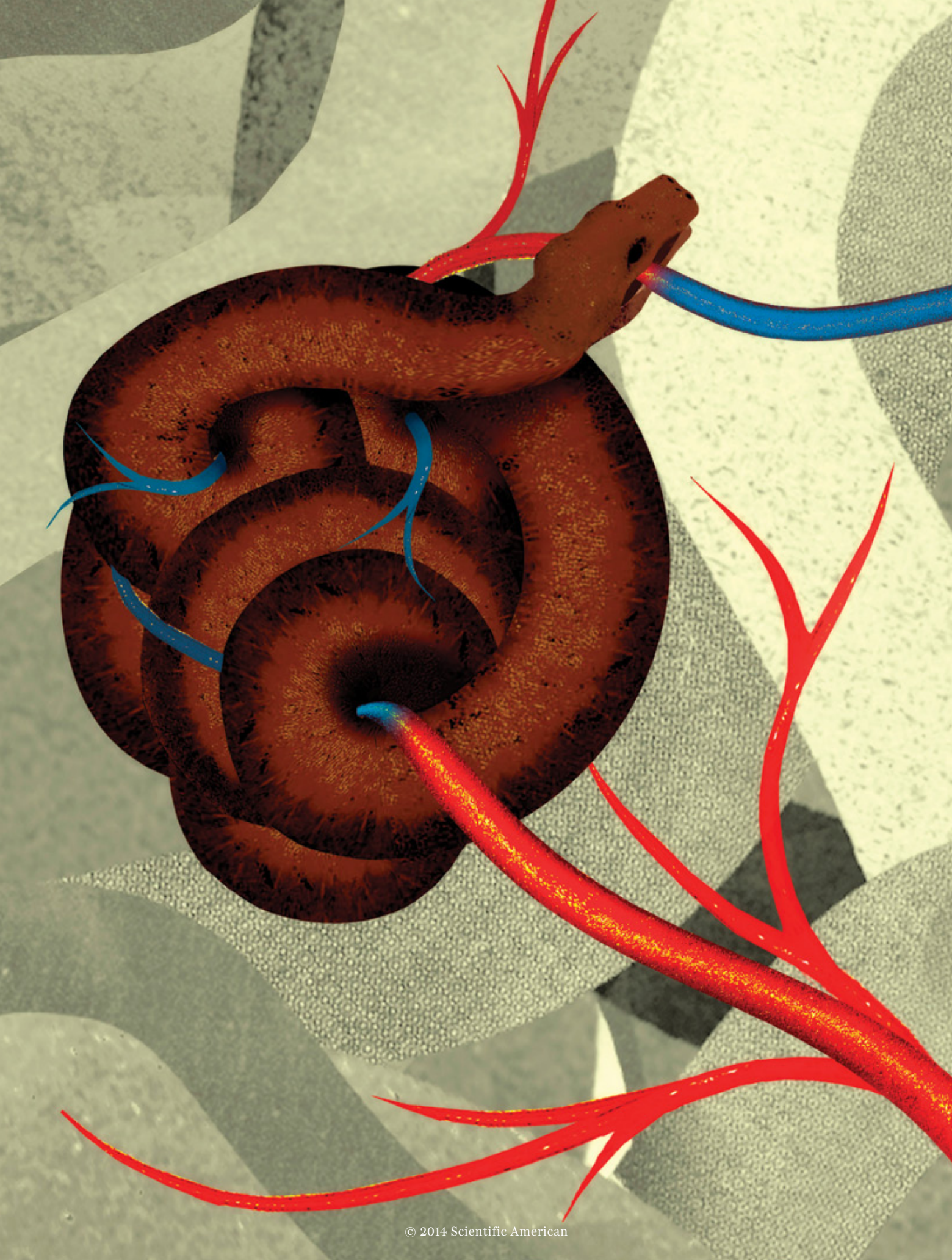


MEDICINE

An Indirect Way to Tame Cancer

Cells and a stiff material called the matrix can squeeze blood vessels in tumors and thus block delivery of cancer-fighting drugs to malignant cells. Now researchers may have a way to reopen vessels and restore the drugs' power

By Rakesh K. Jain

Illustration by Brian Stauffer

Rakesh K. Jain is Andrew Werk Cook Professor of Tumor Biology and director of the Edwin L. Steele Laboratory for Tumor Biology in the radiation oncology department of Massachusetts General Hospital and Harvard Medical School. He is a member of the National Academy of Sciences, the National Academy of Engineering and the Institute of Medicine, one of only 20 people ever to have been elected to all three bodies.

FOR NEARLY 40 YEARS, I HAVE BEEN WORKING ON FIGHTING CANCER FROM AN unusual angle. Trained initially as an engineer, I see tumors in part as a physics challenge and ask: How do their structural features promote their growth and keep cancer-fighting drugs from working effectively?

More than two decades ago, for instance, my co-workers and I, then at Carnegie Mellon University, revealed that structural abnormalities in tumor blood vessels interfere with drug delivery to malignant cells in a mass. These vessels tend to be overly twisty and porous, and the porosity leads fluid and drugs in the blood to leak out as blood enters a mass. The fluid then exerts an outward pressure that causes it and the drug molecules to ooze out of the tumor into the surrounding tissue. We later showed that reducing the leakiness could also lower this so-called interstitial fluid pressure and improve drug distribution in the tumor, thereby enhancing responses to various treatments meant to attack cancer cells.

More recently, our research has demonstrated that fluid pressure is not the only troubling physical force at work. Tumors are a mash-up of malignant cells, nonmalignant cells, and blood and lymph vessels, all embedded in a fibrous material known as the extracellular matrix. The solids—the matrix and cells—can squash the lymph and blood vessels. This compression, known to physicists and engineers as solid stress, may reduce or halt blood flow to many parts of the tumor, which can, in turn, reduce drug delivery and also set up conditions that foster cancer progression. Meanwhile the matrix—which is abnormally stiff in tumors and is more abundant in some cancers than in others—can directly impede the dissemination of anticancer drugs throughout a mass.

Knowing all the worrisome roles played by the tumor matrix, my colleagues and I have lately been searching for ways to diminish it. We have now found an approach that appeals to us in part because it relies on a class of medicines already known to be safe: certain drugs prescribed widely for high blood pres-

IN BRIEF

In a tumor, cells and a material called the matrix can squeeze blood vessels shut, preventing them from delivering anticancer drugs to many parts of the mass. The matrix can also directly retard dispersion of cancer-fighting agents through a tumor. **Squashing of blood vessels** can, moreover, deprive tumors of oxygen, an effect that can increase the aggressive behavior of cancer cells.

Evidence in mice indicates that depleting the matrix with a drug already used to control blood pressure can improve the perfusion of anticancer drugs in a tumor and improve survival rates.

This drug is now being tested in humans, and efforts are under way to find an agent that will deplete the matrix more effectively without lowering blood pressure too much.

sure. Human studies are under way to test such treatment in a type of pancreatic cancer that is one of the most matrix-rich and hardest-to-treat malignancies.

Of course, we cannot promise that matrix-depleting drugs will prove revolutionary. Cancer is actually many different diseases, all of them wily. But if the agents work as we hope, they could become a powerful new ally in the fight to prolong the lives of people stricken by cancers that too often defy eradication.

UNDER THE HOOD

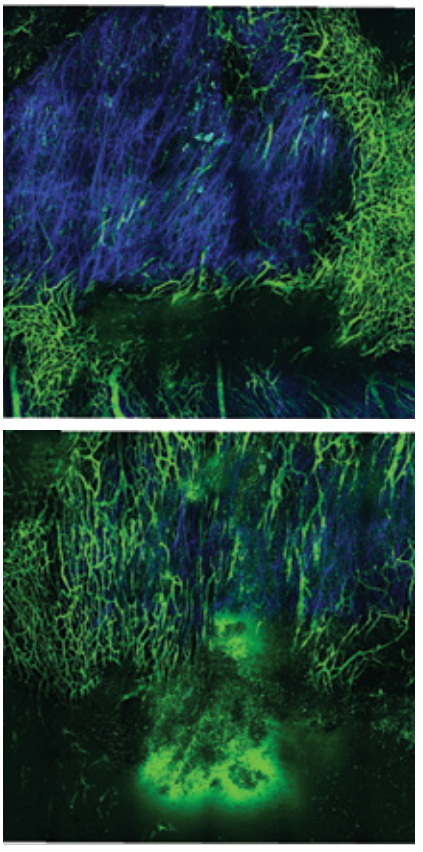
I BEGAN THINKING ABOUT interfering with the matrix after I learned that the compression of blood and lymph vessels in tumors causes a startling array of troubling effects. For instance, lymph vessels normally remove excess fluids from tumors and other tissues. When lymph vessels inside a tumor get squeezed shut, they cannot drain liquid that has leaked from the tumor blood vessels, and so fluid pressure increases. Meanwhile the compression reduces the already compromised ability of blood vessels to distribute blood—and thus oxygen, tumor-fighting immune cells and anticancer drugs—throughout a malignancy and leaves many areas deprived of oxygen.

This oxygen scarcity, or hypoxia, might sound like it would be a good thing, blocking a tumor's abillity to grow. In reality, however, it can be particularly nefarious. Oxygen deprivation in a tumor can spur malignant and even normal cells to secrete proteins that suppress the activity of tumor-fighting immune cells. One such protein, called vascular endothelial growth factor, or VEGF, also increases the leakiness of blood vessels, thereby further reducing blood flow in tumors and adding to the fluid pressure. Hypoxia, moreover, converts some immune cells from cancer fighters to cancer accomplices.

That is not all. Hypoxia favors survival of more malignant cells (those best able to invade tissues and spread) over less malignant ones, because the less dangerous cells tend to commit suicide when oxygen is scarce. What is worse, a dearth of oxygen can increase the invasive tendencies of cancer cells by, for example, inducing them to make proteins that help them travel away from the original mass. And oxygen deprivation undermines the functioning of many anticancer drugs.

The matrix also causes trouble in ways that do not involve oxygen deprivation and reduced drug delivery. My colleagues and I have recently discovered that mechanical compresssion can reprogram some cancer cells to become "leaders" that essentially start marching into nearby tissues and inducing other cells to follow. What is more, in a vicious cycle, compression and hypoxia can each prod dedicated matrix-producing cells, such as fibroblasts, to up their activity and can spur certain cancer cells to secrete matrix components even though nonmalignant versions of those cells do not paricipate in matrix production.

To be sure, my group understood the consequences of hypoxia even before we began work on the matrix, and we made an early priority of finding ways to reduce it. We first proposed about 13 years ago that "normalizing" the vessels—making them less twisted and leaky—would improve blood perfusion through the tumor and reduce fluid pressure, thereby reducing hypoxia and its effects and facilitating delivery of drugs and immune cells. We have now provided compelling evidence supporting this hypothesis in both animals and humans. Indeed, we have shown that restoring some normalcy to blood vessels—which can be achieved with inhibitors of new blood vessel formation (so-called antiangiogenic drugs)—is accompanied by increased blood flow and oxygen delivery through brain tumors and, crucially, can increase some patients' survival time. This mechanism can also explain increased survival in patients with colon, lung and kidney cancer who received the antiangiogenic drug bevacizumab together with chemotherapy (drugs that kill the rapidly dividing cancer cells) or immunotherapy (treatments that are meant to enhance the body's immune response against tumors).



MATRIX (*blue*) **in a mouse tumor decreased (*top to bottom*), and blood flow increased (*green at center*), in response to a matrix-depleting agent. In other animal tests, such changes have improved the efficacy of anticancer drugs.**

Researchers continue to optimize the approach, but it will never be enough on its own because fluid pressure is not what compresses blood and lymph vessels in tumors; the matrix and cells in a tumor do that. (When fluid pressure increases around leaky vessels, fluid seeps back through the pores, rather than collapsing the vessels [*see box on page 52*].) Antiangiogenic drugs cannot open vessels that are clamped shut by the matrix and cells. That is where our work on diminishing the matrix and thus alleviating the solid, compressive stress comes in.

Before searching for drugs that might deplete the matrix, we first wanted a better idea of how tumors differ in their abundance of the material and in how much stress the solid components exert. We found that cancers vary in this respect, although a look at many human tumor masses under the microscope told us that most harbor some collapsed vessels.

The extent of collapse depends in part on the stage of tumor progression and the location. Being in a confined space, for

FROM "ANGIOTENSIN INHIBITION ENHANCES DRUG DELIVERY AND POTENTIATES CHEMOTHERAPY BY DECOMPRESSING TUMOR BLOOD VESSELS," BY VIKASH P. CHAUHAN ET AL., IN *NATURE COMMUNICATIONS*, VOL. 4, ARTICLE NO. 2516; OCTOBER 1, 2013

instance, will increase compressive stress and the number of vessels that are partially or totally collapsed. The kind of tumor plays a role as well. The most common type of pancreatic cancer (pancreatic ductal adenocarcinoma), for instance, usually has relatively few cancer cells, which constitute less than 5 percent of the mass, and contains a lot of matrix and fibroblasts. Other cancers, though (such as medulloblastoma, the most common pediatric brain cancer), typically have relatively little matrix. Additional work has shown that, in general, tumors with a high ratio of matrix and fibroblasts to cancer cells—termed desmoplastic—tend to be least responsive to drug therapy, suggesting that reducing the amount of matrix in such masses might improve the odds that the drugs will reach their targets and thereby work better than usual.

FIRST TESTS

MY GROUP'S INITIAL EFFORTS at finding agents able to minimize the matrix were aided by a chance discovery. The matrix consists of protein fibers (mainly composed of collagen) and of gel-like components, such as hyaluronan. At one time, investigators thought that the gel-like molecules played a bigger role in interfering with drug delivery through tumors than collagen did. But in 2000 we found, to our surprise, that the stiffness of the tissue, which is a function of how much collagen it contains, is more important. We also found that breaking up the fibers with a collagen-degrading enzyme—collagenase—greatly increased distribution of a 150-nanometer particle meant to stand in for a drug, even in the most penetration-resistant tumors. (We tested particles of that size as proxies for the nanoscale medicines that are increasingly being studied as targeted cancer cell killers but that so far have seen only modest success.) Following up on this discovery, we showed that tumors in mice shrank more when we injected the masses with a collagenase along with 150-nanometer viral particles meant to kill cancer cells than when we injected the viral particles without collagenase.

As interesting as that result was, we knew that administering an enzyme that would degrade collagen throughout the body would be problematic in humans: collagen gives structure to our bones and tissues. We needed a safer drug that worked in tumors without producing widespread effects. But what?

We soon considered a hormone called relaxin, which women produce during pregnancy. Relaxin inhibits collagen synthesis and enhances its breakdown, and mothers-to-be make a lot of it with no ill effects. We therefore wondered whether it might be used to decrease collagen in tumors.

In 2002 we treated tumor-bearing mice with relaxin for two weeks. Sure enough, it reorganized collagen, making it more porous and improved dispersion through the tumors of large molecules that we used as stand-ins for drugs. Others confirmed our findings with different tumors. But then we learned of research indicating that that relaxin could enhance the progression of some tumors, such as those in the prostate. Given the disparity of findings and the risks involved, we knew we could never test such a drug for cancer therapy in humans.

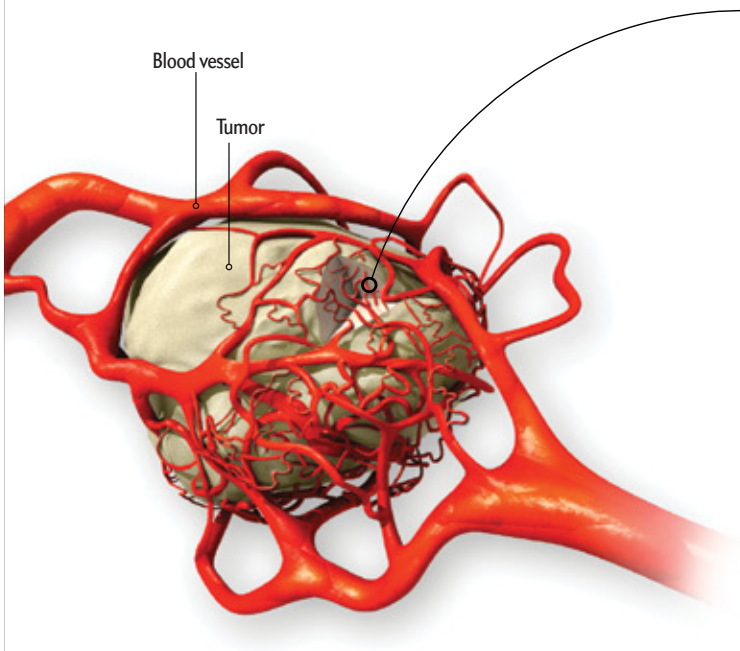
BETTER LUCK THIS TIME

DISAPPOINTED, WE STARTED to search for other agents. We decided to focus on attacking one key player involved in collagen synthesis—a protein named transforming growth factor beta. We found a possible way to do that when we realized that a class of medicines commonly used to treat hypertension (high blood pressure) not only lowers blood pressure but, usefully for us, has a second effect in the body: inhibiting the growth factor's activity. What is more, these widely prescribed agents—which lower blood pressure by inhibiting a hormone called angiotensin II—also impair the function of a second molecule, involved in stabilizing collagen. We knew that various angiotensin inhibitors, including one called losartan, reduce levels of several forms of collagen in laboratory animals that have excessive amounts of extracellular matrix and can reverse such excess in the kidneys and hearts of hypertensive patients. But we could not find any published research addressing the effect of these

BARRIERS TO DRUG DELIVERY

Forces to Be Reckoned With

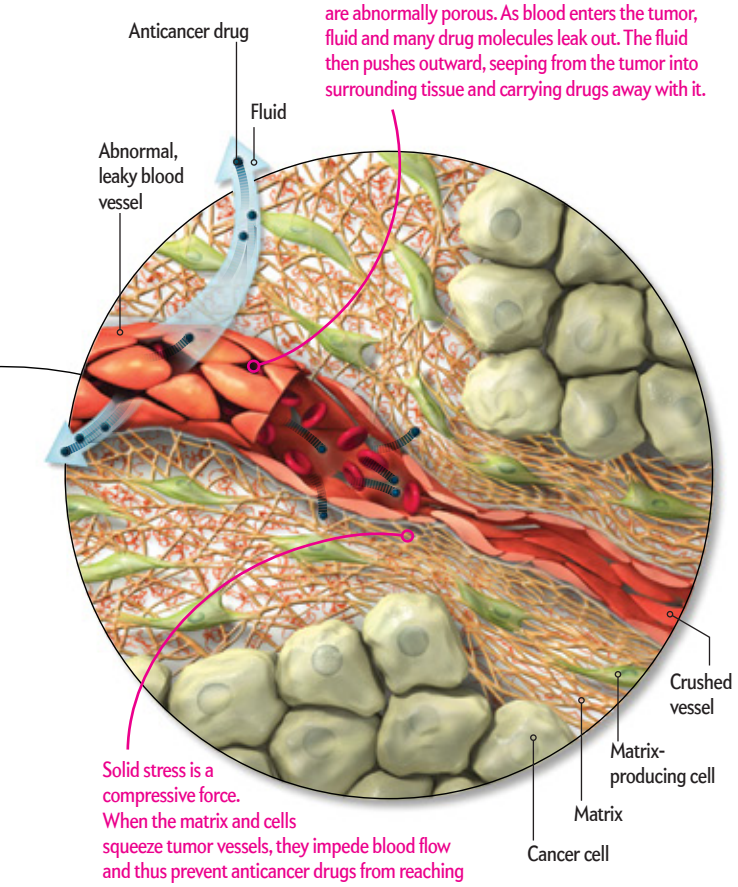
In theory, anticancer drugs delivered to a tumor via the bloodstream would reach everywhere in the mass and attack all cancer cells within it. But forces exerted by fluid and solids in the tumor—including those known as fluid pressure and solid stress—can be high enough to block the drugs from reaching many of the cells they are meant to kill (*right*). Cancer specialists already have access to agents that can help reduce fluid pressure. And now, as the author explains in this article, researchers think they may also have a way to reduce the solid stress, which is exerted by the matrix and cells (*far right*).



Illustrations by Emily Cooper

The Barriers

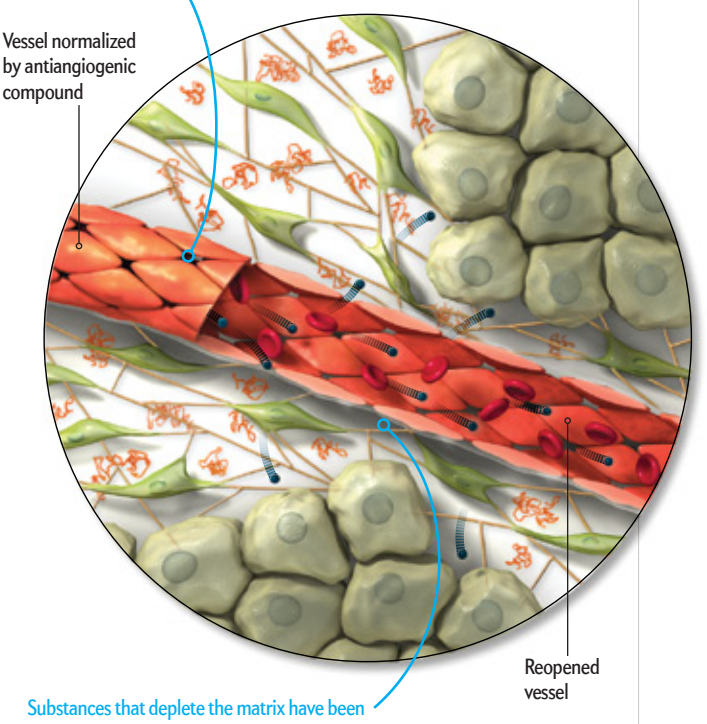
Fluid pressure is often high because tumor vessels are abnormally porous. As blood enters the tumor, fluid and many drug molecules leak out. The fluid then pushes outward, seeping from the tumor into surrounding tissue and carrying drugs away with it.



Solid stress is a compressive force. When the matrix and cells squeeze tumor vessels, they impede blood flow and thus prevent anticancer drugs from reaching malignant cells beyond the crushed region. At the same time, the matrix can trap drug molecules, further limiting their dispersal in a mass. Crushing of blood vessels can also starve tumors of oxygen, an effect that can promote a cancer's spread and hinder immune attacks on it (*not shown*).

Solutions

"Antiangiogenic" medicines can reduce fluid pressure and have been used in cancer care for about 10 years. They are best known for inhibiting the formation of new tumor blood vessels. But they can also "normalize" blood vessels, making them less leaky, so that less fluid seeps out and drugs can penetrate farther into a tumor.



Substances that deplete the matrix have been shown in mice to reduce solid stress and thus enhance tumor blood flow and the dispersal of anticancer drugs. These matrix-depleting substances include a common blood pressure medicine that is now being tested in patients with pancreatic cancer to see if it will improve the effectivenesss of anticancer drugs.

drugs on collagen levels or on compressive stress in tumors.

To see if angiotensin blockers might diminish the matrix in tumors and thus improve the distribution of drugs that attack malignant cells, we gave losartan for two weeks to mice bearing four different types of matrix-rich tumors: pancreatic ductal adenocarcinoma, breast cancer, the skin cancer melanoma and cancer arising from connective tissue (sarcoma). We saw two encouraging effects. Collagen decreased in the tumors, and the 100-nanometer particles we delivered as proxies for cancer cell–killing drugs suffused tumors more fully than usual. We concluded that better penetration by the proxies occurred because of reductions in the collagen content. Follow-up studies in rodents, published in 2011, proved the case with actual nanomedicines: the FDA-approved drug Doxil (about 100 nanometers in diameter) and viral particles (about 150 nanometers) that kill cancer cells.

During the course of our research, we also discovered that the higher the losartan dose, the greater the decrease in collagen. Such dose dependence is a good sign that a drug being tested accounts for an observed effect. The finding implied as well that doses of losartan higher than those we tested earlier might decrease collagen so much that the blood vessels in even matrix-rich tumors would open up enough to allow anticancer drugs to flow readily through tumor vessels and reach areas of the masses that formerly received no blood. Indeed, in mice, doubling the dose depleted collagen in matrix-rich breast and pancreatic tumors, opened up blood vessels and improved the delivery and efficacy not just of nanoscale drugs but also of standard chemotherapies used to treat these cancers.

We then wondered whether high-enough doses of losartan or other antihypertensives would increase the effectiveness of conventional chemotherapy and nanomedicines in humans with cancer. We do not have a definitive answer yet, but we have reason to be encouraged. Reviews of past studies involving cancer patients who also had hypertension, and thus received both cancer therapy and blood pressure medicines, imply that certain antihypertensive agents do seem to improve outcomes somewhat. One analysis of past research indicated, for example, that in combination with the anticancer drug gemcitabine, inhibitors of angiotensin or of certain related enzymes increased overall survival in pancreatic ductal adenocarcinoma patients by about six months relative to the survival achieved with chemotherapy alone.

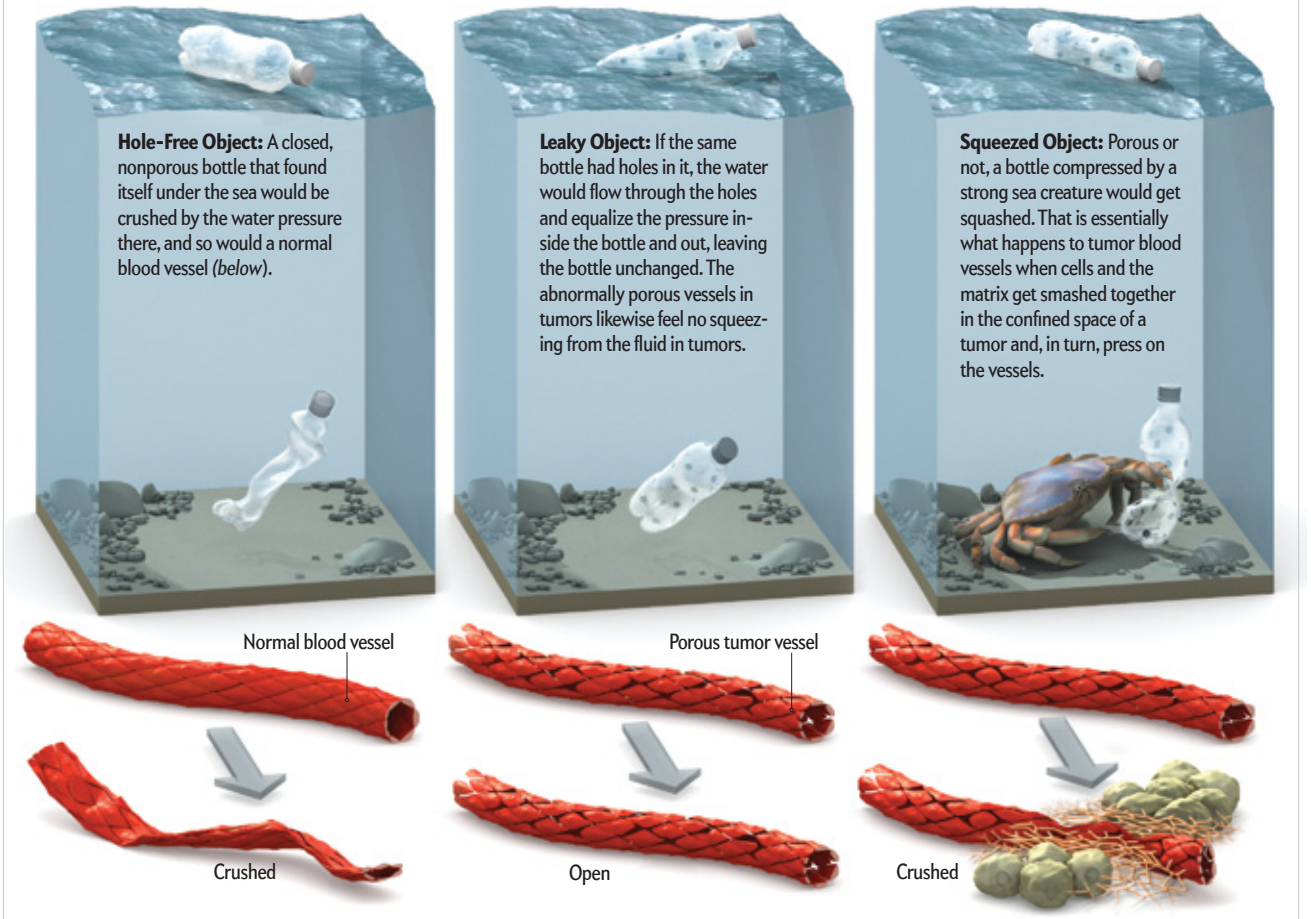
Of course, retrospective studies have their limitations, but the data in cancer patients who were treated for hypertension are consistent with our findings in mice and provide a basis for testing angiotensin blockers as matrix-depleting agents in humans. Accordingly, a group at Massachusetts General Hospital has initiated a trial of losartan with standard chemotherapy in patients with pancreatic ductal adenocarcinoma, which has a five-year survival rate of less than 6 percent. (I am not involved in this trial.) The results could be available in a couple of years. In the future, if all goes well, I can imagine improving patient care by delivering a combination of therapies that would include vessel-normalizing drugs (such as VEGF blockers), matrix-depleting agents and targeted cancer cell killers.

As is true of most medicines, antihypertensive drugs have some drawbacks. They cannot be given to people who have certain kidney diseases or who have low blood pressure. Even for patients with normal blood pressure, the doses need to be carefully monitored to avoid severe drops in blood pressure. These problems might be addressed by finding ways to alter angiotensin-blocking agents so that they retain the ability to diminish the matrix but do not also lower blood pressure. My colleagues and I are pursuing that goal. Still, tumors tend to develop resistance to most medicines. Whether they will show resistance to losartan or other angiotensin blockers is not known.

TUMOR PHYSICS 101

Why Only Solids Squeeze Tumor Vessels

People are often surprised to learn that only the matrix and cells in tumors squeeze blood vessels shut; the fluid buildup does not play a role in that effect. The author likes to explain the logic by analogy to a plastic soft-drink bottle dropped into the ocean.



SOURCE: LANCE L. MUNN *Edwin L. Steele Laboratory for Tumor Biology, Harvard Medical School and Massachusetts General Hospital*

SCIENTIFIC AMERICAN ONLINE Watch a video demonstrating the compressive stress in tumors at ScientificAmerican.com/feb2014/matrix

To improve treatment, researchers need to not only gain a better understanding of cancer's genetic underpinnings but also consider the physical forces in tumors.

ALTERNATIVES

WHAT ABOUT PATIENTS who cannot take antihypertensives or whose tumors do not respond well or persistently to them? Specifically targeting the nonfibrous, hyaluronan molecules in tumors might be another way to attack the matrix. Hyaluronan is abundant in about 25 percent of human tumors, such as pancreatic ductal adenocarcinomas and breast, colon and prostate cancers. We have recently shown that an enzyme that depletes it, a hyaluronidase, can indeed reduce solid stress in tumors grown in mice. We have shown as well that losartan can reduce hyaluronan in tumors. Others have demonstrated that a hyaluronidase can decompress blood vessels. Based on the latter studies, a formulation of the enzyme (called PEGPH20) is now in a clinical trial for pancreatic cancer. We and other groups have also had some success in the lab with certain other drugs known to act in part by affecting the matrix.

To perfect matrix-depleting therapy, researchers need ways to measure the response of the matrix to various test agents. Do substances that disrupt the tumor matrix actually reduce mechanical compression? Which ones are most effective? And does the degree of reduction make a difference to the success of more traditional cancer drugs delivered at the same time? Progress is being made on this front as well. A new imaging method, known as second-harmonic generation, should help investigators see and measure collagen in tumors. In addition, my colleagues and I have found a relatively simple way to gauge compressive stress in a tumor: When a tumor is cut in half, the halves spontaneously swell. Measuring the swelling and applying mathematical formulas we developed reveals the amount of stress the interior was under.

I am sometimes asked if depleting the matrix would make it easier for cancer cells to metastasize—to move through the matrix into blood and lymph vessels and then out into other parts of the body. Similarly, people wonder if digesting the matrix or otherwise opening vessels and improving blood flow through a tumor would help tumor cells escape into the circulation or promote tumor growth by delivering more nutrients to cancer cells, or both. These concerns need further study, but several observations suggest that therapies able to ease compressive stress and otherwise normalize vessels would *not* foster tumor growth and metastasis. Why? On one hand, it is true that nutrients would reach tumor cells, which would also be freer to move around; on the other hand, the oxygen deprivation that promotes tumor progression, impairs immune responsiveness and lowers the efficacy of many therapies would be reduced. Moreover, greater quantities of delivered drugs and potentially more immune cells would be fanning out through the tumor and in the normalized, more open blood vessels to counteract any tumor-friendly effects of the therapy. Ongoing animal and human studies will show which of these effects are most powerful.

FOLLOW THE LOGIC

BACK WHEN MY COLLEAGUES and I first started considering angiotensin blockers for combating cancer, others we consulted discouraged us from pursuing this line of work. Because the agents *reduce* blood pressure, the thinking went, they would cause tumor blood flow to go down, not up. Furthermore, studies involving delivery of angiotensin—which, in contrast to angiotensin blockade, *elevates* blood pressure—found increased tumor blood flow in many studies of mice and humans. But that work did not consider the compressive effects of the matrix, and a trial assessing the effectiveness of angiotensin therapy for treating cancer in patients failed. A few years later we explained the failure: the drug enhanced blood flow only transiently, presumably because compressive stress quickly closed off the affected vessels.

As cancer researchers look to the future, we need to not only gain a better understanding of the genetic and cellular underpinnings of cancer but also consider the consequences of physical forces in tumors. We need to exploit all this knowledge to fully discern the laws that govern tumor progression and learn how to improve cancer detection and treatment. Solid tumors exploit physical forces for their survival. It is time for us to exploit our own knowledge of physics to fight back. SA

Disclosure of commercial ties: *Rakesh K. Jain co-founded, has equity in, and sits on the board of directors of XTuit, a company that is developing anticancer therapies. XTuit and Massachusetts General Hospital have applied for drug patents based on the work summarized in this article. Jain also receives grants and consulting fees from and advises several other companies involved in cancer research.*

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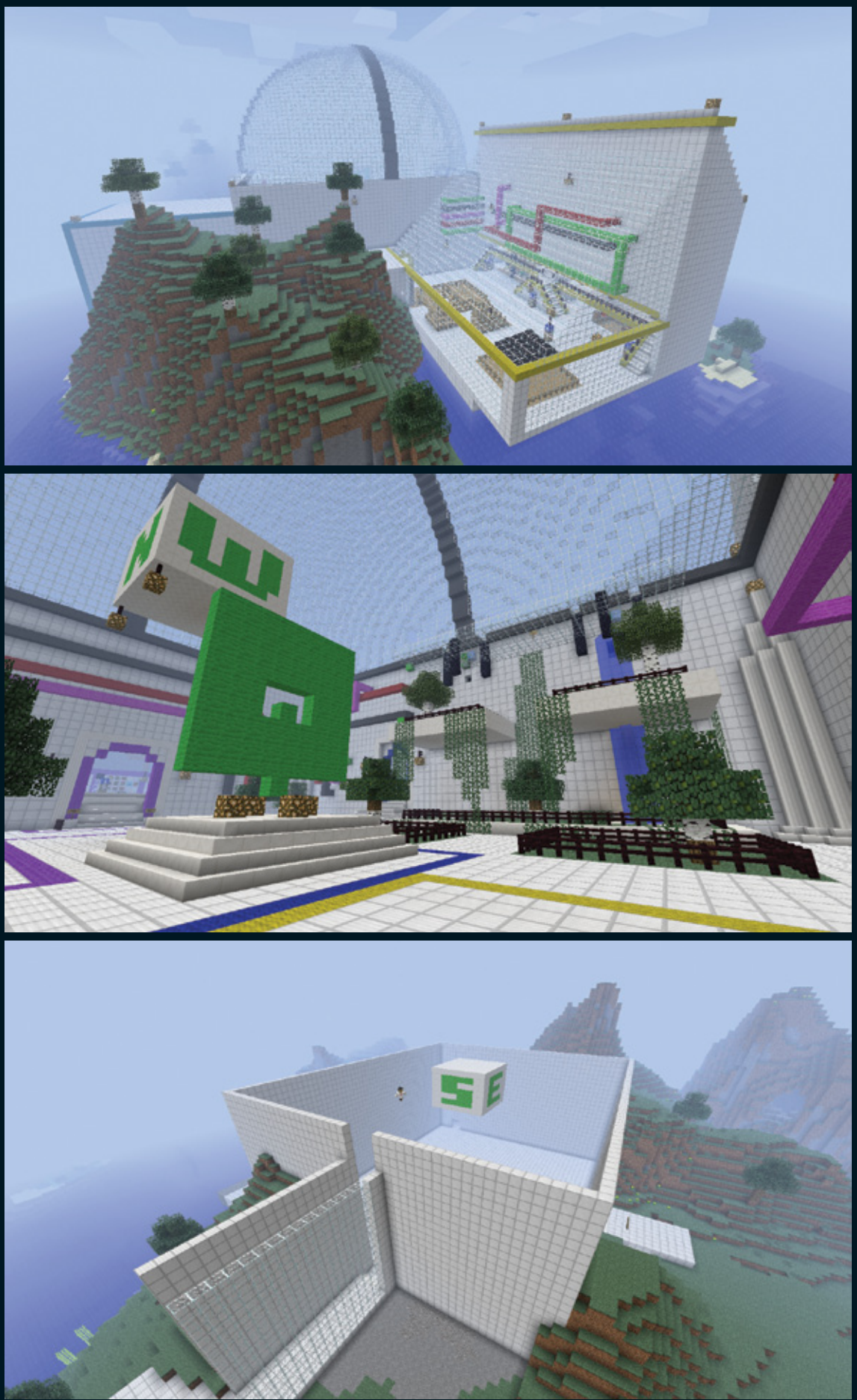

QCRAFT, a modification to the game Minecraft, introduces players to entanglement and other quantum oddities.

INFORMATION TECHNOLOGY

Video games could transform education. But first, game designers, teachers and parents have to move beyond both hype and fear

By Alan Gershenfeld

Alan Gershenfeld is co-founder and president of E-Line Media, a publisher of computer and video games, and a Founding Industry Fellow at Arizona State University's Center for Games & Impact. He is presenting his work on games for social good at this year's World Economic Forum Annual Meeting in Davos, Switzerland.

In 1993, the year I began my career in video games, the public face of the industry was Mortal Kombat. In this martial-arts fighting game, two players would pummel each other until one opponent was sufficiently stunned—and then deliver a "Fatality" move. One character could grab his opponent's head and then rip his spinal cord out of his still standing body. Not surprisingly, parents, teachers and politicians were horrified. Congress held hearings about the game and its influence on youth. The episode led to the creation of the Entertainment Software Rating Board, which today rates games based on their age appropriateness.

My friends and family thought I was crazy for working in the game industry, particularly because I had left a good career in independent filmmaking to do it. They were convinced that video games were frivolous at best, dangerous at worst. Yet when I started my work as a studio executive at Activision, a popular video game publisher, it quickly became clear that games were much more diverse and textured than most people realized. They were not only an emerging entertainment medium—they were a new art form.

At the core, video games are about verbs, what the player *does* in a game. While most people focus on the action-game verbs—running, jumping, fighting, shooting—I have always been fascinated by the verbs used in adventure, strategy, simulation and puzzle games. These games are about exploring, evaluating, choosing, deciding and solving. For example, Spycraft, an action game we developed with William Colby, former head of the CIA, and Oleg Kalugin, a former major general of the KGB, confronted players with complex moral and ethical choices based on real-life experiences. In the simulation game Civilization: Call to Power, players had to make complex decisions about how to build and sustain an empire by balancing cultural, diplomatic, military and scientific advancements.

Although these games had many enthusiastic fans, they were low profile compared with the big action games. By the mid-1990s the public associated video games with first-person-shooter games, in which players careened through three-dimensional environments, mowing down enemies with extravagant weapons. Once it was discovered that the high school shooters in the Columbine massacre of 1999 were avid fans of this genre, video games were again vilified.

Today the gap in how video games are perceived is wider than ever. On one hand, conferences, articles and best-selling books are making the case that games and "gamification"—applying the principles of game design to solve real-world challenges—can save the planet. On the other hand, parents struggle with the amount of time their kids spend on digital media—roughly eight hours a day on average. And it is hard for parents to watch their children spend hours gleefully annihilating virtual humans with heavy artillery and not be concerned.

Yet the fact remains that video games have great potential to help confront the educational challenges of the 21st century. My company, E-Line Media, is working with the National Science Foundation, the Smithsonian Institution, the U.S. Agency for International Development, the Bill & Melinda Gates Foundation, the MacArthur Foundation, the AMD Foundation, the Defense Advanced Research Projects Agency, the White House Office of Science and Technology Policy, Intel, Google, the Massachusetts Institute of Technology's Center for Bits and Atoms, and Arizona State University's Center for Games & Impact, to name a few, all in an effort to figure out how to use video games to improve education. We are learning that it will take a good deal of R&D to get this right.

IN BRIEF

New research shows that video games have great educational potential. A good game can exercise higher-order skills—evidence-based reasoning, problem solving, collaboration—in ways that traditional pedagogy often does not.

But at the moment the hype exceeds the reality. Game developers must work with educators and scientists to design games for inside and outside the classroom that deliver educational benefits—and that kids want to play.

PAGE 54: COURTESY OF QCRAFT.ORG

STUDENTS at the Quest to Learn school in New York City play Gamestar Mechanic, which introduces them to game design—a creative process that exercises many of the higher-order skills emphasized in the Common Core curriculum.

COURTESY OF E-LINE MEDIA (*comic scenes*); COURTESY OF INSTITUTE OF PLAY (*children playing game*)

THE CLASS OF 2024

TEN YEARS FROM NOW today's second graders will graduate from high school in a world of some eight billion people. As adults, they will have to adapt to climate change, water scarcity, urbanization and other complex challenges. They will have to do jobs that do not currently exist, master technologies that have not yet been developed, and build skills that cannot be replaced by technology or outsourced to the cheapest labor. They will need to be scientifically literate and socially adept. They will need to be able to understand complex systems, think critically, propose solutions based on evidence (sometimes emerging and conflicting), and persist despite challenges.

Too many schools do a poor job of fostering these abilities. Most students enter elementary school with a natural curiosity about how the world works, but all too often, by the end of middle school, we have beaten this out of them. Every eight seconds an American public high school student drops out of school; over the next decade that alone will cost the nation an estimated $3 trillion in lost wages, productivity and taxes. Forty-six percent of college students fail to graduate with any credential within six years.

Clearly, for many kids, traditional education is neither relevant nor engaging. Digital games, on the other hand, captivate them. Ninety-seven percent of American teenagers regularly play video games. Fortunately, even games that seem to have no redeeming value can deliver positive, lasting neuropsychological effects. Daphne Bavelier, a psychologist at the University of Geneva, has shown that violent action games can, over time, increase a player's brain plasticity and learning capacity, improve vision and perceptually motivated decision making, sharpen a person's ability to tune out distraction, and strengthen the ability to mentally "rotate" objects.

Games are different from other popular media in that they are interactive and participatory. They enable players to step into different roles (scientist, adventurer, inventor, political leader), confront problems, make choices and explore the consequences. They enable players to advance at their own pace and to fail in a safe environment. Most significant, they give players *agency*—the ability to make a difference in both virtual and real-world environments.

Scientists are discovering a powerful alignment between good game design and effective learning. This research is emerging at a time of great disruption in education. Low-cost tablets and laptops are becoming ubiquitous in schools, but most teachers are still not sure how to use them in the classroom. Schools nationwide are working to implement the new Common Core standards and Next Generation Science Standards, which focus on higher-order skills, but traditional curricula and pedagogy are proving ineffective at delivering them.

Game-based learning has the potential to help tackle many of these challenges. Educators can use games to rethink curricula. Students can use them to exercise critical thinking, problem-solving skills, creativity and collaboration. Games can put the joy and wonderment back into science and scientific inquiry.

That is the good news. The bad news is that a large gap exists between the potential and the reality. Most game-based-learning projects have great difficulty making the transition from research into widely used educational products. As a result, the rhetoric around games and learning can feel overhyped.

My colleague Michael Angst and I founded E-Line Media to help close this gap. But it will take more than one company. The best game designers in the industry will have to work together with scientists and educators to build games informed by the most recent research into learning, behavior and neuroscience.

GAMES IN THE CLASSROOM

GAMES WILL HAVE the deepest impact on learning when they become a meaningful part of the school experience. There are a couple of ways this can happen—with "bounded" games that one plays and finishes (a strategy game that can be won, for example) and by using the principles of game design to restructure learning.

New research is enhancing our understanding of both. For example, scientists at the M.I.T. Education Arcade, in collaboration with the developers of a financial-literacy game called Celebrity Calamity, have shown how a bounded game can be a useful precursor to formal learning. The experiment involved two learning sequences: one in which students first played the game and then listened to a lecture and one in which the order was reversed. They found that students who went straight to the lecture did not know what to listen for, whereas students who played the game first had better context and greater motivation.

Teachers who grew up playing games are particularly adept at finding ways to integrate game play into the classroom. As an example, two social studies teachers in Texas, frustrated by their students' hatred of history, developed a middle school history

IN THE GAME Never Alone (*Kisima Ingittchuna*), a young Inupiat girl must stop Blizzard Man, an anthropomorphization of a deadly storm based on Alaska Native storytelling tradition. At the right, a concept sketch in which the land comes to life.

curriculum inspired by the commercial video game Civilization. They called it Historia. Working on paper, teams of students led fictional civilizations, competing alongside (and sometimes against) the great empires of the past. Students researched history to understand how their decisions would impact the economic, military and cultural strength of their civilization. Initially the teachers encountered resistance from parents and administrators, but once standardized test scores started improving, the dissent quickly disappeared. At E-Line, we are now working on a digital version of Historia, which we will pilot this spring and release this fall.

As it turns out, making a good video game also requires a complex set of higher-order skills—thinking analytically and holistically, experimenting with and testing out theories, creating and collaborating with peers and mentors. That is why the M.I.T. Media Lab developed a programming language, Scratch, that enables kids as young as kindergartners to build games. Microsoft has developed a similar tool called Kodu. And high schools and colleges are increasingly offering instruction in tools used in professional game creation such as Unity, Flash and Java.

At E-Line, our contribution to this genre is Gamestar Mechanic, which we are developing in partnership with the MacArthur Foundation and the New York City–based nonprofit Institute of Play. The game is designed for students between the ages of eight and 14. Working solo or in groups, they log on to a PC or Mac and learn the fundamentals of game design by playing and fixing broken games. On a community site, they can publish and collaborate on games. They can review games, reflect on their own ideas and defend their design decisions. Since Gamestar Mechanic was launched in the fall of 2010, more than 6,000 schools and after-school programs have started using it. Students have published more than 500,000 original games, which have been played more than 15 million times in 100 countries.

Game designers are also adapting commercial games for the classroom. SimCityEdu, for example, is an educational version of the famous simulation game SimCity, created through a partnership among the Bill & Melinda Gates Foundation, the MacArthur Foundation, the game company Electronic Arts, the Entertainment Software Association, the Institute of Play, the publisher Pearson and the Educational Testing Service, which administers the SAT. The company Valve has also developed an educational version of its popular game Portal, in which the player is dropped into a mysterious laboratory and has to solve a series of puzzles to survive. The educational version, called Teach with Portals, is designed to make "physics, math, logic, spatial reasoning, probability, and problem solving interesting, cool and fun."

EDUCATION BY STEALTH

KIDS ARE UNLIKELY TO EMBRACE Call of Duty: Calculus in their discretionary playtime. Nevertheless, we believe there is a large audience for games that explore challenging themes and that open new worlds—as long as they are truly great games.

There are precedents in other media. In the film industry, for example, Participant Media has had success making movies that "inspire and accelerate social change." Examples include *Good Night, and Good Luck, Syriana* and *Lincoln*.

We think this same approach can work with games. Many game designers have families of their own and would rather use their craft to empower youth than to work on yet another $50-million first-person shooter.

At E-Line, our first major project in this field is a collaboration with the Cook Inlet Tribal Council (CITC), a pioneering Alaska Native social service organization. CITC has launched the first U.S.-based indigenous-owned video game company, Upper One Games. Together we are developing a new genre—game-based cultural storytelling—that emphasizes cultural heritage and intergenerational wisdom. The first consumer game we will release is the action-adventure game Never Alone (*Kisima Ingittchuna*), in which the player will take on the role of a young Inupiat girl facing a struggle for survival. Along with her companion, a young fox, the player must overcome obstacles and fears in the harsh and beautiful Arctic landscape. The game is framed as a series of interconnected stories told by elders to youth; both the narrative and core game-play mechanics explore how interdependence, adaptation and resiliency are critical for survival in challenging circumstances. It will be available for game consoles (Sony PlayStation and Microsoft Xbox) as well as for PCs and Macs.

So far, though, the best example of a game that transcends commercial and educational boundaries has to be Minecraft. It is a phenomenon unlike any that I have seen in my career. Originally developed by Swedish programmer Markus "Notch" Persson, the game has become a global phenomenon, with more than 25 million players, mostly tweens. Minecraft players roam freely and

COURTESY OF E-LINE MEDIA

SCIENTIFIC AMERICAN ONLINE See clips from the new crop of educational games at ScientificAmerican.com/feb2014/games

Realizing the full educational potential of video games will involve addressing the good and the bad. Many teachers and parents are still skeptical.

build Lego-like worlds, either individually or collaboratively. In "Survival" mode, the player must build shelter before it gets dark and the bad guys come out. To do so, the player must find the resources ("mine") and make tools ("craft"). Once safe from the bad guys—or in the game's enemy-free "Creative" mode—players build almost anything. A quick whirl through Minecraft creations on YouTube will reveal models of virtually every iconic building on the globe—the Eiffel Tower, the Taj Mahal and, my favorite, a scale model of China's Forbidden City, built from nearly 4.5 million blocks, complete with a roller coaster to take you on a tour.

Not only is Minecraft immersive and creative, it is also an excellent platform for making almost any subject area more engaging. We recently worked on a project with Google, the California Institute of Technology, TeacherGaming (co-founded by Joel Levin, a private school teacher in New York City who began using Minecraft in the classroom shortly after the game was released and quickly gained a global following as the "Minecraft Teacher") and leading Minecraft "modder" Daniel Ratcliffe to develop qCraft, a modification ("mod") to the game that introduces players to the bizarre world of quantum mechanics.

To demonstrate the concept of observational dependency, qCraft blocks change shape and color depending on who is looking at them and from which direction. Entangled blocks are inextricably linked, even if they are a vast distance apart. Superpositional blocks are more than one thing at once.

On the qCraft blog last November, Levin explained the rationale for the project: "By the time our 7-year-old finishes grad school, quantum computers may be commonplace.… Some of the hardest problems in medicine, aerospace, statistics, and more will be tackled by machines using qubits instead of bits.… It is our firm belief that when a young person who has played qCraft encounters these challenging concepts again, they will have an increased intuitive understanding."

THE NEXT MOVE

REALIZING THE FULL educational potential of games will involve addressing the good and the bad. Many parents, teachers and policy makers are still skeptical.

An ongoing concern is violence—the question of whether playing violent video games leads to real-world violent behavior. The issue is highly polarized. The game industry points to countries such as Japan and South Korea, avid consumers of violent games that also have some of the lowest rates of gun violence in the world. They also highlight multiple studies showing that while playing violent games may increase short-term aggressive behavior, there is no correlation to the type of violent behavior exhibited by, for example, school shooters. On the other side of the debate, many parents will refer to a cluster of studies that reinforce some of the connections between games and violence. They will argue that because games can have positive learning effects, does it not stand to reason that they can have negative effects as well?

The fact is that violent behavior is a complex problem that is driven by a variety of environmental and biological determinants. We need to create a research agenda to objectively study the impact that games have in a variety of contexts. This research would help industry, policy makers, parents and teachers, along with law-enforcement and mental health professionals, to maximize the benefits and minimize the drawbacks of the medium.

An increasing number of parents also express concern about the amount of time their children spend playing games. Digital media consumption is like food consumption—it is important to have a balanced diet, and each person's diet is different. The more informed and engaged the parent, the better the outcome for the child. By playing games with their kids, parents can become more savvy observers; they can tell whether their child is learning to code in Minecraft or playing a 50th Hunger Games death match (a popular Minecraft mod inspired by Suzanne Collins's book trilogy). Innovative approaches to game design can also help. Games can be optimized for shorter play cycles, or they can incorporate real-world activities—exercise tracked through an accelerometer, for example—into game-play loops.

Over the next few decades everything about video gaming will become more intense. Technology and design advances will make video games ever more realistic, fantastical and ubiquitous. We will see gaming extend into consumer virtual-reality devices, wearable computing, and beyond. These new technologies will unlock opportunities to use games for social good. They are also likely to intensify the concerns that parents and policy makers already have. That is why it is so important that, starting now, we give video games the proper attention they deserve. SA

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ANIMAL BEHAVIOR

Brainy birds

Chickens are smart, and they understand their world, which raises troubling questions about how they are treated on factory farms

By Carolynn "K-lynn" L. Smith and Sarah L. Zielinski

Carolynn "K-lynn" L. Smith is a research fellow at Macquarie University in Sydney, Australia. Her research investigates communication and cognition in animals ranging from giant cuttlefish to elephants. She is the joint recipient of a 2010 Australian Museum Eureka Prize.

Sarah L. Zielinski is a freelance science writer in Washington, D.C. Her work has appeared in *Science*, *Science News* and *Smithsonian*, among other publications.

IN THE ANIMAL KINGDOM, SOME CREATURES ARE SMARTER THAN OTHERS. BIRDS, IN PARTICULAR, exhibit many remarkable skills once thought to be restricted to humans: Magpies recognize their reflection in a mirror. New Caledonian crows construct tools and learn these skills from their elders. African grey parrots can count, categorize objects by color and shape, and learn to understand human words. And a sulfur-crested cockatoo named Snowball can dance to a beat.

Few people think about the chicken as intelligent, however. In recent years, though, scientists have learned that this bird can be deceptive and cunning, that it possesses communication skills on par with those of some primates and that it uses sophisticated signals to convey its intentions. When making decisions, the chicken takes into account its own prior experience and knowledge surrounding the situation. It can solve complex problems and empathizes with individuals that are in danger.

These new insights into the chicken mind hint that certain complex cognitive abilities traditionally attributed to primates alone may be more widespread in the animal kingdom than previously thought. The findings also have ethical implications for how society treats farmed chickens: recognizing that chickens have these cognitive traits compels moral consideration of the conditions they endure as a result of production systems designed to make chicken meat and eggs as widely available and cheap as possible.

CHATTY CHICKENS

IT HAS TAKEN RESEARCHERS almost a century to figure out what is going on in the brains of chickens. The first inklings emerged from studies conducted in the 1920s, when Norwegian biologist Thorleif Schjelderup-Ebbe established that the birds have a dominance system, which he named the "pecking order" after noting that chickens will enforce their leadership by administering a sharp peck of the beak to underlings whenever they get ideas above their station.

The next major breakthrough in understanding the chicken mind came several decades later. The late Nicholas and Elsie Collias, both at the University of California, Los Angeles, categorized the birds' calls and determined that chickens have a repertoire of about 24 different sounds, many of which seem to be specific to certain events. For example, when faced with a threat from above, such as a hungry eagle, the birds crouch and emit a very quiet, high-pitched "eeee." The clucking sound that most people associate with chickens is actually one they use when encountering a ground predator. The discovery of food elicits an excited series of "dock dock" sounds from males, especially when a judgmental female could be listening.

These early findings suggested that more happens in the chicken's walnut-size brain than one might think. The vocalizations appeared to encode specific information intended to evoke a particular response from onlookers. Yet connecting these sounds and movements with their true meaning proved difficult until the development, in the 1990s, of technology that allowed researchers to test their hypotheses more rigorously. It was then that the late Chris Evans of Macquarie University in Sydney, Australia, and others began to use digital audio-recording devices and high-resolution televisions to test the function of chickens' array of sounds under controlled conditions. In essence, they created a virtual reality for the birds, surrounding a test cage with TVs that allowed them to change what a chicken encountered—a companion, a competitor, a predator—and to record how it responded to a variety of situations. A test chicken might see a simulated hawk flying overhead, or a fox running toward it from the side, or a rooster making a series of dock-dock sounds.

IN BRIEF

Mounting evidence indicates that the common chicken is much smarter than it has been given credit for.

The birds are cunning, devious and capable of empathy. And they have sophisticated communication skills.

That chickens are so brainy hints that such intelligence is more common in the animal kingdom than once thought.

This emerging picture of the chicken mind also has ethical implications for how society treats farmed birds.

PRECEDING PAGE: CARLTON DAVIS *Trunk Archive*

FACTORY-FARMED CHICKENS, such as these hens on a farm in Fleurus, Belgium, often live in extremely crowded conditions.

YVES LOGGHE *Ap Photo*

This virtual reality led to a truly astonishing revelation: the sounds or movements an individual chicken makes convey specific information, and other chickens understand it. A chicken need not see an aerial predator, for instance, to behave as if one was there; it needs only to hear the warning call from another bird. The chickens' calls are "functionally referential," as behaviorists would say—meaning that they refer to specific objects and events broadly in the way that words used by people do. In a chicken hearing the calls, the sounds appear to create a mental picture of that particular object, prompting the bird to respond accordingly—whether to flee a predator or approach a food source.

The virtual world also revealed that individual chickens tailor their messages for their audience. A rooster that sees a threat overhead, for example, would make an alarm call if he knows a female is nearby, but he would remain silent in the presence of a rival male. Females are equally selective, only sending up an alarm when they have chicks.

Taken together, these findings suggested the sounds did not simply reflect a bird's internal state, such as "frightened" or "hungry." Instead the chickens interpreted the significance of events and responded not by simple reflex but with well-thought-out actions. Chickens, it seems, think before they act—a trait more typically associated with large-brained mammals than with birds.

BY HOOK OR BY CROOK

THE REFERENTIAL CALLS showed that chickens are more cognitively sophisticated than they have been given credit for. The research also raised an intriguing question: If these birds have the ability to communicate information about environmental events, might they also withhold that news or even broadcast misinformation when they stand to benefit from such deceitful behavior? Further insights have come from studies of other forms of chicken signaling.

Scientists have known since the 1940s that the birds perform complex visual displays in connection with the discovery of food. The most prominent of these displays is a series of actions collectively called tidbitting, in which an alpha rooster twitches his head rapidly from side to side and bobs it up and down, picking up and dropping food over and over again to signal to a female that he has found something tasty. This performance is the main way he lures a mate. Scientists thought the subordinate males, for their part, focus on keeping a low profile, so as to avoid attracting negative attention from the alpha. Yet some observations of chickens in their social groups hinted that the pecking order of the birds might not be quite as orderly as researchers initially thought. In fact, mounting evidence indicated that chickens could be devious bastards.

Human observers initially missed this underlying drama because interactions between members of the flock are short and often secretive; the birds prefer to hide in the tall grass and among the bushes. At the same time, it is just not possible for a single person to monitor all the chickens at the same time. To minimize those difficulties, one of us (Smith) came up with a solution she called "Chicken Big Brother."

Smith and her colleagues wired the outdoor aviaries at Macquarie University—large outdoor spaces with lots of vegetation, surrounded by nets on all sides—with multiple high-definition cameras and an array of microphones to catch every move and sound the birds made. They then analyzed the resulting recordings.

As expected, the alpha in any group would crow to show he was the master of the territory. He would perform the tidbitting display to attract the ladies. And he would make alarm calls to warn the flock of danger from above.

It was the subordinates that provided the twist. The team expected that these males should keep to themselves, to avoid the harassment of being chased, pecked and spurred by the alpha if they dared to make a play for his girl. Yet the cameras and microphones revealed a more complex story. These lesser males employed surreptitious tactics in a way previously thought impossible for the birds: they performed only the visual part of tidbitting—making the head motions without making the dock-dock sound—thus creating a new signal that could quietly attract a mate while sidestepping the wrath of the alpha rooster.

The fact that the subordinate males modify the tidbitting signal in this way to secretly seduce the hens demonstrated a behavioral flexibility that shocked researchers. But they had yet to plumb the full depths of the birds' deviousness.

To examine the animals' behavior more closely, they added more technology to their tool kit. The chickens' vocalizations were often so subtle that Smith and the other researchers were unable to catch them, even with the extensive camera-and-microphone setup. They needed a way to record every call as it was made and heard by each of the individual chickens.

Ideally, they would outfit the chickens with little backpacks carrying lightweight wireless microphones similar to those reporters wear when working out in the field. But where to find the right materials for those packs? Bras, Smith thought, could do the trick. She began a hunt for old ones with easy-to-latch hooks and preferably colored black so they would not stand out against the feathers. Smith cut off the hooks and adjustable straps and attached these parts to the microphone to create a harness. Once strapped to a bird's waist, the jury-rigged apparatus—affectionately dubbed Chicken Big Brother 2.0—would record what the chicken said and heard.

Smith was particularly keen to take a closer look at how the animals respond to danger. The previous research showing that males would sometimes call out when they saw an aerial predator, such as a hawk, was puzzling because making those squeals would place the rooster at greater risk of getting noticed and attacked himself. Scientists had assumed that the male's need to protect his mate and offspring was so critical that making the call was worth the risk. Yet Smith wondered if other factors influence the calling behavior.

It turns out they do. Using Chicken Big Brother 2.0 to eavesdrop on even the quietest communications revealed that males sometimes made calls for selfish reasons. The birds monitored the danger to themselves and their rivals and were more likely to call if they could both minimize their own risk and increase a rival's. A male calls more often if he is safe under a bush and his rival is out in the open, at risk of being picked off by a swooping predator. If the rooster is lucky, he will protect his girl, and another guy will suffer the consequences.

This strategy is known as risk compensation, and it is yet another skill that chickens have in common with humans. Many of us will take on more risk if we perceive a mitigating factor. Peo-

FINDINGS

The Virtual Chicken Experiments

The knowledge that chickens will watch one another on television inspired one of us (Smith) and her colleagues to create a 3-D animated rooster using the same rendering technology employed in movies such as *Skyfall* and *Titanic*. This virtual rooster allowed the team to test the meaning of the birds' displays and their perceptions of one another. It also solved the age-old question of why roosters have wattles.

The wattle is that dangling flap of skin that hangs loosely from a rooster's beak. When a male performs his tidbitting display—a series of head movements that he uses to tell potential mates that he has found food—the wattle swings back and forth, even smacking him in the side of the head if he gets too enthusiastic.

Decades of research had failed to find any benefit to the male's having a wattle. Smith suspected that the flap of skin might make a male's tidbitting display more obvious and give him an edge in attracting the females, but she could not test her idea by cutting off the appendage and seeing how a female reacted. Instead she created an animated rooster that would tidbit on command for a live hen and then altered the flexibility and size of the wattle on her animated bird to test how the females would react.

The wattle, it turned out, acts like a red flag to the females, making it easier for a hen to spot the male who has the food. For the male, the ornament may cost him a bit in terms of his health because a bigger wattle comes with more testosterone, which weakens the immune system, but the cost is worth it in the long run because it gets him the girls.

Sometimes the chickens' intelligence made studying them challenging. On multiple occasions a bird would subvert an experiment by answering a different question than the one the researcher was posing. In a test of the tidbitting display, Smith had created a setup in which a hen got a chance to watch a video of a male with food. To do so, the female had to wait behind a door that had been rigged with a remote-controlled servo stripped from a toy car. One hen that wore an orange band with the numbers 07 (and thus affectionately dubbed "007") was notorious for getting into trouble. While waiting for the researcher to open the door via remote control, 007 grew impatient and began examining the release mechanism closely, turning her head from side to side. After a few moments, she carefully plucked the wire that controlled the latch. The door opened, and 007 got what she wanted: to be close to the guy and his food. After that single trial, she would never wait again. Although the researchers changed the latch configuration several times, 007 was always able to solve the puzzle and escape before her turn.

—C.L.S. and S.L.Z.

SCIENTIFIC AMERICAN ONLINE Watch a video of the virtual rooster at ScientificAmerican.com/feb2014/chickens

ple will drive faster when wearing a seat belt, for example, or when in a car equipped with antilock brakes. Male chickens will likewise take more risks if they feel more secure.

MOTHER HEN

THE CHICKEN'S LIST of cognitive skills continues to grow with each scientific discovery. Giorgio Vallortigara of the University of Trento in Italy has shown that young chicks have the ability to distinguish numbers and use geometry. Given a half-completed triangle, for example, chicks can identify what the shape should look like with all its parts. And research published in 2011 by Joanne Edgar of the University of Bristol in England and her colleagues revealed a softer side of these sometimes Machiavellian birds, demonstrating that they are capable of feeling empathy.

In Edgar's experiment, mother hens watched as their chicks received a harmless puff of air that ruffled their downy plumage. The chicks perceived the puff as a threat and showed classic signs of stress, including increased heart rate and lowered eye temperature. Intriguingly, their mothers also became upset simply by observing their chicks' reaction. They showed the same signs of stress the chicks exhibited even though the hens themselves did not receive the puff of air and the chicks were in no obvious danger. The hens also made more clucking calls to their chicks. These findings indicate that chickens can take the perspective of other birds—an ability previously seen in only a handful of species, including ravens, squirrels and, of course, humans.

The chicken's flexibility and adaptability, derived from its social red junglefowl ancestor, may have been part of its undoing.

The fact that the common chicken, which is not closely related to other bird species known for their braininess, has such advanced cognition suggests something interesting about the origin of intelligence. Perhaps it is rather more common in the animal kingdom than researchers have thought, emerging whenever social conditions favor it as opposed to being a rare, difficult-to-evolve trait.

For its part, the chicken presumably inherited its cognitive prowess from its wild ancestor, the red junglefowl, which lives in the forests of southern and Southeast Asia. There the ancestral chicken society consisted of long-term, semistable groups of four to 13 individuals of varying ages. A dominant male and a dominant female headed each group, and as in many other societies, those in charge got what they wanted, whether it be food, space or sex, mostly by keeping their subordinates in line. Males spent much of their time strutting their stuff for the females and providing them with food; females carefully observed the males, judging them on their actions and remembering what each had done in the past; they shunned the ones that were deceptive or nasty. A rooster's reputation was important to his long-term success with the hens, and competition for the females was fierce.

Competition within the flock was not the only source of pressure on the birds' mental capacity. They also faced a range of threats from outside the flock—including predators such as foxes and hawks—each of which necessitated a different escape strategy. These conditions forced the fowl to develop clever strategies for dealing with one another and the dangers around them, as well as ways to communicate about all these situations. Those characteristics are still present in the domestic chicken.

That such a litany of abilities belongs to animals that humans eat by the billions naturally raises questions about how they are treated. Birds that would typically live in small flocks in the wild can be penned in with up to 50,000 others. A potential 10-year life span is shortened to a mere six weeks for chickens raised for meat. They are killed so young because these birds have been genetically selected for such fast growth that allowing them to become any older would subject them to heart disease, osteoporosis and broken bones. Egg layers fare little better, living only 18 months in a space about the size of a sheet of printer paper.

The chicken's flexibility and adaptability, derived from its social red junglefowl ancestor, may have been part of its undoing, letting the birds survive even under the unnatural and intense conditions in which humans now raise them. This type of farming will likely continue as long as most people are unconcerned about where their food comes from and unaware of chickens' remarkable nature.

Consumers have begun to effect change, however. In Europe and some U.S. states, such as California, new laws are being passed that require improved housing conditions for egg-laying chickens, largely driven by buyer demand for better animal welfare, as well as healthier food. In Australia, producers now actually highlight the positive conditions under which they raise their animals, competing for a growing population of ethical consumers. Yet there is still more to be done. The conditions under which meat chickens are raised have largely gone unscrutinized.

Researchers have just begun to elucidate the true nature of chicken intelligence, but one thing is already certain: these birds are hardly the "dumb clucks" people once thought them to be. SA

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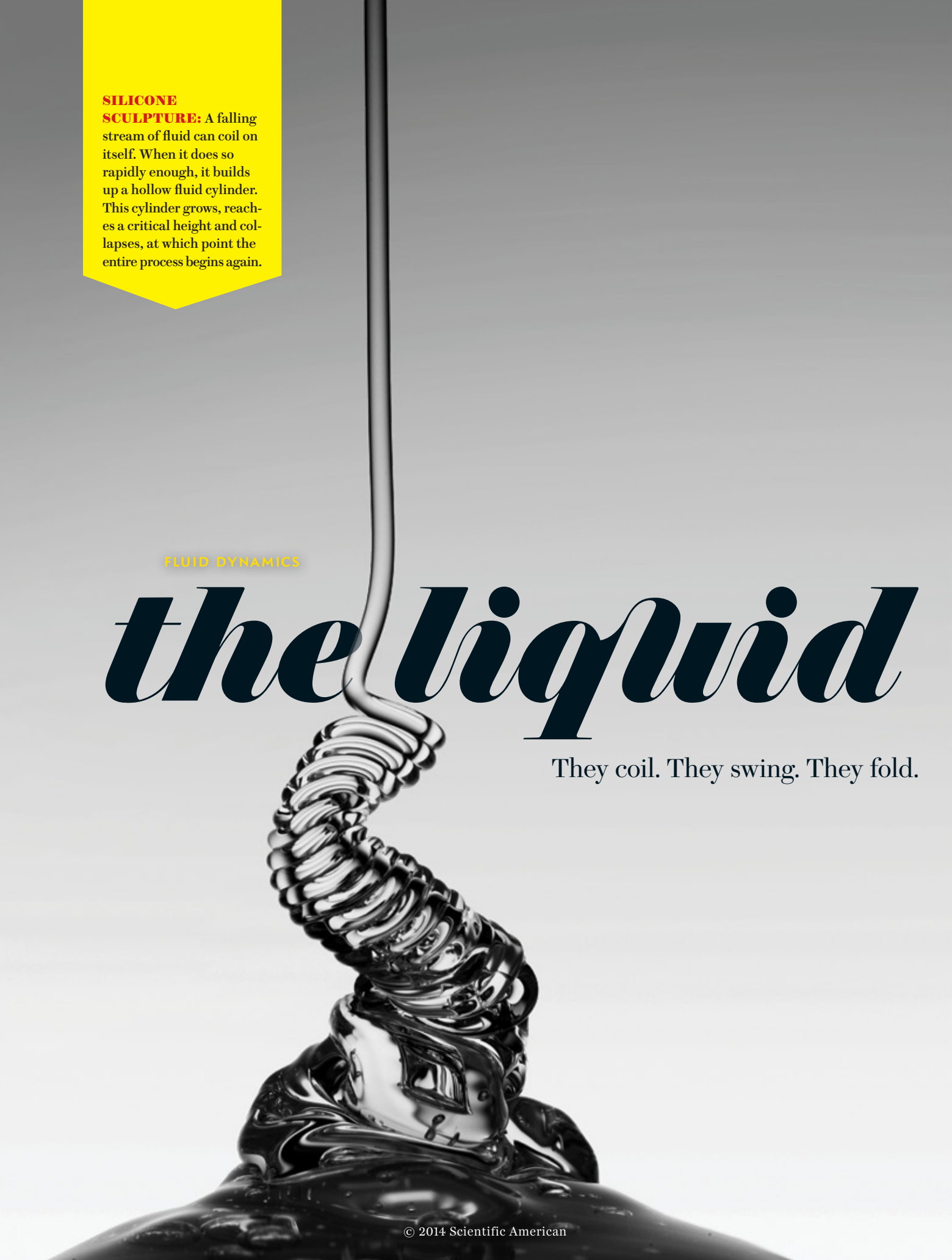


SILICONE SCULPTURE: A falling stream of fluid can coil on itself. When it does so rapidly enough, it builds up a hollow fluid cylinder. This cylinder grows, reaches a critical height and collapses, at which point the entire process begins again.

FLUID DYNAMICS

the liquid

They coil. They swing. They fold.

Neil M. Ribe is a physicist specializing in fluid mechanics and the physics of the earth's interior. He is director of the FAST laboratory in Orsay, France. His other interests include the history of science (with a focus on optics and color theory) and music (piano and singing).

Mehdi Habibi is a visiting scientist in the physics department of the University of Amsterdam, before which he was a professor at the Institute for Advanced Studies in Basic Sciences in Zanjan, Iran. In his spare time, he enjoys swimming and mountain climbing.

Daniel Bonn is an experimental physicist working on fluid mechanics. He is a professor at the University of Amsterdam; during part of the research described in this article, he was a CNRS researcher at L'École Normale Supérieure in Paris. In his free time, he is an avid sailor.

rope trick

They meander. Streams of honey, oil and other viscous fluids can do things that physicists still don't fully understand

By Neil M. Ribe, Mehdi Habibi and Daniel Bonn

IN BRIEF

When dribbled onto a surface, viscous fluids such as honey coil into a helix and form what look like miniature baskets. Only recently have physicists systematically studied the process and its unexpected complexity.

Four distinct styles of coiling can occur depending on the balance of gravitational, frictional and inertial forces on the descending stream. Additional behaviors, such as folding, occur in less viscous fluids.

Strange phenomena such as spiral waves of bubbles and "sewing"—the latter occurs when the fluid stream and surface are in relative motion, as in Jackson Pollock's action painting—have yet to be explained fully.

Photographs by Damien Ropero

IF YOU LIKE HONEY ON YOUR TOAST AT BREAKFAST, YOU ARE READY TO PERFORM ONE OF THE SIMPLEST and most beautiful experiments in the physics of fluids. Plunge a spoon into the honey jar, take it out and then hold it vertically, several centimeters above the toast. The thin stream of falling honey does not approach the toast directly but instead builds up a whirling helical structure. In the late 1950s the resemblance to a pile of coiled rope led the first investigators of this phenomenon, George Barnes and Richard Woodcock, to call it the liquid rope-coil effect.

The three of us had long been fascinated by this effect but never found the opportunity to study it until 10 years ago, when Ribe and Bonn discovered their shared interest by chance at a scientific workshop in Paris. At the time, Bonn had a collaboration with the Institute for Advanced Studies in Basic Sciences in Zanjan, Iran, so we invited Habibi and several others—including, at different times, Ramin Golestanian, Maniya Maleki, Yasser Rahmani and Seyed Hossein Hosseini—to complete the team.

Together we developed a controlled version of the breakfast-table experiment, using silicone oils rather than honey because they come in a broad range of viscosities. Viscosity is a measure of how thick a fluid is—how much it resists flowing because of internal friction. With our apparatus, we vary the flow conditions (such as the rate at which the fluid streams downward and the height from which it drops) and see how they affect the coiling frequency (how fast the descending column of fluid wraps around).

When we began, we expected coiling to be an all-or-nothing affair that either happened or did not depending on the experimental conditions. We were therefore totally unprepared for the wealth of unexpected behavior that we found. For instance, for a slow flow rate, we found that the farther the fluid fell, the slower it coiled. Yet for higher flow rates, we found just the opposite: as the fall height increased, the frequency also increased rapidly. Moreover, when the fall height was fixed at a certain value, the coiling rope jumped back and forth in a seemingly random way between two states with different frequencies.

In parallel with the experiments, we developed a mathematical model to identify the basic principles at work. The starting point was Newton's laws of motion written in a form appropriate for a slender liquid rope whose length is much greater than its diameter. Two main types of forces act on any piece of such a rope: the downward pull of gravity and the internal viscous, or frictional, forces. The rope can deform in three distinct ways—stretching, bending and twisting—and each of these has an associated viscous force that opposes it. The shape of the rope depends on the relative magnitudes of all these forces as well as the inertia of the fluid (that is, mass times acceleration). The surface tension force, important for many other fluid flows, turned out to have only a minor effect here.

Do the Twist

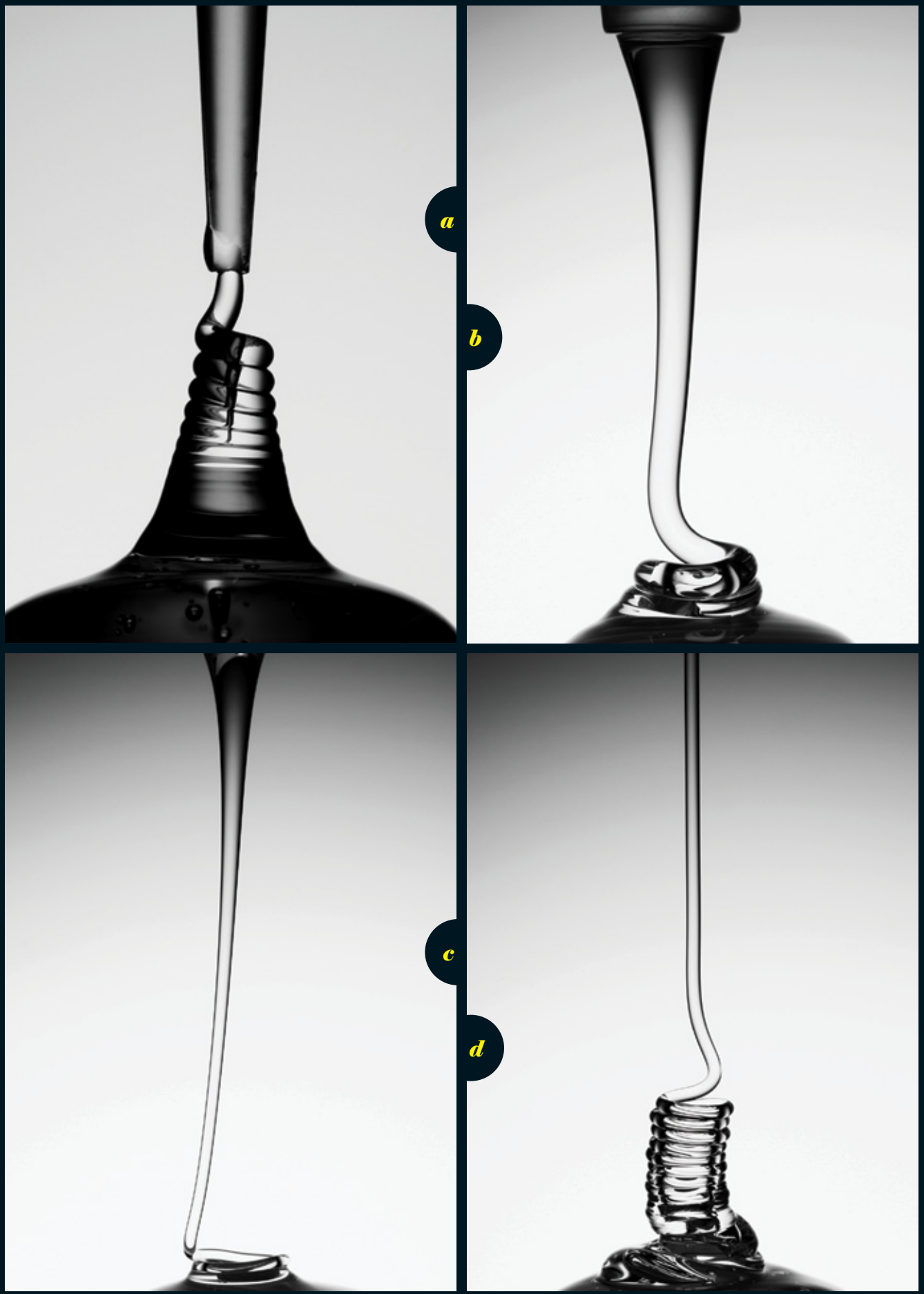
Falling streams of thick fluid can coil in four distinct styles depending on the balance of gravity, inertia and viscous (frictional) forces. In these examples, the authors dribbled silicone oil onto a metal plate of variable height. The stream had a diameter of 0.7 millimeter and flowed at 0.23 milliliter per minute. Oils of the viscosity used here (100,000 centistokes, or cSt) would require a couple of minutes to drain off a spoon. By comparison, water at room temperature has a viscosity of 1 cSt; honey, 10,000 cSt.

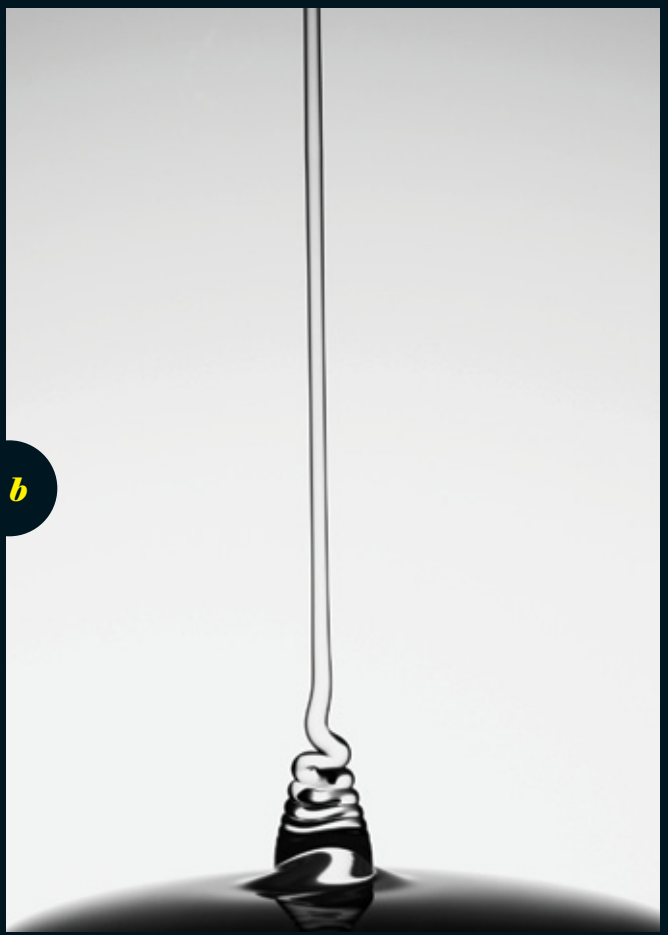
***a* Viscous mode.** When falling from a low height—4 to 8 mm—the rope behaves like toothpaste squeezed slowly from a tube. The fluid coils so slowly that both gravity and inertia are negligible relative to viscous forces. The dominant viscous force is the one that resists bending.

***b* Gravitational mode.** In the height range of 1.5 to 7 cm, gravity becomes a factor. The rope has a two-part structure, with a long tail above and a shorter coil below. In the tail, gravity balances the viscous resistance to stretching, whereas in the coil it balances the viscous resistance to bending. The force balance in the tail makes it behave like a hanging chain that is pulled sideways at its lower end by the coil.

***c* Pendulum mode.** In the height range of 7 to 12 cm, the tail swishes back and forth like a pendulum, albeit a somewhat unusual one, because its mass is spread out rather than concentrated in a single hanging weight. For most heights, the tail is unable to swing freely because its motion is driven at the bottom by coil formation. But for certain heights the imposed frequency matches one of the tail's natural pendulum frequencies—a self-reinforcing situation called resonance. The tail then whirls in a wide circle.

***d* Inertial mode.** Above 15 cm, the tail is almost perfectly vertical because the coil no longer exerts a significant sideways pull on it. Within the coil the viscous force that resists bending is balanced almost entirely by inertia, with gravity playing only a minor role.





Beyond Simple Coiling

Runny fluids, unlike the thick, viscous kind, are able to do much more than just coil. In these examples, the authors used oils with viscosities from 400 to 6,000 cSt—runnier than honey but thicker than water.

***a* Stagnation flow.** For relatively low viscosity, short fall heights and high flow rates, the fluid falls straight down and spreads out equally in all directions over the plate. These conditions apply to common household fluids such as water and olive oil. That said, even these fluids can be made to coil under the right conditions. If you could pour olive oil from a height of 10 cm at a rate of 1 mL over 40 minutes, it would coil.

***b* Rotary folding.** The rope folds back on itself periodically while the entire folding pattern itself rotates about a vertical axis, creating a twisting effect.

***c* Supercoiling.** Supercoiling is the technical term for what happens to twisted telephone cords, which experience large secondary coiling on top of the tightly coiled structure they already have. In the case of fluids, the descending stream creates a hollow cylinder, which in turn coils as a whole. The secondary coiling is more sedate, occurring about a tenth as fast as the primary coiling.

Spiral Bubble Waves

We discovered this galaxylike pattern by chance while doing experiments with a high-viscosity (30,000 cSt) silicone oil at a high flow rate (0.14 mL per second) and low fall heights (3 to 4 cm). The spirals always have five branches. They occur because the center of the coil is not fixed but instead moves along a circular orbit of its own, creating crossing points between successive loops of the coiling rope where air bubbles are easily trapped. The position of the trapping point migrates slowly around a circle while previously formed bubbles are carried radially outward by the fluid spreading over the plate. It is the sum of these two motions that produces the spirals.

Solving the equations proved to be challenging. In most textbook problems of physics, the boundaries of the system are specified, and the student's task is to determine what is going on inside them. In contrast, liquid rope coiling is what physicists call a "free boundary" problem, in which the shape of the boundary is part of the problem we are trying to solve. With care, we were able to show that coiling in highly viscous fluids can occur in four distinct modes, each involving a different force balance [*see box on page 68*].

SPIRAL BUBBLE WAVES

HAVING MAPPED OUT the general types of coiling, we imagined that we had a fairly complete picture—but we were wrong. Further experiments, conducted in an exploratory way with no preconceived ideas, revealed remarkable new phenomena.

The first was the appearance of beautiful spiral waves of air bubbles in the thin layer of fluid that spreads away from the coiling rope [*see box above*]. They form when the successive loops of the rope are slightly offset from one another, trapping small air pockets. We still do not understand, however, why the spirals have precisely the shape they do or why they only occur for narrow ranges of fluid viscosity, flow rate and fall height.

We also played with silicone oils of much lower viscosity. These fluids coiled more quickly—up to 2,000 times per second—so we needed high-speed cameras to record their behavior. The fluids could coil and even fold in much more complex ways [*see box on opposite page*]. A given state would persist indefinitely if left undisturbed yet would suddenly switch to another if we gave the apparatus a strong tap with our knuckles.

In all the above experiments, the thin stream of liquid fell onto a stationary surface. But new effects can arise if the surface and the source of the liquid move relative to each other—as observed by Jackson Pollock in his action painting and by manufacturers of textiles using molten polymer threads. Our colleagues Keith Moffatt, Sunny Chiu-Webster and John Lister, all then at the University of Cambridge, experimented with these situations using what amounts to a fluid sewing machine, which extrudes a single thread of viscous fluid onto a horizontal belt moving at a constant speed. At high speeds, the dragged thread leaves a straight trace on the belt. But as the belt slows down, more complex, unsteady patterns emerge, such as meandering, alternating loops, double coiling and even a W shape.

We still have a long way to go before we understand liquid ropes fully. A top priority is to understand the physical mechanism behind spiral bubble waves. Why does the center of the coil start to move in a separate orbit? Another goal is to model the complex secondary coiling that occurs in lower-viscosity fluids. We also plan to extend our exploration to more exotic systems, including complex fluids with nonstandard responses to applied forces, as well as electrically charged fluids coiling at microscales and nanoscales in an electric field. Judging by our past experience, many more surprises are in store for us. SA

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SCIENTIFIC AMERICAN ONLINE Find instructions for running your own coiling experiments and links to videos of liquid rope coiling at ScientificAmerican.com/feb2014/coils

Why you should not be surprised when long shots, miracles and other extraordinary events occur—even when the same six winning lottery numbers come up in two successive drawings

By David J. Hand

MATHEMATICS

NEVER SAY NEVER

A SET OF MATHEMATICAL LAWS THAT I CALL THE IMPROBABILITY PRINCIPLE TELLS US THAT WE should not be surprised by coincidences. In fact, we should *expect* coincidences to happen. One of the key strands of the principle is the law of truly large numbers. This law says that given enough opportunities, we should expect a specified event to happen, no matter how unlikely it may be at each opportunity. Sometimes, though, when there are really many opportunities, it can look as if there are only relatively few. This misperception leads us to grossly underestimate the probability of an event: we think something is incredibly unlikely, when it's actually very likely, perhaps almost certain.

Adapted from The Improbability Principle: Why Coincidences, Miracles, and Rare Events Happen Every Day, *by David J. Hand, by arrangement with Scientific American/Farrar, Straus and Giroux, LLC (North America), Transworld (UK), Ambo|Anthos (Holland), C. H. Beck (Germany), Companhia das Letras (Brazil), Grupa Wydawnicza Foksal (Poland), Locus Publishing Co. (Taiwan), AST (Russia).*

How can a huge number of opportunities occur without people realizing they are there? The law of combinations, a related strand of the Improbability Principle, points the way. It says: the number of combinations of interacting elements increases exponentially with the number of elements. The "birthday problem" is a well-known example.

The birthday problem poses the following question: How many people must be in a room to make it more likely than not that two of them share the same birthday?

The answer is just 23. If there are 23 or more people in the room, then it's more likely than not that two will have the same birthday.

Illustration by Paul Blow

Now, if you haven't encountered the birthday problem before, this might strike you as surprising. Twenty-three might sound far too small a number. Perhaps you reasoned as follows: There's only a one-in-365 chance that any particular other person will have the same birthday as me. So there's a 364/365 chance that any particular person will have a different birthday from me. If there are n people in the room, with each of the other $n - 1$ having a probability of 364/365 of having a different birthday from me, then the probability that all $n - 1$ have a different birthday from me is $364/365 \times 364/365 \times 364/365 \times 364/365 \ldots \times 364/365$, with 364/365 multiplied together $n - 1$ times. If n is 23, this is 0.94.

Because that's the probability that none of them share my birthday, the probability that at least one of them has the same birthday as me is just 1 – 0.94. (This follows by reasoning that either someone has the same birthday as me or that no one has the same birthday as me, so the probabilities of these two events must add up to 1.) Now, 1 – 0.94 = 0.06. That's very small.

Yet this is the wrong calculation to consider because that probability—the probability that someone has the same birthday as you—is not what the question asked. It asked about the probability that *any* two people in the same room have the same birthday as *each other*. This includes the probability that one of the others has the same birthday as you, which is what I calculated above, but it also includes the probability that two or more of the other people share the same birthday, different from yours.

This is where the combinations kick in. Whereas there are only $n - 1$ people who might share the same birthday as you, there are a total of $n \times (n - 1)/2$ pairs of people in the room. This number of pairs grows rapidly as n gets larger. When n equals 23, it's 253, which is more than 10 times as large as $n - 1 = 22$. That is, if there are 23 people in the room, there are 253 possible pairs of people but only 22 pairs that include you.

So let's look at the probability that none of the 23 people in the room share the same birthday. For two people, the probability that the second person doesn't have the same birthday as the first is 364/365. Then the probability that those two are different *and* that a third doesn't share the same birthday as either of them is $364/365 \times 363/365$. Likewise, the probability that those three have different birthdays *and* that the fourth does not share the same birthday as any of those first three is $364/365 \times 363/365 \times 362/365$. Continuing like this, the probability that none of the 23 people share the same birthday is $364/365 \times 363/365 \times 362/365 \times 361/365 \ldots \times 343/365$.

This equals 0.49. Because the probability that none of the 23 people share the same birthday is 0.49, the probability that some of them share the same birthday is just 1 – 0.49, or 0.51, which is greater than half.

David J. Hand is an emeritus professor of mathematics and senior research investigator at Imperial College London. He is a former president of the Royal Statistical Society and author of *Statistics: A Very Short Introduction* (Oxford University Press, 2008).

WINNING THE LOTTERY

FOR ANOTHER EXAMPLE of how a seemingly improbable event is actually quite probable, let's look at lotteries. On September 6, 2009, the Bulgarian lottery randomly selected as the winning numbers 4, 15, 23, 24, 35, 42. There is nothing surprising about these numbers. The digits that make up the numbers are all low values—1, 2, 3, 4 or 5—but that is not so unusual. Also, there is a consecutive pair of values, 23 and 24, although this happens far more often than is generally appreciated (if you ask people to randomly choose six numbers from 1 to 49, for example, they choose consecutive pairs less often than pure chance would).

What was surprising was what happened four days later: on September 10, the Bulgarian lottery randomly selected as the winning numbers 4, 15, 23, 24, 35, 42—exactly the same numbers as the previous week. The event caused something of a media storm at the time. "This is happening for the first time in the 52-year history of the lottery. We are absolutely stunned to see such a freak coincidence, but it did happen," a spokeswoman was quoted as saying in a September 18 Reuters article. Bulgaria's then sports minister Svilen Neikov ordered an investigation. Could a massive fraud have been perpetrated? Had the previous numbers somehow been copied?

In fact, this rather stunning coincidence was simply another example of the Improbability Principle, in the form of the law of truly large numbers amplified by the law of combinations. First, many lotteries are conducted around the world. Second, they occur time after time, year in and year out. This rapidly adds up to a large number of opportunities for lottery numbers to repeat. And third, the law of combinations comes into effect: each time a lottery result is drawn, it could contain the same numbers as produced in *any* of the previous draws. In general, as with the birthday situation, if you run a lottery n times, there are $n \times (n - 1)/2$ pairs of lottery draws that could have a matching string of numbers.

The Bulgarian lottery that repeated numbers in 2009 is a six-out-of-49 lottery, so the chance of any particular set of six numbers coming up is one in 13,983,816. That means that the chance that any particular two draws will match is one in 13,983,816. But what about the chance that *some* two draws

IN BRIEF

What we think of as extremely unlikely events actually happen around us all the time. The mathematical law of truly large numbers as well as the law of combinations help to explain why. **With only 23 people** in a room, the probability that two of them share the same birthday is 0.51—greater than 50 percent. **The Bulgarian** lottery randomly selected the winning numbers 4, 15, 23, 24, 35, 42 on September 6, 2009. Four days later it selected the same numbers again. The North Carolina Cash 5 lottery produced the same winning numbers on July 9 and 11, 2007. Strange? Not according to probability.

SCIENTIFIC AMERICAN ONLINE See probabilities of your chances for getting ill at ScientificAmerican.com/feb2014/hand

among three draws will match? Or the chance that *some* two draws among 50 draws will match?

There are three possible pairs among three draws but 1,225 among 50 draws. The law of combinations is coming into play. If we take it further, among 1,000 draws there are 499,500 possible pairs. In other words, if we multiply the number of draws by 20, increasing it from 50 to 1,000, the impact on the number of pairs is much greater, multiplying it by almost 408 and increasing it from 1,225 to 499,500. We are entering the realm of truly large numbers.

How many draws would be needed so that the probability of drawing the same six numbers twice was greater than one half—so that this event was more likely than not? Using the same method we used in the birthday problem results in an answer of 4,404.

If two draws occur each week, making 104 in a year, this number of draws will take less than 43 years. That means that after 43 years, it is more likely than not that some two of the sets of six numbers drawn by the lottery machine will have matched exactly. That puts a rather different complexion on the Bulgarian spokeswoman's comment that it was a freak coincidence!

And that's just for one lottery. When we take into account the number of lotteries around the world, we see that it would be amazing if draws did not occasionally repeat. So you won't be surprised to learn that in Israel's Mifal HaPayis state lottery, the numbers drawn on October 16, 2010—13, 14, 26, 32, 33, 36—were exactly the same as those drawn a few weeks earlier, on September 21. *You* won't be surprised to learn that, but scores of people flooded Israel's talk radio programs with calls to complain that the lottery was fixed.

The Bulgarian lottery result was unusual in that the duplicate sets of numbers occurred in consecutive draws. But the law of truly large numbers, combined with the fact that there are many lotteries around the world regularly rolling out their numbers, means we shouldn't be too surprised—and so we shouldn't be taken aback to hear that it had happened before. For example, the North Carolina Cash 5 lottery produced the same winning numbers on July 9 and 11, 2007.

Another, rather frustrating way in which the law of combinations can generate lottery matches is illustrated by what happened to Maureen Wilcox in 1980. She bought tickets containing the winning numbers for both the Massachusetts State Lottery and the Rhode Island Lottery. Unfortunately for her, however, her ticket for the Massachusetts Lottery held the winning numbers for the Rhode Island Lottery, and vice versa. If you buy tickets for 10 lotteries, you have 10 chances of winning. But 10 tickets mean 45 pairs of tickets, so the chance that one of the 10 tickets will match one of the 10 lottery draws is more than four times larger than your chance of winning. For obvious reasons, this is not a recipe for obtaining a vast fortune because matching a ticket for one lottery with the outcome of the draw for another wins you nothing—apart from a suspicion that the universe is making fun of you.

Maureen Wilcox bought tickets that held the winning numbers for both the Massachusetts and the Rhode Island lotteries. Unfortunately for her, the ticket for Massachusetts had the winning numbers for Rhode Island, and vice versa.

The law of combinations applies when there are many interacting people or objects. Suppose, for example, that we have a class of 30 students. They can interact in various ways. They can work as individuals: there are 30 of them; they can work in pairs—there are 435 different pairs; they can work in triples—there are 4,060 possible different triples; and so on, up to, of course, them all working together—there is one set of all 30 students working together.

In total, the number of different possible groups of students that could be formed is 1,073,741,823. That's more than a billion, all just from 30 students. In general, if a set has n elements, there are $2^n - 1$ possible subsets that could be formed. If $n = 100$, the result is $2^{100} - 1$, which is approximately equal to 10^{30}, a truly large number in anyone's terms.

But if even 10^{30} isn't large enough for you, consider the implications of the World Wide Web, which has around 2.5 billion users, any and all of whom can interact with any of the others. This gives 3×10^{18} pairs and $10^{750,000,000}$ possible groups of interacting members. Even events with very small probabilities become almost certain if you give them that many opportunities to happen.

Next time you experience a seemingly strange coincidence, think of the Improbability Principle.

MORE TO EXPLORE

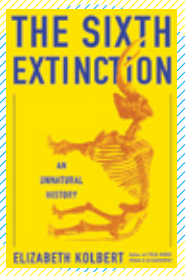
Duelling Idiots and Other Probability Puzzlers. Paul J. Nahin. Princeton University Press, 2000.

Symmetry and the Monster: One of the Greatest Quests of Mathematics. Mark Ronan. Oxford University Press, 2006.

FROM OUR ARCHIVES

Miracle on Probability Street. Michael Shermer; Skeptic, August 2004.

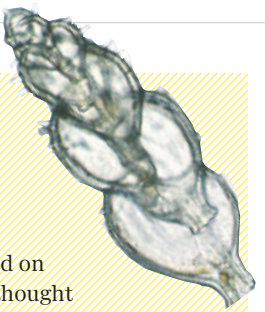
The Science of Murphy's Law. Robert A. J. Matthews; April 1997.



The Sixth Extinction: An Unnatural History

by Elizabeth Kolbert. Henry Holt, 2014 ($28)

Of all the species to have ever lived on earth, more than 90 percent are thought to be extinct. Most of them perished sometime over the past half a billion years, in one of the five major mass extinctions that have profoundly reshaped the world. Kolbert, a contributing writer for the *New Yorker,* argues that we are now in the midst of a sixth extinction, one distressingly of our own making. Part travelogue, part exegesis of extinction's history and literature, each chapter focuses on a single already vanished or critically endangered species and the scientists who study it, revealing a planetary crisis through heartrending close-up portraits of the Sumatran rhinoceros, the little brown bat, the Panamanian golden frog and other unlucky creatures. Fittingly, the book closes with a short chapter on *Homo sapiens* and an unflinching refusal to sugarcoat the ways we have broken our world.



OCEAN acidification threatens foraminifera and other shell-making creatures with extinction.

The Perfect Theory: A Century of Geniuses and the Battle of General Relativity

by Pedro G. Ferreira. Houghton Mifflin Harcourt, 2014 ($28)

University of Oxford professor Ferreira begins this "biography of general relativity" with a profession of his "lifelong love affair" with Albert Einstein's grandest theory. He writes this almost apologetically because despite its revolutionary linkage of gravity with space and time and its remarkable success in explaining the universe's evolution, general relativity has not always been a popular research topic. Indeed, for decades it was an "almost irresponsible calling," eclipsed throughout much of the 20th century by the wild successes of quantum physics. Many of its greatest triumphs, from black holes to the big bang, were at first steadfastly opposed by notable physicists, often Einstein himself. In *The Perfect Theory,* Ferreira masterfully portrays the science and scientists behind general relativity's star-crossed history and argues that even now we are only just beginning to realize its vitality as a tool for understanding the cosmos.

Extreme Medicine: How Exploration Transformed Medicine in the Twentieth Century

by Kevin Fong. Penguin Press, 2014 ($27.95)

With degrees in medicine, astrophysics and engineering, Fong has dedicated as much of his life to discussing the health challenges of space travel as he has to treating trauma patients. In *Extreme Medicine,* he writes of those challenges as well as more terrestrial medical advancements that have pushed the boundaries of possibility. "While our medical pioneers weren't concerned with geographical conquest," he writes, "they were very much in the business of exploration." From the tale of a young woman revived after hours without a heartbeat in an icy Nordic river to stories of World War II soldiers who served as early guinea pigs for facial skin grafting, Fong interweaves historical accounts with engrossing stories of clinical doctors charting new territories to save their patients. In each case, their encounter with physical extremes powered rapid medical advances. The next frontier to push science forward, Fong writes, may be sending humans to Mars. The book shows how, "by probing the very limits of our biology, we may ultimately return with a better appreciation of precisely how our bodies work, what life is, and what it means to be human."

—Rachel Feltman

Me, Myself, and Why: Searching for the Science of Self

by Jennifer Ouellette. Penguin, 2014 ($16)

How can we learn who we really are? For science journalist, *Scientific American* blogger and veteran author Ouellette, the journey of self-discovery involved genome sequencing, brain imaging, psychological analysis and even a hallucinogenic trip. In *Me, Myself, and Why,* Ouellette takes her readers from Gregor Mendel's pea plants to the personal genome-sequencing services of the 21st century. Adopted as an infant, she provides a unique view on the importance of nurture versus nature, and her sharp sense of humor makes for an enjoyable read. Ouellette admits that she failed to find a succinct answer to her multitude of questions about the self, but, she writes, "That's not the point. Ultimately, the story is not about the destination. It's about everything learned along the way."

—R.F.

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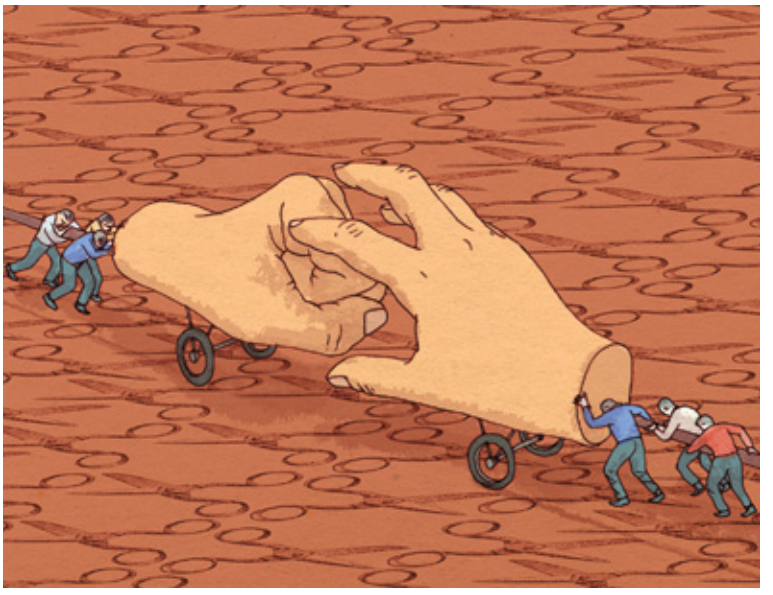
E. R. DEGGINGER Science Source

Michael Shermer is publisher of *Skeptic* magazine (www.skeptic.com). His next book is *The Moral Arc of Science*. Follow him on Twitter @michaelshermer

Heavens on Earth

Can a scientific utopia succeed?



"There is no scientific law that prevents 100 people who find each other on the Internet from coming together for a month, or 1,000 such people from coming together for a year. And as that increases to 10,000 and 100,000 and beyond, for longer and longer durations, we may begin to see cloud towns, then cloud cities, and ultimately cloud countries materialize out of thin air." So says Stanford University lecturer Balaji Srinivasan in an article published online by *Wired* in November 2013. In a talk at the annual conference held by the Silicon Valley start-up-funding organization Y Combinator, he revealed his inspiration to be the classic 1970 book *Exit, Voice, and Loyalty* by the late economist Albert Hirschman: when firms, nations and other organizations begin to stagnate and decline, members or citizens can employ one of two strategies for change—*voice* their opinions for reform; *exit* and start anew.

Which strategy is best? It depends on whether the change is brought about through violence or resistance. University of Denver political scientist Erica Chenoweth and her colleague Maria Stephan compared violent and nonviolent revolutions and reforms since 1900. They found that "from 1900 to 2006, nonviolent campaigns worldwide were twice as likely to succeed outright as violent insurgencies." And: "This trend has been increasing over time, so that in the last 50 years nonviolent campaigns are becoming increasingly successful and common, whereas violent insurgencies are becoming increasingly rare and unsuccessful." Only a small percentage of a population is necessary to bring about change: "No single campaigns failed after they'd achieved the active and sustained participation of just 3.5 percent of the population." And if they surpassed the 3.5 percent threshold, all were nonviolent and "often much more inclusive and representative in terms of gender, age, race, political party, class, and the urban-rural distinction." It's a faster track to the 3.5 percent magic number when you are more inclusive and participation barriers are low. Plus, nonviolent resistance does not require expensive guns and weapons.

We should keep these data in mind when evaluating utopian schemes. Theists and postmodernist critics of science often label the disastrous Soviet and Nazi utopias as "scientific." But science was a thin patina covering a deep layer of counter-Enlightenment pastoral paradisiacal fantasies of racial ideology grounded in blood and soil, as documented in Claudia Koonz's 2003 book *The Nazi Conscience* (Belknap Press) and in Ben Kiernan's 2007 book *Blood and Soil* (Yale University Press). Such utopias can rack up high body counts with a utilitarian calculus in which everyone is presumed to be happy forever. As Harvard psychologist Steven Pinker explains in *The Better Angels of Our Nature* (Viking, 2011), people who oppose a utopia "are the only things standing in the way of a plan that could lead to infinite goodness. How evil are they? You do the math."

Which brings us back to Srinivasan, who envisions techno-utopian schemes such as *Star Trek,* in which replicators produce everything anyone could want or need (much like the promise of 3-D printers today). Is this realistic? In his and Steven Kotler's 2012 book *Abundance* (Free Press), X Prize founder Peter H. Diamandis says that "humanity is now entering a period of radical transformation in which technology has the potential to significantly raise the basic standard of living for every man, woman and child on the planet. Within a generation, we will be able to provide goods and services, once reserved for the wealthy few, to any and all who need them." PayPal co-founder Peter Thiel has helped bankroll the Seasteading Institute, whose mission is "to establish permanent, autonomous ocean communities to enable experimentation and innovation with diverse social, political, and legal systems." Google CEO Larry Page has suggested setting aside regions of the world for political and social experimentation. SpaceX CEO Elon Musk has outlined colonies on Mars where new social systems could be tried.

I am skeptical of these schemes but not cynical about them. New ideas have to come from somewhere. As long as a techno-utopia is based in reality and one can opt out, what's the harm? As English poet Robert Browning wrote, "Ah, but a man's reach should exceed his grasp,/Or what's a heaven for?" SA

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Illustration by Izhar Cohen

The ongoing search for fundamental farces

Steve Mirsky is off this month (more than usual). This column about copying previously published material originally ran in April 2002. He also hosts the *Scientific American* podcast Science Talk.

Copy That

Technology is making it harder for word thieves to earn outrageous fortunes

It was the best of times, it was the worst of times,[1] it was the *New York Times*. Specifically, it was a *Times* article that discussed computer programs and other techniques designed to root out plagiarism.[2] The article revealed that there is now software that can look for a lengthy passage, like a string of pearls,[3] in a new document that is identical to a passage in a previously published work. In another method, every fifth word from sample passages is removed, and the author has to fill in the blanks[4] to reveal his or her familiarity with the work. These high-tech ways to spot literary theft will surely rob copycats of the sleep that knits up the raveled sleave of care.[5]

When I first read the *Times* article, I remember thinking, it's a good thing[6] and attention must be paid.[7] After all, as a writer, I find plagiarism to be a constant concern. (Although from time to time, I have to admit, I shall consider it.[8]) Of course, it can be hard to define. When you steal from one author, it's plagiarism; if you steal from many, it's research.[9] One might say that a writer should neither a borrower nor a lender be.[10] On the other hand, imitation is the sincerest form of flattery.[11]

I shall never believe that God plays dice with the world.[12] Therefore, the plagiarized passages that programs pinpoint are probably purposeful and potentially punishable.[13] There is grandeur in this view of life.[14] I think.[15]

Plagiarism is a central issue of science[16] as well. Relying on the work of others is the lifeblood of scientific research. Indeed, if I (who had the chance to learn physics that Newton never dreamed of) have seen further, it is by standing on the shoulders of giants.[17] One might even say that I have always depended on the kindness of strangers[18] in this regard.

But employing the findings of other researchers is one thing; claiming such findings as one's own is intellectual murder most foul.[19] So when in the course of human events,[20] a case of plagiarism is revealed, it represents a clear and present danger[21] to intellectual liberty. And naturally, eternal vigilance is the price of liberty.[22] It is thus incumbent on all researchers to say, "Let me make this perfectly clear[23]: I am not a crook.[24]" SA

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1. Dickens, Charles. *A Tale of Two Cities,* opening lines.
2. Eakin, Emily. "Stop, Historians! Don't Copy That Passage! Computers Are Watching!" in the *New York Times,* January 26, 2002.
3. Miller, Glenn. Song title.
4. Rayburn, Gene. *The Match Game,* television program (1962–1969, 1973–1984).
5. Shakespeare, William. *Macbeth,* Act 2, Scene 2.
6. Stewart, Martha.
7. Miller, Arthur. *Death of a Salesman,* end of Act 1.
8. Spock, Mr. (with beard), to Captain Kirk on the transporter pad. *Star Trek,* episode 39, "Mirror, Mirror."
9. Mizner, Wilson.
10. Shakespeare, William. *Hamlet,* Act 1, Scene 3.
11. Colton, Charles Caleb.
12. Einstein, Albert, according to *Bartlett's Familiar Quotations.*
13. After "Peter Piper."
14. Darwin, Charles. *On the Origin of Species,* closing paragraph.
15. Descartes, René. "*Cogito, ergo sum.*"
16. "Science" refers to the enterprise by which human beings attempt to discover basic truths about the universe. It is, however, also the name of a journal published by the American Association for the Advancement of Science.
17. Attributed to Isaac Newton but probably existed in some form earlier.
18. Williams, Tennessee. *A Streetcar Named Desire,* Scene 11.
19. Shakespeare, William. *Hamlet,* Act 1, Scene 5.
20. Declaration of Independence, opening paragraph.
21. Holmes, Oliver Wendell, Supreme Court justice. *Schenck v. United States,* 1919.
22. Phillips, Wendell. 1852 speech to the Massachusetts Antislavery Society, paraphrasing John Philpot Curran, who in 1790 said, "The condition upon which God hath given liberty to man is eternal vigilance."
23. Nixon, Richard M., 37th U.S. president. On numerous occasions.
24. Ibid., about the Watergate scandal.

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FROM THE AMERICAN PEOPLE

CENTER FOR INTERNATIONAL DISASTER INFORMATION

February 1964

Danger from Tobacco

"'Cigarette smoking is causally related to lung cancer in men; the magnitude of the effect of cigarette smoking far outweighs all other factors.' This unqualified statement in the report issued January 11 by the Public Health Service answered a question that had been debated for more than a decade. The first large-scale statistical studies showing the harmfulness of cigarettes were published in 1954. In the nine years since these studies were reported, more than 300,000 Americans have died of lung cancer. Throughout the nine-year period the cigarette industry placed its faith in a single argument: A statistical association between cigarette smoking and disease does not prove a cause-and-effect relation."

Danger from Movies

"It is possible to suggest that the observation of aggression is more likely to induce hostile behavior than to drain off aggressive inclinations; that, in fact, motion picture or television violence can stimulate aggressive actions by normal people as well as by those who are emotionally disturbed. I would add an important qualification: such actions by normal people will occur only under appropriate conditions. The experiments point to some of the conditions that might result in aggressive actions by people in an audience who had observed filmed violence. —Leonard Berkowitz"

Berkowitz is currently professor emeritus in psychology at the University of Wisconsin–Madison.

February 1914

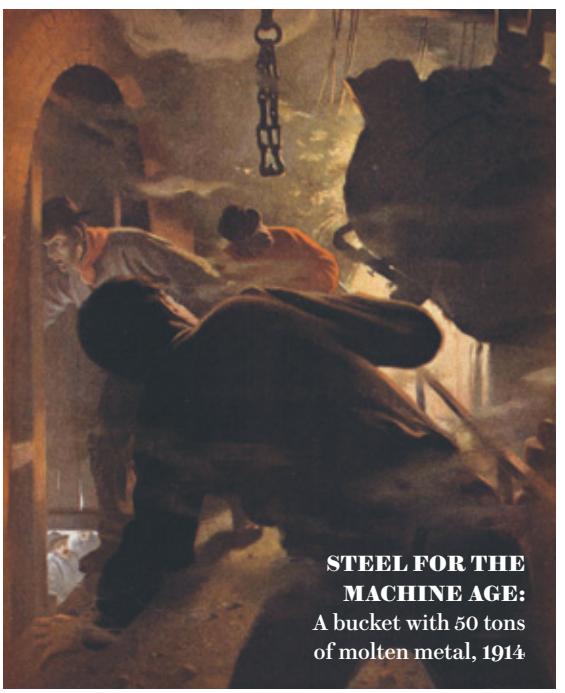
Existence of the Ether

"The notion of a universal medium, permeating all space, has undergone many vicissitudes. At the present time there are at least three theories: one considers the ether as an incompressible medium, very rigid and very dense; another considers it composed of particles much smaller than electrons; and the third denies its existence altogether and seeks to eradicate it from the list of physical theories. It is this last theory which gains more and more adherents day by day. And once more we see reappearing the mysterious, and rather terrifying, notion of the absolute 'nothingness' of outer space which one imagined to be successfully abolished by the introduction of the ether."

Big Steel

"The writer recently had occasion to visit the works of the Illinois Steel Company at South Chicago, and was struck by the 'safety first' atmosphere that pervaded the whole works. Safety signs in five languages were set up at all points in the works where there was a possibility of accident. Not only that, but the men themselves seemed imbued with the safety spirit and enthusiastic in their support of safety methods. Our illustration shows a huge ladle containing fifty tons of molten metal."

For a slide show on engineering with iron and steel in 1914, see www.ScientificAmerican.com/feb2014/steel-1914



STEEL FOR THE MACHINE AGE: A bucket with 50 tons of molten metal, 1914

February 1864

Politics of the Metric System

"English Toryism is up in arms at the proposition to introduce the decimal system of weights and measures in England. This proposition, which was earnestly urged upon the general consideration of Christendom at the recent National Congress, in Berlin, and in which the Hon. S. B. Ruggles [of the New York City Chamber of Commerce] represented the United States, has been brought before the House of Commons by Mr. William Ewart. The Tory organ in the weekly press of London, the *John Bull,* denounces it as 'absurd and impudent,' and as 'an idea which could only enter the heads of dunces, Whigs, and revolutionary tyrants.'"

The metric system had been introduced in revolutionary France in 1799.

America and Measurement

"Messrs. Editors: The following reflection occurs upon reading an account of the French metrical system. The time and money expended in propagating and maintaining our chaotic system are sufficient to give collegiate education to the whole population. —J. Edi."

Heard through the Grapevine

"California raisins are the greatest novelty. They are equal to the best imported and don't cost as much. Very few have appeared in the Atlantic States, but in course of time they will drive the foreign fruit from the market."

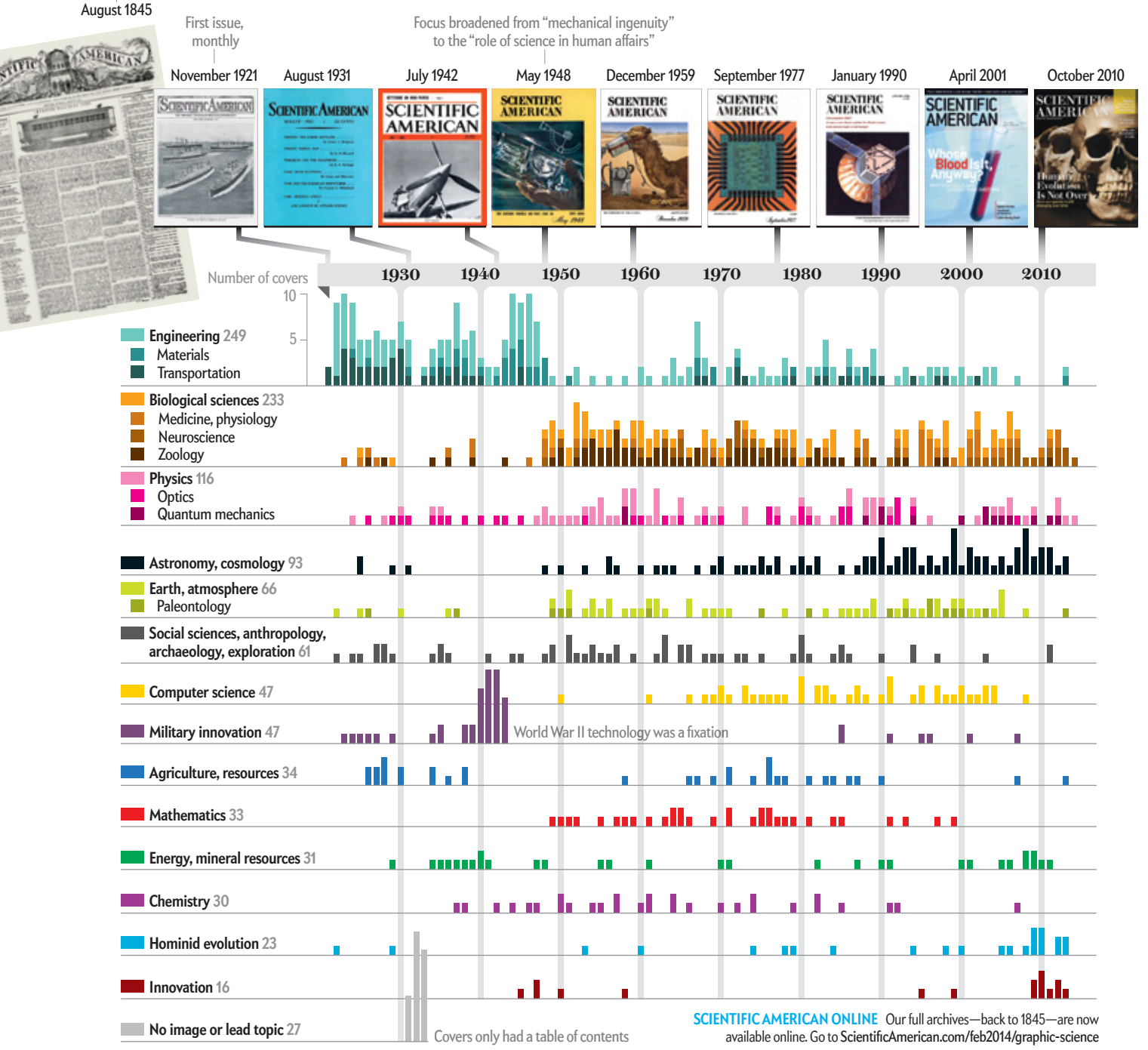
SCIENTIFIC AMERICAN, VOL. CX, NO. 6; FEBRUARY 7, 1914

How Science Evolves

Scientific American covers reveal a shift from practical to provocative

When our magazine went monthly in 1921, it was published as a journal of "practical information"—one definition of "scientific." Since then, cover topics have reflected science's progress. Engineering and other applied sciences predominated until after World War II, when attention turned to the natural world (biology) and later to theoretical pursuits (physics, astronomy). Today neuroscience and evolution are surging—and raising controversial questions.

—Jen Christiansen and Mark Fischetti



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Graphic by Jen Christiansen

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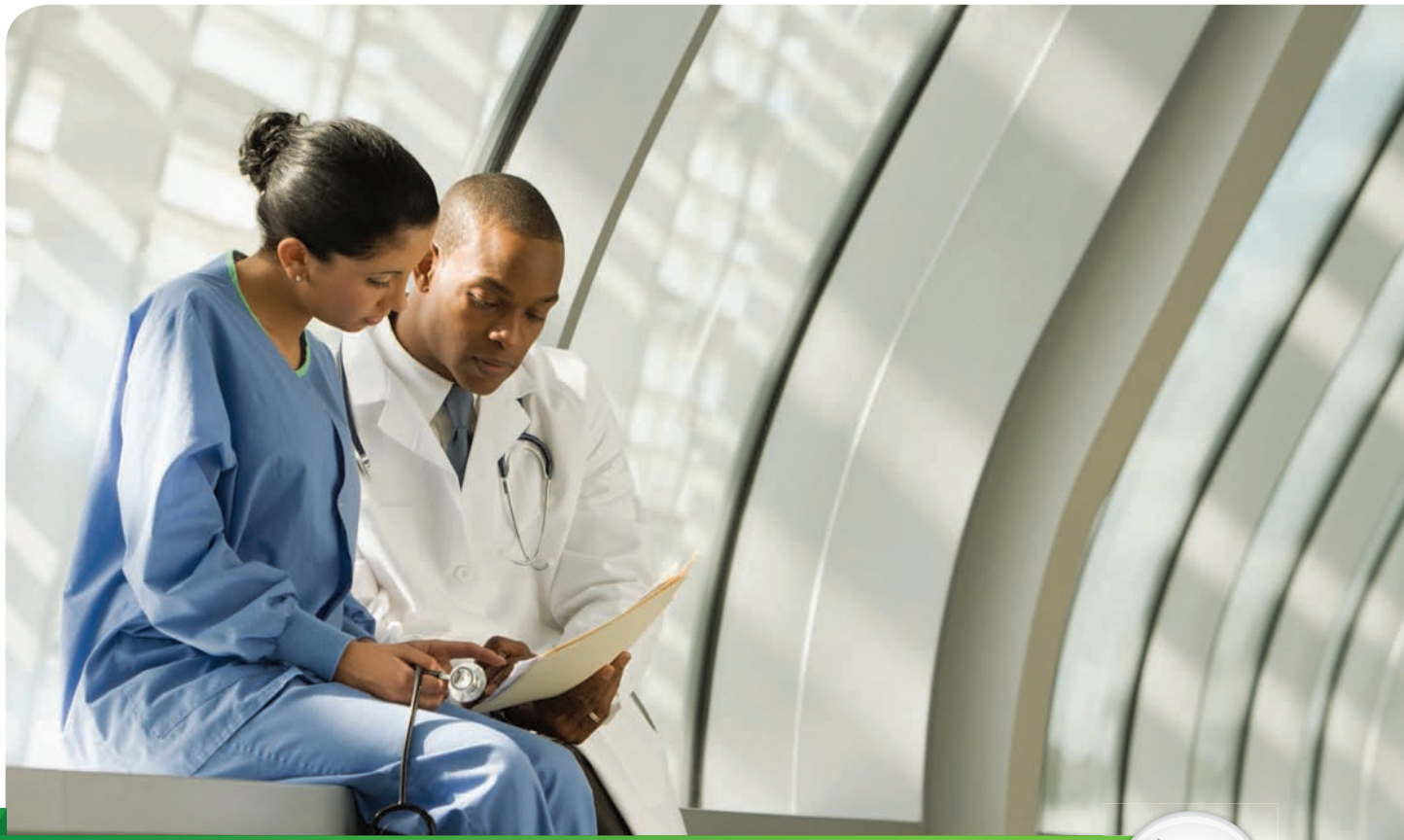

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