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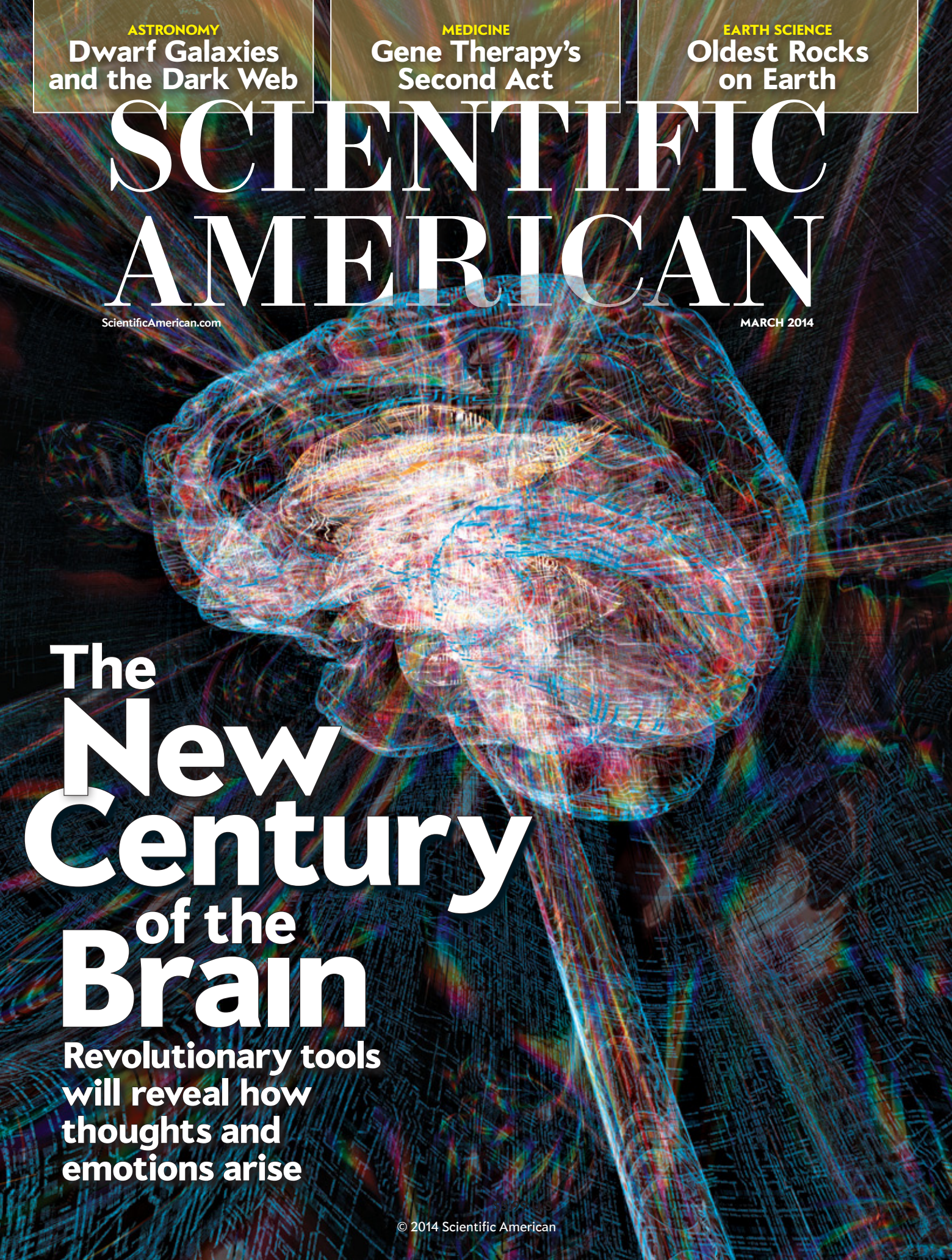

The New Century of the Brain

Revolutionary tools will reveal how thoughts and emotions arise

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ON THE COVER

Scientific tools for doing research on the brain—the world's most complex machine—are too blunt or else overly fine to provide a deep understanding of how the activity of neurons leads to perception and thought. The need for developing better technologies that can record or control brain circuits has recently become a central focus of neuroscience. Image by Bryan Christie.

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A Summit for Science

This year's meeting of the American Association for the Advancement of Science focused on "Meeting Global Challenges: Discovery and Innovation" and featured a diverse array of speakers, from actor and science communicator Alan Alda to former energy secretary Steven Chu. *Go to www.ScientificAmerican.com/mar2014/aaas*

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

The Brain Beckons

In 1990 Congress and President George H. W. Bush proclaimed the beginning of the "Decade of the Brain," intended "to enhance public awareness of the benefits to be derived from brain research." Improvements in imaging technologies were giving us better ways to peer at the workings of the inner universe inside our noggins. Researchers used the imaging to further probe correlations between types of thinking and increased blood flow or neural electrical activity, indirect indicators of areas of the brain at work. In the press coverage of studies, we all saw lots of lovely colorized pictures of certain brain areas "lighting up" when some kind of processing was thought to be involved. If it wasn't a complete way of understanding such a complex organ, with its billions of neurons and trillions of neural connections, at least it was a start.

As a longtime observer of brain research (I oversaw the launch of our sister magazine, *Scientific American Mind,* which celebrates its 10th anniversary later this year), I have been eagerly tracking such developments. Now we are moving into a new era, one that will be less marked by (of necessity, given the tools that have been available) the reductionist strategy of trying to understand the role of this or that chunk of brain tissue and more by a network-focused understanding of the complex systems involved in any activity.

Already *Scientific American* authors have described their research in such areas as the neural-circuit underpinnings of mental illnesses (see "Faulty Circuits," by Thomas R. Insel; April 2010) and simulating the human brain (see "The Human Brain Project," by Henry Markram; June 2012), among others. Last year the Obama administration announced the Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative, with a funding level of more than $100 million in 2014. It joins the Human Brain Project, a $1.6-billion, 10-year effort funded by the European Union.

In our cover story, starting on page 38, neuroscientist Rafael Yuste and geneticist George M. Church preview exciting tools for probing our wetware anticipated in this, "The New Century of the Brain." The challenge: understanding the buzz of 86 billion neurons, by which properties such as thought and emotion arise. The tools: innovative technologies such as arrays of tens of thousands of electrodes for recording brain cell activity and light-activated chemical switches that turn a neural circuit on or off. I can hardly wait to see what's next. SA

Entries Open

Scientists ages 13 to 18: Entries for the 2014 Google Science Fair—and a chance to win the $50,000 *Scientific American* Science in Action prize—are now open. The award honors a project that can make a practical difference by tackling an environmental, health or resources challenge. Entries are open until May 11. For more, visit **www.ScientificAmerican.com/science-in-action.** —*M.D.*

Illustration by Nick Higgins



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November 2013

PERILS OF E-READING

"Why the Brain Prefers Paper," by Ferris Jabr, is a fascinating study on how the brain reads paper versus e-texts. The differences seem to call for further study, especially given the increasing reliance on online, high-stakes testing in education. These tests involve a lot of reading, even the math tests. If studies show a definite decrease in comprehension when people read e-texts, then we are doing a disservice to our students, teachers and schools by imposing less beneficial testing on them. Even though online testing may be more efficient, the consequences of poor testing results would be catastrophic.

Robert Hanna
Choctaw, Okla.

DON'T TEXT AND DRIVE

After describing a recent study that found that texting by hand and hands-free by voice were equally bad for driving in "Crash Text Dummies" [TechnoFiles], David Pogue writes that "the results surprised me." It would, in fact, be *very* surprising if they had showed any difference: the reason that driving performance is impaired when people are making phone calls and texting, hands-free or not, is that such tasks require attention. That's why a sensible driver would, say, stop talking when navigating a curvy ramp.

Jianjian (J.J.) Qin
California State University, Sacramento

"Driving performance is impaired when people make phone calls or text, hands-free or not, because such tasks require attention."

Jianjin (J.J.) Quin
California State University, Sacramento

Currently there is a misconception that voice-activated texting is safe. Furthermore, some believe laws forbidding texting by drivers are unenforceable. I agree with the second point, but there is a foolproof solution: pass laws requiring that all texting devices include a GPS with a default that stops the texting function from working when the device is in motion.

J. G. McCully
via e-mail

HUMANS AND EXTINCTION

In "King of Beasts," Lars Werdelin makes an interesting case for the influence of early humans, who arose in Africa around two million years ago, on the decline of large carnivore species in that continent around the same time. How does the decline compare with species diversity of large carnivores everywhere else, where there were no humans until much later, such as in North America?

David Smith
St. John's, Newfoundland and Labrador

WERDELIN REPLIES: Each continent has to be viewed separately because history and environment, as well as the time of appearance of Homo, *differ. Overall, there is support in most parts of the world for a reduction in large carnivore diversity coincident with the appearance of* Homo. *This is clearest in the Americas, where the debate over whether humans or climate caused Late Pleistocene extinctions has raged for decades (the truth is probably a combination of these two factors, including a trophic cascade caused by human-mediated extinctions of large carnivores).*

In Europe, there is a reduction in large carnivore diversity that coincides with the first permanent settlements of Homo *in the continent, about 800,000 to 700,000 years ago, although this needs further research. The situation in Asia is unclear because of the existence of very few well-dated localities in the critical time period (1.8 million to 1.5 million years ago).*

TABLET TEACHING

An interview with Maryanne Wolf, "A Is for App," by Ferris Jabr [Advances], describes Wolf and her colleagues' work in designing a tablet-based system to teach children to read, which they have been testing in the Ethiopian villages of Wonchi and Wolonchete.

I have a question for Wolf: Did you consider using the tablets to help the children in Wonchi and Wolonchete learn to read and write their own mother tongue before teaching them to read English?

Jimmie Davis
via e-mail

WOLF REPLIES: We reflected a great deal on the fact that it is generally easier to learn to read in one's own first language. The kind of apps we want for teaching the precursors of reading, however, are not available in these children's first language, Oromo, or most languages. Even in English, there are too few apps that address what we call the "reading brain circuit."

Furthermore, the children's parents wanted them to learn English as much as they wanted them to learn to read because it would enhance their later economic opportunities and would also be the second language taught in their schools, should they ever be able to attend them.

Finally, we are currently developing our own apps that teach oral and written vocabulary in English and Oromo. And two of our goals involve developing templates for how to design apps in any language that best represent our knowledge of the reading brain and forming communications networks around the globe in which children can teach one another the words that describe their worlds.

ELECTRONIC MEDICAL RECORDS

In "Data Glitches Are Hazardous to Your Health" [Science Agenda], the editors decry

I LOVE

ROBOTS

I'M GOOD AT

BUILDING THINGS

I WANT TO

HELP MY GRANDMOTHER

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IT'S YOUR TURN TO CHANGE THE WORLD

that no centralized body is keeping track of errors in electronic medical records.

It should be noted that all the examples they cite are manual-entry errors committed by humans. While they should be identified as much as possible, there is no particular benefit in separating other errors from such e-record errors, and they should be included in error tabulations that already exist, along with, say, hospital-acquired infections.

A more pervasive problem with electronic records is the cacophony of systems that are unable to "talk" with one another, with many older computerized records not being readable by current software.

EDWIN G. TAFT
via e-mail

CARBON SEQUESTRATION

In "The One-Stop Carbon Solution," Steven L. Bryant proposes sequestering carbon dioxide by injecting it into hot brine from deep underground and sending it back.

Coal-fired power plants are a major source of CO_2. But sequestration schemes do not solve other problems the plants pose.

Coal combustion releases chromium and arsenic (carcinogens), lead and mercury (neurotoxins), and dioxins and furans (endocrine disruptors).

For this and other reasons, Canadian doctors support a complete phaseout of this dirty fossil fuel. Pipe dream? Ontario will be closing its last coal plant in 2014.

GIDEON FORMAN
Executive director, Canadian Association of Physicians for the Environment

GAMBLING ADDICTION

I was delighted with Ferris Jabr's article on disordered gambling, "Gambling on the Brain" [The Science of Health]. What has historically been referred as "problem gambling" is now appropriately regarded as an addictive disorder that can be identified and treated. More states are addressing this downside of adult gaming and affiliating with the National Council on Problem Gambling, which advocates for programs and services to aid such individuals and operates a national Helpline at 800-522-4700.

GEORGE SEWELL
Program director, Helpline operations
Louisiana Problem Gamblers Helpline

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/mar2014

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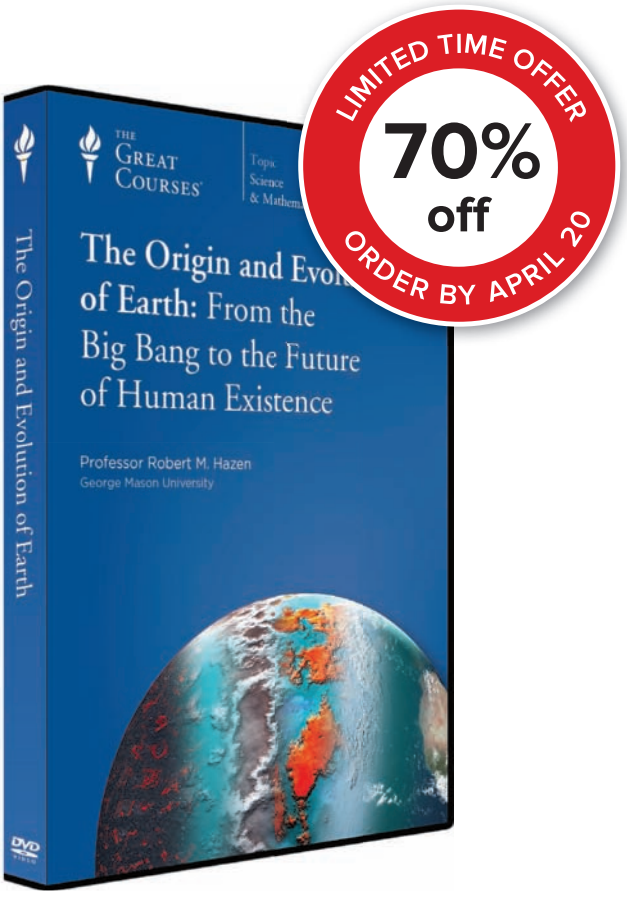

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Free Willy—And All His Pals

Orcas and elephants are smart, social and way too large for captivity

Having finally joined the rest of the world in severely restricting medical testing on chimpanzees, the U.S. is currently relocating hundreds of government-managed chimps to sanctuaries. One reason for these changes is that the animals are not as essential to biomedical research as they used to be—we have learned to use genetically engineered mice and cell cultures instead. For many people, an even more persuasive argument is that performing medical research on chimpanzees is inhumane because, like us, they are highly intelligent, emotional and self-aware.

As with chimps, the intelligence of orcas and elephants is undeniable. Boasting some of the most intricate brains around, all three animals have recognized themselves in mirrors, indicating that they, too, have a concept of self. All are cooperative problem solvers. Teams of orcas sometimes hunt by producing and directing waves at icebergs to knock seals and penguins into the water. Elephants are also adept toolmakers, fashioning switches with which to shoo flies and chewing bark into balls to plug small drinking holes, thereby preventing evaporation.

Chimps, killer whales and elephants are just as dependent on companionship as we are. A killer whale mother stays with most of her descendants throughout life, sometimes shepherding as many as four generations. Related matrilines, each of which has its own dialect, unite in pods, which merge into clans, which intermingle in large communities—akin to tribes and nations.

Likewise, related elephant mothers and their offspring form tight-knit clans in which they share parenting duties and shield children from predators. When a clan member dies, elephants mourn—there is no other word for it. At Kenya's Samburu National Reserve, zoologist Iain Douglas-Hamilton and his team witnessed elephants from various families tending to an ailing matriarch named Eleanor. Another matriarch used her tusks to lift Eleanor to her feet when she collapsed. Even after Eleanor died, elephants repeatedly visited and caressed her body. Cynthia Moss and other researchers have also reported elephants sprinkling their dead with soil and covering them with branches and leaves.

A number of other species share similar humanlike traits, among them gorillas, orangutans, dolphins and porpoises. What distinguishes orcas and elephants—what makes holding them in captivity so uniquely fraught—is one of the same features that makes them so attractive to zoo-goers: their immense size. African elephants can weigh as much as 15,000 pounds and are used to traveling between watering holes and feeding sites hundreds of miles apart. Confined elephants often spend their time standing around in cramped quarters. Killer whales can reach a length of 32 feet and a weight of 22,000 pounds. The approximately four dozen orcas now in captivity are forced to trade the ocean for a bathtub. At Miami Seaquarium, the aging Lolita lives in a tank that is not even twice as wide as she is long.

These tortuous conditions inflict serious physical and psychological damage on such smart and sensitive animals. Zoo elephants die young, often after becoming obese and infertile. They frequently develop psychological tics such as swaying and head bobbing. Citing ethical reasons, several large zoos in the U.S., Canada, the U.K. and India have closed their elephant exhibits.

Captive orcas are unusually aggressive, biting and ramming one another as well as trainers. Many researchers think the animals behave this way because they are so stressed; some have suggested that longtime confinement makes cetaceans psychotic. In February 2010 SeaWorld orca Tilikum pulled 40-year-old senior trainer Dawn Brancheau underwater, shook her violently, scalped her and severed her spine. It was the second time he had killed a trainer. Wild orcas have never killed anyone.

Orcas and elephants are not the only intelligent species that deserve our respect and attention, but they face unique hardships in captivity. Even though many zoos and sea parks raise awareness about the plight of animals in the wild, the suffering of captive orcas and elephants in particular overshadows this worthy goal. Some currently confined individuals may not survive if released, but the ones that can be, should be, and captive breeding programs should be terminated. SA

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Illustration by Marc Scheff

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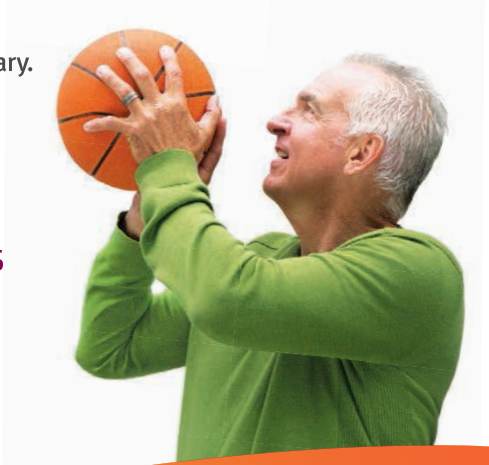

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What is the most important information I should know about ELIQUIS (apixaban)?

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

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

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

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

While taking ELIQUIS:

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

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

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

ELIQUIS (apixaban) is not for patients with artificial heart valves.

What is ELIQUIS?

ELIQUIS is a prescription medicine used to reduce the risk of stroke and blood clots in people who have atrial fibrillation.

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

Who should not take ELIQUIS?

Do not take ELIQUIS if you:

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

What should I tell my doctor before taking ELIQUIS?

Before you take ELIQUIS, tell your doctor if you:

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

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

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

How should I take ELIQUIS (apixaban)?

Take ELIQUIS exactly as prescribed by your doctor. Take ELIQUIS twice every day with or without food, and do not change your dose or stop taking it unless your doctor tells you to. If you miss a dose of ELIQUIS, take it as soon as you remember, and do not take more than one dose at the same time. **Do not run out of ELIQUIS. Refill your prescription before you run out. Stopping ELIQUIS may increase your risk of having a stroke.**

What are the possible side effects of ELIQUIS?

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

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

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

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

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

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Based on 1289808 / 1298500 / 1289807 / 1295958
December 2012
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Walter Willett is a professor of epidemiology and nutrition and chair of the department of nutrition at the Harvard School of Public Health. He is also a professor of medicine at Harvard Medical School.

The Case for Banning Trans Fats

The FDA's new policy on these deadly artificial fatty acids is long overdue

In November 2013 the U.S. Food and Drug Administration made the welcome, belated determination that partially hydrogenated oils—the primary source of trans fats—could no longer be "generally regarded as safe." At press time, the ruling is preliminary but expected to become permanent. If it does, it will virtually eliminate industrially produced trans fats in the U.S, saving thousands of lives every year, with minimal cost to industry.

In 1901 German chemist Wilhelm Normann discovered the process of partial hydrogenation, which converts inexpensive liquid vegetable oils into shortenings and margarines and creates trans fats as a by-product. Because these cheaper, longer-lasting products mimicked the traditional cooking fats of European and North American cuisines, many countries quickly incorporated them into their food supplies. In 1912 the inventors of partial hydrogenation received the Nobel Prize. It took decades for scientists to realize how deadly trans fats could be, partly because the food industry and the cardiovascular prevention community dismissed concerns over adverse effects on health, but the evidence continued to mount.

In 1980 my colleagues and I set out to examine in greater detail the relation between intake of trans fats and risk of coronary heart disease. We included trans fats in a comprehensive assessment of diet in the Nurses' Health Study cohort of more than 100,000 women and developed a regularly updated database of the trans-fat content of foods. After eight years of follow-up and after accounting for known risk factors for heart disease, we found that women with the highest intake of trans fats had a 50 percent higher risk of hospitalization or death attributable to coronary heart disease. Margarine, the primary source of trans fat in 1980, was also associated with greater risk.

Around the same time, Dutch researcher Martijn Katan and his colleagues were investigating the metabolic effects of trans fats among healthy volunteers in carefully controlled feeding studies lasting several weeks. They found that trans fat and saturated fat increased "bad" LDL cholesterol to a similar degree—but unlike any other type of fat, trans fat also reduced "good" HDL cholesterol. Other researchers confirmed these findings and documented additional adverse metabolic effects, including increases in blood concentrations of triglycerides and inflammatory factors. Calculations suggested that eliminating industrially produced trans fats would prevent up to 20 percent of avoidable cardiac disease deaths in the U.S.

By 2003 the FDA found the evidence compelling enough to require that trans fats be included on food labels. Most manufacturers responded by eliminating them entirely. Soon thereafter New York City banned their use in restaurants, and other cities nationwide followed. By 2012 approximately 75 percent of trans fats had been removed from the U.S. food supply. Blood cholesterol levels responded nationally, just as expected.

The U.S. Centers for Disease Control and Prevention has estimated that the 25 percent of trans fats still coursing through the American food supply account for approximately 7,000 premature deaths a year. The FDA's recent decision would prevent those deaths. The food industry most likely will take the new ruling in stride. It has already phased out the large majority of trans fats, and in Denmark they have already been banned for a decade, proving that full elimination is feasible.

The FDA's action is cause for some celebration. It means that the efforts of many scientists from many disciplines will soon lead to the elimination of a major cause of premature death. Because of the FDA's global leadership role, the ruling is even likely to stimulate similar changes worldwide. But we should not get too carried away. It is sobering that it has taken more than a century for this moment to arrive. The case of trans fats should provoke us to consider how future risks might be prevented, detected or eliminated more quickly. SA

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Illustration by Wesley Allsbrook

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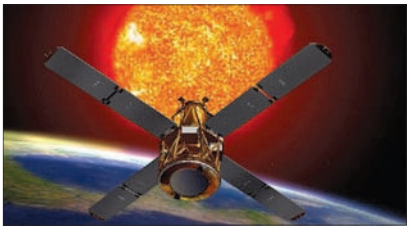

Astronomy

Speaker: John Brown, Ph.D.

Our High Energy Sun

Eruptions on the sun are dramatic events that have consequences on Earth, such as aurorae (Northern and Southern Lights), as well as disrupted power grids and satellite communications. Learn about the solar science advances that were enabled by NASA's RHESSI spacecraft from the mission's U.K. co-investigator.

Comet-Sun Impacts

The sun is continually pummeled by impacting cosmic debris, and has close encounters with more than 100 comets a year. Learn how these sun-plunging supersonic snowballs interact with the Hellish conditions near the sun, and the possible terrestrial consequences of a large comet–sun impact.

Gravity, Black Holes & White Rabbits

Through the lens of magic tricks, learn what gravity is and how it affects the universe, particularly black holes — the strongest sources of gravity and the most bizarre objects in the cosmos. We'll explore space-time distortion, gravitational lensing, Hawking radiation, multiverse creation, and other cosmic mysteries.

A Historical Tour of Scottish Astronomy

The Scots and their ancient ancestors have recorded aspects of the sky since before the pyramids of Egypt. We'll discuss highlights from the work of some early great astronomers, such as James Gregory, Alexander Wilson and others, and explore the great modern astronomical heritage they created.

Plant Biology

Speaker: Daniel Chamovitz, Ph.D.

What a Plant Knows

Take a captivating journey into the sensory lives of plants, and discover the surprising similarities between humans and green, leafy organisms. Highlighting the latest research in plant science, we'll look into the sensory lives of different types of plants, and even consider whether plants are aware.

Hunger and the Quest to Feed the World

More than half of the world's population suffers from some form of food insecurity. Rapid increases in global population, increased demand for food, and dwindling agricultural resources have put critical strains on our ability to feed the world. We'll examine the problem and some ideas to address it.

A Rational Look at GMO Food

Many of us are concerned by food labeled "GMO." But is GMO food inherently inferior to organic food? We'll examine what happens when GMO technology turns plants into factories, and delve into the scientific basis of genetic engineering with a view toward how it influences our lives.

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The Scientific Life

Hear the story of a life in science from a researcher who started as a graduate student studying beta-carotene in bacteria, and became director of an institute trying to solve issues of world hunger. Learn about the hypotheses that have powered the science throughout, and the experiments and findings behind them.

Theoretical Physics

Speaker: Frank Close, Ph.D.

Antimatter: Facts and Fiction

The Big Bang produced matter and antimatter in equal amounts, yet there is very little antimatter in our universe. Where has all the antimatter gone? Could antimatter solve the world's energy problems, or even make the ultimate weapon of mass destruction? The answer to both questions is no — learn why.

Nothing: Mysteries of the Vacuum

If you take away the Earth, moon and stars, what remains? The concept of the void — nothing — has alarmed and fascinated humans from the dawn of time. We'll move from the philosophical speculations of early civilizations to the cutting edge thinking of modern science to ask: Can we understand nothing?

Neutrino: Ghost Particle of the Cosmos

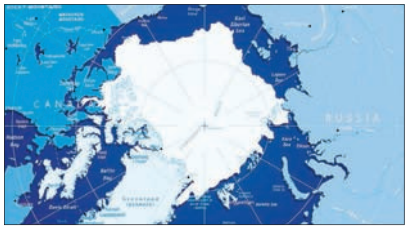
Ghostly neutrino particles stream through Earth by the billions as if it wasn't there. This is the story of how these extraordinary particles were sought and found — a story of heroic endeavor, of lifetimes spent chasing the near-impossible — and the scientific revelations neutrinos have enabled.

A Lopsided Universe

Nature produces structured asymmetric patterns prolifically: Even human life is lopsided, with spherical embryos somehow giving rise, ultimately, to creatures whose inner organs are asymmetric. This is the story of a quest for the origins of structure in nature, which has culminated in the discovery of the Higgs Boson particle.

The Story of the Higgs Boson

Roughly 50 years ago a new theory of the basic structure of matter was inspired by the work of Peter Higgs and others. In July 2012, Higgs's boson was finally found. Hear the story behind this amazing discovery, and delve into the ideas that inspired it.



History of Science

Speaker: Edward Larson, Ph.D.

Scientific Exploration of the Arctic

Scientists and geographers knew virtually nothing about the Arctic until 150 years ago, when Fridtjof Nansen and his protégé Roald Amundsen became legends by exploring this mysterious territory. While cruising through the beginning of the Arctic in Scandinavia, we'll follow their exploits as they opened the Arctic for science.

Amundsen, Scott, and Science in the Antarctic

The Antarctic was a mystery to humanity until the Royal Society-backed expeditions of Robert Scott and Ernest Shackleton, followed by Roald Amundsen's entry in the field. We'll follow the adventure and the science of the early research at the South Pole.

The Evolution Controversy

Creationism has changed, creationists say, but has it? Rooted in supposed biblical truths, almost by definition creationism cannot evolve, but creationist tactics do. We'll explore the world of modern creation science, intelligent design, and the 21st-century American battle over teaching evolution.

The Neo-Darwinian Synthesis

Charles Darwin was central to the story of modern evolutionary theory, but he wasn't its founder. We'll trace this grand breakthrough from Lamarck and the dawn of evolutionary science through Darwin to the modern neo-Darwinian synthesis of the 1930s, when genetics finally explained how evolution operated.

Robotics

Speaker: Alan Winfield, Ph.D.

Robotics: The State of the Art

Robots are moving out of factories and into homes, hospitals and offices. Robots are now mobile and working alongside humans. We'll delve into the state-of-the-art in intelligent robotics, defining what a robot is through examples from current research. Learn how the latest robots differ drastically from earlier generations.

A Brief History of Robotics

Trace the history of robotics from Classical Greece to the modern day, from Aristotle's early reference to the idea of an intelligent tool that could replace human labor, to Leonardo da Vinci's programmable automata, and W. Grey Walter's 1940s robot "tortoises," regarded as the first autonomous electronic mobile robots.

Robot Ethics

Like any transformative technology, intelligent robotics has the potential for huge benefit, but is not without ethical or societal risk. We'll explore whether there are situations where robots should be banned, and the issue of whether intelligent robots themselves could or should be ethical.

The Thinking Robot

Could robots ever truly think like humans, or have feelings? We'll explore how intelligent present-day intelligent robots really are, and the future prospects of designing robots that not only have increased abilities, but also have a sense of self.

ADVANCES

Dispatches from the frontiers of science, technology and medicine

NEUROSCIENCE

The Brain's Fix-It Brigade

Naturally occurring "exosomes" show promise for repairing nerve damage

An active lifestyle improves brain health, scientists have long believed. The studies bear this out: physical, intellectual and social activity—or "environmental enrichment," in the parlance—enhances learning and memory and protects against aging and neurological disease. Recent research suggests one benefit of environmental enrichment at the cellular level: it repairs brain myelin, the protective insulation surrounding axons, or nerve fibers, which can be lost because of aging, injury or diseases such as multiple sclerosis. But how does an enriched environment trigger myelin repair in the first place?

The answer appears to involve naturally occurring membrane-wrapped packets called exosomes. A number of different cell types release these little sacs of proteins and genetic material into the body's fluids. Loaded with signaling molecules, exosomes spread through the body "like messages in a bottle," says R. Douglas Fields, a neurobiologist at the National Institutes of Health. They target particular cells and change their behavior. In animal studies, exosomes secreted by immune cells during environmental enrichment caused cells in the brain to start myelin repair.

Researchers think exosomes might find use as biomarkers for diagnosing diseases or as vehicles to deliver cancer drugs or other therapeutic agents.

The exosomes produced during environmental enrichment carry microRNAs—small pieces of genetic material—which appear to instruct immature cells in the brain to develop into myelin-making cells called oligodendrocytes. When researchers at the University of Chicago withdrew exosomes from the blood of rats and administered them to aging animals, the older rats' myelin levels rose by 62 percent, the team reported in February in *Glia*.

The researchers also discovered how to generate exosomes outside the body, making them on demand for potential therapies. By stimulating immune cells from bone marrow, the group was able to "mimic Mother Nature's environmental enrichment in a dish," says Richard Kraig, a professor of neurology at Chicago.

Kraig's team is now exploring how to craft exosomes into a treatment for multiple sclerosis. The lab-grown exosomes stimulated myelin production in a sample of rat brain tissue intended to simulate multiple sclerosis damage, returning myelin levels to 77 percent of normal, Kraig and his colleagues recently reported in the *Journal of Neuroimmunology*.

The next step is to see if exosomes harvested from immune cells work as effectively in live animals with the disease, says team member Aya Pusic, a Ph.D. candidate in neurobiology. With any luck, Pusic says, the research could progress to human tests in five years. —*Debra Weiner*

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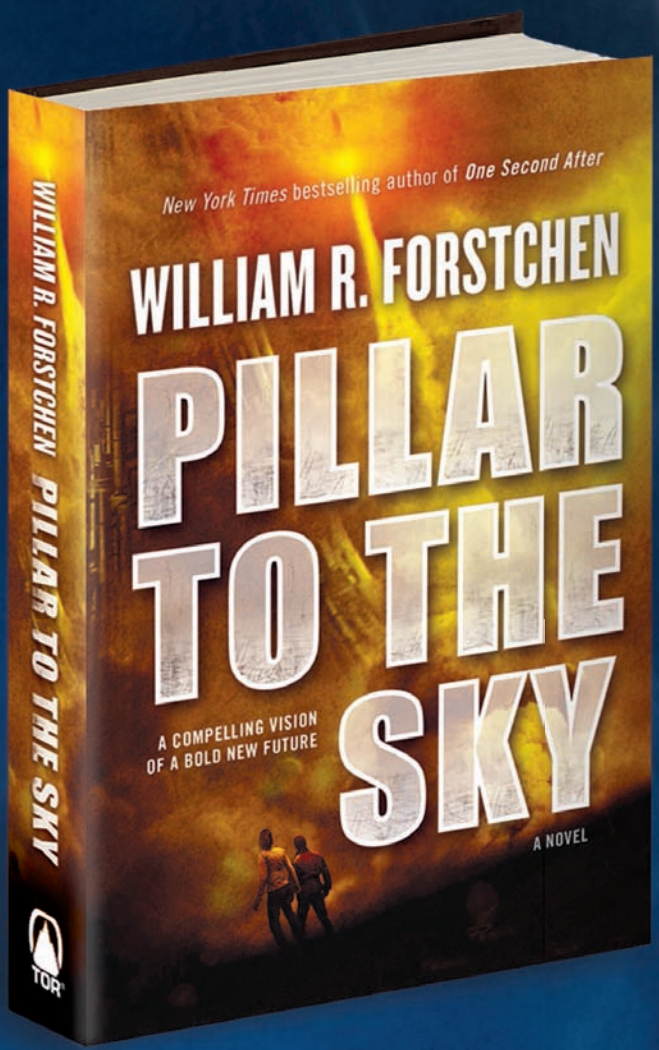
From the author of the *New York Times* bestseller *One Second After* comes

A magnificent NASA-inspired work of fiction



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Pandemic drought, skyrocketing oil prices, dwindling energy supplies, wars of water scarcity threaten the planet...

...and the world's last, best hope lies in a utopian scheme to harvest the infinite energy of the sun. However, three courageous people must first construct a vertiginous elevator, over 22,000 miles high, which offers limitless access to space. This pillar to the sky will require revolutionary advances in science, including the ultimate mastery of nanotechnology, and will face brutal opposition. Wealthy, powerful people want it demolished, its builders killed. A fast-paced thriller, *Pillar to the Sky* will keep you up long into the night but will also remind you that we are capable of greatness and can once again "slip the surly bonds of Earth."

WILLIAM R. FORSTCHEN, PhD, is a professor in North Carolina. His areas of expertise include the history of technology. He is the author of the acclaimed, bestselling science-based thriller, *One Second After.*

"Snappy storytelling that is utterly engaging. The concepts are intriguing—the possibilities endless."
—Steve Berry
New York Times bestselling author of *The King's Deception*

"The story of a world sinking into apocalypse, which can only be saved by a radical and terrifying experiment.... A fascinating, fiercely passionate, razor-sharp thriller full of innovative insights, high-tension suspense, and cutting-edge science."
—Douglas Preston
#1 *New York Times* bestselling author of *Impact*

CONSERVATION

The Rain Forest of Alabama

An extinction crisis is quietly unfolding in the southeastern U.S.

In a popularity contest, the homely little catfish known as the chucky madtom stands no chance against majestic, endangered sport fishes such as the Chinook salmon. Yet the catfish's plight is far more dire: none have been seen in the wild since 2004.

Conservation groups are putting the spotlight on lowly species such as the chucky madtom in a bid to bring attention to the plight of aquatic creatures in the southeastern U.S. Some 70 kinds of snails and mussels, along with two fishes and a crayfish from the region, are believed to have gone extinct. Dozens of other species, including the chucky madtom, are on the brink, devastated by agricultural chemicals, dams and invasive species. Sediment-laden runoff has also taken a toll, particularly on filter feeders. "If water conditions never improve, then they'll just die," says Tierra Curry, a biologist at the Center for Biological Diversity.

Thanks to the Southeast's stable geology, its wealth of isolated river basins and a lack of Ice Age glaciers, the region is a locus of aquatic biodiversity. The majority of the freshwater mussel, snail and fish species in the U.S. can be found there.

Many animals suffered when hydropower dams started popping up. The construction of seven dams on the Coosa River in Alabama from 1914 to 1967 proved uniquely harmful, wiping out an estimated three dozen species.

More recent threats include increased water withdrawals for human use and mountaintop-removal mining. "It's the conservation crisis that nobody hears about," says Paul D. Johnson, program supervisor at the Alabama Aquatic Biodiversity Center. "It's certainly unequaled in the United States. There's nothing close to this."

A few southeastern mussels received endangered status in 2013, but higher-profile species gobble up most of the available funding. In 2012 the U.S. government spent roughly $500 million to protect steelhead trout and Chinook salmon alone, compared with around $13.5 million total on all freshwater snails and mussels. "For them to really survive," Curry says, "it's going to take cash."

—Jesse Greenspan

ENVIRONMENT

Flame Out

Chemical fire retardants will be with us for years to come

California unwittingly prescribed a harmful chemical cocktail for the country in the 1970s, when it adopted rules meant to suppress fires from lit cigarettes. The regulations required foam used in upholstery to withstand a 12-second exposure to a small, open flame, triggering the widespread use of flame retardants. The effects reached well beyond the state, as manufacturers opted to adhere to a single safety standard rather than producing one set of products for California and another for the rest of the U.S.

The California rules, it turned out, were based on distorted science. Research has found that flame retardants are less effective than previously thought and pose potentially serious health risks. One class of chemicals, polybrominated diphenyl ethers, has been linked to cancer, reproductive problems and lower IQ in children. In January new rules took effect in California that free furniture manufacturers to cut back on the amount of flame retardants in their chairs and sofas. The new standards require that upholstered furniture resist exposure to a lit cigarette rather than an open flame. The change does not bar manufacturers from using flame retardants, but it makes it feasible to avoid their use.

How the industry responds remains to be seen. Even if manufacturers phased them out entirely, the chemicals would linger in the environment. Studies have shown that flame retardants in furniture leach into homes and then accumulate in the body. The chemicals also wind up in waterways and aquatic organisms.

And then there is the fact that furniture can last for generations, says Linda Birnbaum, director of the National Institute of Environmental Health Sciences. "I'm thinking of my 25-year-old couch," she says, "and I still love it."

—Dina Fine Maron

RAYMOND GRASSO *Getty Images (top);* JOEL SARTORE *Getty Images (bottom)*

COMMENT AT ScientificAmerican.com/mar2014

PALEONTOLOGY

Ancient Burial

In their treatment of the dead, Neandertals were a lot like us

Around 60,000 years ago, in a small limestone cave in what is now central France, Neandertals dug a grave and laid an elderly member of their clan to rest. That is the picture emerging from the archaeological site that yielded the famous La Chapelle-aux-Saints Neandertal skeleton in 1908, and it has important implications for understanding the behavior and cognitive capacity of our closest evolutionary relatives.

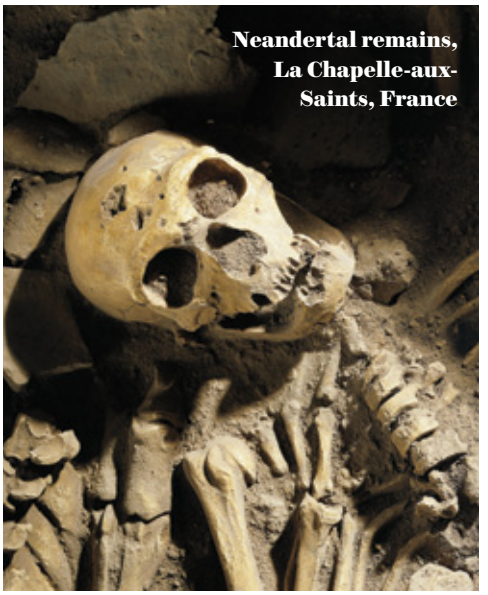
Some archaeologists have long argued that a number of Neandertal sites preserve evidence of burials, a practice considered to be a key feature of modern human behavior. But critics have countered that the sites were excavated long ago using outmoded techniques that obscure the facts.

In recent years researchers have found compelling evidence that Neandertals had other modern practices, such as decorating their bodies and making sophisticated tools. They did such things before anatomically modern humans invaded their turf, suggesting that Neandertals developed cultural traditions independently, rather than learning them from savvy newcomers.

A reexcavation of the French cave has recovered more Neandertal bones and teeth, as well as stone tools and animal remains. William Rendu of New York University and his colleagues found a number of features indicating that the pit containing the Neandertal skeleton was at least partially modified for the purposes of burial, as opposed to being an entirely natural depression. They also observed that whereas the animal remains appear to have been gnawed on by carnivores, the Neandertal bones exhibit no such damage, suggesting that the corpse was covered rapidly, as would occur if it were intentionally buried. Rendu and his colleagues reported their findings in January in the *Proceedings of the National Academy of Sciences USA*.

Ironically, the original La Chapelle-aux-Saints discovery in the early 20th century gave rise to the Neandertals' unfortunate reputation as dumb brutes. Shortly after the find, French paleontologist Marcellin Boule reconstructed the skeleton to show a stooped, slouching individual with bent knees, a short neck and a low, sloping skull. Thus, the image of the oafish caveman was born. Scientists later determined that the skeleton was in fact that of an aged male who suffered from severe arthritis.

—Kate Wong



Neandertal remains, La Chapelle-aux-Saints, France

BY THE NUMBERS

1%

Accuracy to which astronomers have now measured the scale of our universe. Galaxies tend to appear in clumps separated by a standard distance—a consequence of oscillations that reverberated through the early universe. Researchers working on the Baryon Oscillation Spectroscopic Survey have now measured that distance, and therefore the scale of cosmic structure, with unprecedented accuracy.

GETTY IMAGES (*top*); SOURCE: "THE CLUSTERING OF GALAXIES IN THE SDSS-III BARYON OSCILLATION SPECTROSCOPIC SURVEY: BARYON ACOUSTIC OSCILLATIONS IN THE DATA RELEASE 10 AND 11 GALAXY SAMPLES," BY LAUREN ANDERSON ET AL. PREPRINT PUBLISHED ONLINE DECEMBER 17, 2013 *http://arxiv.org/abs/1312.4877* (*bottom*)

PHYSICS

Leaden Treasure

Scientists draw battle lines over metal salvaged from ancient shipwrecks

Archaeologists and physicists both covet ancient Roman lead—for very different reasons. Old lead is pure, dense and much less radioactive than the newly mined metal, so it makes ideal shielding for sensitive physics experiments. But it also has historical significance—and many archaeologists object to melting down 2,000-year-old ingots.

"Are these experiments important enough to destroy parts of our past, to discover something about our future?" asks Elena Perez-Alvaro, an archaeology graduate student at the University of Birmingham in England, who wrote a paper on the dilemmas involved in the journal *Rosetta*.

Romans once used the lead to make coins, pipes, construction materials and weapons. Today private companies collect it from shipwreck sites and pass it on to customers—many of whom are physicists. "We may lose all ancient Roman lead—and therefore the information about ancient technology, shipping, trade, et cetera, it can offer—if its use for this kind of purpose becomes widespread," says University of Birmingham archaeologist John Carman.

Physicists argue that using the metal is prudent in key applications, such as in pursuit of dark matter, the material theorized to make up more than one quarter of the universe's mass. "None of us takes it casually—you don't want historical artifacts to be destroyed unnecessarily," says physicist Blas Cabrera of Stanford University. Cabrera is the spokesperson of the Super Cryogenic Dark Matter Search in Minnesota, which uses the lead for shielding its detector.

And in physics, ancient lead can help solve mysteries that long predate the Romans. "These experiments can reveal some of the most fundamental properties of the universe and answer questions such as what are we and where we come from," says physicist Fernando Gonzalez-Zalba of the University of Cambridge. "I think it's worth it." —*Clara Moskowitz*

BY THE NUMBERS

1.3 million

Number of galaxies for which researchers will have collected spectra when the Baryon Oscillation Spectroscopic Survey wraps up this year. Each spectrum—a detailed breakdown of a galaxy's light—helps to determine its distance from the Milky Way and improves cosmologists' measures of the universe.

GETTY IMAGES (*top*); SOURCE: "THE CLUSTERING OF GALAXIES IN THE SDSS-III BARYON OSCILLATION SPECTROSCOPIC SURVEY: BARYON ACOUSTIC OSCILLATIONS IN THE DATA RELEASE 10 AND 11 GALAXY SAMPLES," BY LAUREN ANDERSON ET AL. PREPRINT PUBLISHED ONLINE DECEMBER 17, 2013 http://arxiv.org/abs/1312.4877 (*bottom*)

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THIS IS THE AGE OF TAKING ACTION. VIAGRA.

VIAGRA is prescription medication to treat erectile dysfunction (ED).

IMPORTANT SAFETY INFORMATION BELOW.

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.

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

The blue diamond tablet shape is a registered trademark of Pfizer Inc.

VIAGRA® (sildenafil citrate) tablets

IMPORTANT FACTS

VIAGRA® (sildenafil citrate) tablets (vi-AG-rah)

IMPORTANT SAFETY INFORMATION ABOUT VIAGRA

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.

NEED MORE INFORMATION?

- This is only a summary of important information. Ask your doctor or pharmacist for complete product information OR
- Go to **www.viagra.com or call (888) 4-VIAGRA (484-2472).**

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TECHNOLOGY

Sun Chaser

A hybrid concept car would use solar power for short trips

Solar-powered cars have been little more than an experimental novelty to date. Expensive batteries, relatively inefficient energy conversion and the scarcity of sunny days in many regions have made photovoltaic passenger vehicles impractical.

Ford is looking to change that. A version of its plug-in C-MAX Energi hybrid, unveiled at the Consumer Electronics Association's recent International CES in Las Vegas, would use roof-mounted solar panels to charge a lithium-ion battery. The battery would power the car for trips of up to 34 kilometers, after which the hybrid's gasoline engine would kick in. "This is the world's first plug-in vehicle that doesn't need to be plugged in," says Mike Tinskey, Ford's global director of vehicle electrification and infrastructure.

The concept car gets a boost from an accompanying 20-square-meter acrylic canopy equipped with lenses that act as a giant magnifying glass, directing intense rays to the car's solar panels. Using sensors and cameras, the car would track the sun's position and autonomously reposition itself under the canopy for optimal exposure. The system enables the car to charge up to eight times faster than simply parking in the sun, Tinskey says.

Ford obviously has some kinks to work out if the concept is to ever see the light of day, much less a sales floor. The cost of the solar cells, tracking system and canopy are an open question. And the vehicle's repositioning system could pose logistical and safety problems. Would the average driveway accommodate a robotically rolling car? And what is to stop it from inadvertently running over an object in its path—such as a person's foot or a dozing cat?

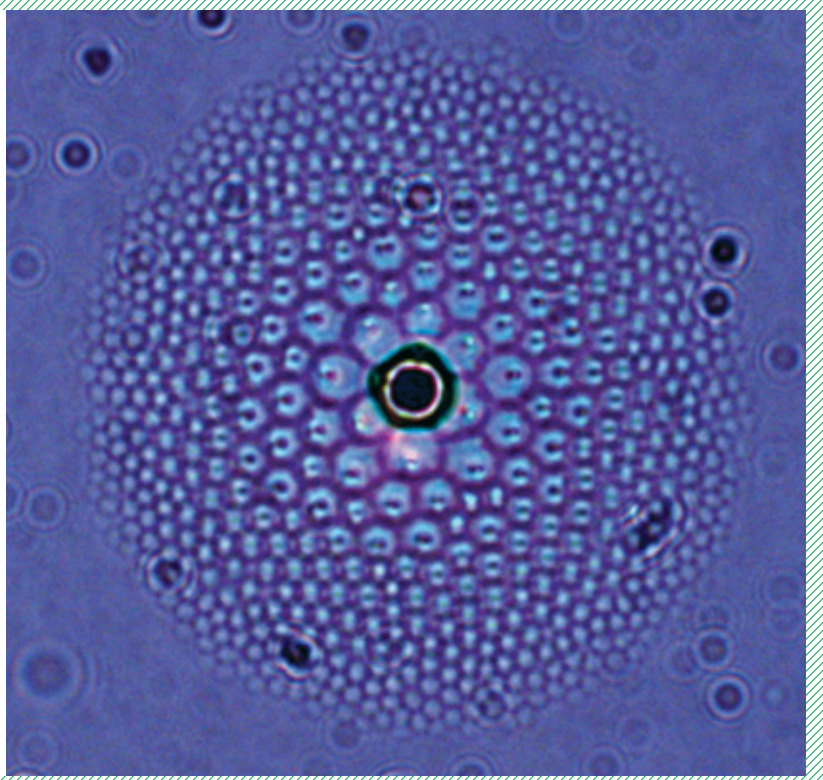
Despite the hurdles, the hybrid marks a promising automotive move—going cordless and energy-independent at the same time. *—Larry Greenemeier*

COURTESY OF FORD MOTOR COMPANY (*top*); COURTESY OF MOHAMED GHARBI *University of Pennsylvania* (*bottom*)

WHAT IS IT?

Liquid crystals, as the name suggests, occupy a state somewhere between a liquid and a solid. Researchers long ago learned how to exploit the unique properties of liquid crystals by manipulating the crystals' rod-shaped molecules to control light in digital displays. Now a University of Pennsylvania team has developed a new optical approach. When the researchers dropped a silica bead into a layer of liquid crystals, capillary forces drew the crystals into hundreds of tiny petals around the bead to form the flowerlike pattern pictured here. The work was detailed in *Physical Review X*.

The self-assembling petals collectively act as a compound lens that focuses light much like a fly's eye. The lens could find use in solar panels, boosting the collection of sunlight, or could form the tip of a fiber-optic probe to give surgeons a better view inside our bodies. *—Annie Sneed*



***Aedes albopictus* mosquito**

SUSUMU NISHINAGA *Science Source*

INFECTIOUS DISEASE

Trouble Knocking

A nasty mosquito-borne virus spreads to the Western Hemisphere

Given a choice between dengue fever and another mosquito-borne disease called chikungunya fever, most would choose dengue. Neither has an available vaccine or specific treatment, but chikungunya is far more debilitating.

The disease has long been a problem in Africa and southern Asia, causing high fever and severe joint pain. The name "chikungunya," meaning roughly "that which bends up" in the Makonde language of southeastern Africa, describes the doubled-over posture of the afflicted.

Now the virus is drawing closer to the U.S. The World Health Organization recently reported the first outbreak of chikungunya in the Western Hemisphere, on the Caribbean island of St. Martin. As of early January, there were 99 confirmed cases on the island, as well as a smattering of cases on other Caribbean isles. The U.S. Centers for Disease Control and Prevention warns that the virus could spread to other islands and the surrounding mainland in the coming months or years. The flow of tourist traffic through the region also heightens the risk of an outbreak in the U.S.

Just how chikungunya reached St. Martin has not been determined. The earliest patients diagnosed had not recently left the island, so they most likely acquired the disease locally. One plausible explanation is that a traveler contracted the disease in another region of the world and brought it back to St. Martin, where a local mosquito spread the virus to others. (All it takes to spread chikungunya is for a female *Aedes aegypti* or *Aedes albopictus* mosquito to feed on an infected person's blood and then bite someone else.) Another, less likely, option is that an infected mosquito traveled to St. Martin, perhaps as a stowaway on a ship or plane.

"We know the area has the right mosquitoes to potentially transmit chikungunya, so you could question, 'why not before now' or 'why not a year from now,'" says Erin Staples, an expert in vector-borne diseases at the CDC. "This just happened to be the right combination of factors."

—Dina Fine Maron

COMMENT AT ScientificAmerican.com/mar2014

BIOCHEMISTRY

Growing Hair in a Dish

Researchers are testing treatments for baldness on lab-grown locks

Cell biologist Desmond Tobin spends his days harvesting organs from cosmetic surgery patients. But Tobin is not after kidneys or other vital parts. Instead he collects swatches of skin removed from behind the ear during face-lift procedures. Crucially for Tobin, the skin samples contain the miniature organs, known as follicles, that produce hair.

At the Center for Skin Sciences at the University of Bradford in England, Tobin carefully extracts the follicles and uses them to replicate human hair growth in a petri dish.

With the harvested follicles, investigators such as James V. ("Vince") Gruber, global director of research and development at Lonza Consumer Care, can test the effectiveness

of new hair and skin products without relying on laboratory animals. Gruber explained his work at the annual meeting of the Society of Cosmetic Chemists last December.

Two different molecules show promise for potential hair-loss treatments, Gruber said. A yeast peptide appears to reverse senescence—when follicle cells linger in a dormant state and cease to replicate. And an antioxidant called an isoflavone increases collagen and elastin concentrations, which strengthen the skin matrix holding the follicles in place.

Tobin and Gruber have thus far focused on hair that has been chemically forced into senescence. The next step is to determine if follicles naturally heading toward dormancy could be persuaded to return to an active state. —*Rebecca Guenard*

Illustrations by Thomas Fuchs

ECOLOGY

No-Fly Zone

Is slaughtering birds the best way to keep the wildlife away from airplanes?

TONY CORDOZA *Getty Images*

In 2012, on the flat, grassy grounds of John F. Kennedy International Airport, wildlife-control agents killed 10,123 birds. The species "depredated" at JFK, which lies just northeast of the Jamaica Bay Wildlife refuge in the New York City borough of Queens, included thousands of gulls, hundreds of starlings and mourning doves, and a smattering of more majestic species such as ospreys and the American kestrel. The long-running JFK depredation program is just one of many efforts around the globe to prevent dangerous, expensive collisions between birds and aircraft.

Perhaps modern forensic tools could lead to a less deadly approach. The DNA found in carcasses of birds killed by aircraft illuminates new ways to control wildlife at airports, a team of Australian scientists suggests.

The forensic investigation began with a call from airport employees in Perth to Michael Bunce, then at Murdoch University. "Look, we've got an entire freezer full of birds," he recalls airport staffers telling him. "Do you want them?" Soon he and his colleagues had 77 bird carcasses to work with.

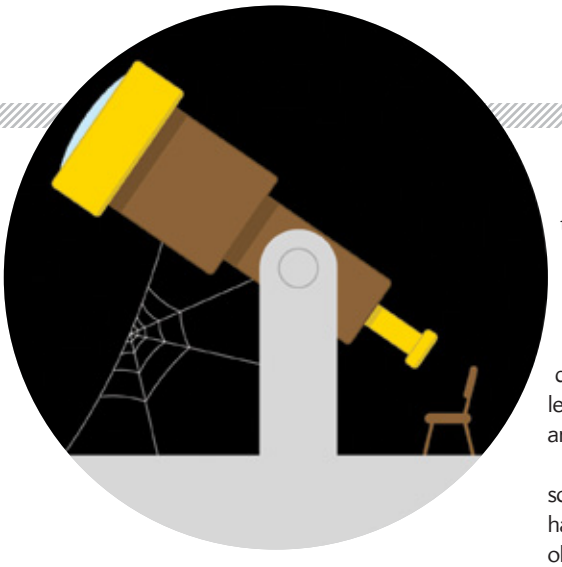
The researchers began scooping out the contents of the birds' digestive tracts and sequencing the DNA. In a 2013 study published in *Investigative Genetics*, Bunce and his colleagues matched the genetic sequences with known species of mice, crayfish and grasshoppers, as well as various grasses.

Such genetic analyses could inform how ground crews manage an airport's ecology to deter birds. "If there's available food for them, what do you do?" Bunce says. "Are you better off netting off waterways, poisoning for rodents or applying insecticides?" In Perth, his findings led the airport to install netting in waterways to control an invasive mosquito fish. Even if such research stops only one or two bird strikes, Bunce says, "it pays for itself many times over." —*Peter Andrey Smith*

SPACE

Lonely Dwarf Planets

The boom in finding Pluto's peers nears its end



For decades Pluto was the undisputed heavyweight champion in the far reaches of the outer solar system. Now astronomers know that the beloved world is just one of many known dwarf planets, most of which orbit the sun out beyond Neptune.

The discoveries that led to Pluto's demotion from planet to dwarf planet arrived in a rapid burst that peaked about a decade ago. Between 2002 and 2007 astronomer Mike Brown of the California Institute of Technology and his colleagues discovered several major objects, including the dwarf planets Eris, Makemake and Haumea (although another group also claims credit for Haumea). Since that flurry of activity, the discovery of large objects in the outer solar system has stalled, even though Brown's group left broad swaths of the sky unsearched.

The reason? Most of the big, bright objects have already been found, according to a new study. Megan Schwamb, a former graduate student of Brown's, now at the Academia Sinica in Taiwan, conducted a large-scale survey of the outer solar system, then extrapolated from the search to estimate the total numbers of objects. "It says that there are about 12," Schwamb says, adding that nine are already known. "That's really telling us that we are pretty complete on the inventory of bright dwarf planets." Schwamb and her colleagues published their findings in January in the *Astronomical Journal*.

Even though astronomers have not scanned the entire sky, they appear to have covered the areas laden with bright objects. It is possible, however, that a dwarf planet has escaped notice, says Darin Ragozzine of the Florida Institute of Technology. The starry plane of the Milky Way could obscure a dwarf planet, he notes, but it is unlikely that several await discovery.

"We had this golden age of finding these dwarf planets," Schwamb observes. "That era is over." But there may be similar objects farther out that are just too faint to spot today. "They're lurking in the shadows waiting for someone to detect them," she adds.

—*John Matson*

PSYCHOLOGY

Thought Control

Imagination triggers some of the same physical mechanisms involved in actual sight

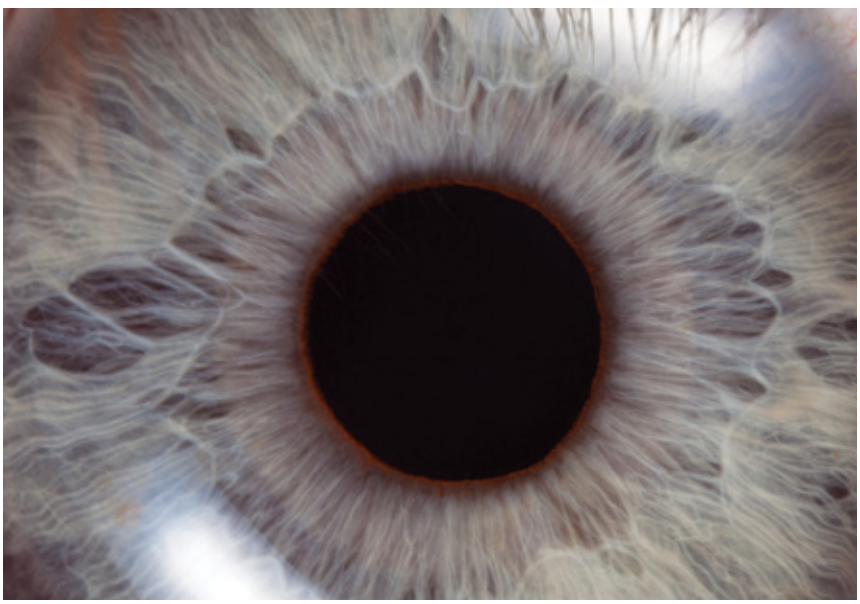
Most people don't spend much time pondering the diameter of their pupils. The fact is that we don't have much control over our pupils, the openings in the center of the irises that allow light into the eyes. Short of chemical interventions—such as the eyedrops ophthalmologists use to widen their patients' pupils for eye exams—the only way to dilate or shrink the pupils is by changing the amount of available light. Switch off the lamp, and your pupils will widen to take in more light. Step out into the sun, and your pupils will narrow.

Mechanical though they may be, the workings of pupils are allowing researchers to explore the parallels between imagination and perception. In a recent series of experiments, University of Oslo cognitive neuroscientists Bruno Laeng and Unni Sulutvedt began by displaying triangles of varying brightness on a computer screen while monitoring the pupils of the study volunteers. The subjects' pupils widened for dark shapes and narrowed for bright ones, as expected. Next, participants were instructed to simply imagine the same triangles. Remarkably, their pupils constricted or dilated as if they had been staring at the actual shapes. Laeng and Sulutvedt saw the same pattern when they asked subjects to imagine more complex scenes, such as a sunny sky or a dark room.

Imagination is usually thought of as "a private and subjective experience, which is not accompanied by strongly felt or visible physiological changes," Laeng says. But the new findings, published in *Psychological Science,* challenge that idea. The study suggests that imagination and perception may rely on a similar set of neural processes: when you picture a dimly lit restaurant, your brain and body respond, at least to some degree, as if you were in that restaurant.

The new experiments complement popular methods for studying consciousness by providing visual stimulation to participants without their awareness. Joel Pearson, a cognitive neuroscientist at the University of New South Wales in Australia, explains that mental imagery research takes the opposite approach, allowing subjects conscious awareness of a mental image without the accompanying stimulation. Perhaps by combining the two approaches, scientists can better understand how consciousness works.

—Jason G. Goldman



PETER A. KEMMER Getty Images

COMMENT AT ScientificAmerican.com/mar2014

HEALTH

Rapid Response

The food we eat quickly changes the bacterial makeup in our gut

You are what you eat, and so are the bacteria that live in your body.

Microbiologists have known for some time that different diets produce different gut flora, but new research indicates that the changes take hold with startling quickness. Bacterial populations shift measurably in the first few days following a big shift in what we eat, according to a recent study.

Researchers assigned volunteers to two diets—one based on animal products such as meat, eggs and cheese and one based on vegetables. Almost immediately the gut microbiome responded. The animal diet, for instance, curbed the numbers of microbes that break down carbohydrates from plants and boosted levels of organisms that can tolerate bile, which helps to digest fats. "What we thought might take days, weeks or years began to happen within hours," says Eugene Chang, a professor of medicine at the University of Chicago, who did not contribute to the study.

The rapid changes could have been very useful for ancient humans, notes study co-author Lawrence David, an assistant professor at the Duke Institute for Genome Sciences & Policy. A forager's diet could vary widely based on what food sources were available, and the microbiome's ability to adapt would ensure maximum nutrient absorption. David and his colleagues published their findings in *Nature*. (*Scientific American* is part of Nature Publishing Group.)

The microbes may not be uniformly beneficial, however. Subjects eating animal products saw a significant uptick in *Bilophila wadsworthia*, a bacterium known to contribute in mice to colitis, or inflammation of the colon. But David cautions that it is too soon to advocate for specific dietary changes. "We're anticipating that people will try to draw conclusions about which diet is better from this," David says. "And we want to address that it's very difficult to come to any health-related judgment based on this study." —*Rachel Feltman*

PROFILE

NAME
Ernest J. Moniz

TITLE
U.S. Secretary of Energy

LOCATION
Washington, D.C.

Q&A

The Storm Next Time

The energy secretary talks about buffering infrastructure against the next Hurricane Sandy

When extreme weather events hit, energy infrastructure is often the first thing to fail. As the world adapts to climate change, resilient infrastructure may prove key. Last December, SCIENTIFIC AMERICAN talked with the U.S. energy secretary at New York City start-up Urban Electric Power, which aims to decentralize electricity infrastructure and enhance its resilience by installing batteries for energy storage across the grid.

Why do we need batteries in the grid? There are several reasons. It's about absorbing intermittent sources such as solar and wind. Clearly, one can do other things to help balance those kinds of intermittent supplies, like integrating natural gas. But obviously, storage gives you massive flexibility. As we go more and more to smart grids and grids with intelligence, integrating distributed storage will also be important.

But if the home of the future has fuel cells and photovoltaics on the roof, do we even need the grid? Certainly for a well-developed economy like the U.S., it's not going to be one or the other. I think there will always be a place for some large, base-load power plants, even as we have an increased emphasis on distributed generation. Of course, when you go to other places in the world, the balance can be quite different. You might start from the distributed side and then, perhaps, integrate into a larger system, depending on the economy.

In the context of a developed country, if you can provide energy services with less need for supply and infrastructure, then you are better off. That comes down to efficiency, things such as LEDs, where the cost drop has been incredible. The price is now coming below $10 retail, and with $125 to $130 lifetime energy-cost savings—that's getting to be a deal that's hard to turn down. To me, it's just clearly the future of lighting.

What's next? In 2014 there is going to be a focus on infrastructure. In the climate context, it's the question of resilience of energy infrastructure against, well, Hurricane Sandy and events of that type. Although I do want to emphasize that when we are looking at resilience, it will be broader than just extreme weather events. It will also be cyber as well as physical threats.

Are you having fun? Absolutely.

You like the job so far? I like any job that I'm doing.

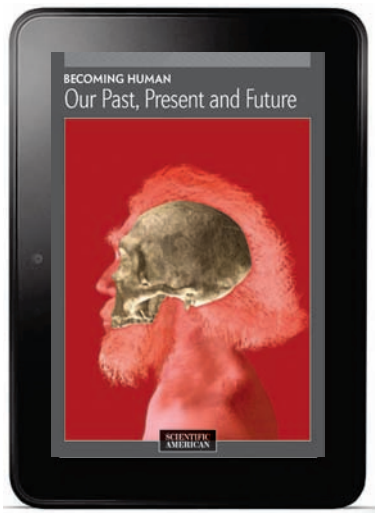
But they can't all be fun. This one is fun? They're all fun. I make them all fun. —*David Biello*

REDUX PICTURES

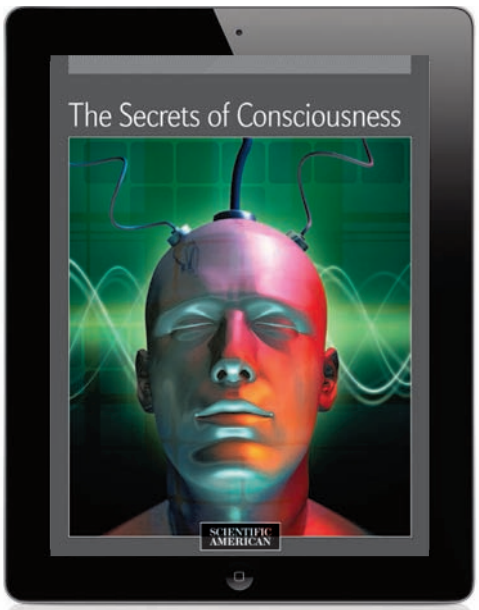
COMMENT AT ScientificAmerican.com/mar2014

EBooks that raise your tablet IQ

Science to enrich your life in a format to fit your lifestyle
From the Editors of Scientific American



We humans are a strange bunch. We have self-awareness and yet often act on impulses that remain hidden. We were forged in adversity but live in a world of plenty. How did we get here? What is to become of us? To these age-old questions, science has in recent years brought powerful tools and reams of data.



Consciousness is an enigmatic beast. It's more than mere awareness—it's how we experience the world, 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 this discussion, using available medical technology to explore just what separates so-called "mind" from brain.

Advances in technology often concur with times of war—the nuclear bomb is an iconic example. The need to develop a weapon before the Nazis changed the rules of warfare forever. Today each advance from drones to computer systems to biological weapons demands a re-thinking of where the vulnerabilities lie and how severe any collateral damage would be.

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Katherine Harmon Courage is a contributing editor at *Scientific American* and author of the book *Octopus! The Most Mysterious Creature in the Sea* (Current/Penguin Group, 2013).

Space: The Final Medical Frontier

Are overeager space tourists endangering their health?

Keeping people healthy in space has been a major challenge since the first days of spaceflight. That is partly why NASA has always favored the crème de la healthy crème of human specimens for its missions. Now, however, the burgeoning business of commercial spaceflight is poised to open the galaxy's doors to a much larger—and unhealthier—pool of passengers. If private spaceflight companies keep their promise to allow people of average health to fly, space tourism could become a $1.3-billion industry with more than 25,000 customers by 2021, according to consulting firm Futron Corporation. Virgin Galactic has already booked at least 680 reservations for a two-and-a-half-hour-long trip, with about four minutes spent in what is technically "space"—just more than 100 kilometers above Earth's surface. And a Russian company called Orbital Technologies hopes to build a space hotel equipped for five-day stays at more than 320 kilometers above the highest suite on Earth.

Fewer than a dozen paying customers have made the journey into space so far. We can guess at the kinds of medical problems new waves of space tourists may encounter, however, by examining the experiences of professional astronauts between the 1960s and today. Major health issues for these explorers have included weakened bones and muscles, poor vision, nausea and insomnia. In addition to all these risks, untrained tourists will almost certainly face a wider array of "health problems that you haven't had to deal with in space before," says Jeffrey Jones, a member of the Center for Space Medicine at Baylor College. Even a brief sojourn into space could present serious health concerns for the elderly and those with high blood pressure because of the enormous compression the body endures during takeoff and reentry. Longer voyages will likely aggravate many common medical disorders—including asthma, heart disease and cancer—that would usually disqualify someone from a NASA flight.

Currently there are no federal or state regulations that determine who is eligible for commercial spaceflight, so companies are free to set their own no-fly standards. A Virgin Galactic spokesperson says "most people" will be allowed to fly with them. Some doctors have begun drawing up screening guidelines for those who hope to vacation among the stars; others are considering how to modify a few Earth-bound medical procedures so that, if necessary, they can be applied in space.

NEW PRESSURE

THE ISSUES TO BE TACKLED are formidable. In the past half a century, researchers have learned that space travel changes just about every system in the human body. Launch and reentry place people under strong gravitational forces (*g*-forces), a measure of the stress to which the body is subjected during acceleration. High *g*-forces make the heart work extra hard to circulate blood, especially to the brain (which is one reason high *g*-forces can cause people to lose consciousness). Some commercial spaceflight companies have offered to help customers prepare for the intense strain by whipping them around in a giant centrifuge machine, but the training is not mandatory.

Orbiting Earth in free-fall at, say, 28,000 kilometers per hour and about 400 kilometers above the planet's surface—as is the case for the International Space Station—creates a state of weightlessness. On Earth, gravity keeps the bulk of our fluids in our lower half. When we are weightless, fluids spread out more evenly, draining from the legs and filling up the chest and head. In the process, fluid disperses through the inner ear tubes that help us keep our balance, resulting in nausea, which—even more than pain—is notoriously difficult to ignore and, if followed by vomiting, can lead to severe dehydration. Despite learning techniques to tolerate nausea, professional astronauts often feel queasy during the first days of a flight, so we can expect plenty of sick-to-their-stomach civilians.

Increased fluid in the head is also responsible for one of the most frequent complaints among astronauts after the all too common "space sickness": poor eyesight. All of that excess cranial

Illustration by O.O.P.S.

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ASTROBIOLOGY

- NASA's OSIRIS-Rex Mission
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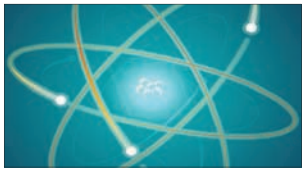

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pressure can flatten the back of the eyeball and thus blur vision.

In addition to shifting fluids, prolonged weightlessness weakens the skeleton. Because astronauts are no longer walking or performing other weight-bearing activities, bone loses between 1 and 2 percent of its mineral density each month in space, says Jeffery Sutton, director of the National Space Biomedical Research Institute. As an added danger, calcium that leaches from bone can contribute to kidney stones—nuggets of minerals that can painfully obstruct the urinary tract.

Muscles also deteriorate in microgravity because they no longer have to work to support the body throughout the day. Although exercise in space can help slow such decay, fluid redistribution becomes a problem once again. Unusually high levels of lactic acid—which is responsible for cramps and aches during a workout—pool in the muscles of space exercisers, cutting their routines short.

Particularly concerning is how space alters the body's hardest-working muscle: the heart. Marlene Grenon of the University of California, San Francisco, and her colleagues have discovered that after just 24 hours in a simulated microgravity environment, the cells that line blood vessels change shape, adhere in different ways and use a different mix of genes than usual.

Space travel takes its toll on the mind as well as the body. Getting a good night's rest in microgravity can be difficult because of persistent lights and sounds on a spacecraft and the eerie feeling of weightlessness. In several grounded simulations of long-term space travel, astronauts living in close quarters occasionally became depressed and foggy. Considering how aggravated airline passengers can get after a flight across the Atlantic, sending a group of space tourists on a seven-month trip to Mars, as the Mars One organization wants to do, might be asking for mutiny.

GALAXY OF WOES

SPACE TOURISTS of average and poor health are bound to face a whole host of medical concerns on top of what even a NASA Adonis must worry about. Most commercial spaceflight customers are likely to be at least middle-aged, which means many will have high blood pressure and heart disease, common disorders for their age range.

Fluid redistribution is particularly dangerous for people with heart disease. As fluids move to the chest and head, rising pressure in the skull bumps up the risk of bursting blood vessels and damaging brain tissue. Similarly, increasing pressure inside the lungs from extra fluid can trigger an asthma attack—a sudden and acute constriction of the airways.

Even motion sickness could be extra dangerous to people with existing cardiovascular disorders. The dehydration, panting and racing blood pressure that come with excessive use of the barf bag, Jones points out, tire the cardiovascular system, which, if already weakened, could culminate in a heart attack. Some scientists have begun studying the heart in rats that are half-suspended (often by their tail), which somewhat mimics the fluid redistribution that happens in microgravity. So far they have learned that after a month—even in this experimental environment—the animals' heart muscle itself changes, becoming larger and less efficient; similar cardiac deconditioning has been reported in human astronauts.

Like microgravity, another one of the greatest dangers to space tourists is something they cannot see with their own eyes: radiation. Giant magnetic fields surrounding Earth deflect electromagnetic energy emanating from stars and black holes that would otherwise incinerate us. Once you leave Earth's magnetosphere behind, you are exposed to all that energy, which shreds DNA and can cause mutations that make a healthy cell start multiplying uncontrollably, leading to cancer.

Supremely healthy astronauts can spend hundreds of days in space without terribly increasing their rates of cancer. But if Mars One is serious about setting up colonies on the Red Planet, it will have to protect its passengers from radiation on the voyage—as well as at the atmosphereless destination. And skittering particles and electromagnetic waves could unfavorably tip the scales for anyone with a genetic predisposition to cancer.

FINAL FRONTIER MEDICINE

PINPOINTING WHO IS VULNERABLE to illness in space is still not enough to guarantee the well-being of space travelers. We must also learn how to adapt medical procedures we have perfected on Earth.

Dorit Donoviel, deputy chief scientist at the National Space Biomedical Research Institute, and her colleagues are exploring easy, noninvasive techniques as alternatives to standard medical practice in space. Traditionally doctors check for a change in brain pressure by sticking a needle into the spinal column or directly into the skull—a procedure that might not fly in space, especially without an attending physician. Instead Donoviel has been trying to gauge changes in internal pressure by recording how sound waves travel through the eye sockets and ear canals. And infrared light, which is absorbed and refracted differently by healthy and injured tissue, might be able to identify internal bleeding. Portable diagnostic devices based on infrared or ultrasound signals would be far more likely to make it to space than the bulky and heavy machines used for MRIs and CT scans.

In the meantime, a report published in 2012 in *BMJ* recommends that primary care clinicians start getting ready to evaluate patients who want to try commercial spaceflight. Conditions such as heart disease, uncontrolled asthma or high blood pressure should merit a warning and explanation of risks from a physician. Researchers are also devising simple ways to get hopeful tourists as healthy as possible before they ever set foot onboard a spacecraft. Low-tech solutions such as making sure people are well nourished and properly hydrated in the weeks before launch might go a fair way toward ensuring an emergency-free flight.

Virgin Galactic says it will offer customers three days of training that will include "physical tests" and "a medical screening" but is not disclosing the precise criteria used to approve tourists for flight, if any. For now the onus falls mainly on tourists and their doctors to take precautions. As a consolation to anyone who must stay grounded, just remember: there's so much to discover on our planet. I hear Iceland is out of this world. SA

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

Future Imperfect

Asimov's forecast from 1964 shows how far we still have to go

Predictions about technology's future are almost always doomed. According to *2001: A Space Odyssey,* for example, humans should be making flights to the outer reaches of our solar system. Per *1984,* by now we should have become a society of brainwashed drones, toiling under constant surveillance for faceless overlords. Clearly, that would never—hey, wait a second!

Nevertheless, Isaac Asimov, the revered science-fiction author, made a stab at describing our lives today—back in 1964. In a *New York Times* article 50 years ago, Asimov called his vision "Visit to the World's Fair of 2014." Now it is, in fact, 2014. Shall we dust off his little time capsule and see how well his predictions fared?

You might assume that his projections fall into two categories: the ones that came to pass and those that didn't. Give the guy credit for anticipating self-driving cars, video calling, the widespread use of nuclear power and single-duty household robots. (He didn't exactly name the Roomba, but he did at least propose "robots for gardening work.")

Asimov also worried at length about overpopulation, estimating the 2014 world population to be 6.5 billion and the U.S. population to reach 350 million. He came very close; the actual world population is about 7.1 billion, and the U.S.'s tally is 317 million.

And, yes, he also got a lot wrong. He foresaw underground and underwater homes becoming popular, along with "transportation that makes the least possible contact with the surface"—cars and boats that levitate on jets of compressed air.

His weirdest prophesies concern our desperate suffering "from the disease of boredom," once robotics and automation have taken away most of our jobs. "The lucky few who can be involved in creative work of any sort will be the true elite of mankind, for they alone will do more than serve a machine." If technology ever does buy us more leisure time, technology will also expand to fill it. (A streaming Netflix movie, anyone?)

But many of Asimov's prognostications also fall into a third category that you might not have expected: technologies that are indeed feasible today—but aren't yet commonplace.

By now he thought that windows would be little more than "an archaic touch," thanks to the popularity of glowing wall panels. Sure, we have flat-screen technology—but we still like to look outside at real grass, sky and squirrels.

In downtown areas, he predicted moving sidewalks. We've built those at airports but skipped them on city streets.

He also figured that our diets would include "processed yeast and algae products" such as "pseudosteak"—an item that might give even tofurkey converts pause. And he foresaw moon colonies established by 2014, with Mars colonies already in the planning stages. In each case, what kept his hopeful prediction from coming true has not been technological; instead we seem to lack the will, desire or courage to make them a reality.

His dream of "large solar-power stations" operating in the desert has been slow to arrive. But stations are finally being built, as economic and political obstacles fall.

Another example: he gives us, the future humans, more credit than we deserve for tackling overpopulation. It must have seemed logical to anticipate "a worldwide propaganda drive in favor of birth control"—but opposition to contraception remains strong.

Asimov's predictions illustrate three lessons for those who would predict the future. First, almost every new technology takes longer to arrive than sci-fi writers imagine.

Second, you'll never hit all the big ones; the history of technology is framed by enormous zigs or zags—consider, for instance, the Internet—that not even Asimov saw coming.

And third, many attractive or logical developments never materialize, thanks to our own human failings. The fault, dear Isaac, is not in our engineering but in ourselves. SA

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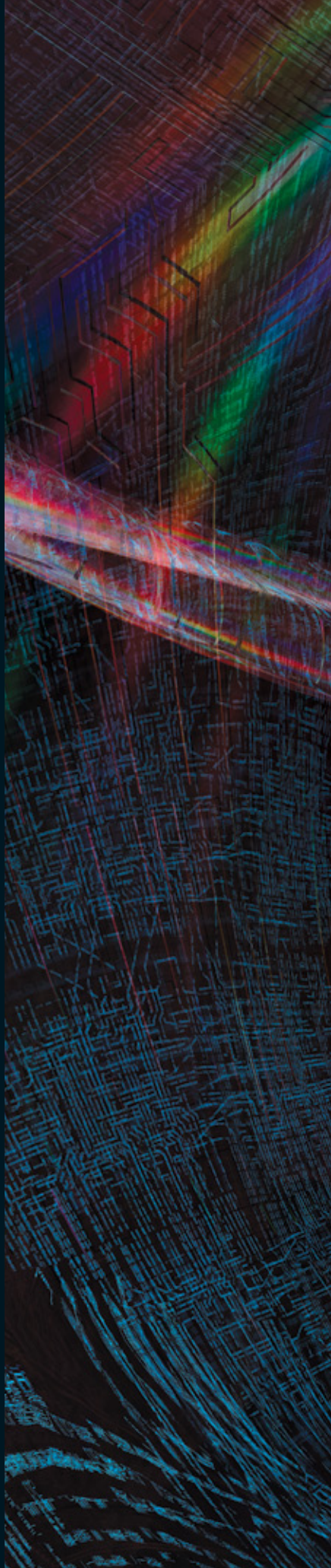
NEUROSCIENCE

THE NEW CENTURY OF THE BRAIN

Big science lights the way to an understanding of how the world's most complex machine gives rise to our thoughts and emotions

By Rafael Yuste and George M. Church



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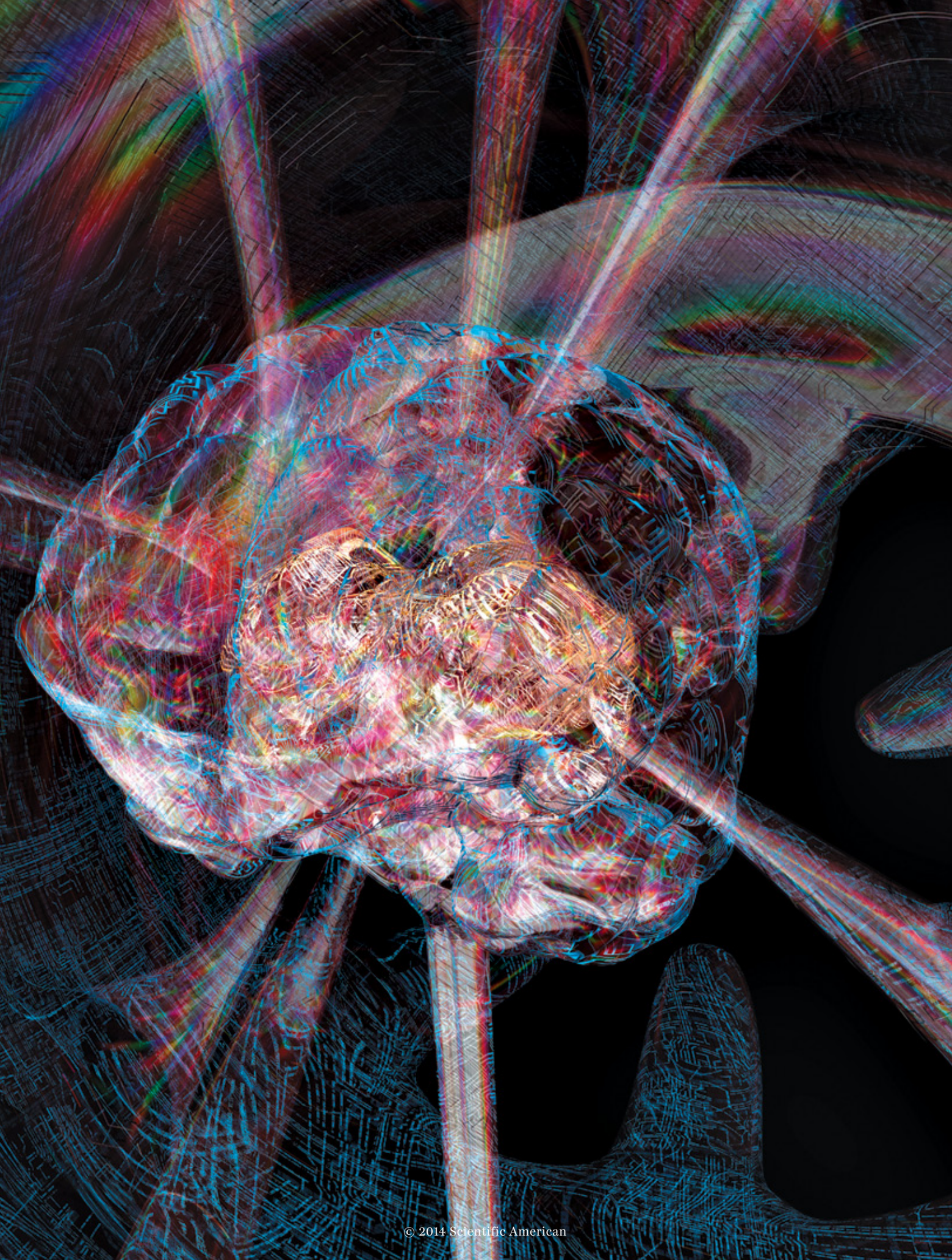


Rafael Yuste is a professor of biological sciences and neuroscience at Columbia University and co-director of the Kavli Foundation's Institute for Brain Science. He is a recent winner of the NIH Director's Pioneer Award.

George M. Church is a professor of genetics at Harvard University and founder of PersonalGenomes.org, an open-access source for data on human genomes, neuroimaging, and behavioral and cognitive traits. He serves on *Scientific American*'s board of advisers.

DESPITE A CENTURY OF SUSTAINED RESEARCH, BRAIN SCIENTISTS REMAIN IGNORANT of the workings of the three-pound organ that is the seat of all conscious human activity. Many have tried to attack this problem by examining the nervous systems of simpler organisms. In fact, almost 30 years have passed since investigators mapped the connections among each of the 302 nerve cells in the roundworm *Caenorhabditis elegans*. Yet the worm-wiring diagram did not yield an understanding of how these connections give rise to even rudimentary behaviors such as feeding and sex. What was missing were data relating the activity of neurons to specific behaviors.

The difficulty in establishing a link between biology and behavior in humans is still more acute. The media routinely report on scans showing that specific brain locations light up when we feel rejected or speak a foreign language. These news stories may give the impression that current technology provides fundamental insights into how the brain works, but that impression is deceiving.

A noteworthy example of the mismatch is a much publicized study identifying single brain cells that fired an electrical impulse in response to the face of actor Jennifer Aniston. Despite the hoopla, the discovery of a "Jennifer Aniston neuron" was something like a message from aliens, a sign of intelligent life in the universe but without any indication about the meaning of the transmission. We are still completely ignorant of how the pulsing electrical activity of that neuron influences our ability to recognize Aniston's face and then relate it to a clip from the television show *Friends*. For the brain to recognize the star, it probably has to activate a large ensemble of neurons, all communicating using a neural code that we have yet to decipher.

The Jennifer Aniston neuron also exemplifies the crossroads neuroscience has reached. We already have techniques to record the activity of single neurons in living humans. But to advance meaningfully, the field needs a new set of technologies that will enable investigators to monitor and also alter the electrical activity of thousands or even millions of neurons—techniques capable of deciphering what the pioneering Spanish neuroanatomist Santiago Ramón y Cajal called "the impenetrable jungles where many investigators have lost themselves."

Such breakthrough methods could, in principle, begin to bridge the gap between the firing of neurons and cognition: perception, emotion, decision making and, ultimately, consciousness itself. Deciphering the exact patterns of brain activity that underlie thinking and behavior will also provide critical insights into what happens when neural circuitry malfunctions in psychiatric and neurological disorders—schizophrenia, autism, Alzheimer's or Parkinson's.

Calls for a technological leap in studying the brain have started to be heard outside the laboratory. Indeed, the Obama administration announced last year that it was establishing a large-scale initiative: the Brain Research through Advancing Innovative Neurotechnologies Initiative, or simply the BRAIN Initiative, the most visible big science effort of the president's second term.

The BRAIN Initiative, with an initial funding level of more than $100 million in 2014, targets development of technologies to record signals from brain cells in much greater numbers and even from whole areas of the brain. BRAIN complements other large neuroscience projects outside the U.S. The Human Brain Project, funded by the European Union, is a 10-year, $1.6-billion effort to

IN BRIEF

The brain—and the way it gives rise to conscious thought—remains one of the great mysteries in all of science.

To better understand the brain, neuroscientists need new tools for analyzing the functioning of neural circuits.

Technologies that either record or control the activity of brain circuits may address these needs.

The Obama administration has a large-scale initiative under way to promote development of these technologies.

develop a computer simulation of the entire brain. Ambitious neuroscience research projects have also been launched in China, Japan and Israel. The global consensus that is now propelling investment in brain science recalls other postwar science and technology initiatives focused on pressing national priorities: nuclear power, atomic weaponry, space exploration, computers, alternative energy and genome sequencing. The Century of the Brain is now upon us.

THE TV SCREEN PROBLEM

TRACKING HOW BRAIN CELLS compute the concept of Jennifer Aniston—or anything comparable that we encounter through subjective experience or perceptions of the outside world—is currently an insurmountable obstacle. It requires moving from measuring one neuron to gaining an understanding of how a collection of these cells can engage in complex interactions that give rise to a larger integral whole—what scientists call an emergent property. The temperature or solidity of any material or the magnetic state of a metal, for instance, emerges only from the interactions of a multitude of molecules or atoms. Consider carbon atoms. The same atoms can bond to create either a diamond's durability or the softness of graphite, which exfoliates so easily it forms words on paper. Whether hard or soft, these emergent properties depend not on the individual atoms but on the set of interactions among them.

The brain, too, probably exhibits emergent properties that are wholly unintelligible from inspection of single neurons or even from a coarse, low-resolution picture of the activity of large groups of neurons. The perception of a flower or the retrieval of a childhood memory may be discerned only by observing the activity of brain circuits that pass electrical signals along intricate chains of hundreds or thousands of neurons. Although neuroscientists have long been familiar with these challenges, they still lack the tools to record the activity of the individual circuits that underlie a perception or a memory or that give rise to complex behaviors and cognitive functions.

What it takes to perceive a flower may only be discerned by observing the activity of brain circuits that pass electrical signals along chains of thousands of neurons.

One attempt to overcome this bottleneck involves assembling a map of the anatomical connections, or synapses, among neurons—an endeavor called connectomics. The recently launched Human Connectome Project in the U.S. will provide a structural wiring diagram of the brain. But, as with the roundworm, that map is only a starting point. By itself, it will be unable to document the constantly varying electrical signals that produce specific cognitive processes.

To make such a recording, we need wholly new methods of measuring electrical activity that go beyond existing technologies—which provide either a precise picture of the activity of relatively small groups of neurons or else sweeping imagery of large brain areas but without the resolution required to identify specific brain circuits switching on or off. Fine-scale recordings are made currently by inserting needlelike electrodes into the brains of laboratory animals to record the firing of a single neuron, the electrical impulse triggered after the cell receives chemical signals from other neurons. When a neuron is properly stimulated, the voltage across the cell's outer membrane reverses. This voltage shift induces membrane channels to usher in sodium or other positively charged ions. The inflow, in turn, produces an electrical "spike" that travels down the cell's long projection—the axon—spurring it to send a chemical signal of its own to other neurons and thus continue to propagate the signal. Recording from just one neuron is analogous to trying to follow the plot of a high-definition movie while viewing only a single pixel, making viewing all but impossible. It is also an invasive technique that can cause tissue damage when electrodes penetrate brain tissue.

At the other end of the spectrum, methods that track the collective activity of neurons across the whole brain are also inadequate. In the familiar electroencephalograph (EEG), invented by Hans Berger in the 1920s, electrodes sit on the skull and measure the combined electrical activity of more than 100,000 nerve cells underneath—the EEG records the oscillating "waves" of rising and falling amplitude over a few milliseconds, although it cannot resolve whether any individual neuron is active. Functional magnetic resonance imaging (fMRI)—producing the splotches of color illuminating active brain areas—records activity throughout the brain noninvasively but only slowly and with poor spatial resolution. Each image element, or voxel (a three-dimensional pixel), is a composite of about 80,000 neurons. Moreover, fMRI does not track neuronal activity directly but records only secondary changes in blood flow within voxels.

To gain a picture of emergent patterns of brain activity, investigators need new sensing devices that can record from assemblages of thousands of neurons. Nanotechnology, with novel materials that sometimes measure less than the dimensions of individual molecules, may assist in making large-scale recordings. Prototype arrays have been built that incorporate more than 100,000 electrodes on a silicon base; such devices could record the electrical activity of tens of thousands of neurons in the retina. Further engineering of this technology will allow stacking of these arrays into three-dimensional structures, shrinking the electrodes to avoid damage to tissue and lengthening shafts to penetrate deep within the cerebral cortex, the brain's outermost layer. These developments could make it possible to record tens of thousands of neurons in a human patient while discerning the electrical properties of each cell.

Electrodes are only one way to track the activity of neurons. Methods that move beyond electrical sensors are making their way into the lab. Biologists, borrowing from technologies developed by physicists, chemists and geneticists, are beginning

to visualize living neurons in awake animals going about their daily paces.

A hint of what might be in store came last year, when Misha Ahrens of the Howard Hughes Medical Institute's Janelia Farm Research Campus in Ashburn, Va., used a larval zebra fish to perform microscopic whole-brain imaging. The zebra fish is one of neurobiologists' favorite organisms because the species is transparent in its larval state, allowing for easy inspection of the fish's innards, including the brain. In the experiment, the neurons of the zebra fish were genetically engineered to fluoresce when calcium ions entered the cell after it fired. A novel type of microscope illuminated the zebra fish brain by projecting a sheet of light over the entire organ while a camera took second-by-second snapshots of the neurons lighting up.

The technique used, called calcium imaging, which was pioneered by one of us (Yuste) to record the electrical activity of neural circuits, enabled the recording of 80 percent of the zebra fish's 100,000 neurons. It turns out that when the fish was at rest, many regions of the nervous system of the larval zebra fish switched on and off in mysterious patterns. Ever since Berger introduced the EEG, researchers have known that the nervous system is essentially always active. The zebra fish experiment gives hope that newer imaging technologies could help tackle a major challenge in neuroscience—the understanding of the persistent, spontaneous firing of large groups of neurons.

The zebra fish experiment is just the beginning because neuroscientists require still better technologies to discover how brain activity gives rise to behavior. New types of microscopes need to be designed to image simultaneously neuronal activity in three dimensions. In addition, calcium imaging operates too slowly to track the rapid firing of neurons and is also unable to measure the inhibitory signals that tamp down electrical activity in the cell.

Neurophysiologists, working side by side with geneticists, physicists and chemists, are trying to improve optical techniques that—instead of sensing calcium—record neuronal activity directly by detecting changes in membrane voltage. Dyes that alter their optical properties as voltage fluctuates—either deposited on the neuron or integrated through genetic engineering into the cell membrane itself—could improve on calcium imaging. This alternative technique, known as voltage imaging, may ultimately enable researchers to record the electrical activity of every neuron in an entire neural circuit.

Voltage imaging is still in its infancy, however. Chemists need to enhance the ability of the dyes to change color or other characteristics as a neuron fires. The dyes must also be designed to ensure that the chemicals do not damage the neuron. Already, though, molecular biologists are building genetically encoded voltage sensors; these cells read a genetic sequence to produce a fluorescent protein that is delivered to the cells' outer membrane. Once there such proteins can change the degree to which they fluoresce in response to alterations in a neuron's voltage.

As with electrodes, advanced nonbiological materials borrowed from nanotechnology may help. In place of organic dyes or genetic indicators, a new type of voltage sensor can be made of quantum dots—small semiconductor particles that exhibit quantum-mechanical effects and can be precisely tailored in their optical properties, such as the color or intensity of the light emitted. Nanodiamonds, another novel material imported from quantum optics, are highly sensitive to changes in electrical fields that occur as a cell's electrical activity fluctuates. Nanoparticles could also be combined with conventional organic or genetically engineered dyes to produce hybrid molecules in which a nanoparticle could serve as an "antenna" to amplify low-intensity signals produced by fluorescent dyes when a neuron is activated.

GOING DEEP

ANOTHER IMPOSING TECHNICAL CHALLENGE to visualizing neuronal activity is the difficulty of delivering light to, and collecting it from, neural circuits deep below the surface of the brain. To solve this problem, neurotechnology developers are beginning to undertake collaborations with researchers in computational optics, materials engineering and medicine who also need to see through solid objects noninvasively, whether skin, skull or the inside of a computer chip. Scientists have long known that some of the light that hits a solid object gets scattered and that the scattered photons may, in principle, reveal details of the object from which it is reflected.

For example, the light from a flashlight on one side of a hand shines through, exiting as a diffuse glow yet without giving any clue about the location of the bones or vasculature underneath the skin. But information about the path the light takes through the hand has not been lost entirely. The disordered waves of light scatter and then interfere with one another. This light pattern can be imaged with a camera, and new computational methods can then reconstruct an image of what lies within—a technique used last year by Rafael Piestun and his colleagues at the University of Colorado Boulder to see through an opaque material. These methods might be combined with other optical techniques, including those used by astronomers to correct image distortions caused by the atmosphere's effects on starlight. So-called computational optics may help visualize the fluorescent glow from dyes that light up when subsurface neurons fire.

Some of these new optical techniques have already been used successfully to image the inner reaches of animal or human brains with a piece of the skull removed, enabling scientists to see more than a millimeter into the cortex. And with further refinement, these techniques might potentially offer a way to look through the thickness of the skull. But see-through optical imaging will not penetrate far enough to detect structures deep within the brain. Yet another recent invention may help address this problem. In a technique called microendoscopy, neuroradiologists currently insert a narrow but flexible tube into the femoral artery and then maneuver it to many parts of the body, including the brain, allowing microscopic light guides inserted in the tube to do their work. In 2010 a team at the Karolinska Institute in Stockholm demonstrated an "extroducer"—a device that allows the artery or vessel through which the endoscope is threaded to be safely perforated, which makes any part of the brain, not just the vasculature, accessible for inspection by various imaging or electrical recording technologies.

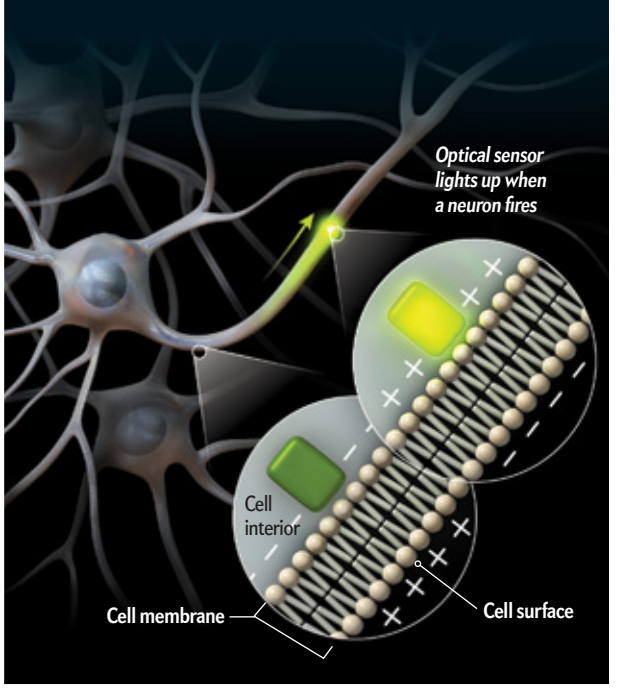
Electrons and photons are the most obvious candidates for recording brain activity, though not the only ones. DNA technology could also play a critical role in a still distant future for monitoring neuronal activity. One of us (Church) has gained inspiration from the field of synthetic biology, which tinkers with biological materials as if they were machine parts. As research goes forward, lab animals could be genetically engineered to synthesize a "molecular ticker tape"—a molecule that changes in spe-

Listening in on Millions of Neurons

Neuroscientists need more efficient and less intrusive ways to observe brain circuits, in which electrical signals pass from one neuron to the next. A range of technologies—some in use, others just a glint in a researcher's eye—may enable scientists to record from thousands, even millions, of neurons. They will replace slow and imprecise methods that often require invasive electrical probes.

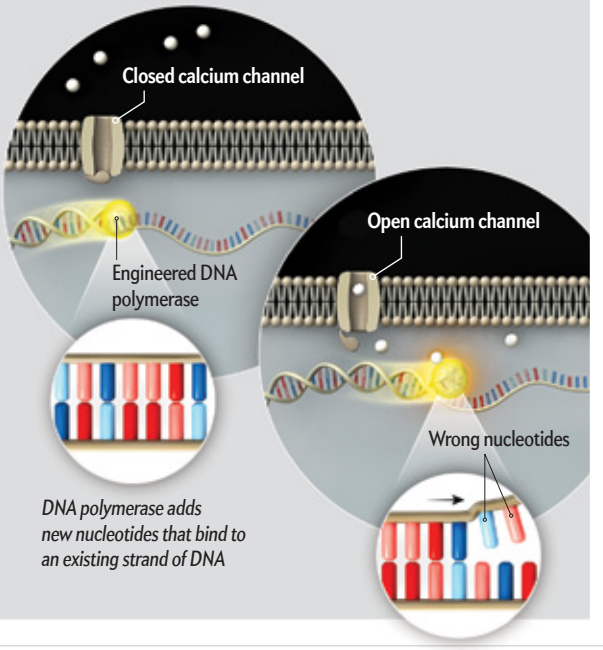
Voltage Imaging

This technique implants a dye into a neuron to determine if the cell is active. This sensor fluoresces when the electrical field across the cell membrane flips its charge as an electrical signal passes by. A detector (*not shown*) registers the event and may also monitor the activity of many other neurons, labeled with the same dye.



DNA Ticker Tape

A radically new approach—a molecular ticker tape—would, in one scenario, place a single strand of DNA with a known sequence of letters, or nucleotides, inside a cell but near its surface. An enzyme, DNA polymerase, would then add new nucleotides that bind to form a double-stranded molecule (*left*). When a neuron fires, an influx of calcium ions coming through a newly opened membrane channel would cause the enzyme to add the wrong nucleotides (*right*), an error that could be detected when the DNA strand is later sequenced.



cific, detectable ways when a neuron becomes active. In one scenario, the ticker tape would be made by an enzyme called a DNA polymerase that starts off by continuously building a long strand of DNA that binds to another strand consisting of a preestablished sequence of nucleotides (the "letters" that are the building blocks of DNA). An influx of calcium ions, generated after the neuron fires, would then cause the polymerase to produce a different sequence of letters—in short, causing "errors" in the expected placement of nucleotides. The resulting double strand of nucleotides could be sequenced later from each neuron of the brain of an experimental animal. An innovative technique called fluorescent in situ sequencing would yield a record of different patterns of changes, the errors from the original ticker tape, corresponding to either the intensity or the timing of each of many neurons in a given volume of tissue. In 2012 the Church lab reported on the feasibility of this idea using a DNA ticker tape altered by magnesium, manganese and calcium ions.

Down the road, synthetic biology envisages the prospect of artificial cells acting as biological sentinels that patrol the human body. A genetically engineered cell could serve as a biological electrode, much smaller than a hair's width in diameter, that could be placed near a neuron to detect its firing. This pattern of firing could be recorded by a nanosize integrated circuit inside the synthetic cell—"electronic dust," which could transmit the collected data by a wireless link to a nearby computer. These nanosize devices, a hybrid concoction of electronic and biological parts, might be powered by an external ultrasound transmitter or even from within the cell using glucose, adenosine triphosphate or another molecule.

TOGGLING ON OR OFF SWITCHES

TO UNDERSTAND WHAT IS HAPPENING in the brain's vast web of neural circuitry, researchers need to do more than just snap photographs. They must switch selected groups of neurons on or off at will to test what the cells are doing. Optogenetics, a technique widely adopted by neuroscientists in recent years, involves using animals that have been genetically engineered so that their

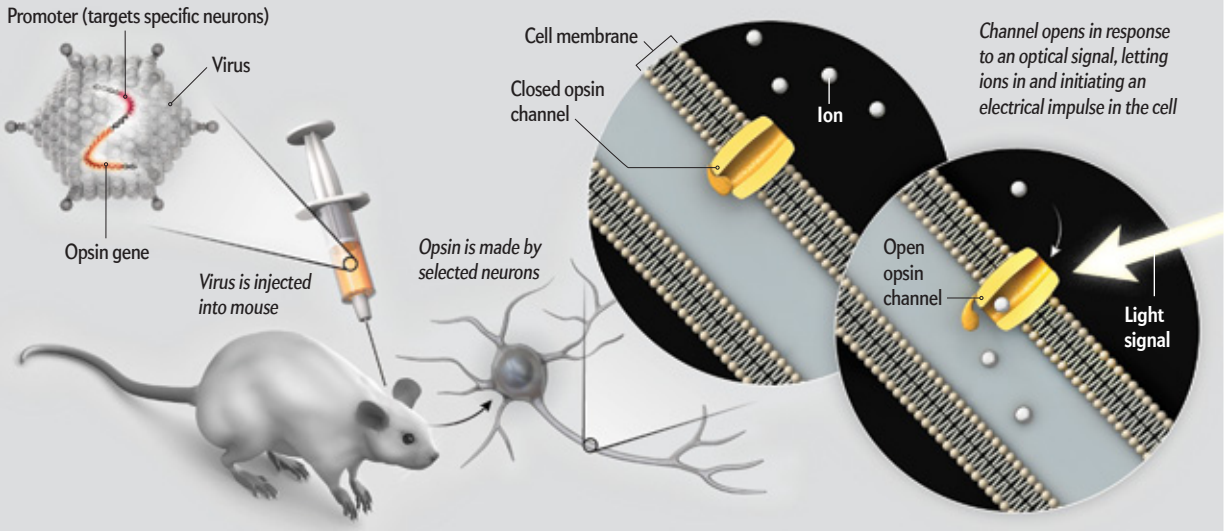
Illustrations by Emily Cooper

Installing a Neural Light Switch

Beyond observing electric currents flowing through circuits, neuroscientists increasingly want to turn individual circuits on and off at will so they can learn how to control specific forms of brain activity. One day these nascent technologies, two of which rely on optical signals (*below*), may quell epileptic seizures or parkinsonian tremors.

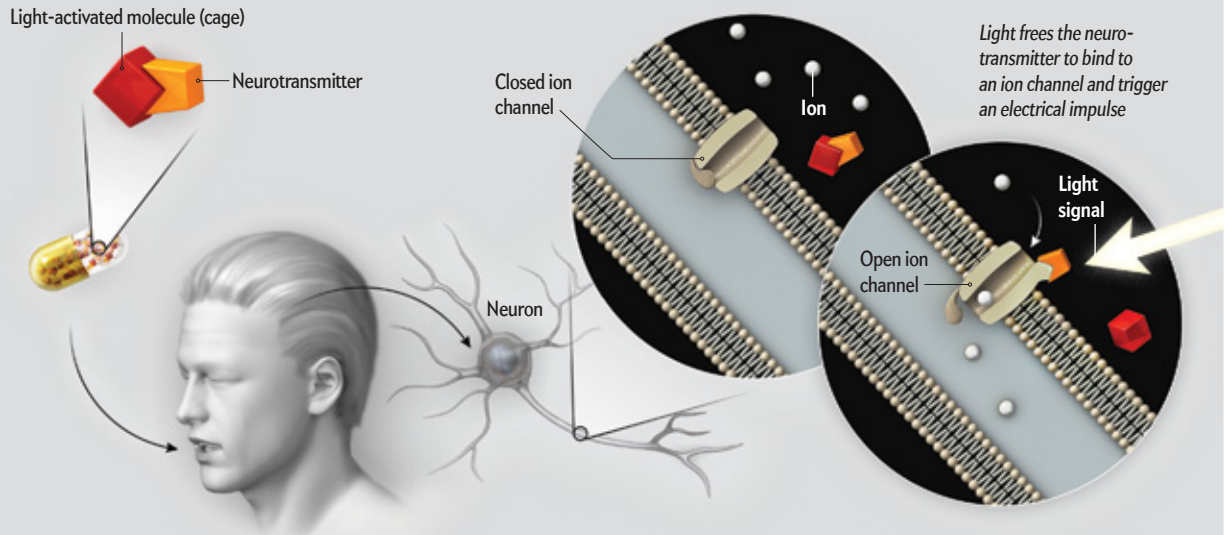
How Optogenetics Works

As the name implies, optical signaling and genetic engineering combine to activate a brain circuit in a living animal. First, a gene for a light-sensitive protein, an opsin, is placed inside a virus that, after injection into an animal, delivers the gene into neurons. Promoter DNA in the inserted genetic material ensures that only certain neurons make the opsin, an ion channel, and insert it in their surface membranes. A signal from an optical fiber inside a mouse skull opens the channel, allowing charged ions to enter the neuron and triggering a current through the cell.



How Optochemistry Works

An alternative technique known as optochemistry avoids the need for cumbersome genetic engineering. A patient would first swallow a pill that contains a light-activated molecule—a cage—that attaches to a neurotransmitter, which regulates a neuron's activity. After the pill's content reached the brain, a pulse of light from an endoscope, or one delivered from outside the skull, would detach the neurotransmitter, which would go on to bind to and open a channel on the cell membrane that lets ions enter. The ions would then trigger the firing of the neuron, sending an electrical impulse traveling into the cell.



SCIENTIFIC AMERICAN ONLINE Watch Yuste give a TEDMED talk about brain mapping at ScientificAmerican.com/mar2014/brain-map

neurons produce light-sensitive proteins derived from bacteria or algae. When exposed to light of a particular wavelength, piped in through an optical fiber, these proteins cause neurons to either switch on or shut down. Researchers have applied the technique to activate neural circuits involved in pleasure and other reward responses and in the impaired movements characteristic of Parkinson's. They have even used optogenetics to "implant" false memories into mice.

The need for genetic engineering means that optogenetics may require lengthy approval protocols before it can be tested, or used as a therapy, in humans. A more practical alternative for some applications has been demonstrated by attaching neurotransmitters, the chemicals that regulate the activity of neurons, to a light-sensitive chemical called a "cage." Once exposed to light, the cage breaks apart, and the chemical escapes and becomes active. In a 2012 study, Steven Rothman of the University of Minnesota, in collaboration with the Yuste lab, placed ruthenium cages joined to GABA, a neurotransmitter that ratchets down neural activity, on the exposed cerebral cortex of rats that were chemically induced to produce epileptic seizures. Shining a pulse of blue light on the brain released the GABA and caused the seizures to abate. Similar "optochemical" approaches are currently used to probe the function of selected neural circuits. If further developed, they might serve as therapies for some neurological or mental disorders.

A long path still stretches from basic research to clinical applications. Each new idea for the large-scale measurement and manipulation of neural activity will have to be tested in fruit flies, roundworms and rodents before moving on to humans. An intensive effort could allow researchers to image and optically control a large number of the 100,000 neurons in a fruit fly brain within perhaps five years. Instruments to capture and modulate the neural activity of the brain of an awake mouse might not be possible for up to 10 years. Some technologies, such as thin electrodes to correct malfunctions in neural circuits in depressed or epileptic patients, could find their way into medical practice in the next few years, whereas some will take a decade or more.

As neurotechnologies grow in sophistication, investigators will need improved ways to manage and share enormous compilations of data. Imaging the activity of all the neurons in a mouse cortex could generate 300 terabytes of compressed data in an hour. But this is by no means an insurmountable task. Elaborate research facilities, akin to astronomical observatories, genome centers and particle accelerators, could acquire, integrate and distribute this type of digital data flood. Just as the Human Genome Project spawned the field of bioinformatics to cope with sequencing data, the academic discipline of computational neuroscience could decode the workings of entire nervous systems.

The ability to analyze petabytes of data will do more than bring order to floods of new information; it could lay the groundwork for new theories about how the cacophony of nerve firings translates into perception, learning and memory. The mega data analysis may also help confirm or dispel theories that could not be tested before. One intriguing theory postulates that the many neurons involved in the activity of a circuit develop particular sequences of firing known as attractors that may represent emergent brain states—a thought, a memory or a decision. In one recent study, a mouse had to make decisions about whether to traverse one section or another of a virtual maze projected on a screen. That action switched on dozens of neurons that exhibited dynamic changes in activity that resembled that of an attractor.

A better understanding of neural circuits could improve diagnosis of brain diseases from Alzheimer's to autism and give a deeper understanding of their causes. Instead of diagnosing and treating these conditions based on symptoms alone, doctors could look for specific alterations in the activity of particular neural circuits found to underlie each disorder and administer therapies to correct those abnormalities. By extension, knowledge about the roots of disease will likely translate into economic benefits for medicine and biotechnologies. As with the genome project, ethical and legal issues will need to be dealt with, particularly if this research leads to ways of discerning or altering mental states—outcomes that would necessitate careful safeguards for patient consent and privacy.

For the various brain initiatives to succeed, however, scientists and their backers must stay closely focused on the goal of imaging and controlling neural circuitry. The idea for the BRAIN Initiative grew from an article in the journal *Neuron* in June 2012. In it, we and our colleagues suggested a long-term collaboration among physicists, chemists, nanoscientists, molecular biologists and neuroscientists to develop a "brain activity map" derived by applying new technologies to measure and control the electrical activity of entire brain circuits.

We would urge that as the ambitious BRAIN project evolves, our original emphasis on tool building be retained. The scope of brain research is vast, and the BRAIN Initiative could easily devolve into a composite wish list that attempts to satisfy the broad-ranging interests of neuroscience's many subdisciplines. It could thus become nothing more than a supplement to already existing projects pursued by many individual labs working independently.

If this occurs, progress will be haphazard, and major technical challenges may never be met. We need collaboration among academic disciplines. Building instruments to image voltage in millions of neurons simultaneously throughout entire brain regions may be achieved only by a sustained effort of a large interdisciplinary team of researchers. The technology could then be made available at a large-scale, observatorylike facility shared by the neuroscience community. We are passionate about retaining a focus on new technology to record, control and decode the pattern of electrical spikes that are the language of the brain. We believe that without these new tools, neuroscience will remain bottlenecked and fail to detect the brain's emergent properties that underlie a virtually infinite range of behaviors. Enhancing the ability to understand and use the language of spikes and neurons is the most productive way to derive a grand theory of how nature's most complex machine functions. SA

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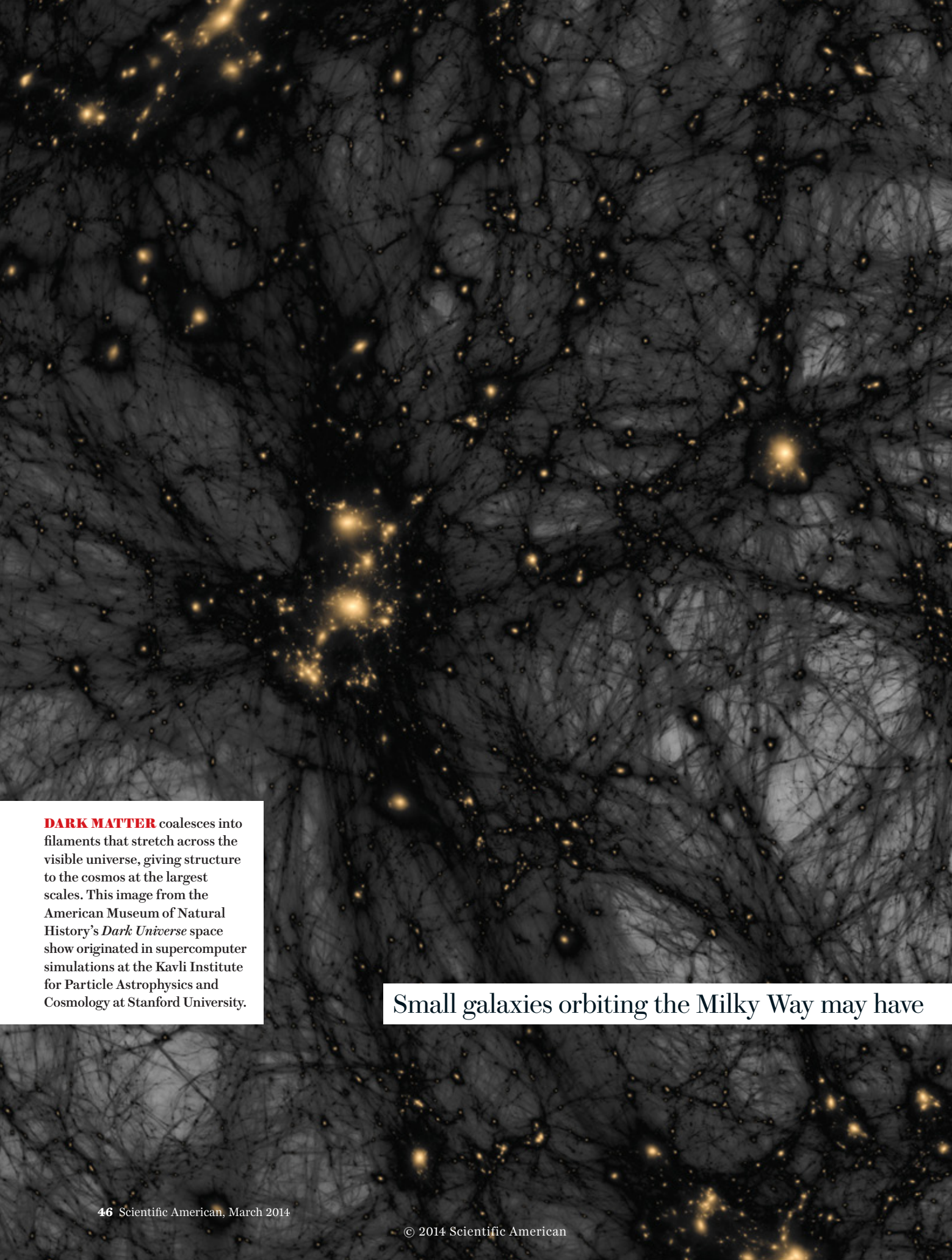


DARK MATTER coalesces into filaments that stretch across the visible universe, giving structure to the cosmos at the largest scales. This image from the American Museum of Natural History's *Dark Universe* space show originated in supercomputer simulations at the Kavli Institute for Particle Astrophysics and Cosmology at Stanford University.

Small galaxies orbiting the Milky Way may have

ASTRONOMY

Dwarf Galaxies and the Dark Web

arrived via dark matter superhighways stretching across the universe

By Noam I. Libeskind

Noam I. Libeskind is an astrophysicist who creates computational models of the universe at the Leibniz Institute for Astrophysics Potsdam in Germany.

"Nonsense! Hot air! Balderdash!"

blurted out Pavel Kroupa, an astrophysicist at the University of Bonn in Germany, as I stood at the head of the lecture hall. I was just a graduate student at the time, applying for postdoctoral research positions. I had come to Bonn to give a 45-minute talk on my investigations of the small satellite galaxies surrounding the Milky Way. I had helped develop a theory that explains why these mysterious objects are located in what appears to be a straight line stretching across the sky—an unexpected and extremely puzzling alignment. Kroupa, it appeared, was not swayed by my arguments.

Most galaxies like the Milky Way are surrounded by dozens of small satellite galaxies that orbit around them. These galaxies are extremely faint—only the brightest and closest of them have been spotted flying around the Milky Way and our next-door neighbor, the Andromeda galaxy. But these dwarf satellite galaxies do not just fly around haphazardly. Instead they all sit on a thin plane, seen edge on [*see box on opposite page*].

This alignment comes as a surprise. Computer simulations that model how galaxies evolve have predicted that every direction in the sky should contain roughly the same number of satellite galaxies. Such a spherical arrangement was long thought to be a natural consequence of dark matter, a mysterious substance that interacts with ordinary matter only through the force of gravity. Astronomers believe dark matter pervades the universe and plays a key role in galaxy formation and expansion of the cosmos.

Yet the puzzle of dwarf galaxy alignment has been so vexing that it has led some astronomers, including Kroupa, to question whether dark matter really exists after all. "Dark matter has failed," he said, interrupting my talk, "since its prediction that satellites should be spherically distributed around the Milky Way is clearly in direct contradiction with what we observe."

I was presenting a different view, one that attempts to explain the peculiar alignment of galactic satellites by pointing to cosmic structures of dark matter that are far larger than our Milky Way. Although a few skeptics like Kroupa remain unconvinced, recent work, including my own research, shows how enormous webs of dark matter can account for the unique alignment of satellite galaxies in the sky.

MISSING MATTER

THE DARK MATTER at the center of this debate was first postulated in an effort to explain other puzzling features of galaxies. In the 1930s the great astronomer Franz Zwicky wanted to weigh the Coma cluster, a huge group of around 1,000 galaxies. He started out by measuring the speed with which the galaxies in Coma move. To his surprise, he found enormous speeds—thousands of kilometers per second—fast enough to rip the cluster apart. Why was the cluster not tearing itself up? Zwicky concluded that the cluster must be filled with additional unseen matter that holds the galaxies together with its gravitational force. This missing substance has subsequently been named "dark matter."

Since Zwicky's first suggestion some 80 years ago, signs of dark matter have popped up all over the universe, in nearly every galaxy observed. In our own Milky Way, astronomers infer its existence from the motion of the stars on the galaxy's outskirts. Like the galaxies in the Coma cluster, these stars move too quickly to be held in by all the matter that we see. The dozen or so dwarf galaxies of the Milky Way appear to contain even greater abundances of dark matter.

Dark matter's pervasiveness has solidified belief in its existence. In fact, most cosmologists believe dark matter constitutes around 80 percent of all matter, outweighing normal atoms by around five to one.

This abundance of dark matter implies that it should play a dramatic role in how the universe evolves. One way to study this evolution is through the use of computer models. Beginning in the 1970s, researchers in the field of computational cosmology have attempted to simulate the history of the universe using computer codes. The technique is straightforward: Define an imaginary box in a computer. Place imaginary point particles (that represent clumps of dark matter) in a near-perfect lattice inside the box. Calculate the gravitational pull on each particle from every other particle in the box and move each particle according to the net gravity it feels. Iterate this process for 13 billion years.

IN BRIEF

Theories of galaxy formation say that our Milky Way should be surrounded by a spherical halo of small satellite galaxies. Yet searches for these satellites have come up short, leading some to question basic tenets of cosmology.

The satellites that astronomers have found tend to align in a plane that cuts across the Milky Way.

New simulations explain the lack of galaxies and their alignment by appealing to a large web of dark matter.

PRECEDING PAGES: COURTESY OF AMERICAN MUSEUM OF NATURAL HISTORY

The strategies have grown significantly more complicated since the 1970s, but this basic technique is still used today. Four decades ago the codes could handle just a few hundred particles. Now state-of-the-art computer simulations can successfully model billions of particles in a volume approaching the size of the observable universe.

Computer simulations of the cosmos have been an incredibly useful way to investigate individual galaxies, but they have created some notable puzzles. For example, computer models conclude that the pervasive dark matter in the so-called halo that surrounds the Milky Way should pull gas and dust into individual clumps. These clumps should contract under the force of gravity, eventually forming stars and dwarf galaxies. In the case of the Milky Way, the prevalence of dark matter implies that we should expect to see thousands of small galaxies. Yet when we look out at the night sky, we observe only a few dozen. The failure to find them was first identified in the 1990s and has since become known as the missing satellites problem.

In the intervening years, astronomers have devised a few potential solutions to this dilemma. First and foremost, perhaps not all the satellites seen in simulations correspond directly to real satellite galaxies. The smallest clumps of dark matter may lack the mass (and gravitational pull) to capture gas and form stars. In this line of thinking, the observed satellite galaxies are the visible tip of a dark iceberg: hundreds, if not thousands, of dark satellites, devoid of stars, may exist in our vicinity. We just can't see them.

Second, even if small dark matter clumps do create stars, those stars may be too faint for our telescopes to see. In this scenario, as technology advances and telescopes become more sensitive, astronomers will find more satellites. Indeed, in the past seven years the number of satellites known to be orbiting the Milky Way has doubled.

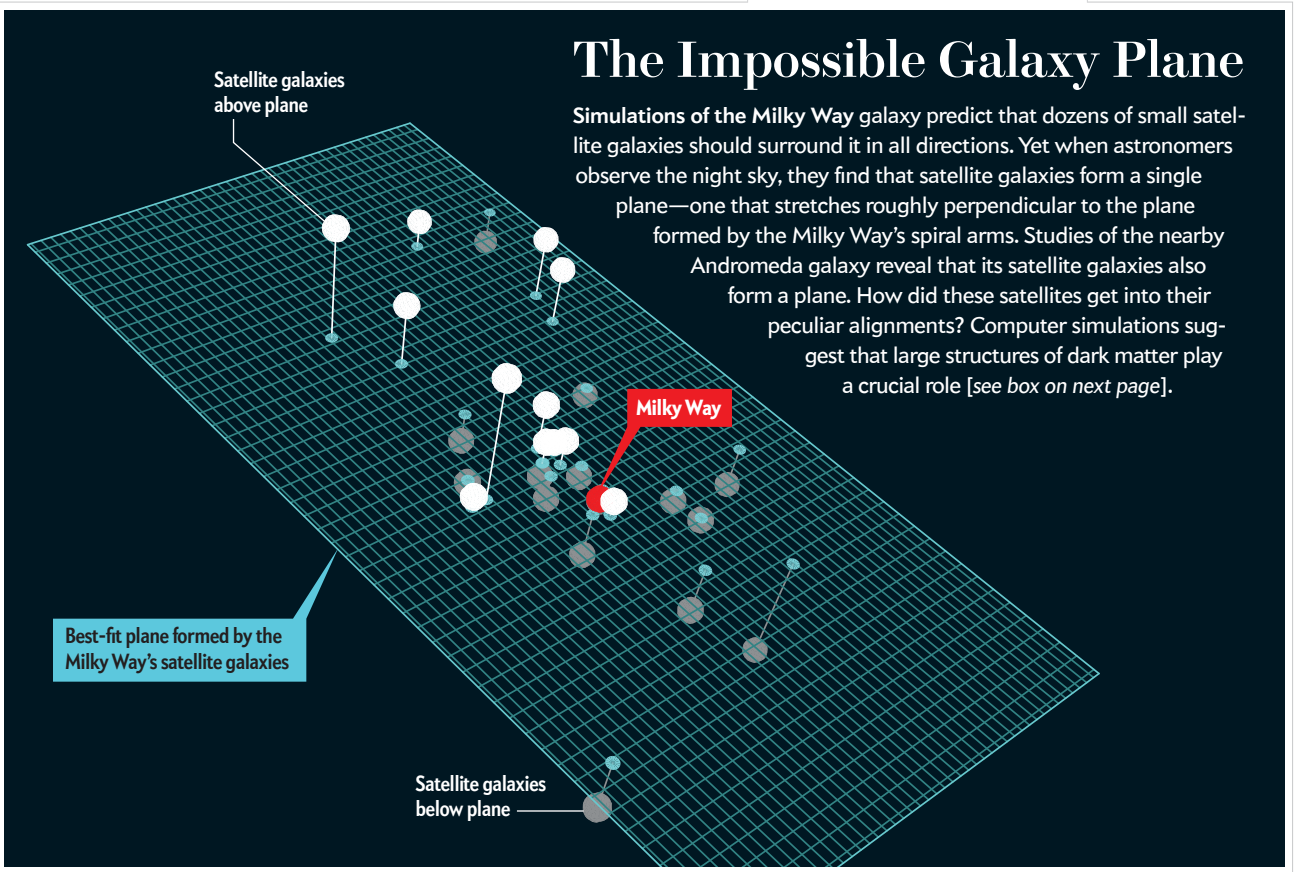
In addition, the disk of the Milky Way could be blocking our view of certain satellite galaxies. This disk is essentially a dense plane of stars so bright that it looks like a continuous white fluid to the naked eye (hence, the "Milky" Way). It would be exceedingly difficult to find a satellite hidden behind the disk, just as it is difficult to see the moon during the day—the light from the disk simply drowns out the faint light from the satellite.

Taken together, these arguments largely settled the missing satellite problem for most astrophysicists and saved the idea of dark matter from one of its most serious observational challenges. Yet the peculiar alignment of satellite galaxies continued to baffle researchers.

RETURN OF THE DWARF THREAT

IN SEVERAL PAPERS in the late 1970s and early 1980s, Donald Lynden-Bell, an astrophysicist at the University of Cambridge, noted that many of the satellite galaxies orbiting the Milky Way appeared to sit on a single plane. How could this odd arrangement be explained? In 2005 Kroupa and his group at Bonn convinced the world that the alignment could not be random. They assumed that dark matter satellites were evenly distributed around the

GALACTIC GEOGRAPHY

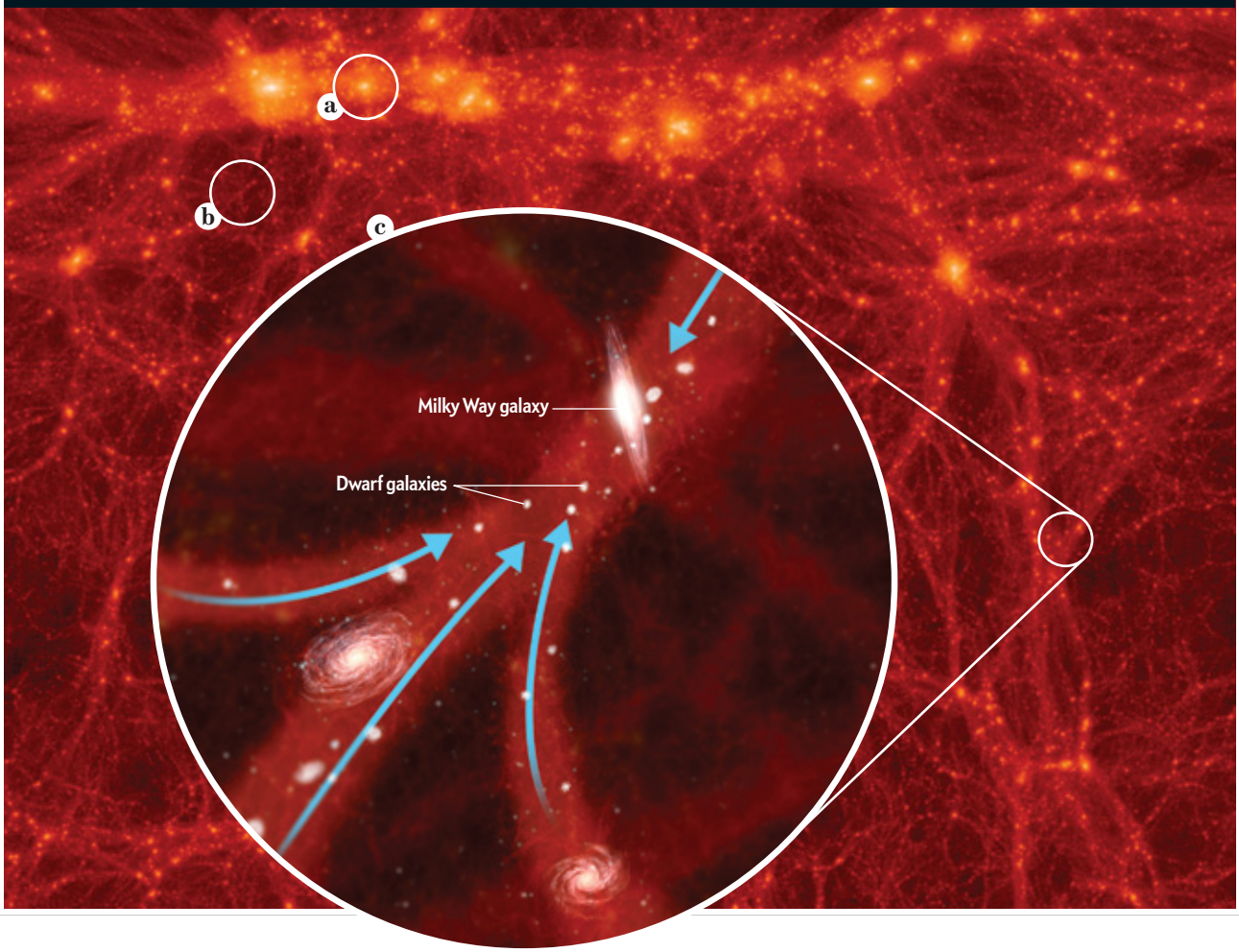


SOURCE: "DWARF GALAXY PLANES: THE DISCOVERY OF SYMMETRIC STRUCTURES IN THE LOCAL GROUP," BY MARCEL S. PAWLOWSKI, PAVEL KROUPA AND HELMUT JERJEN, IN *MONTHLY NOTICES OF THE ROYAL ASTRONOMICAL SOCIETY*, VOL. 435, NO. 3; NOVEMBER 1, 2013

Graphic by Jan Willem Tulp

Cosmic Superhighways of Dark Matter

In the roughly 14 billion years since the big bang, the dark matter that pervades our universe has coalesced into what cosmologists call the cosmic web, an enormous structure of filaments and nodes. Dark matter pulls in nearby gas and dust, forming massive galaxies such as our Milky Way in the nodes where the density of dark matter is highest (a). In filaments, the density of dark matter is lower, and only smaller dwarf galaxies form (b). Over time, the strong gravitational pull of the nodes tends to attract material in the filaments, pulling dwarf galaxies toward large galaxies (c). From our point of view inside the Milky Way, the dwarf galaxies appear to lie in a plane running perpendicular to the galaxy.



Milky Way, as the computer simulations predicted, and that only one in 100 of these dwarfs was large enough to create stars and visible galaxies. Given these entirely reasonable assumptions, they asked, how often would we expect to find a system like the Milky Way, where the illuminated galaxies happen to be located all in a row? The answer caused an earthquake in cosmology: the probability was less than one in a million.

If dark matter guided the formation of galaxies, Kroupa argued, the dwarf satellites would never all be found on this one impossible plane. In the paper describing his results, Kroupa put forth his own solution. The only way out, he wrote, was if the Milky Way's satellites did not form as a consequence of the clumping of dark matter. Dark matter, he said, does not exist.

As a good theorist, Kroupa proposed an alternative. He suggested that satellites were galactic debris, the remains of an older progenitor galaxy that long ago flung past the Milky Way. Just as an asteroid breaks up and leaves a trail of debris as it flies through Earth's atmosphere, perhaps the satellites of the Milky Way similarly had their origins in material stripped from a larger progenitor.

For example, Kroupa said, when we look out into the cosmos, we can see that a number of colliding galaxies show long bridges of material known as tidal arms. Often the tidal arms contain small dwarf galaxies that condense out of the streaming material. Under the right conditions, the nature of the ripping ensures that the stripped material will end up in a thin plane, just like the satellites of the Milky Way.

Kroupa's explanation was elegant, simple—and above all,

COURTESY OF STEFAN GOTTLÖBER, GUSTAVO YEPES, ANATOLY KLYPIN, ARMAN KHALATYAN AND CLUES-PROJECT.ORG

SCIENTIFIC AMERICAN ONLINE Watch a simulation of the cosmic web at ScientificAmerican.com/mar2014/cosmic-web

Illustration by Ron Miller (inset)

controversial. It quickly came under attack. For one, the stars in the satellites of the Milky Way are moving far too quickly to be held together by ordinary matter alone. Dark matter must be holding them together, just as it holds the Milky Way together. (In fact, observations suggest that the dwarf satellites of the Milky Way are among the most dark matter–dominated galaxies in the universe.) The tidal dwarf galaxy scenario implies that these galaxies are devoid of dark matter, leaving open the question of what keeps them from flying apart.

The observed satellite galaxies are just the tip of a dark iceberg: hundreds, if not thousands, of dark satellites may exist in our vicinity. We just can't see them.

Secondly, just as car crashes destroy cars, collisions between disk galaxies destroy the disks. The final result of a galactic collision is almost always a formless blob of stars. The Milky Way has a crisp structure and a fairly thin disk. We observe no indication that it suffered through any merger or collision in the recent past.

THE DARK WEB

AN ALTERNATIVE SOLUTION to the unusual alignment of dwarf galaxies requires looking farther out into the cosmos. The computational simulations that began in the 1970s do not just model the evolution of individual galaxies. They model huge volumes of the universe. When we explore these simulations on the largest scales, we see that galaxies are not randomly distributed. Instead they tend to aggregate into a well-defined filamentary network known as the cosmic web. We clearly see the predicted structure when we look up to the skies with large-scale astronomical surveys.

The cosmic web is composed of magnificent sheets of millions of galaxies, hundreds of millions of light-years across. Cigar-shaped filaments connect these sheets. In between the filaments lie massive voids where no galaxies reside. Large galaxies such as the Milky Way tend to anchor the web at spots where multiple filaments intersect [*see box on opposite page*].

As a graduate student at Durham University in England, I had been creating computer simulations of these dense regions when I brought a plot of recent results into the office of my research adviser, Carlos Frenk. The model I had been working on traced the formation of the Milky Way and its environs for the past 13 billion years of cosmic history. Frenk scrutinized the plots for a moment, shook the papers and exclaimed, "Drop everything! The satellite galaxies you are studying are all sitting on Kroupa's impossible plane!" Our model was not reproducing the earlier predictions of computer simulations—an evenly distributed halo of satellite galaxies around the Milky Way. Instead the computer was predicting the formation of a plane of satellites that was very close to what astronomers observe. We felt that our simulations were beginning to crack the mystery of how the dwarf satellites came to adopt such an odd configuration.

"Why don't you trace the satellites back in time and see where they came from?" Frenk proposed. We had the final result; now it was time to examine the intermediate steps in the simulation.

When we examined the simulation in reverse, we saw that the dwarf satellites did not originate in the region immediately surrounding the Milky Way. They tended to come together a little farther away, inside of filaments in the cosmic web. Filaments are regions of the cosmos with higher densities than the cosmic voids; as such, they will attract nearby dust and gas and collect them into nascent galaxies.

Once these dwarf galaxies form, gravity pulls them in the direction of the most massive nearby region—in our case, the Milky Way. Because the Milky Way lies at a node where filaments intersect, the dwarf galaxies travel through the filament that birthed them as they accelerate in our direction. Filaments, in other words, serve as cosmic superhighways of dark matter. When we gaze up at the sky and see dwarf galaxies in a single plane moving in the same direction, we are essentially looking at oncoming galactic traffic.

A NEW TEST

SOME SCIENTISTS such as Kroupa remain skeptical. Computer models seem to reproduce the observed conditions around the Milky Way with sufficient precision, but the general theory should be also able to describe the neighborhood around other galaxies.

The theory faces a new test. In January 2013 astronomers mapping the regions around the nearby Andromeda galaxy found an even thinner sheet of satellites: a vast plane one million light-years across and just 40,000 light-years thick—around the same dimensions of a laptop computer. The sheet also appears to be rotating in just the way that Kroupa's tidal scenario would predict. Computer simulations such as my own, however, have not yet been able to reproduce the alignment of galaxies that we see around Andromeda.

Yet the serious problems with Kroupa's tidal theory remain—it, too, is at odds with observations. History has shown that in stalemates such as these, definitive solutions will only come with more data. As Albert Einstein once remarked, "Nature did not deem it her business to make the discovery of her laws easy for us." SA

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FROM OUR ARCHIVES

The Dark Side of the Milky Way. Leo Blitz; October 2011.

MEDICINE

GENE THERAPY'S SECOND ACT

A decade and a half after a series of tragic setbacks led to critical reevaluations, scientists say gene therapy is ready to enter the clinic

By Ricki Lewis

Illustration by Kotryna Zukauskaite

Ricki Lewis is a science writer with a Ph.D. in genetics. She is author of several textbooks, many magazine articles and the book *The Forever Fix: Gene Therapy and the Boy Who Saved It* (St. Martin's Press, 2012).

Gene therapy may finally be living up to its early promise. In the past six years the experimental procedure for placing healthy genes wherever they are needed in the body has restored sight in about 40 people with a hereditary form of blindness. Doctors have seen unprecedented results among another 120-plus patients with various cancers of the blood—several of whom remain free of malignancy three years after treatment. Researchers have also used gene therapy to enable a few men with hemophilia, a sometimes fatal bleeding disorder, to go longer without dangerous incidents or the need for high doses of clotting drugs.

The positive results are even more impressive considering that the field of gene therapy essentially ground to a halt 15 years ago, following the untimely death of Jesse Gelsinger, a teenager with a rare digestive disorder. Gelsinger's immune system reacted to the gene treatment he received by launching a counterattack of unexpected ferocity that killed him. Gene therapy's preliminary successes in the 1990s, it turns out, had fueled unreasonably high expectations among doctors and researchers—and perhaps a bit of hubris.

This and other setbacks forced scientists to rethink some of their approaches, as well as to be more realistic about gene therapy's feasibility for treating various conditions in people. Investigators curbed their hopes and returned to basic research. They examined potentially fatal side effects such as those experienced by Gelsinger and learned how to avoid them. And they paid more attention to explaining the risks and benefits to volunteers and their families.

The turning point, in the view of many observers, came six years ago, when doctors treated then eight-year-old Corey Haas for a degenerative eye disorder that caused his sight to deteriorate. The gene therapy they used allowed the defective retina of Haas's left eye to make a protein that his body could not otherwise produce. Within four days he took a trip to the zoo and found, to his delight and astonishment, that he could see the sun and a hot-air balloon. Three years later he underwent the same treatment in his right eye. Now Haas sees well enough to go turkey hunting with his grandfather.

Although gene therapy is still not available in hospitals and clinics, that is likely to change in the next decade. Europe approved its first gene treatment, for a rare but extremely painful

IN BRIEF

Early excitement about gene therapy experiments in the 1990s triggered unrealistic expectations about the technology's potential in humans.

After several tragic setbacks, researchers spent the next few years refining their understanding of the fundamental biology and techniques involved.

New, safer treatments are now poised to enter the clinic. Europe approved its first gene therapy in 2012. The U.S. may follow by 2016.

disorder called familial lipoprotein lipase deficiency, in 2012. At the end of 2013 the National Institutes of Health removed some of the regulatory speed bumps that the agency now considers unnecessary. The first U.S. approval of a commercial gene treatment, some industry watchers predict, may come in 2016. Gene therapy, after its lost decade, is at last beginning to fulfill its destiny as a revolutionary medical treatment.

HEARTBREAK

THE EARLY FAILURES OF GENE THERAPY highlight how difficult it is to establish a safe and efficient means of delivering genes to the target tissue. Too often the safest delivery systems were not very effective, and some of the most effective systems turned out not to be very safe, setting off either an overwhelming immune reaction, as in Gelsinger's case, or the development of leukemia, as in other instances.

To understand what triggered these side effects and to figure out how to lessen the risks of their occurrence, scientists focused on the most common delivery system for gene therapy: engineering a virus to act as a kind of microscopic injection gun.

For starters, researchers remove some of the virus's own genes to create room for the healthy genes that they want to deliver to a patient. (This step also has the added benefit of preventing the virus from making copies of itself once inside the body, which increases the chances of an immune reaction.) Then the customized viruses are injected into that person, where they insert the new genes into various places in cells, depending on the type of virus being used.

By the time Gelsinger volunteered for a clinical trial, the delivery system of choice consisted of adenoviruses, which in their natural state can cause mild upper respiratory infections in people. Scientists at the University of Pennsylvania determined that the best chance for success was to inject the viruses into the liver, where the cells that normally make the digestive enzyme Gelsinger was missing are located. They packaged a working copy of the gene for that enzyme into stripped-down adenoviruses. Then they injected one trillion of these viruses—each with their custom payload—directly into Gelsinger's liver.

Once in Gelsinger's body, however, some of the viruses took a tragic detour. They entered the liver cells as planned, but they also infected huge numbers of macrophages, the large wandering cells that serve as sentries for the immune system, and the dendritic cells that announce an invasion. The immune system responded by destroying each infected cell, a violent process that ultimately ravaged Gelsinger's body from the inside out.

The ferocity of the immune response took investigators by surprise. None of the 17 volunteers who had previously undergone treatment for the same disorder had exhibited such severe side effects. Researchers knew that adenoviruses could provoke an immune response, but apart from a study of a slightly different reengineered virus in which a monkey died, they did not realize how explosive the reactions could be. "Humans are much more heterogeneous than colonies of animals," says James Wilson of the University of Pennsylvania, who developed the viral delivery system used in the clinical trial in which Gelsinger had participated. "What we saw in that trial was one individual out of 18 who had a very exaggerated host response." In hindsight, it seemed that it would have been wiser to inject fewer—billions rather than one trillion—gene-bearing viruses into his body. The researchers were also criticized for not informing Gelsinger and his family about the monkey's death so that they could make up their own minds about whether it was an unrelated event.

Gelsinger's death was not the only gene therapy tragedy. Soon after, treatment for another disorder—called severe combined immunodeficiency X1, or SCID-X1—triggered five cases of leukemia, including one death, in 20 children. Once again the gene delivery system turned out to be at fault. In this instance, however, the microscopic injection gun in question consisted of a retrovirus, a kind of virus that inserts its genetic payload directly into the DNA of a cell. The exact placement of the therapeutic genes is a bit haphazard, however, and the retrovirus sometimes inserted its payload into an oncogene—a gene that can cause cancer under certain circumstances.

The decades-long path to successful gene therapy is far from complete. But recent advances have moved the experimental approach closer to being a mainstream treatment for some disorders.

RETHINKING THE TECHNOLOGY

GIVEN THE PROPENSITY OF ADENOVIRUSES to provoke lethal immune reactions and of retroviruses to trigger cancer, investigators began paying more attention to other viruses to see if they offered better results. They soon focused on two more widely suitable entrants.

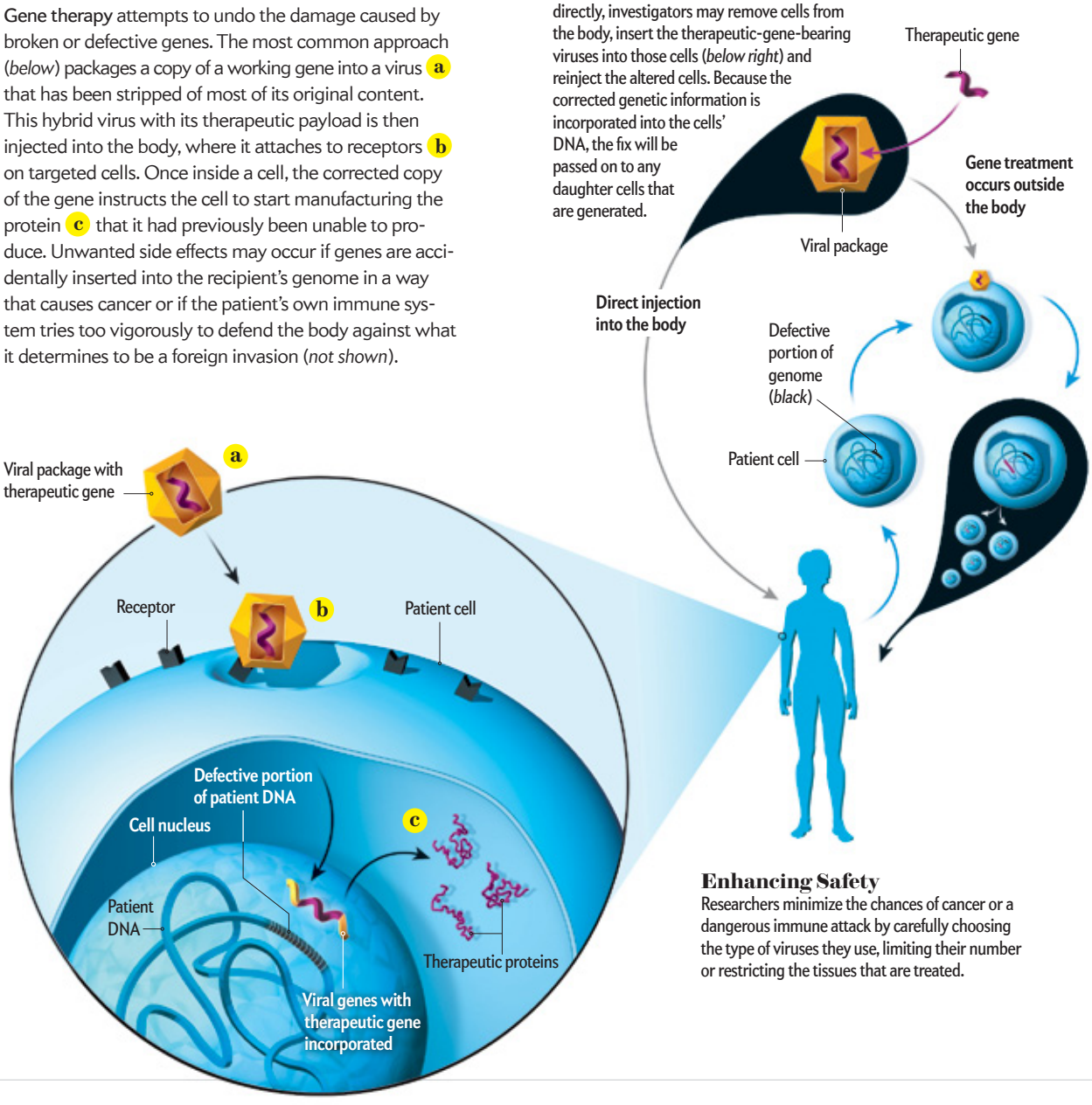
The first new delivery system, adeno-associated virus (AAV), does not make people sick (although most of us have been infected by it at one time or another). Because it is so common, it is unlikely to cause extreme immune reactions. This virus has another feature that should also help minimize side effects: it is available in several varieties, or serotypes, that favor specific types of cells or tissues. For example, AAV2 works well in the eye, whereas AAV8 prefers the liver, and AAV9 slips into heart and brain tissue. Researchers can choose the best AAV for a specific body part, decreasing the number of individual viruses that need to be injected and thus minimizing the chances of an overwhelming immune response or other unwanted reaction. Plus, AAV depos-

How to Fix a Defective Gene

Gene therapy attempts to undo the damage caused by broken or defective genes. The most common approach (*below*) packages a copy of a working gene into a virus **a** that has been stripped of most of its original content. This hybrid virus with its therapeutic payload is then injected into the body, where it attaches to receptors **b** on targeted cells. Once inside a cell, the corrected copy of the gene instructs the cell to start manufacturing the protein **c** that it had previously been unable to produce. Unwanted side effects may occur if genes are accidentally inserted into the recipient's genome in a way that causes cancer or if the patient's own immune system tries too vigorously to defend the body against what it determines to be a foreign invasion (*not shown*).

Two Delivery Choices

In addition to injecting viruses into patients directly, investigators may remove cells from the body, insert the therapeutic-gene-bearing viruses into those cells (*below right*) and reinject the altered cells. Because the corrected genetic information is incorporated into the cells' DNA, the fix will be passed on to any daughter cells that are generated.



Enhancing Safety

Researchers minimize the chances of cancer or a dangerous immune attack by carefully choosing the type of viruses they use, limiting their number or restricting the tissues that are treated.

its its genetic payload outside the chromosomes, so it cannot accidentally cause cancer by interfering with oncogenes.

Adeno-associated virus was first used in a clinical trial in 1996, on cystic fibrosis. Since then, 11 serotypes have been identified, and their parts have been mixed and matched to engineer hundreds of seemingly safe and selective delivery tools. Current studies are evaluating AAV-borne gene therapy for several brain diseases, including Parkinson's and Alzheimer's, and for hemophilia, muscular dystrophy, heart failure and blindness.

The second, rather more surprising new gene vector is a stripped-down version of HIV—the virus that causes AIDS. Once you look beyond HIV's reputation as a killer, its advantages for gene therapy emerge. As a member of the *Lentivirus* genus of retroviruses, it evades the immune system and—crucial for a retrovirus—does not typically disturb oncogenes.

After the genes that make HIV lethal are removed, the viral packaging that remains "has a large capacity," says Stuart Naylor, formerly chief scientific officer at Oxford Biomedica in England, which is pursuing "gene-based medicines" for eye diseases. Unlike the smaller AAV, "it's great for installing multiple genes or big,

SCIENTIFIC AMERICAN ONLINE Watch an animation about gene therapy in the liver at ScientificAmerican.com/mar2014/gene-therapy-video

Illustration by Tami Tolpa

chunky genes," he says. "There's no toxicity and no adverse immune reaction." Stripped-down lentiviruses are now being used in a number of clinical trials, including treatments for adrenoleukodystrophy—the disease featured in the 1992 movie *Lorenzo's Oil*. To date, a few of the boys who have received this treatment have become healthy enough to return to school.

Although clinical trials using AAV and HIV are on the rise, researchers have also redirected or modified the older viral delivery systems so that they can be used in limited circumstances. For example, non-HIV retroviruses are now genetically edited so that they inactivate themselves before they can trigger leukemia.

Even adenovirus, which caused Gelsinger's death, is still in clinical trails as a gene therapy vector. Investigators restrict its use to parts of the body where it is unlikely to cause an immune response. One promising application is to treat "dry mouth" in patients undergoing radiation for head and neck cancer, which damages the salivary glands, located just under the surface of the inside of the cheek.

The NIH is running a small clinical trial that involves inserting a gene that creates channels for water into the glands. Because the glands are small and contained, and the experimental design calls for 1,000-fold fewer viruses than were used on Gelsinger, the chances of an immune overreaction are reduced. In addition, viruses that do not hit their target cells should wind up in a patient's drool, either swallowed or spit out, with little chance of irking the immune system. Since 2006, six of 11 treated patients have been shown to produce significantly more saliva. Bruce Baum, a dentist and biochemist who led the research before he retired, calls the results "cautiously encouraging."

NEW TARGETS

EMBOLDENED BY THESE SUCCESSES, medical researchers have moved beyond treating hereditary diseases to trying to reverse genetic damage that naturally occurs over the course of a lifetime.

Scientists at the University of Pennsylvania, for example, are using gene therapy to tackle a common childhood cancer known as acute lymphoblastic leukemia (ALL).

Although most children with ALL respond to standard chemotherapy, about 20 percent do not. Researchers are turning to gene therapy to turbocharge these children's immune cells to seek out and destroy the recalcitrant cancer cells.

The experimental approach is particularly complex and is based on so-called chimeric antigen receptor (CAR) technology. Like the chimera of Greek mythology that is made up of different animals, a chimeric antigen receptor consists of two molecules from the immune system that are not normally found together. Some immune cells, known as T cells, are then outfitted with these chimeric antigen receptors, which allow the cells to target proteins that are found in greater numbers on a leukemia cell. The fully armed and deployed T cell then destroys the cancer cell. The first test subjects were adults with chronic leukemia, who responded favorably. The next attempt, with a child, exceeded the researchers' wildest dreams.

Emily Whitehead was five in May 2010, when she was diagnosed with leukemia. Two rounds of chemotherapy did not work. In the spring of 2012 "she was given a [third] chemotherapy dose that would have killed an adult, and she still had lesions in her kidneys, liver and spleen," says Bruce Levine, one of Whitehead's doctors. The girl was days from death.

Doctors took a sample of Whitehead's blood and isolated some of her T cells. They then injected the sample with lentiviruses that had been outfitted with the appropriate genes. After a rocky start, which fortunately responded to treatment, Whitehead quickly improved. Three weeks after treatment, a quarter of the T cells in her bone marrow bore the genetic correction. Her T cells began homing in on the cancer cells, which soon vanished. "In April she had been bald," Levine recalls. "By August she went to her first day of second grade."

Although Whitehead's modified cells might not last forever—in which case doctors can repeat the treatment—this beautiful girl with shaggy brown hair has been free of cancer for about two years. And she is not alone. By late 2013 several groups of researchers reported that they had used the CAR technique on more than 120 patients, for Whitehead's form of leukemia and three other blood cancers. Five adults and 19 of 22 children have achieved remission, meaning that they are currently cancer-free.

INTO THE CLINIC

WITH SAFER VIRAL DELIVERY SYSTEMS in hand, gene therapy specialists are now tackling the greatest challenge that any new drug faces: earning the approval of the U.S. Food and Drug Administration. This daunting step requires so-called phase III clinical trials, which are designed to assess efficacy in a larger group of volunteer patients and typically take one to five years to complete (the time varies widely). As of the end of 2013, about 5 percent of approximately 2,000 clinical trials for gene therapy had reached phase III. One of the furthest along is aimed at Leber congenital amaurosis—the condition that was robbing Haas of his sight. So far several dozen patients have had corrective genes inserted into both eyes and are now able to see the world.

China was the first country to approve a gene treatment, in 2004, for head and neck cancer. In 2012 Europe approved a gene therapy–based drug called Glybera to treat familial lipoprotein lipase deficiency. Working copies of the mutant gene wrapped in AAV are injected into the leg muscles. Netherlands-based company UniQure is in early talks with the FDA about approval in the U.S. One potential stumbling block: the price tag for a single curative dose is $1.6 million, but that cost may come down as researchers develop more efficient procedures.

As with many medical technologies, the decades-long path to successful gene therapy has been circuitous and is far from complete. But as gene therapy accumulates more success stories such as Corey Haas and Emily Whitehead, it is moving closer to becoming a mainstream medical treatment for some disorders and a promising new option for others. SA

MORE TO EXPLORE

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EARTH SCIENCE

THE OLDEST ROCKS ON EARTH

One team of scientists thinks ancient rocks discovered in northern Canada give us a window onto the planet's infancy and the birth of life itself. Another team thinks they're not that special

By Carl Zimmer

IN BRIEF

Rocks recently retrieved along the northeastern edge of Hudson Bay in Canada may be the oldest ever found, but scientists are arguing whether the age is 3.8 billion or 4.4 billion years. The older date would put the rocks close to the time when Earth formed. **Resolving the debate** depends on improving methods for dating atoms on small rock samples formed from the primordial Earth.

If the rocks are 4.4 billion years old, they may provide strong clues about how Earth's surface took shape, when the oceans arose and how soon after those events life began.

Photograph by Travis Rathbone

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

The Nuvvuagittuq greenstone belt doesn't look like a battlefield.

It lies in peaceful, roadless isolation along the northeastern edge of Hudson Bay in Canada, more than 20 miles from Inukjuak, the nearest human settlement. From the shoreline, the open ground swells into low hills, some covered by lichens, some scraped bare by Ice Age glaciers. The exposed rocks are beautiful in their stretched and folded complexity. Some are gray and black, shot through with light veins. Others are pinkish, sprinkled with garnets. For most of the year the only visitors here are caribou and mosquitoes.

But this tranquil site is indeed a battleground—a scientific one. For almost a decade rival teams of geologists have traveled to Inukjuak, where they have loaded canoes with camping gear and laboratory equipment and trekked along the coast of the bay to the belt itself. Their goal: to prove just how old the rocks are. One team, headed by University of Colorado geologist Stephen J. Mojzsis, is certain that the age is 3.8 billion years. That is pretty ancient, though not record setting.

Jonathan O'Neil, who leads the competing team at the University of Ottawa, argues that the Nuvvuagittuq rocks formed as long as 4.4 billion years ago. That would make them by far the oldest rocks ever found on Earth. And that is not the least of it. Rocks that old would tell us how the planet's surface formed out of its violent infancy and just how soon after that life emerged—a pivotal chapter in Earth's biography that has so far remained beyond reach.

The first half a billion years of Earth's history—from its formation 4.568 billion years ago to four billion years ago—was a time when water rained down to create the oceans, when the first dry land heaved above the surface of the sea to form continents. It was a time when comets and asteroids crashed into Earth and when a failed planet the size of Mars may have collided with ours, creating the moon from the wreckage. But geologists have very few clues about the timing of these events, such as a few specks of minerals that suggest oceans might have formed before the moon. They find themselves in much the same situation as biographers of ancient Greek philosophers, trying to squeeze as much meaning as they can from scraps of parchment and secondhand stories.

If O'Neil is right and Nuvvuagittuq's rocks are indeed 4.4 billion years old, they will read not like scraps but like entire books. Thousands of acres of the minerals are waiting to be studied, perhaps holding answers to long-running mysteries. Did plate tectonics start early on, or did Earth mature for hundreds of millions of years before the continents and ocean crust began moving around? What was the chemistry of the youngest oceans and the atmosphere? And how soon did life emerge after Earth formed?

If Mojzsis is right, the earliest chapter in Earth's history will remain shut for now. If O'Neil is right, the rocks of Nuvvuagittuq are among the most precious treasures of geology.

IMPRISONED IN STONE

LIKE THE ROCKS that make up much of Earth's crust, the rocks at Nuvvuagittuq generally arose in one of two ways. In some cases, fine particles settled to the bottom of oceans, where they were gradually pressed into layers of sedimentary rock. In other cases, molten magma rose from Earth's mantle, cooling and crystallizing into igneous rock as it ascended.

Only tiny portions of ancient crust in places such as Nuvvuagittuq have remained intact, whereas the rest has vanished. Some rocks were slowly eroded by rain and wind and delivered back to the ocean for new sedimentation. Many others were carried back down under Earth's crust by tectonic plates sinking into the hot mantle, where the rocks melted, their original identity wiped out like an ice cube tossed into a warm pond. Their atoms mixed into the magma and rose again as fresh, young stone.

Rocks on the early Earth were also wiped out by giant asteroids that smashed into the planet and melted large fractions of the crust. About 4.4 billion years ago one collision—called the Giant Impact—hurled a huge amount of material into orbit, which became the moon. "The Giant Impact probably made a real mess of Earth," says Richard W. Carlson of the Carnegie Institution for Science. "You would not have wanted to be here. You might want to have watched it from Venus."

Given that so much ancient rock was destroyed in one way or another, it is not surprising that samples are rare. That is why the Nuvvuagittuq findings are so prized—and so hotly contested. Just a few other sites around the world have provided samples that are 3.8 billion years old. The oldest is from the tundra of the Northwest Territories, dating back 3.92 billion years.

The rarity of early rocks has driven geologists to look for other clues to what the planet was like in its first few hundred million years. Some of those clues have come from tiny crystals called zircons. These rugged, zirconium-based minerals will sometimes form in cooling magma. When the resulting rocks later erode away, some of the zircons may remain intact, even as they settle back on the ocean floor and are incorporated into younger sedimentary rocks.

The chemical bonds that make up zircons can trap radioac-

STONE OF CONTENTION: Jonathan O'Neil (*left*) insists his rocks are a record 4.4 billion years old. Stephen J. Mojzsis says 3.8 billion.

tive atoms such as uranium. The decay of those atoms acts like a clock that geologists can use to measure the age of the zircons. The crystals also trap other chemicals, which can provide a few clues to what Earth was like when they formed. "Zircons are great because they're time capsules," Mojzsis says.

In the outback of Australia, geologists have found sedimentary rocks that are sprinkled with immensely old zircons. Some of the zircons (but not the surrounding rock) date back as far as 4.4 billion years, making them the oldest traces of geologic history ever found. Scientists have squeezed remarkable information from these tiny gems since their discovery in 2001. Their structure suggests that the rock in which they originally formed solidified about four miles below the surface. Mojzsis and his colleagues have found chemical fingerprints of water in some of the Australian zircons, too.

The information that scientists can extract from sedimentary zircons is vastly better than nothing, but it is vastly less than they could get from the original rock in which the zircons grew. Rock contains many other minerals, which together can reveal far more about what Earth was like when it formed. "Unless you have the rocks, you don't have the complete story," says Larry Heaman of the University of Alberta. Which brings us back to Nuvvuagittuq.

SHEER LUCK

IN THE LATE 1990S the Quebec government launched a massive geologic expedition to make the first detailed maps of the northern reaches of the province. The region has an onionlike geology, with ancient cores of continental crust surrounded by layers of younger rock. Much of the rock proved to be around 2.8 billion years old. But Pierre Nadeau, then a Ph.D. candidate at Simon Fraser University in British Columbia, brought back a sample that dated back 3.8 billion years. By sheer luck, he had been sent to the Nuvvuagittuq greenstone belt. "Finding these rocks is like having a jewel dropped in my lap," Nadeau's co-worker Ross Stevenson told the BBC in 2002 after they released their results.

Other geologists began to make the long journey to Nuvvuagittuq. Among those pilgrims was O'Neil, who was earning his Ph.D. at McGill University. He was struck by the chemical similarity between the Nuvvuagittuq rocks and 3.8-billion-year-old rocks in Greenland. Perhaps they belonged to the same ancient landmass.

To probe the chemistry, O'Neil teamed up with Carlson from the Carnegie Institution, who is an expert at precision measurements of ancient rocks. The only clear way to determine if a specific stone from Nuvvuagittuq is ancient or not is to date it. To do so, scientists count the levels of radioactive isotopes trapped inside a stone. Radioactive isotopes are variations of atoms that were part of the dusty cloud from which our solar system was born. They became incorporated into solidifying planets and meteorites, and when rocks on Earth crystallized, they became imprisoned inside. As time passed, the isotopes gradually broke down at a regular, clocklike pace. Measuring the levels remaining today reveals a rock's age.

In a Carnegie Institution lab, O'Neil and Carlson tallied up the concentrations of different isotopes. That is when they realized something was very strange about the Nuvvuagittuq samples. Among the isotopes was one known as neodymium 142. It forms from the breakdown of samarium 146. There is no natural samarium 146 left on Earth, because its half-life is short, by some estimates only 68 million years. "It's long gone," Carlson says. "Samarium 146 was present when Earth formed because it was injected by the supernova that started the solar system. But then it decayed away within 500 million years."

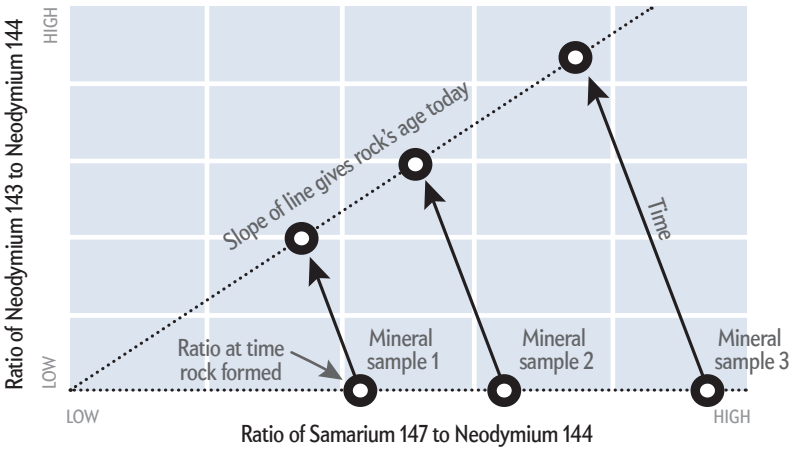
Carlson and his colleagues found that different Nuvvuagittuq rocks had different proportions of neodymium 142 and other neodymium isotopes. That variation could have come about only if the rocks formed at a time when there was still samarium 146 on

Photographs by Travis Rathbone (left) and Jamie Kripke (right)

How to Date a Rock

Measuring the levels of atoms in a rock can reveal its age. When rocks first harden from molten material, they trap variations, or isotopes, of radioactive atoms inside their structure. Over millions of years radioactive isotopes slowly break down at a steady, clocklike and unique rate into another isotope. For example, samarium 147 (the "parent") decays into neodymium 143 (the "daughter"). The number of parent atoms gradually decreases, and the number of daughter atoms increases.

Some stable atoms related to the daughter also get trapped, however, such as neodymium 144. Stable atoms do not break down, so their abundance stays the same over time. Plotting the ratio of parent atoms to stable atoms, and the ratio of daughter atoms to stable atoms, for different minerals in the rock creates a line on a graph (*above right*). The slope of the line gives the rock's age: the steeper the slope, the more the decay and the older the age.



Researchers used several such methods to date the rocks of the Nuvvuagittuq greenstone belt in Canada. There is always some margin of error, of course, so they have also evaluated results of a more complex method that compares two clocks: the ratio of uranium 238 to lead 206 and the ratio of uranium 235 to lead 207.

By the way, the famous "radiocarbon-dating" method often used by archaeologists works on a similar principle, but because the carbon 14 isotope decays relatively quickly, it can point back only to about 60,000 years ago. —*The Editors*

Earth. O'Neil, Carlson and their colleagues compared the proportions to estimate just how long ago the rocks had formed. The number was one none of them had anticipated: 4.28 billion years. To their surprise, they had discovered the oldest rocks on Earth.

"This was totally not what we were expecting to find," O'Neil says. He and his colleagues reported their discovery in 2008. Since then, they have analyzed other samples and now estimate that the Nuvvuagittuq rocks are as old as 4.4 billion years.

OLD—OR OLDEST EVER?

O'NEIL AND HIS COLLEAGUES first announced their results at a geology conference in Vancouver. Mojzsis can still remember the shock he felt at the news: "My jaw drops. I look around, and people are stunned. I think, 'This is peculiar.'"

Mojzsis had particular reason to be surprised. He was among the few geologists who had traveled to Nuvvuagittuq to follow up on Nadeau's research. Mojzsis and his colleagues had identified a vein of igneous rock that had thrust through the crust after the crust had formed. It turned out to contain zircons. Back home in Colorado, Mojzsis and his colleagues determined that the zircons were 3.75 billion years old—a result that squared nicely with Nadeau's original estimates of 3.8 billion years.

Now O'Neil was standing before Mojzsis and the rest of the scientific community, declaring that the Nuvvuagittuq rocks were half a billion years older.

Mojzsis's collaborator Bernard Bourdon of the École Normale Supérieure in Lyon, France, asked for some of O'Neil's samples and tested them again. The measurements of neodymium were correct. Still, "it didn't make sense to me," Mojzsis says.

So, in 2011, Mojzsis and his students returned to Nuvvuagittuq to study the site further. They mapped the terrain and layers of rock around the samples O'Neil had dated. In the rocks that were reportedly 4.4 billion years old, they saw bright green bands of quartzite. That, Mojzsis decided, offered a way to test whether the Nuvvuagittuq rocks were the oldest on the planet.

Geologists have seen similar arrangements in much younger formations. They occur when underwater volcanoes spread molten rock across the ocean floor. Sometimes the volcanoes die down, and sediments from the land settle on top of the igneous rocks. Then the volcanoes rev up again, burying the sedimentary rock in a fresh layer of igneous rock.

If that was the case in Nuvvuagittuq, then the quartzite had come from sediments from an ancient landmass during one of those volcanic pauses. And if that quartzite had zircons, those zircons would have to be older than the surrounding volcanic rock because they had a much longer history.

"We were on our hands and knees crawling over many outcrops," Mojzsis says. After days of hunting, they found two patches of quartzite with zircons—one of which yielded thousands of the tiny minerals. When they brought those zircons back to Colorado, Mojzsis found that they were 3.8 billion years old. That is precisely what they would *not* expect to find in rocks that were 4.4 billion years old.

Mojzsis's group also approached the question of Nuvvuagittuq's age from other scientific directions. They used another clock to date the rocks, for example, based on the decay of lutetium into hafnium. Once again they came up with 3.8 billion years.

All this evidence has led Mojzsis to a new narrative of Nuv-

SOURCE: JONATHAN O'NEIL

SCIENTIFIC AMERICAN ONLINE To learn more about dating fossils, see the video *How Does Radiocarbon Dating Work?* at ScientificAmerican.com/mar2014/zimmer

vuagittuq. Around 4.4 billion years ago some molten rock rose toward Earth's surface and turned solid. As it crystallized, it captured some short-lived radioactive samarium 146 that still existed in the early Earth. But then the ancient crust was pulled back down into the mantle. The material heated up to the point where it was no longer rock, but all of it did not get mixed into the surrounding mantle. A bit of it remained a distinct blob with its own peculiar levels of neodymium. Finally, 600 million years later, volcanic activity pushed the material back to the surface, creating rock that incorporated some of the ancient blob, along with the blob's 4.4-billion-year-old signature.

"That melt itself can have a memory of a previous existence," Mojzsis says. As a result, a rock that is only 3.8 billion years ago can appear to be 4.4 billion years old.

ZIRCON MYSTERY EXPLAINED

MOJZSIS AND HIS COLLEAGUES have been presenting these results at geologic conferences, sometimes in the same sessions where O'Neil is presenting the opposing view—that the rocks formed 4.4 billion years ago and simply have remained there in Earth's crust ever since. O'Neil's team has returned to Nuvvuagittuq, building up its collection of ancient rocks from 10 to about 50. None of the new data have clashed with the original estimation for the age of the site. O'Neil also rejects the evidence that Mojzsis and his colleagues have used to argue that Nuvvuagittuq is only 3.8 billion years old. "We have strong disagreement about the geology of the region," O'Neil says.

Take the quartzite layer where Mojzsis found his zircons. In formations as old as those of Nuvvuagittuq, it is not simple to identify what kind of rock makes up a formation, because it has been deformed so much over billions of years. O'Neil does not think the quartzite band is quartzite at all. Instead, he argues, it is a vein of magma that pushed itself into the ancient rock 3.8 billion years ago. The age of its zircons thus has no bearing on the age of the surrounding rock. "There's nothing bizarre or unusual" about his own rocks, O'Neil says. "They're just really old."

Heaman, himself an expert on old rocks, thinks that O'Neil and his colleagues have made a good case. "I think their evidence is compelling," he says. "They've done their due diligence." But Heaman also thinks that some uncertainty will endure until scientists can find another way to date the rocks. It is possible that a few minerals are lurking in the contested Nuvvuagittuq rocks that contain uranium and lead. That combination is the most reliable way to tell ancient time because scientists have vast experience with it. "If somebody were able to go out there and find the right material and get an old date, then the scientific community [would] be more accepting of the idea that there's some ancient crust exposed there," Heaman says.

WHEN LIFE FORMED

IF THE NUVVUAGITTUQ ROCKS are indeed 4.4 billion years old, O'Neil believes they have the potential to open a wide window on the early Earth because they would have formed shortly after the Giant Impact. The Australian zircons were also forming at that time, several miles down into the mantle. But O'Neil argues that the Nuvvuagittuq rocks formed on the surface. "The geochemistry of these rocks really looks like an ocean floor," he says.

If that is true, it confirms that Earth acquired an ocean not long after the Giant Impact. O'Neil also finds that the chemistry of the rocks is remarkably similar to seafloor rocks that formed much more recently. That would suggest that when the world's oceans first arose, they were not drastically different than they are today. O'Neil even believes that the rocks show signs of plate tectonics, suggesting that this process started very early in the planet's history.

There is an even more exciting prospect if the Nuvvuagittuq rocks formed on the ocean floor 4.4 billion years ago: they could shed light on the origin of life. Right now the fossil trail runs cold at 3.5 billion years ago. In rocks younger than that, scientists find preserved bacteria. In rocks older than that, they have found none.

But fossils are not the only traces that life can leave behind. As bacteria feed on carbon, they can alter the balance of carbon isotopes in their environment, and that imbalance can be preserved in rocks that form at the time. Some researchers have claimed that the 3.8-billion-year-old rocks from Greenland carry that imbalance, a signature of life.

That still leaves no evidence of life for the first 700 million years of Earth's existence. Scientists thus cannot say whether life got a quick start on Earth shortly after the planet formed or if it was delayed for hundreds of millions of years. They also have yet to figure out where life began on the planet. Some researchers have suggested that biological molecules emerged in deserts or tidal pools. Others have contended that deep-sea hydrothermal vents were the original nurseries.

If the Nuvvuagittuq rocks formed on the ocean floor 4.4 billion years ago, they are the perfect material to study to tackle these big questions. O'Neil hopes to collaborate with researchers to see whether the rocks could have formed at hydrothermal vents. "We cannot ignore these rocks. It's the ideal place where life could have formed," he says.

Finding the earliest traces of life is an obsession of Mojzsis, too, but he will not be looking in Nuvvuagittuq for them. "I'll spend the rest of my career pursuing that jabberwocky," he says.

Mojzsis does see an important benefit arising from his disagreement with O'Neil and others, however. As they spar, they are developing better methods for dating old rocks in general. "It's really an amazing debate," Mojzsis says. Future generations of geologists who venture into the remote corners of the world and bring back enigmatic samples will be able to use those methods to finally lift the curtain back on the early Earth. And on that point, at least, O'Neil and Mojzsis agree. "All these small enclaves of old rocks are probably all over the place," O'Neil says. "They're just really easy to miss." SA

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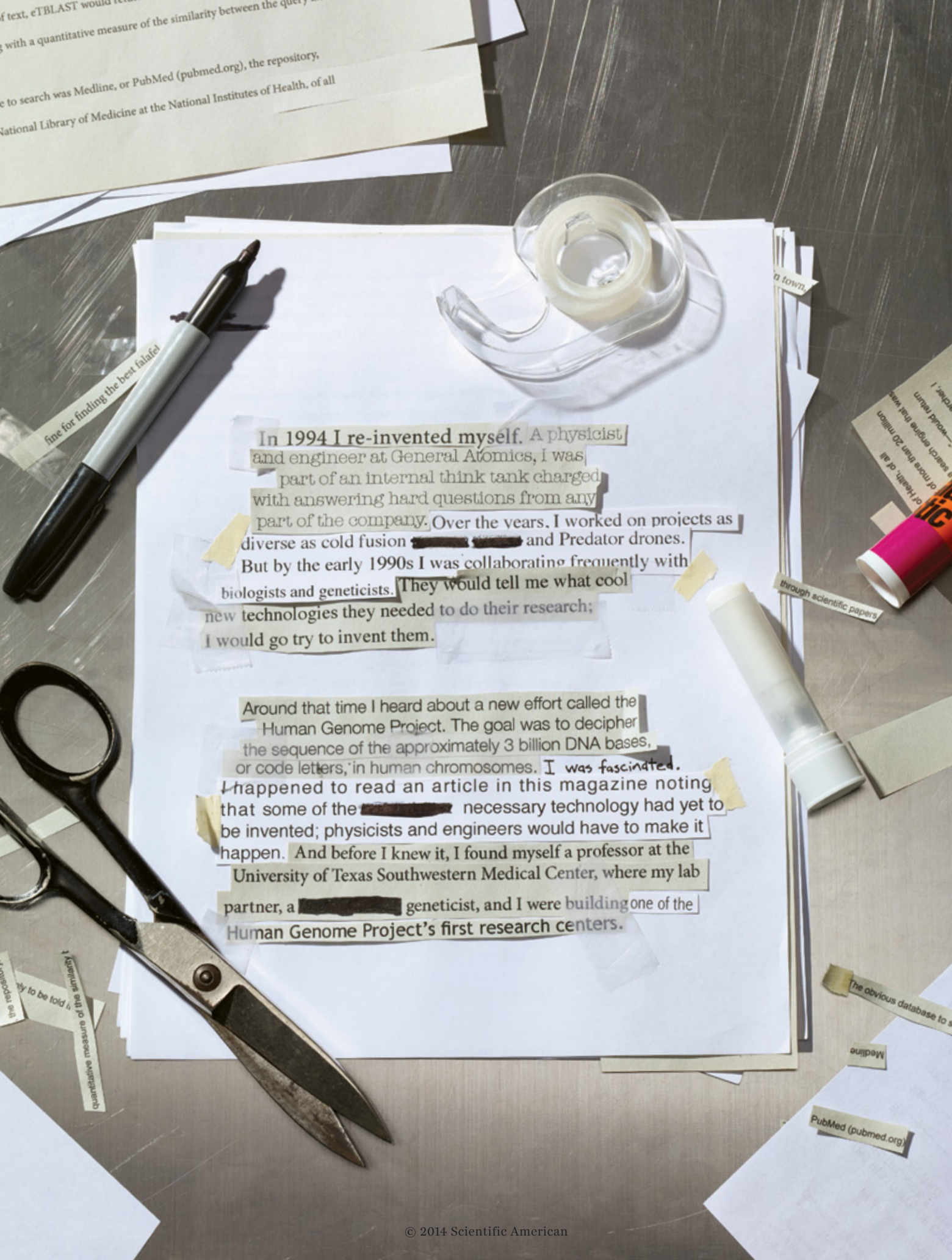

The author wanted to build software that would navigate medical jargon. He ended up uncovering widespread plagiarism and hundreds of millions of dollars in potential fraud

By Harold "Skip" Garner

INFORMATION TECHNOLOGY

THE Case of the STOLEN WORDS

IN 1994 I REINVENTED MYSELF. A physicist and engineer at General Atomics, I was part of an internal think tank charged with answering hard questions from any part of the company. Over the years, I worked on projects as diverse as cold fusion and Predator drones. But by the early 1990s I was collaborating frequently with biologists and geneticists. They would tell me what cool new technologies they needed to do their research; I would go try to invent them.

Around that time I heard about a new effort called the Human Genome Project. The goal was to decipher the sequence of the approximately three billion DNA bases, or code letters, in human chromosomes. I was fascinated. I happened to read an article in this magazine noting that some of the necessary technology had yet to be invented. Physicists and engineers would have to make it happen. And before I knew it, I found myself a professor at the University of Texas Southwestern Medical Center, where my scientific partner, a geneticist, and I were building one of the Human Genome Project's first research centers.

Everything was different there. My colleagues spoke a different language—medicine. I spoke physics. In physics, basic equations govern most everything. In medicine, there are no universal equations—just many observations, some piecewise understanding and a tremendous amount of jargon. I would attend seminars and write down huge lists of words I had never heard and then spend hours afterward looking them up. To read a scientific paper, I had to have a medical dictionary on hand.

Frustrated with my inability to understand any contiguous piece of text, I decided to develop software to help me. I wanted a search engine that would take a chunk of text and return references for further reading, abstracts and papers that would quickly get me up to speed on the topic at hand. It was a tough problem. Search engines for the Web were just emerging. They were fine for finding the best falafel restaurant in town, but they could not begin to digest a paragraph containing multiple interrelated concepts and point me to related readings.

With some students and postdocs, I set about studying text analytics, and together we developed a piece of software called eTBLAST (electronic Text Basic Local Alignment

Photographs by Adam Voorhes

Search Tool). It was inspired by the software tool BLAST, used to search DNA and protein sequence databases. A query for BLAST was usually a series of 100 to 400 DNA letters and would return longer sequences that included those codes. The query for eTBLAST would be a paragraph or page—typically 100 words or more. Designing the search protocol was harder than designing software to seek a string of letters because the search engine could not merely be literal. It also had to recognize synonyms, acronyms and related ideas expressed in different words, and it had to take word order into account. In response to a query consisting of a chunk of text, eTBLAST would return a ranked list of "hits" from the database it was searching, along with a measure of the similarity between the query and each abstract found.

The obvious database to search was Medline (available from PubMed at pubmed.org), the repository, maintained by the National Library of Medicine at the National Institutes of Health, of all biological research relevant to medicine. It contains the title and abstract of millions of research papers from thousands of peer-reviewed journals. Medline had a search engine that was keyword-based, so a query of a few words—for example, "breast cancer genes"—would return plenty of hits, often with links to full papers. But as a newly converted biomedical researcher, I did not even know how to start many of my searches.

The first versions of eTBLAST took hours to compare a paragraph of a few hundred words against Medline. But the software worked. Using eTBLAST, I could make my way through scientific papers, mastering their meaning paragraph by paragraph. I could pop a graduate student's thesis proposal in and quickly get up to speed on the pertinent literature. My research partners and I even spoke with Google about commercializing our software, only to be told it did not fit with the company's business model.

Then events took a strange turn. A couple of times I found text in student proposals that was identical to text in other, uncited papers. The students received remedial ethics training. I received a research question that would change my career: How much of the professional biomedical literature was plagiarized?

DÉJÀ VU

WHEN I SET OUT TO EXPLORE this new question, the research on plagiarism in biomedicine consisted of anonymous surveys. In the most current survey I found, researchers admitted to plagiarizing 1.4 percent of the time. But the accuracy of that number depended on the honesty of the survey respondents. With eTBLAST, we could find out whether they were telling the truth.

Once we had enough student help and a sufficiently powerful computer, we randomly selected abstracts from Medline and then used them as eTBLAST queries. The computer would compare the query text with the entire contents of Medline, looking for similarities, then return a list of hits. Each hit came with a similarity score. The query was always at the top of the list—100 percent similarity. The second hit typically had a similarity score between the single digits and 30 percent. Occasionally, though, we found that the second and sometimes third hits had scores close to 100 percent. After running a few thousand queries, we started to see that about 5 percent of queries had suspiciously high similarity scores. We reviewed those abstracts by eye to make sure the software was finding things that a human would consider similar. Then we went on to compare the full text of papers that had suspiciously similar abstracts.

Soon we began to find blatant examples of plagiarism—not just recycled phrases but entire papers lifted whole cloth. It was disappointing, even astounding. Sure, we knew that surveys said that 1.4 percent of researchers admit to plagiarism. But it is quite a different thing to see examples of plagiarized papers side by side. For the students in particular, the process was exciting. They felt like crime fighters, and in a sense, they were.

The next step was to scale up the computing and the analysis. To be thorough, we wanted to perform similarity searching on every entry of sufficient length in Medline—at the time, almost nine million entries, each containing an average of 300 words, times nearly nine million comparisons. The task took months and consumed a considerable amount of our lab's computing power. As the results emerged, we analyzed them and placed all the highly similar results in a database we called Déjà Vu.

Déjà Vu began to fill with pairs of highly similar Medline abstracts—about 80,000 pairs that were at least 56 percent similar. The vast majority of these pairs were highly similar for perfectly good reasons—they were updates to older papers, or meeting summaries, for example. But others were suspicious.

We submitted a paper to *Nature* that contained data on the frequency of plagiarism and duplicate publication (sometimes called self-plagiarism), details on the content of the Déjà Vu database and some prime examples. (*Scientific American* is part of Nature Publishing Group.) The editors accepted, but because we referred to some abstracts as plagiarized, the lawyers ripped the paper apart. They had an excellent point: the only people who could make a plagiarism determination were editors and ethics review boards. We could present only facts—the amount of text overlap or similarity between any two pieces of scientific literature. Eventually, with the approval of the lawyers, that is what we did.

When the *Nature* report came out, all hell broke loose. Journal editors were upset because it gave them extra work to do. To protect their copyright, the editors of the original papers had to insist that the plagiarized papers be retracted. The second pub-

Harold "Skip" Garner is a professor of biological sciences, computer science and medicine at Virginia Tech and a serial entrepreneur. He is co-founder of HelioText, a textual analysis firm, and serves on *Scientific American*'s board of advisers.

IN BRIEF

By mining the medical literature with textual analysis software, the author found evidence of widespread plagiarism and potential fraud. Now, he argues, the proliferation of dubious journals has made it easier to publish plagiarized work.

Textual analysis is a useful tool for detecting plagiarism. But it may be time to consider a new model for scientific publishing—perhaps one in which researchers continually edit a single Wikipedia-style electronic corpus.

PRECEDING PAGES: ROBIN FINLAY (*prop styling*)

SCIENTIFIC AMERICAN ONLINE Hear Garner and others talk about plagiarism at ScientificAmerican.com/mar2014/ethics

lisher, of course, was embarrassed. Scientists were angry because our results seemed to expose a flaw in peer review. But everyone grudgingly admitted that this was an important topic and a serious problem. Scientists and clinicians make critical decisions based on what they read in the literature. What did it mean if those decisions were based on tainted studies?

Ultimately we determined that 0.1 percent of professional publications were blatantly plagiarized from the work of others. (We looked only for papers that were nearly identical to one another; there must be many more instances in which small fragments of papers are plagiarized, but because our software searched only abstracts, it would not detect such things.) Some 1 percent were self-plagiarized; one author's work would appear, often nearly verbatim, in as many as five journals. If these percentages seem small, consider that some 600,000 new biomedical papers are published every year.

And before long, we noticed that the publishing process had begun to change. Journal editors started using eTBLAST to check their submissions. I had changed, too. I had evolved again, adding "ethics researcher" to my job description.

MY LIFE AS AN ETHICS COP

THE FIRST BIG PLAGIARISM STUDY was just the beginning. Understanding the causes of plagiarism and their effects on science would require much more work. When is repeated text acceptable? When and why do scientists plagiarize? What other kinds of unethical behavior could textual analysis uncover? So we refined our software, expanded our databases and took on new studies.

Some of our subsequent work revealed unexpected nuances in the plagiarism debate. We found that in some cases, textual similarity is not only acceptable but preferred. In the methods section of a research paper, for example, where the most important consideration is reproducibility of results, unoriginal phrasing serves the important purpose of showing clearly that exactly the same protocol was used.

We also found some truly egregious ethical lapses. In a study published in *Science,* we took the most blatant examples of plagiarism we could find—pairs of papers in which paper B was on average 86 percent identical to paper A—and analyzed them in detail. We e-mailed annotated copies of the papers, along with confidential surveys, to the authors and editors involved with those papers. Were they aware of the similarity? Could they explain it? Ninety percent of the people we contacted responded.

Some of the authors divulged striking ethics violations. Some admitted that they had copied papers while they were reviewing them—and that they had given those papers bad reviews to block their publication. Others blamed the lapse on fictitious medical students. One author said he had plagiarized a paper as a joke. This person happened to be the vice president of the national ethics committee of his country. Unsurprisingly, most of the tainted papers in that bunch have since been retracted.

These were not the last ethics violations we would find. In early 2012 we began looking for instances of double-dipping on grants—that is, getting money from multiple government agencies to do the same work. We downloaded summaries of approximately 860,000 grants from government and private agencies, including the National Institutes of Health, the National Science Foundation, the Department of Defense, the Department of Energy and Susan G. Komen for the Cure, and subjected them to the eTBLAST treatment. The study required 800,000 times 800,000 (roughly 10^{12}) comparisons and supercomputer-level power.

After reviewing the 1,600 most similar grant summaries, we found that about 170 pairs had virtually identical goals, aims or hypotheses. We concluded several things: that double-dipping had been happening consistently for a long time; that it involved America's most prestigious universities; and that the resulting loss to biomedical research was as high as $200 million a year.

THE FUTURE OF SCIENTIFIC PUBLISHING

A SMALL PERCENTAGE of people have always broken societal norms, and scientists are no different. In desperate times, with declining funding and increasingly intense competition for academic positions, some scientists are bound to behave badly. In fact, a recent explosion of dubious, fly-by-night journals has made scientific publishing a Wild West show. It is now easier than ever to find a place to publish your material, even if it is flagrantly plagiarized.

Text analytics gives us a good tool for policing bad behavior. But it could eventually do much more than smoke out plagiarism. It could facilitate entirely new ways of sharing research.

One intriguing idea is to adopt a Wikipedia model: to create a dynamic, electronic corpus of work on a subject that scientists continually edit and improve. Each new "publication" would consist of a contribution to the single growing body of knowledge; those redundant methods sections would become unnecessary. The Wikipedia model would be a step toward a central database of all scientific publications across all disciplines. Authors and editors could use text mining to verify the novelty of new research and to develop reliable metrics for the impact of an idea or discovery. Ideally, instead of measuring a paper's impact by the number of citations it receives, we would measure its influence on our total scientific knowledge and even on society.

At Virginia Tech, where I moved four years ago, we are struggling to keep eTBLAST running, but the software still has thousands of users. My wife and business partner, Kim Menier, and I, meanwhile, are bullish about textual analysis. We are working to apply the kind of paragraph-size similarity searching that uncovered so many instances of plagiarism to other ends, including grant management, market research and patent due diligence. Do we have the next Google on our hands? Who knows? But I speak from experience when I say that textual analysis can be truly revealing. It once proved to me that scientists could be as flawed as the rest of us. SA

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ECOLOGY

The American Chestnut's Genetic Rebirth

A foreign fungus nearly wiped out North America's once vast chestnut forests. Genetic engineering can revive them

By William Powell

ABOUT 70 FEET TALL and six feet in diameter, one of the largest remaining American chestnut trees grows in Oregon (*left*). At the right is a leaf from the species.

William Powell is co-director of the American Chestnut Research and Restoration Program at the S.U.N.Y. College of Environmental Science and Forestry. He is a recent recipient of the Forest Biotechnologist of the Year Award from the Forest Biotechnology Partnership.

IN 1876 SAMUEL B. PARSONS RECEIVED A SHIPMENT OF CHESTNUT SEEDS FROM JAPAN AND DECIDED TO grow and sell the trees to orchards. Unbeknownst to him, his shipment likely harbored a stowaway that caused one of the greatest ecological disasters ever to befall eastern North America. The trees probably concealed spores of a pathogenic fungus, *Cryphonectria parasitica,* to which Asian chestnut trees—but not their American cousins—had evolved resistance. *C. parasitica* effectively strangles a susceptible tree to death by forming cankers—sunken areas of dead plant tissue—in its bark that encircle the trunk and cut off the flow of water and nutrients between the roots and leaves. Within 50 years this one fungus killed more than three billion American chestnut trees.

Before the early 1900s the American chestnut constituted about 25 percent of hardwood trees within its range in the eastern deciduous forests of the U.S. and a sliver of Canada—deciduous forests being those composed mostly of trees that shed their leaves in the autumn. Today only a handful of fully grown chestnuts remain, along with millions of root stumps. Now and then these "living stumps" manage to send up a few nubile shoots that may survive for 10 years or longer. But the trees rarely live long enough to produce seeds because the fungus almost always beats them back down again.

In its prime, the American chestnut was a keystone species, crucial to the health of a multitude of organisms in its ecosystem. Many different birds, insects and small mammals nested in its branches and burrowed into its bark. Bears, deer, turkeys, blue jays, squirrels and other animals ate the large, nutritious chestnuts. After losing so many mature chestnut trees, wildlife populations declined and became less diverse. The oaks that have since replaced the chestnut cannot support as many animals; the acorns they produce are only half as nutritious. And chestnuts once generated larger quantities of nuts than oaks do today, in part because they flowered after frosts that might have destroyed delicate buds.

The American chestnut also had great economic value. Its nuts can be used for food or ethanol fuel. Because the American chestnut grows quickly, has sturdy, straight-grained wood and is very rot-resistant, it provides excellent timber. In fact, if the chestnut were still abundant, most decks would likely be made from its wood instead of from pressure-treated lumber, which often contains heavy metals and other preservatives that endanger the environment and people's health when they find their way into soil and food. Last, the American chestnut has been an especially beloved tree, immortalized in poetry, songs, books, street signs, and the names of many schools, hotels and parks across the country.

We do not have to stand by as the American chestnut becomes a distant memory for most people. The culmination of decades of research suggests that science can restore the tree and all the resources it once offered people and wildlife. After a century of ineffective efforts to combat chestnut blight, two approaches are now meeting with some success. One strategy attempts to create blight-resistant American chestnuts with an ancient horticultural technique: hybridization. By mating American chestnuts with far smaller, fungus-resistant Chinese chestnuts, researchers "backcross" the resulting hybrids with other Ameri-

IN BRIEF

In its prime, before the early 1900s, the American chestnut flourished in the eastern forests of North America, providing shelter and food for many other creatures. Within 50 years, however, a foreign fungus introduced by humans eradicated more than three billion trees.

To revive the American chestnut, some scientists have hybridized it with its more resilient Chinese cousin. A more precise and successful approach inserts genes from wheat and other plants into American chestnuts to yield fungus-resistant trees.

If researchers receive federal approval to plant these transgenic trees in the wild, which could happen in the next five years, the American chestnut will be the first genetically engineered plant used to restore a threatened species to its native range.

PRECEDING PAGES: GARY BRAASH *Getty Images (tree);* JOEL SARTORE *(leaf)*

can chestnuts to Americanize the trees as much as possible while, it is hoped, keeping all the genes responsible for blight resistance. In addition to being rather imprecise, however, backcross breeding requires many generations and thousand of trees to produce individuals suitable for restoration.

For those reasons, my many collaborators and I are focusing on a second approach, which relies on altering the chestnut tree's DNA in a much more exact way than traditional breeding and which has the potential to produce more fungus-resistant trees more quickly. By borrowing genes from wheat and the Chinese chestnut, among other plants, and inserting them into the American chestnut's genome, we have created hundreds of transgenic trees, some of which defend themselves against *C. parasitica* as well as, if not better than, their Asian counterparts. If the U.S. Department of Agriculture, the Environmental Protection Agency, and the Food and Drug Administration approve our trees—which could happen as soon as five years from now—they will be the very first transgenic organisms used to restore a keystone species to its native environment.

Compared with other efforts to revive endangered or extinct species with genetic engineering and related biotechnologies—such as the proposed restoration of the passenger pigeon, thylacine and mammoth—the efforts to reinstate the American chestnut face far fewer hurdles and offer much clearer benefits. Unlike cloned mammoths and pigeons, trees do not require surrogate mothers, parenting or socialization. And as a massive organism that is home to many others, the American chestnut can improve the health of the forest more than any one animal.

PLANT PATHOLOGIST Gary J. Griffin of Virginia Tech uses a hand lens to examine a swollen canker on a chestnut tree infected with a harmful fungus.

GARY BRAASH

SEEDS OF SALVATION

LIKE MANY ADULTS in the U.S. today, all I knew about chestnuts while I was growing up was what I learned from a certain iconic Christmas song. Yet in 1983, when I became a graduate student working with plant pathologist Neal Van Alfen, then at Utah State University, I began to develop a deep appreciation and sympathy for the magnificent chestnut tree and its demise at the hands—or rather the fungal fingers—of an exotic pathogen.

In 1989, when I had moved to the S.U.N.Y. College of Environmental Science and Forestry, Stan Wirsig of the American Chestnut Foundation approached my colleague Charles Maynard and me with a proposition. He wanted to complement the foundation's ongoing chestnut tree hybridization program with a new restoration project focused on genetic engineering, which was a cutting-edge technology at the time and promised a speedier and more precise way to create resistant American chestnuts. One of my tasks was to find a gene that could endow the trees with resistance to *C. parasitica* while Maynard and Scott Merkle of the University of Georgia developed the techniques that would allow us to introduce that gene to chestnut tree embryos—tiny bundles of swiftly multiplying cells that would eventually grow into adult trees. If everything worked as planned, the young trees would grow into sturdy adults with the ability to battle the fungus.

At that time, no one had ever tried to genetically engineer a tree to fight a virulent fungus, but we had a few clues about how to get started. Over the years researchers had learned some important details about how *C. parasitica* damages chestnut trees. The pathogen grows feathery lattices of fungal tissue called mycelial fans that produce oxalic acid, which eats through the tree's bark to make room for the fungal invasion. As the fungus wedges its way into the tree, a canker girdles the trunk.

Initially we focused on finding a way to weaken the mycelial fans. We knew that the immune systems of many plants and animals contain small chains of amino acids known as antimicrobial peptides (AMPs) that can disrupt fungal cells. Using AMP genes in the African clawed frog as a model, we assembled genes from scratch to produce AMP peptides that could fight *C. parasitica*. We hoped that if we could engineer the chestnut trees to produce even small amounts of these AMPs, they would make mycelial fans go slack and thereby render them benign. Such peptides are notoriously unstable molecules, though, so we needed a backup plan.

Around the same time, a then graduate student named Kim Cameron stopped by my office and dropped off a book summarizing many of the studies presented at the recent annual meeting of the American Society of Plant Biologists. When I read about a study conducted by Ousama Zaghmout and Randy Allen, both then at Texas Tech University, I had a eureka moment. The study described a wheat gene for an enzyme called oxalate oxidase (OxO), which breaks down oxalic acid—the very same caustic substance produced by the chestnut blight fungus. Even better, the researchers had worked out a way to introduce this gene into other plants. They put the gene into *Agrobacterium,* a microbe that can inject DNA into the command center of plant cells, and exposed plants to clones of that microbe. The resulting transgenic plants became resistant to an acid-spewing fungus known as *Sclerotinia sclerotorium*. Maybe we could do something similar with the American chestnut.


ULMUS AMERICANA

What Happened to the American Elm?

Throughout the country, the American elm once sheltered many city streets in cathedrals of green. In addition to its beauty, it was a hardy tree, tolerant of the compacted, salty soil and periodic droughts characteristic of urban life. Like the American chestnut, however, this native species fell victim to a virulent fungus from Asia. Although the American elm is not extinct, it is now very rare to see these trees in urban settings.

The American elm succumbed to a fungus known as Dutch elm disease (DED), which is spread by bark beetles. Once in the tree, the fungus grows through tubes of xylem, conduits for water and minerals. The tree attempts to contain the fungus behind walls of tissue, thereby inadvertently clogging its own passageways and depriving itself of sustenance. Through many decades of selective breeding, however, researchers have produced 23 DED-tolerant varieties of American elm, such as the New Harmony, Valley Forge and Liberty elms.

Unfortunately, DED is not the only problem. American elms are also highly vulnerable to another disease known as elm yellows, spread by American leafhoppers carrying phytoplasma bacteria. These microbes destroy the tree's roots and phloem tubes, which transport sugars. An infected elm droops at first and eventually dies. In this case, genetic engineering might be useful. Instead of producing American elms that can resist both DED and elm yellows through many decades of breeding, scientists may be able to engineer immunity in only a few generations, using what we have learned from work on the American chestnut. In fact, some of the same Chinese chestnut genes currently under investigation to save the American chestnut may help defend the American elm against elm yellows. Allison Oakes, a graduate student at the S.U.N.Y. College of Environmental Science and Forestry, is currently exploring this possibility. —*W.P.*

We could not test either approach on chestnuts at that point, because we were still figuring out how to grow the finicky chestnut in the laboratory. So we decided to achieve a proof of principle in a different tree—the hybrid poplar, which was well studied and often used in experiments. Haiying Liang, then a graduate student at the College of Environmental Science and Forestry, would deliver both the *OXO* gene and our AMP gene, and when the trees were old enough, we would infect them with *Septoria musiva,* a fungus that produces a good deal of oxalic acid and can cause leaf spot and canker diseases in hybrid poplars. Most of the trees treated in this way remained relatively healthy. We had made one tree fungus-resistant with genetic engineering. Now we needed to do it with the right tree and the right fungus.

While Liang was conducting the poplar experiments, Linda McGuigan, also then a graduate student at the college, set to work figuring out how to raise chestnut trees from embryos in the lab. Some plants, like carrots and petunias, are remarkably easy to grow in the lab. Provided with enough water, nutrients and certain hormones, they will grow new shoots and roots from a tiny piece of leaf, for example. The American chestnut was not one of these cooperative plants. McGuigan, building on the work of previous students, spent two and a half years learning how to successfully introduce the wheat gene into chestnut embryos using *Agrobacterium* and to subsequently shepherd the embryos into young adulthood in the lab. Usually the cluster of rapidly dividing cells that make up a chestnut tree embryo grow within the protective husk of a chestnut seed that has fallen to the ground, eventually pushing roots through the seed and into the soil and pushing green shoots toward the sun. McGuigan learned how to control lighting, humidity and temperature to mimic what would normally happen inside a chestnut seed and fine-tuned the delivery of various hormone cocktails at different stages of the miniature tree's early development to induce growth of roots and shoots.

In 2006 we were able to plant the first transgenic American chestnut trees in experimental fields sectioned off from the forest. It takes at least two to three years for the trees to reach a size at which we can challenge them with the blight fungus. We had attached the *OXO* gene to a promoter—a kind of genetic switch that controls how often a cell reads the instructions in a gene—to limit the production of OxO to certain tissues. We were hoping the resulting low levels of the enzyme would be sufficient to take on the fungus without causing any unwanted side effects. Unfortunately, we were mistaken. This first line of trees was not able to resist the fungus; they died a little slower than is typical but ultimately succumbed to their illness.

By 2012 we had designed a new promoter for the *OXO* gene and engineered a new line of trees that produced much more of the acid-degrading enzyme. Success! These trees evaded disease almost as well as the Chinese chestnut, which had evolved resistance on its own. We have now developed a way of gauging disease resistance by testing the leaves of chestnut trees that are only a few months old, so we no longer have to wait three years to see if our experiments are working. In this test, we make small cuts in leaves, infect them with fungus and wait for a circle of decaying tissue to spread from the wound. The smaller the spot of death, the more resistant the tree. Some of our newest trees, which make OxO in all their tissues and were planted in the field in 2013, appear to be even more resistant than the Chinese chestnut. We need to confirm this finding as

WILLIAM HARLOW Getty Images

SCIENTIFIC AMERICAN ONLINE Read about how northeastern forests have changed since the demise of the American chestnut tree at ScientificAmerican.com/mar2014/chestnut-forest

the trees get older, but it appears that the gene we borrowed from wheat has exceeded our expectations.

People often ask us why we do not simply find the genes that make the Chinese chestnut resistant and use them instead of the wheat gene. When we first started our research, no one had thoroughly studied the Chinese chestnut genome, and it would have taken too much time and too many resources to locate the numerous different genes responsible for a complex trait like blight resistance. Each of those genes would contribute only a small portion of the tree's ability to battle the fungus, and any one of them would probably have been ineffective as a defense on its own.

At this point, however, scientists have identified 27 genes that might be involved in the Chinese chestnut's blight resistance—the fruits of a recent collaborative effort under the Forest Health Initiative between many researchers at the College of Environmental Science and Forestry, the University of Georgia, Clemson University, Pennsylvania State University, the U.S. Forest Service, North Carolina State University, the Connecticut Agricultural Experiment Station and the American Chestnut Foundation. So far two of these genes each appear to endow trees with an intermediate level of resistance. Testing is ongoing with the other candidate genes. Joseph Nairn of the University of Georgia has also given us copies of two other genes to test: one for a grape enzyme that helps to make resveratrol, which is toxic to fungus, and a pepper gene encoding an AMP that directly inhibits the growth of fungal cells.

Eventually we hope to fortify American chestnuts with many different genes that confer resistance in distinct ways. Then, even if the fungus evolves new weapons against one of the engineered defenses, the trees will not be helpless.

GOING OUT ON A LIMB

TODAY MORE THAN 1,000 transgenic chestnut trees are growing in field sites, mostly located in New York State. The next hurdle for American chestnut restoration involves the federal regulatory process. Before we can plant trees in the forest, the FDA, USDA and EPA will want to make sure that genetically engineered chestnut trees are not significantly different from typical trees in some unexpected way. As opposed to hybridized trees, which are genetically quite different from American chestnuts because they have large chunks of Chinese chestnut DNA, our transgenic trees have only a few new genes. Preliminary tests show that the roots of typical chestnut trees and engineered trees form the same kinds of symbiotic relations with helpful fungi and that similar communities of smaller plants grow underneath the canopies of both modified and unmodified trees. Likewise, the same insect species visit both transgenic and typical chestnut trees, and nuts from both types of trees have the same nutritional composition.

Once such tests are complete, we will petition the USDA, EPA and FDA for the same unregulated status that they give to genetically engineered crops. Here is where the American chestnut will introduce a new dilemma in the usual regulatory process. We are not growing a genetically modified organism on cropland for profit; rather we are producing trees for restoration without monetary gain. Like researchers working on golden rice enriched with a precursor of vitamin A, we are motivated by the public good—and the health of the forest. The EPA generally grants seed companies licenses to sell transgenic seeds, but in our case, we have no one to hold the license and nothing to sell. It is not clear what kind of alternative approval they would give us, but we are determined to set a precedent.

A final hurdle is public acceptance. Encouragingly, many people who are typically opposed to genetic modification make an exception for the American chestnut tree. Some people reason that because humans caused the demise of the chestnut in the first place, humans should fix it. Others are accepting because we are not seeking profit and are not patenting the trees.

Many people are also happy to learn that the environmental risks of American chestnut restoration are negligible. The chances of transgenic chestnut tree pollen spreading introduced genes to other plant species are very small. Pollen from one tree species can fertilize only the same species or a closely related one. The American chestnut has no closely related species in the northern part of its natural range. In the southern parts of its range, chinquapins occasionally cross with American chestnuts. But chinquapins are also infected by chestnut blight and would benefit from some genetic resistance. Ideally, some of the transgenic pollen will spread resistance to at least a fraction of the remaining American chestnut stumps that manage to flower, rescuing as much of their total genetic diversity as possible. If the stumps do benefit, they could spawn a blight-resistant population that, over the centuries, could return this once towering keystone species to its former glory in the eastern forests.

Chestnut blight is not the only enemy of biodiversity that genetic engineering can eradicate. We are losing the battle against many other exotic pests such as the hemlock woolly adelgid—a bug that sucks the sap from hemlock trees—and the emerald ash borer—a metallic green beetle whose larvae tunnel under the bark of ash trees—as well as the pathogens responsible for sudden oak death and walnut thousand cankers disease, to name a few. To turn the tables, we have to act quickly, and in most cases, traditional breeding techniques are just too slow to make a difference. Now, more than ever, we need genetic engineering in our toolbox to maintain diverse and healthy forests.

Completely restoring the American chestnut to its previous status as a king of the forest is a centuries-long endeavor. Once the chestnut trees pass regulatory and public approval, a good place to begin restoration is on reclamation lands. With the help of the Forest Health Initiative and Duke Energy, test plots are now being planted on mine reclamation sites. Other areas might include abandoned farmland and historic locations that once had abundant chestnut trees. And perhaps some individuals will want to have these iconic trees in their own yards. An old Chinese proverb says, "One generation plants a tree, the next generation enjoys its shade." In the case of the American chestnut, we are that first generation. SA

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PSYCHOLOGY

Why Good Thoughts Block Better Ones

While we are working through a problem, the brain's tendency to stick with familiar ideas can literally blind us to superior solutions

By Merim Bilalić and Peter McLeod

Illustration by Danny Schwartz

Merim Bilalić is a professor of cognitive science at the University of Klagenfurt in Austria and a senior research fellow at the University of Tübingen in Germany. His research on the *Einstellung* effect won the British Psychological Society's Award for Outstanding Doctoral Research Contributions to Psychology in 2008.

Peter McLeod is an emeritus fellow at Queen's College at the University of Oxford. He is chair of the Oxford Foundation for Theoretical Neuroscience and Artificial Intelligence.

IN A CLASSIC 1942 EXPERIMENT, AMERICAN PSYCHOLOGIST ABRAHAM LUCHINS asked volunteers to do some basic math by picturing water jugs in their mind. Given three empty containers, for example, each with a different capacity—21, 127 and three units of water—the participants had to figure out how to transfer liquid between the containers to measure out precisely 100 units. They could fill and empty each jug as many times as they wanted, but they had to fill the vessels to their limits. The solution was to first fill the second jug to its capacity of 127 units, then empty it into the first to remove 21 units, leaving 106, and finally to fill the third jug twice to subtract six units for a remainder of 100. Luchins presented his volunteers with several more problems that could be solved with essentially the same three steps; they made quick work of them. Yet when he gave them a problem with a simpler and faster solution than the previous tasks, they failed to see it.

This time, Luchins asked the participants to measure out 20 units of water using containers that could hold 23, 49 and three liquid units. The solution is obvious, right? Simply fill the first jug and empty it into the third one: 23 – 3 = 20. Yet many people in Luchins's experiment persisted to solve the easier problem the old way, emptying the second container into the first and then into the third twice: 49 – 23 – 3 – 3 = 20. And when Luchins gave them a problem that had a two-step solution—but could not be solved using the three-step method to which the volunteers had become accustomed—they gave up, saying it was impossible.

The water jug experiment is one of the most famous examples of the *Einstellung* effect: the human brain's dogged tendency to stick with a familiar solution to a problem—the one that first comes to mind—and to ignore alternatives. Often this type of thinking is a useful heuristic. Once you have hit on a successful method to, say, peel garlic, there is no point in trying an array of different techniques every time you need a new clove. The trouble with this cognitive shortcut, however, is that it sometimes blinds people to more efficient or appropriate solutions than the ones they already know.

Building on Luchins's early work, psychologists replicated the *Einstellung* effect in many different laboratory studies with both novices and experts exercising a range of mental abilities, but exactly how and why it happened was never clear. Recently, by recording the eye movements of highly skilled chess players, we have solved the mystery. It turns out that people under the influence of this cognitive shortcut are literally blind to certain details in their environment that could provide them with a more effective solution. New research also suggests that many different cognitive biases discovered by psychologists over the years—those in the courtroom and the hospital, for instance—are in fact variations of the *Einstellung* effect.

BACK TO SQUARE ONE

SINCE AT LEAST THE EARLY 1990s, psychologists have studied the *Einstellung* effect by recruiting chess players of varying skill levels, from amateur to grand master. In such experiments, researchers have presented players with specific arrangements of chess pieces on virtual chessboards and asked them to achieve a checkmate in as few moves as possible. Our own studies, for instance, provided expert chess players with scenarios in which they could accomplish a checkmate using a well-known sequence

IN BRIEF

The *Einstellung* effect is the brain's tendency to stick with the most familiar solution to a problem and stubbornly ignore alternatives.

Psychologists have known about this mental phenomenon since the 1940s, but only now do they have a solid understanding of how it happens.

In recent eye-tracking experiments, familiar ideas blinded chess players to areas of a chessboard that would have provided clues to better solutions.

called "smothered mate." In this five-step maneuver, the queen is sacrificed to draw one of the opponent's pieces onto a square to block off the king's escape route. The players also had the option to checkmate the king in just three moves with a much less familiar sequence. As in Luchins's water jug studies, most of the players failed to find the more efficient solution.

During some of these studies, we asked the players what was going through their mind. They said they had found the smothered mate solution and insisted they were searching for a shorter one, to no avail. But the verbal reports offered no insight into why they could not find the swifter solution. In 2007 we decided to try something a little more objective: tracking eye movements with an infrared camera. Which part of the board people looked at and how long they looked at different areas would unequivocally tell us which aspects of the problem they were noticing and ignoring.

In this experiment, we followed the gaze of five expert chess players as they examined a board that could be solved either with the longer smothered mate maneuver or with the shorter three-move sequence. After an average of 37 seconds, all the players insisted that the smothered mate was the speediest possible way to corner the king. When we presented them with a board that could be solved only with the three-sequence move, however, they found it with no problem. And when we told the players that this same swift checkmate had been possible in the previous chessboard, they were shocked. "No, it is impossible," one player exclaimed. "It is a different problem; it must be. I would have noticed such a simple solution." Clearly, the mere possibility of the smothered mate move was stubbornly masking alternative solutions. In fact, the *Einstellung* effect was powerful enough to temporarily lower expert chess masters to the level of much weaker players.

The infrared camera revealed that even when the players said they were looking for a faster solution—and indeed believed they were doing so—they did not actually shift their gaze away from the squares they had already identified as part of the smothered mate move. In contrast, when presented with the one-solution chessboard, players initially looked at the squares and pieces important for the smothered mate and, once they realized it would not work, directed their attention toward other squares and soon hit on the shorter solution.

BASIS FOR BIAS

THIS PAST OCTOBER, Heather Sheridan of the University of Southampton in England and Eyal M. Reingold of the University of Toronto published studies that corroborate and complement our eye-tracking experiments. They presented 17 novice and 17 expert chess players with two different situations. In one scenario, a familiar checkmate maneuver such as the smothered mate was advantageous but second best to a distinct and less obvious solution. In the second situation, the more familiar sequence would be a clear blunder. As in our experiments, once amateurs and master chess players locked onto the helpful familiar maneuver, their eyes rarely drifted to squares that would clue them in to the better solution. When the well-known sequence was obviously a mistake, however, all the experts, and most of the novices, detected the alternative.

The *Einstellung* effect is by no means limited to controlled experiments in the lab or even to mentally challenging games like chess. Rather it is the basis for many cognitive biases. English philosopher, scientist and essayist Francis Bacon was especially eloquent about one of the most common forms of cognitive bias in his 1620 book *Novum Organum:* "The human understanding when it has once adopted an opinion … draws all things else to support and agree with it. And though there be a greater number and weight of instances to be found on the other side, yet these it either neglects or despises, or else by some distinction sets aside and rejects…. Men … mark the events where they are fulfilled, but where they fail, though this happen much oftener, neglect and pass them by. But with far more subtlety does this mischief insinuate itself into philosophy and the sciences, in which the first conclusion colours and brings into conformity with itself all that comes after."

In the 1960s English psychologist Peter Wason gave this particular bias a name: "confirmation bias." In controlled experiments, he demonstrated that even when people attempt to test theories in an objective way, they tend to seek evidence that confirms their ideas and to ignore anything that contradicts them.

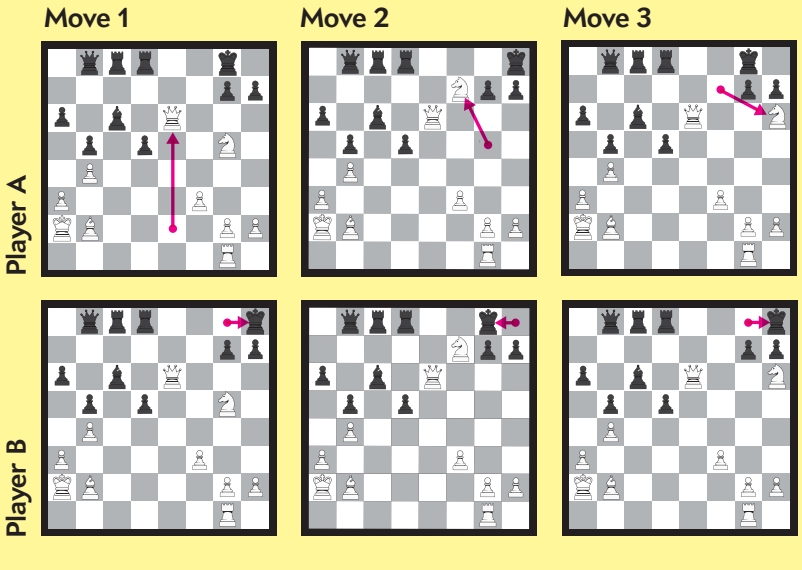
In *The Mismeasure of Man,* for example, Stephen Jay Gould of Harvard University reanalyzed data cited by researchers trying to estimate the relative intelligence of different racial groups, social classes and sexes by measuring the volumes of their skulls or weighing their brains, on the assumption that intelligence was correlated with brain size. Gould uncovered massive data distortion. On discovering that French brains were on average smaller than their German counterparts, French neurologist Paul Broca explained away the discrepancy as a result of the difference in average body size between citizens of the two nations. After all, he could not accept that the French were less intelligent than the Germans. Yet when he found that women's brains were smaller than those in men's noggins, he did not apply the same correction for body size, because he did not have any problem with the idea that women were less intelligent than men.

Somewhat surprisingly, Gould concluded that Broca and others like him were not as reprehensible as we might think. "In most cases discussed in this book we can be fairly certain that biases ... were unknowingly influential and that scientists believed they were pursuing unsullied truth," Gould wrote. In other words, just as we observed in our chess experiments, comfortably familiar ideas blinded Broca and his contemporaries to the errors in their reasoning. Here is the real danger of the *Einstellung* effect. We may believe that we are thinking in an open-minded way, completely unaware that our brain is selectively directing attention away from aspects of our environment that could inspire new thoughts. Any data that do not fit the solution or theory we have already clung to are ignored or discarded.

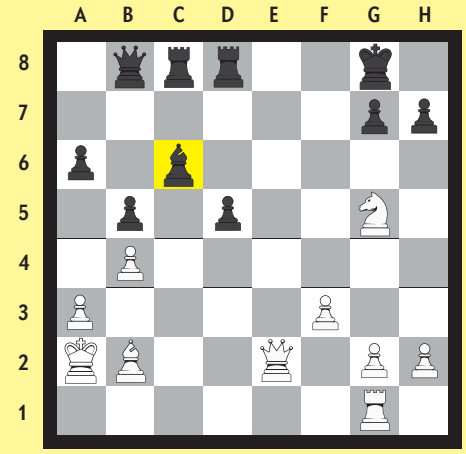
The surreptitious nature of confirmation bias has unfortunate consequences in everyday life, as documented in studies on decision making among doctors and juries. In a review of errors in medical thought, physician Jerome Groopman noted that in most cases of misdiagnosis, "the doctors didn't stumble because of their ignorance of clinical facts; rather, they missed diagnoses because they fell into cognitive traps." When doctors inherit a patient from another doctor, for example, the first clinician's diagnosis can blind the second to important and contradictory details of the patient's health that might change the diagnosis. It is easier to just accept the diagnosis—the "solution"—that is already in front of them than to rethink the entire situation. Simi-

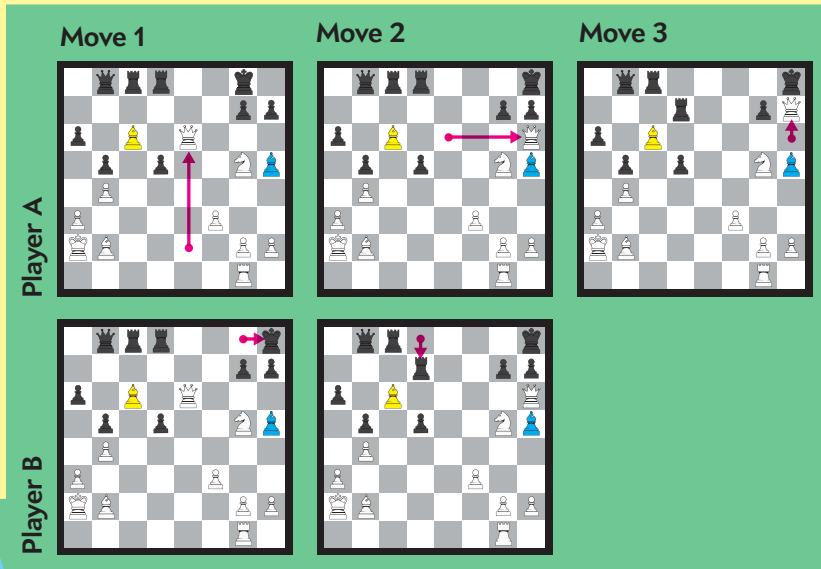
Much More Than Meets the Eye

The intellectually demanding game of chess has proved a wonderful way for psychologists to study the *Einstellung* effect—the brain's tendency to stick with solutions it already knows rather than looking for potentially superior ones. Experiments have shown that this cognitive bias literally changes how even expert chess players see the board in front of them.

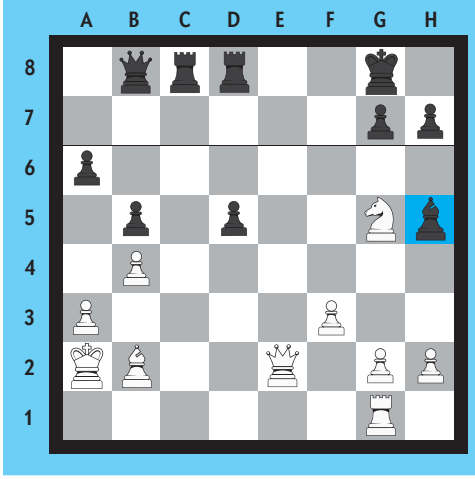


Two-Solution Problem





One-Solution Problem

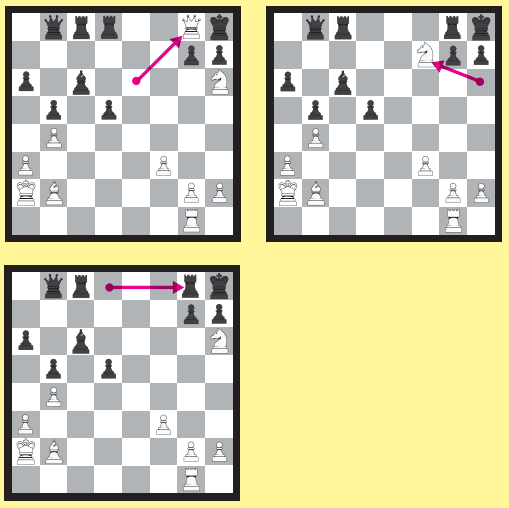


Chess Masters Fail to See the Quickest Path to Victory

In a well-known five-sequence move called smothered mate (*top, yellow*), player A begins by moving his queen from E2 to E6, backing player B's king into a corner. Player A then repeatedly threatens to take B's king with a knight, forcing player B to dodge. As an act of deliberate sacrifice, player A moves his queen adjacent to B's king, allowing player B to take the queen with a rook. To end the game, player A moves his knight to F7, boxing in B's king with no chance of escape. In recent experiments, psychologists presented master chess players with the two-solution board shown above, which could be won using either the smothered mate or a much swifter three-step solution (*middle, green*). The players were told to achieve checkmate as quickly as possible, but once they recognized the smothered mate as a possibility, they became seemingly incapable of noticing the more efficient strategy. When presented with a nearly identical board on which the position of one bishop had shifted (*bottom, blue*), eliminating the smothered mate as an option, the players did recognize the speedier solution, however.

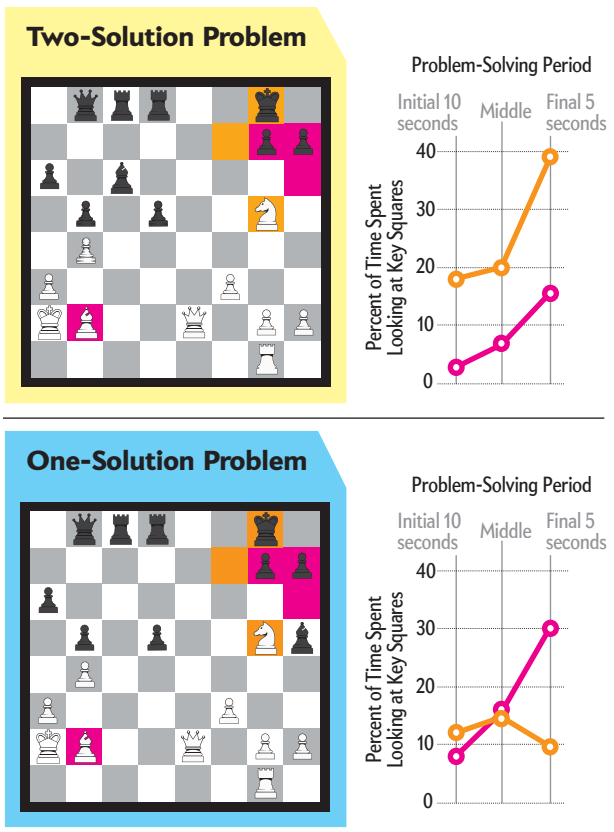
SCIENTIFIC AMERICAN ONLINE See animations of chess moves at ScientificAmerican.com/mar2014/einstellung

Illustration by George Retseck



The Explanation: Tunnel Vision

Eye-tracking devices revealed that as soon as chess players hit on the smothered mate as a solution, they spent far more time looking at squares relevant to that familiar maneuver (*orange*) than at squares pertinent to the more efficient three-step sequence (*magenta*), despite insisting that they were searching for alternatives. Conversely, when the smothered mate was not viable, the players' gaze shifted to regions of the chessboard crucial to the swifter strategy.



larly, radiologists examining chest x-rays often fixate on the first abnormality they find and fail to notice further signs of illness that should be obvious, such as a swelling that could indicate cancer. If those secondary details are presented alone, however, radiologists see them right away.

Related studies have revealed that jurors begin to decide whether someone is innocent or guilty long before all the evidence has been presented. In turn, their initial impressions of the defendant change how they weigh subsequent evidence and even their memory of evidence they saw before. Likewise, if an interviewer finds a candidate to be physically attractive, he or she will automatically perceive that person's intelligence and personality in a more positive light, and vice versa. These biases, too, are driven by the *Einstellung* effect. It is easier to make a decision about someone if one maintains a consistent view of that person rather than sorting through contradictory evidence.

Can we learn to resist the *Einstellung* effect? Perhaps. In our chess experiments and the follow-up experiments by Sheridan and Reingold, some exceptionally skilled experts, such as grand masters, did in fact spot the less obvious optimal solution even when a slower but more familiar sequence of moves was possible. This suggests that the more expertise someone has in their field—whether chess, science or medicine—the more immune they are to cognitive bias.

But no one is completely impervious; even the grand masters failed when we made the situation tricky enough. Actively remembering that you are susceptible to the *Einstellung* effect is another way to counteract it. When considering the evidence on, say, the relative contribution of man-made and naturally occurring greenhouse gases to global temperature, remember that if you already think you know the answer, you will not judge the evidence objectively. Instead you will notice evidence that supports the opinion you already hold, evaluate it as stronger than it really is and find it more memorable than evidence that does not support your view.

We must try and learn to accept our errors if we sincerely want to improve our ideas. English naturalist Charles Darwin came up with a remarkably simple and effective technique to do just this. "I had ... during many years, followed a golden rule, namely, that whenever a published fact, a new observation or thought came across me, which was opposed by my general results, to make a memorandum of it without fail and at once," he wrote. "For I had found by experience that such facts and thoughts were far more apt to escape from memory than favourable ones." SA

MORE TO EXPLORE

Why Good Thoughts Block Better Ones: The Mechanism of the Pernicious *Einstellung* (Set) Effect. Merim Bilalić, Peter McLeod and Fernand Gobet in *Cognition*, Vol. 108, No. 3, pages 652–661; September 2008.

The Mechanism and Boundary Conditions of the Einstellung Effect in Chess: Evidence from Eye Movements. Heather Sheridan and Eyal M. Reingold in *PLOS ONE*, Vol. 8, No. 10, Article No. e75796; October 4, 2013. www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0075796

FROM OUR ARCHIVES

The Expert Mind. Philip E. Ross; August 2006.

The Science of Genius. Dean Keith Simonton; *Scientific American Mind*, November/December 2012.

Caffeinated: How Our Daily Habit Helps, Hurts, and Hooks Us

by Murray Carpenter.
Hudson Street Press, 2014 ($25.95)

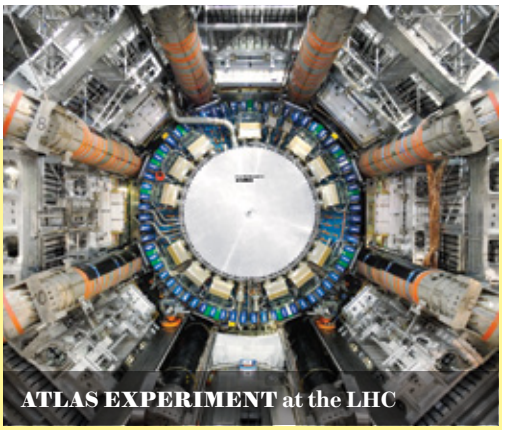
"Let's get personal—this substance courses through my veins as I write these words. It is a drug, and I have been under its influence … for the last 25 years. And I am in good company," writes journalist Carpenter in *Caffeinated*. His book examines the caffeine industry, the coffee and other products it churns out, and the complex effects the chemical has on our bodies. The book is anything but preachy, yet along with acknowledging caffeine's benefits, Carpenter bluntly addresses its dangers, which can include anxiety, panic attacks, disrupted sleep and, if taken in large doses, even death. *Caffeinated* highlights not just the physiological downsides of caffeine but the problems that regulators face in trying to curb what he calls "an industry running wild."

—*Rachel Feltman*

Computing with Quantum Cats: From Colossus to Qubits

by John Gribbin.
Prometheus Books, 2014 ($28.95)

"Within a decade the computer world will be turned upside down" by quantum computers, predicts science journalist Gribbin in *Computing with Quantum Cats*. Today such devices can solve only simple problems and face significant technological challenges. But Gribbin and other proponents of the field see a bright future for machines that are based on the principles of quantum mechanics, particularly the spooky ability of particles to be in multiple states at the same time. These computers should be able to perform calculations many times faster than conventional computers do—if the bugs can be worked out. Gribbin entertainingly illustrates the history of computers, the great minds who have contributed to the field, and what may be in store if quantum computers can fulfill their promise. At the top of the list is cryptography, which stands to be revolutionized if quantum computing can deliver the ability to crack previously unbreakable codes.



COURTESY OF CERN

Particle Fever

by Anthos Media/PF Productions.
Opens March 5 in New York City and March 21 in Washington, D.C.

This documentary, directed by Mark Levinson, accessibly conveys both the science and the human drama behind the largest machine ever built—the Large Hadron Collider (LHC) near Geneva—and its crowning achievement, the discovery of the Higgs boson particle. Viewers feel the physicists' tension and excitement as the first particles circled the LHC's underground tunnels in 2008, along with the researchers' growing anticipation. The ultimate thrill would come four years later, when they saw results confirming that the long-sought Higgs boson had been found.

The Extreme Life of the Sea

by Stephen R. Palumbi and Anthony R. Palumbi.
Princeton University Press, 2014 ($27.95)

From "immortal" jellyfish that age in reverse, to zombie bone worms that eat the skeletons of dead whales, the ocean is full of bizarre characters. Biologist Stephen Palumbi and his science writer son, Anthony, profile the most unusual specimens. Chapters cover the smallest, the oldest, the hottest and the coldest species, among others, and the landscape of strange creatures is brought to life by charming writing. On the sex-switching abilities of the clownfish portrayed in the Disney film *Finding Nemo,* for instance, the authors say, "A real clownfish father who lost his mate would not develop a psychologically complex system of grieving and overprotection. He would simply become Nemo's new mother."

On the Cancer Frontier

by Paul A. Marks and James Sterngold.
PublicAffairs, 2014 ($26.99)

The past 50 years have seen remarkable strides in cancer research and treatment, thanks in part to physician and researcher Marks. Since the 1950s Marks has contributed to the genetic research that has gradually provided a basic understanding of cancer cells. He also pushed to change public perception of the disease, petitioning President Richard M. Nixon to declare a war on cancer. With his co-author, *Wall Street Journal* business reporter Sterngold, Marks recounts his life and work, giving readers insight into cancer treatment's past and glimpses of its future. —*R.F.*

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PROMOTION

The Agenda Setters

Bringing Science to Life

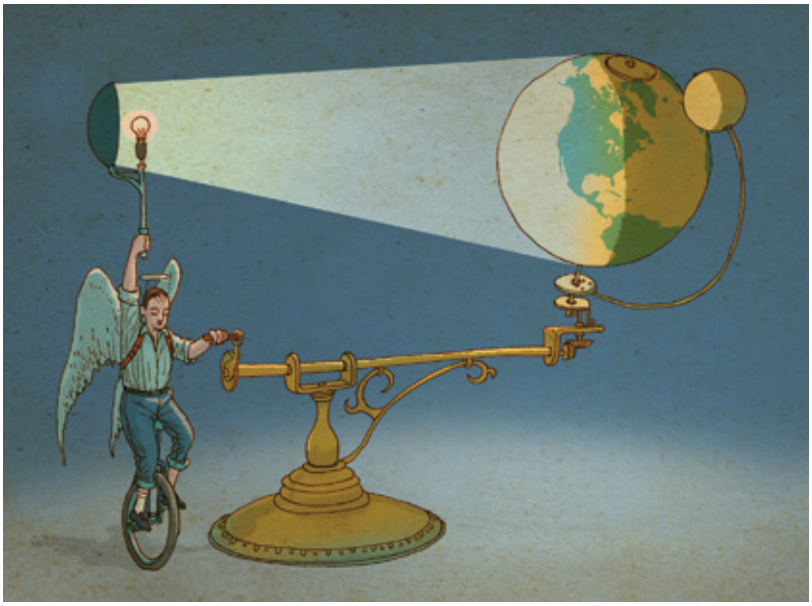
2013 Strategic Foresight Forum

Atlantic Council Headquarters | Washington, DC | December 9-10, 2013

Under the title *Harnessing Disruption*, the 2013 Strategic Foresight Forum convened global thinkers, technologists, corporate leaders, and media to discuss the effects of technological disruption and innovation on the future of politics, the economy, and society. More than 200 participants and speakers tried to find policy and technological solutions to the upcoming food-water-energy crisis; discussed the risks and opportunities emerging from the bio-ICT convergence; assessed the impacts of the third industrial revolution on global unemployment, inequality, and prosperity; and exchanged ideas about the role mega-cities will play in the governance of the international system.

Key speakers included **Brent Scowcroft**, Atlantic Council International Advisory Board Chairman, **Marco Annunziata**, GE Chief Economist, **Andrew McAfee**, MIT Center for Digital Business Principal Research Scientist, **David Tennenhouse**, Microsoft Corporate VP, **Frederick Kempe**, Atlantic Council President & CEO, **Anne-Marie Slaughter**, New America Foundation President & CEO, **Rajiv Shah**, US Agency for International Development Administrator and **Dina Fine Maron**, SCIENTIFIC AMERICAN Associate Editor.

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



The Awe Delusion

What does the magnificence of the universe have to do with God?

After 64-year-old Diana Nyad completed her 110-mile swim from Cuba to Florida in September 2013, she was interviewed by Oprah Winfrey on her *Super Soul Sunday* show in what was to be a motivational reflection on the triumph of will over age. When Nyad announced, "I'm an atheist," Oprah responded quizzically: "But you're in the awe." Puzzled, Nyad responded: "I don't understand why anybody would find a contradiction in that. I can stand at the beach's edge with the most devout Christian, Jew, Buddhist—go on down the line—and weep with the beauty of this universe and be moved by all of humanity. All the billions of people who have lived before us, who have loved and hurt and suffered. So to me, my definition of God is humanity and is the love of humanity." What Oprah said next inflamed atheists: "Well, I don't call you an atheist then. I think if you believe in the awe and the wonder and the mystery, then that is what God is."

This is the soft bigotry of those who cannot conceive of how someone can be in awe without believing in supernatural sources of wonder. Why would anyone think that?

A partial answer may be found in a 2013 study by psychologists Piercarlo Valdesolo of Claremont McKenna College and Jesse Graham of the University of Southern California, published in the journal *Psychological Science*. Research had shown that "awe" is associated with "perceived vastness" (like the night sky or an open ocean) and that "awe-prone" individuals tend to be more comfortable with uncertainty and are less likely to need cognitive closure in some kind of explanation. They "are more comfortable revising existing mental schemas to assimilate novel information," the authors said in their paper. For those who are not awe-prone, Valdesolo wrote in an e-mail, "we hypothesized that the uncertainty experienced by the immediate feeling of the emotion would be aversive (since they are probably not the kinds of people who feel it all the time). This was rooted in theoretical work which argued that awe is elicited when we have trouble making sense of the event we are witnessing, and this failure to assimilate information into existing mental structures should lead to negative states like confusion and disorientation." To reduce the anxiety of awe-inspiring experiences, people who are not prone to awe engage in a process I call "agenticity," or the tendency to believe that the world is controlled by invisible intentional agents.

To test this hypothesis, Valdesolo and Graham divided subjects into three groups. One group saw a video clip of an awe-inspiring scene from the BBC's *Planet Earth,* another watched an emotionally neutral news interview by the late *60 Minutes* correspondent Mike Wallace, and the last group viewed a comedy clip from the BBC's *Walk on the Wild Side*. Subjects then took a survey that measured their belief in God, belief "that the universe is controlled by God or supernatural forces, such as karma," and their feeling of "awe" while watching the video clip. Subjects who saw the *Planet Earth* video experienced the most awe and, while in this state, greater belief in both God and supernatural control. The researchers concluded: "The present results suggest that in the moment of awe, some of the fear and trembling can be mitigated by perceiving an author's hand in the experience."

What are the larger implications of these findings? "We showed that feeling the emotion (which even low awe-prone people are capable of) elicits uncertainty and a subsequent desire to resolve that feeling by explaining events in terms of purpose-driven causal agents," Valdesolo explained. "One interesting hypothesis might be that the dispositionally awe-prone are *less* likely to show our effect since the uncertainty that they feel is not aversive."

This brings me back to Diana Nyad and those of us who find our spirituality in the awe of the natural world without a need for supernatural agenticity. Instead of fear and trembling, we feel wonder and gratitude in discovering that the author's hand is nature's laws and nothing more, but also nothing less. SA

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Illustration by Izhar Cohen

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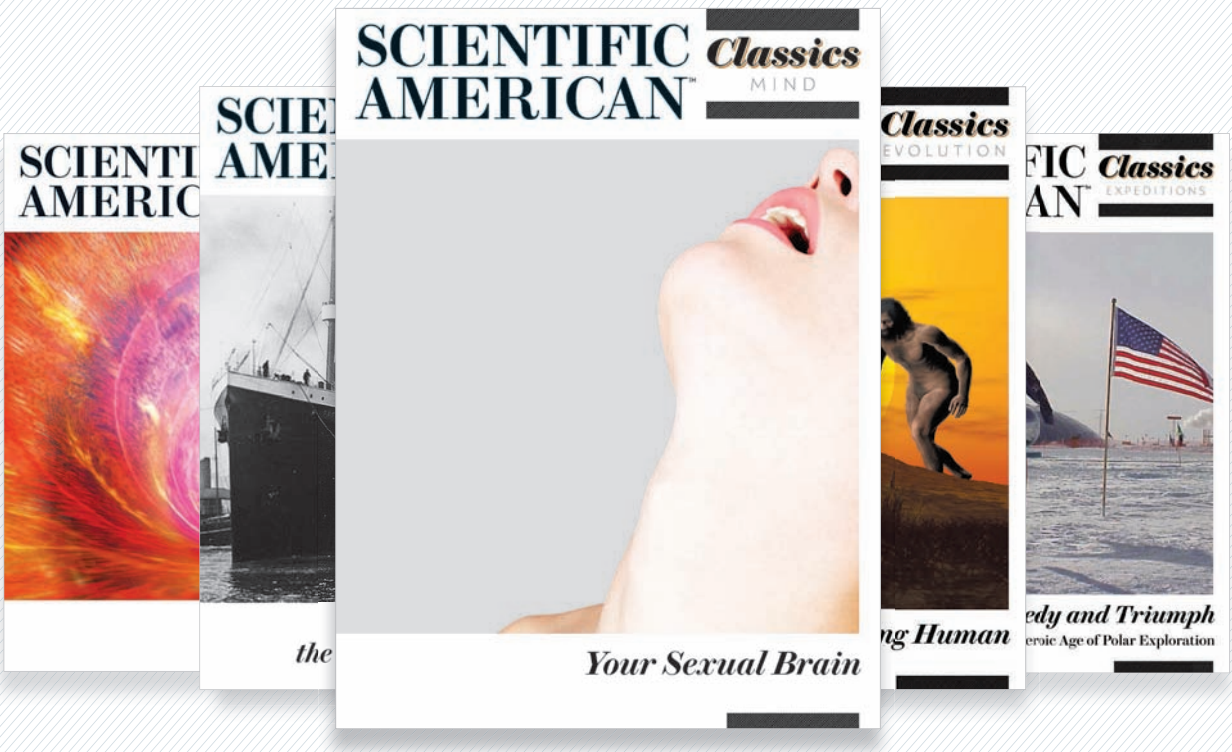

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The ongoing search for fundamental farces

Steve Mirsky has been writing the Anti Gravity column for as long as the age of the third oldest of the "classic range" Glenlivet single malts. He also hosts the *Scientific American* podcast Science Talk.

007 and 7

Fiction's most famous spy seems to have had a major substance abuse problem

Bombed. James Bombed.

That slight revision to Secret Agent 007's famous self-introduction may be in order. A study of James Bond's personal habits, as described in the original series of books by Ian Fleming, finds that Bond drank a lot—way more than is safe. He had a license to kill the entire bottle.

In fact, Bond imbibed so much alcohol that he would be at high risk for "malignancies, depression, hypertension, and cirrhosis," according to the report in the *BMJ,* preabbreviatedly known as the *British Medical Journal*. The Liver and Let Die analysis appeared in the *BMJ*'s infamous Christmas issue, which annually includes the kind of tongue-in-cheek studies that are best conceived after a few drinks.

English emergency physician Graham Johnson of Derby and pediatrician Patrick Davies of Nottingham divvied up the 14 Flemings to perform their study. Nottingham hepatologist Indra Neil Guha was brought in for liver expertise. They sought no funding for the work because "the original books were already owned by two of the study authors." They describe the setting, ordinarily a lab or research medical center, as "the study authors' homes, in a comfy chair." (I'm guessing each home had its own comfy chair, rather than the one chair being shuttled between the domiciles.) They also note that they sought no consent from the study participant, "the barrier to this chiefly being his fictional nature meaning he is unable to give valid consent."

Johnson and Davies's alcohol assay calculated that Bond drank more than four times the recommended maximum for adult beverages. He sucked down an average of some 92 units per week (a unit being 10 milliliters or eight grams of pure ethanol). That average doesn't include days during which he was absolutely incapable of acquiring alcohol—for example, while hospitalized. He also could not drink when incarcerated while some fiend created a Rube Goldberg device to kill him instead of taking the expedient and effective blammo route.

Such drinking habits make accidents a major extra risk. For example, the researchers count that during one dinner with his nemesis Auric Goldfinger, Bond had 18 drinks before somehow driving himself safely home. "Despite his alcohol consumption," the study authors write, "he is still described as being able to carry out highly complicated tasks and function at an extraordinarily high level. This is likely ... pure fiction."

Speaking of complicated tasks performed at a high level, the research team wondered whether, after years of Bond's chronic alcohol abuse, "he would realistically have the capacity to perform (in all aspects of his life)." To make clear their meaning, the authors then referred to a 1987 paper entitled "Sexual Dysfunction in Male Alcohol Addicts: Prevalence and Treatment," published in *Archives of Sexual Behavior*. It seems that most of Bond's alleged conquests may have turned into mere cuddles: the books should have been called *The Spy Who Almost Loved Me, From Russia with Love but the Tennis Kind,* and, of course, *Dr. Oh No*.

(Despite such ample evidence that Bond might have had erectile dysfunction, his randy reputation inspired a 1999 *Saturday Night Live* sketch in which he received a doctor's diagnosis of 107 concurrent sexually transmitted diseases, of which only 53 had been previously identified.)

One clue left by Fleming that Bond had indeed done irrevocable damage to himself through alcohol overindulgence is his famous vodka martini instruction: "shaken, not stirred." The *BMJ* study authors note that "ideally vodka martinis should be stirred, not shaken. That Bond would make such an elementary mistake in his preferences seemed incongruous with his otherwise impeccable mastery of culinary etiquette."

The researchers thus theorize that Bond suffered from alcohol-induced tremor, aka the shakes—if he prepared his own martini, he was unable to stir it without also shaking it. Thus, to hide his infirmity, which could obviously jeopardize his career within Her Majesty's Secret Service, he resorted to making and ordering all his martinis shaken. So that M's faith in him would not be. SA

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Illustration by Matt Collins

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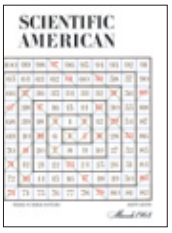
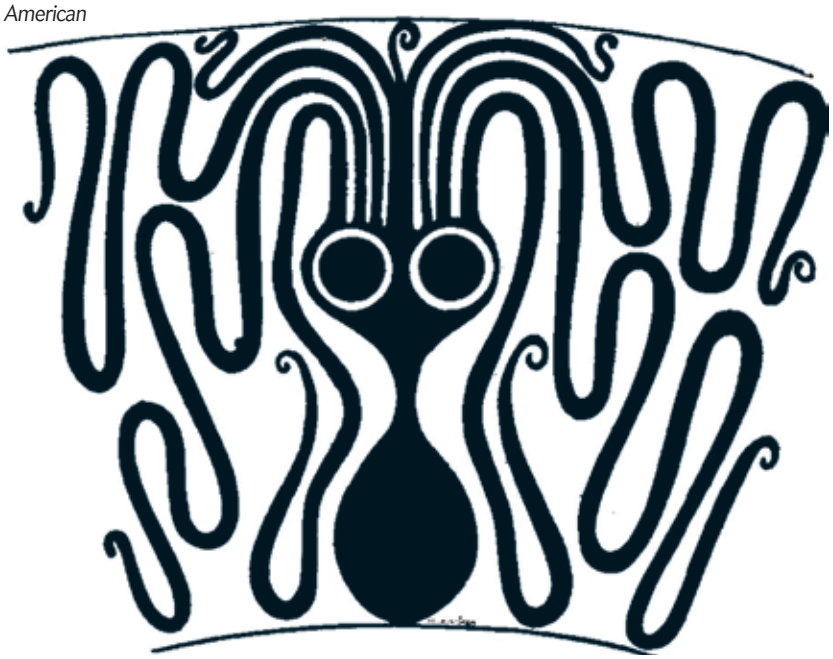


March 1964

Vision Biology

"Students of the visual system came to assume that the retina was like a photographic film, that the whole function of the eye and the optic nerve was to form and then transmit a mosaic of the visual world to the brain, there to form the basis of visual perception. Anatomical investigations have shown, however, that there are many more receptor cells in the retina than there are fibers in the optic nerve. It is thus impossible for every receptor cell to send a separate message to the brain, and the concept that the array of receptor cells is equivalent to the grain of a photographic emulsion must be abandoned."



NATURE IN ART: In 1911 artist Jean Alexis Morin copied paintings on ancient ceramics in the Louvre. In a 1914 article *Scientific American* reproduced his interpretation of the "horrid tentacles" of a cuttlefish, from a Mycenaean drinking vessel made before 1000 B.C.

Through a Darkling Glass

"A reversible photochromic glass has been invented by S. Donald Stookey and William H. Armistead of the Corning Glass Works. Silver halide crystals are precipitated in silicate glass during a cooling and reheating cycle. The particles are much smaller than those in a photographic emulsion; there are some eight million billion of them in a cubic centimeter of the glass. On exposure to light, the crystals change to metallic silver in a matter of seconds and darken—and so does the glass. When the light is reduced or extinguished, the silver halide is reconstituted and the glass clears in a few minutes or hours."

March 1914

Flea Display

"The American Museum of Natural History is fortunate in having secured in Mr. Ignaz Matausch one of these very few and highly exceptional scientific artists to prepare its models. His latest creation is a flea magnified in wax 1,728,000 times the size of the insect in bulk. Although the model excites admiration because of the skillful manner in which it was prepared, it tells nothing of the painstaking preliminary studies which were necessary. Strange as it may seem, no picture has ever been made of the living flea. The insect as it is pictured in text books is a dead insect. To the uninformed it seems a very trivial matter whether a flea is magnified in wax alive or dead. The entomologist knows better."

A New Look at Ancient Art

"M. Morin-Jean [a pseudonym for Jean Alexis Morin], the author of *Le Dessin des Animaux en Grèce,* wields the brush and the pen with equal facility. The French critic's three hundred drawings, one of which is shown in our illustration, acquaint his readers with images culled from painted, engraved and molded Greek, Italiote and Etruscan vases, from the geometric decorations of 800 B.C. and onwards to the decline of the art in southern Italy about 300 B.C."

Thoughts of War

"Let us suppose that two years from now Great Britain, estranged by our breach of faith (in the event it should not be rectified) on the canal tolls question, agreed to maintain an attitude of neutrality, while Germany, by the purchase of a base in the West Indies, challenged our Monroe Doctrine in its relation to the security of the Panama Canal. Let us suppose that, released from anxieties at home, Germany dispatched her whole first line of twenty-six dreadnoughts to the Caribbean. Where should we stand? Against her twenty-six dreadnoughts [battleships] we could oppose twelve."

Such equations would become vitally important when World War I broke out four months later.

March 1864

Patent Dishwashing Machine

"We long ago asserted that the tendency of invention was to lessen the labor of mankind, and predicted that, before a great while, the inventor would invade the precincts of the kitchen. The action has already commenced; we publish herewith what may be called 'a family machine,' for it is designed to wash dishes, clean lamp-chimneys, and scour and sharpen knives, not at one and the same time, however, but by several operations. This machine will have charms for our lady readers, who, we are happy to know, are zealous in the cause of science and 'up' to all the newest improvements (we have several patents now pending by lady inventors)."

SCIENTIFIC AMERICAN SUPPLEMENT, VOL. LXXVII, NO. 1992, MARCH 7, 1914

SCIENTIFIC AMERICAN ONLINE Giant wax flea and more natural history from 1914: ScientificAmerican.com/mar2014/natural-history

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Physician, NASA Astronaut and Venture Capitalist

ALFREDO QUIÑONES-HINOJOSA, M.D.
Immigrant Worker Turned Neurosurgeon and Researcher

J. CRAIG VENTER, PH.D.
Bored Science Student turned Genomics Pioneer, Biologist, and Entrepreneur

FOUNDING & PRESENTING HOST: LOCKHEED MARTIN

AMERICIUM: Northrop Grumman Foundation, Mythbusters, CAT, Chevron Human Energy, Scientific American, Popular Science

NOBELIUM: U.S. Air Force, NewScientist, MedImmune, AAAS, Science Buddies, STEMconnector

BOCKIUM: Larry and Diane Bock

K&L GATESIUM: K&L Gates

EINSTEINIUM: Radio Disney, NSTA, NIH, DC, Kavli Foundation, ResMed Foundation, NASA, Dow, ACS, Universal Technical Institute, MIT Technology Review, Francis Goelet Charitable Lead Trusts, 3M, amazon web services, infoComm 75, Engineering.com, Planetary, Sigma Xi, American Scientist, Farrell Family Foundation

KRYPTON: Agilent Technologies, PBS Kids, Forbes/Wolfe, CrazyEngineers.com, The KidWind Project, Physics Today, U.S. News STEM Solutions, Illumina, Inc., Washington FAMILY Magazine, American Architectural Foundation, National Additive Manufacturing Innovation Institute (NAMII), Microsoft, American Farm Bureau Federation, IEEE-USA, WAMU 88.5 - American University Radio, SEGA

PLATINUM: Center for Biotechnology Education at Johns Hopkins University, CERVIS Technologies, U.S. Environmental Protection Agency, National Institute of Standards and Technology (NIST), SpaceX, Department of Defense, Northern Virginia Technology Council, Xconomy, Children's National Medical Center, FEI, Purdue University, Genentech, Celestron, Federation of American Societies for Experimental Biology, SCOPE, U.S. Department of State, The Scripps Foundation for Science and the Environment, TeenLife Media, Koch Industries, Inc., Georgetown University, ThinkGeek

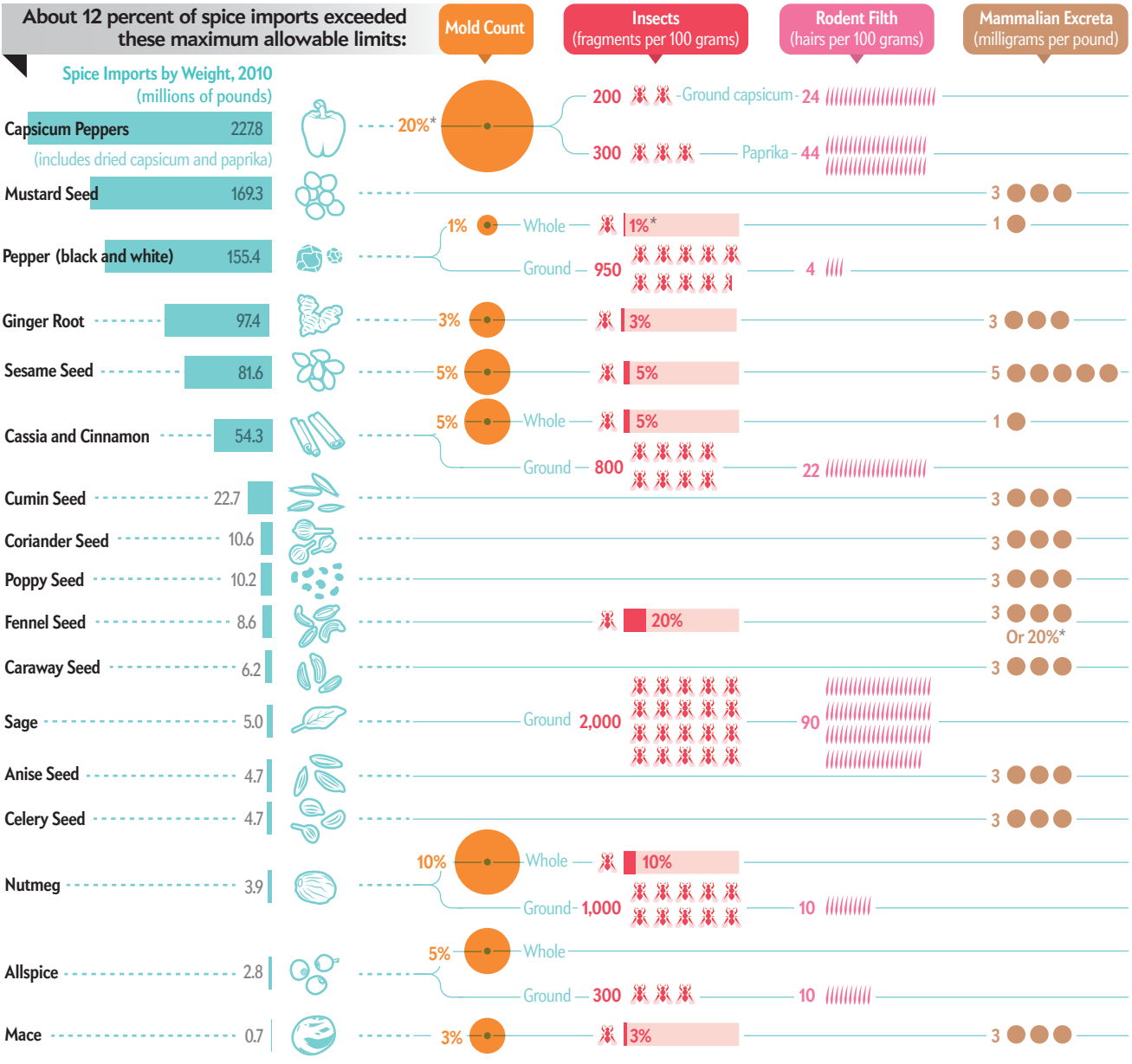
Filth in the Spice Rack

Imported seasonings are rife with all sorts of extras

Some spices contain ingredients you won't find in any recipes. The Food and Drug Administration recently found that spices entering the U.S. are nearly twice as likely as the average FDA-regulated foodstuff to contain *Salmonella* pathogens or unacceptable amounts of filth. Roughly 12 percent of spice imports, which make up the bulk of the U.S. supply, exceeded federal limits on the "maximum levels of natural or unavoidable defects," such as insect body parts and animal hair. In sufficiently small amounts, the FDA reasons, such defects "pose no inherent hazard to health."

Those limits might seem rather loose—a small, two-ounce jar of paprika must contain roughly 170 insect fragments or 25 rodent hairs to be considered adulterated. But whereas the odd instance of egregious filth involves objects large enough to be spotted by consumers, many contaminants are merely microscopic fragments, according to the FDA. —*John Matson*

SCIENTIFIC AMERICAN ONLINE
Delve into the science of food at ScientificAmerican.com/mar2014/graphic-science



SOURCES: "DEFECT LEVELS HANDBOOK," U.S. FOOD AND DRUG ADMINISTRATION *http://1.usa.gov/1BmGxP5 (threshold values)*; *DRAFT RISK PROFILE: PATHOGENS AND FILTH IN SPICES*: U.S. FOOD AND DRUG ADMINISTRATION, 2013 *(import values)*

Graphic by Section Design

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