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MEDICINE
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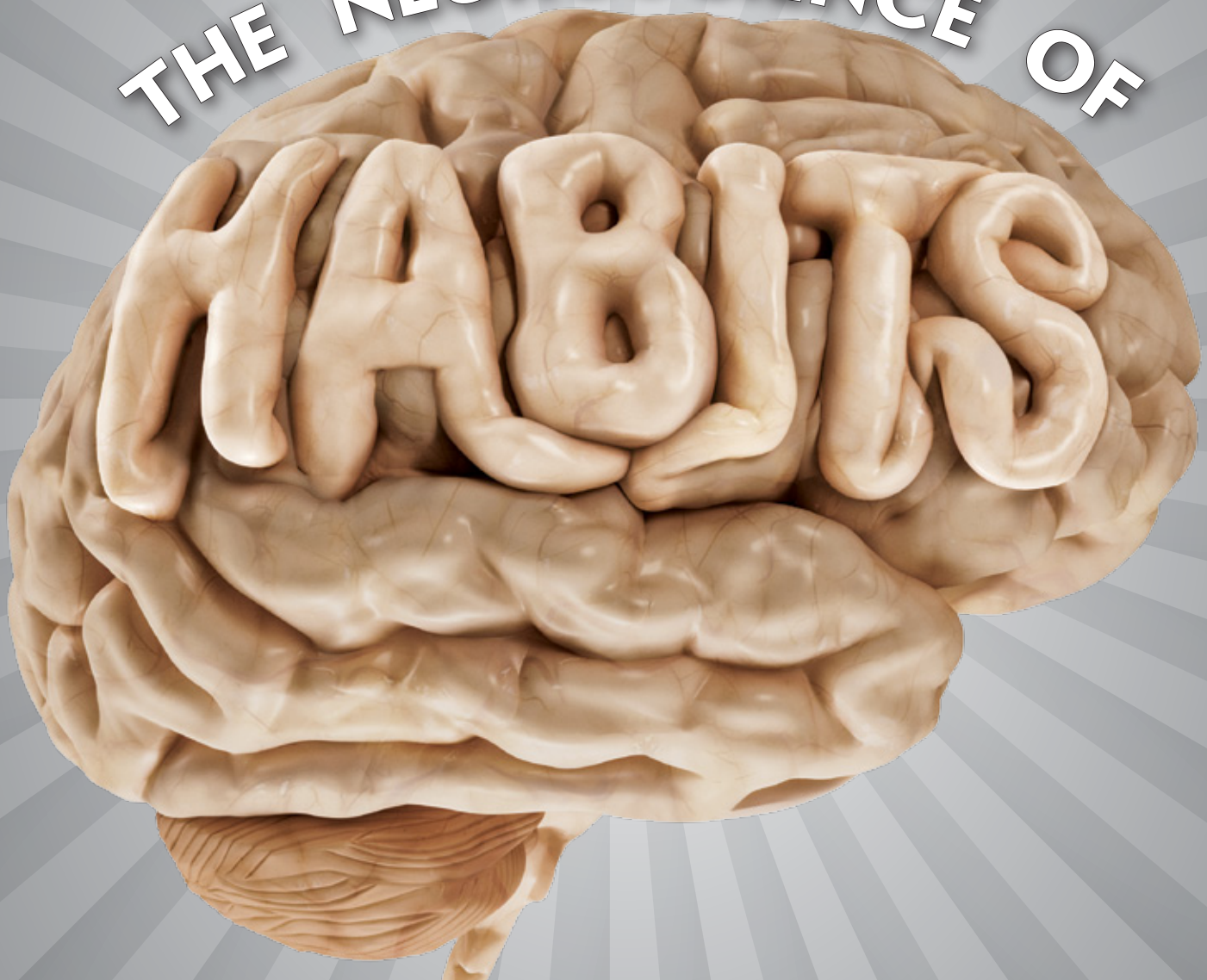
JUNE 2014

THE NEUROSCIENCE OF HABITS



How they form and why they are so hard to change

Being a new mom means getting lots of advice. What I need is information I can trust.

▶ SIMPLICITY When you're having a baby, everyone has opinions to share. But what you really need is reliable information about how to take care of yourself and your baby. That's where UnitedHealthcare comes in. We have a simple program that helps moms stay on track with their doctors and get the right care and guidance—before and after the baby is born.

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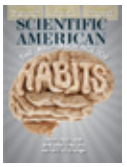
ON THE COVER



Forming good habits and breaking bad ones can be difficult. Why? New experiments by neuroscientists are revealing for the first time how specific brain regions work to lock in or let go of habits. The insights could lead to simple tricks, novel behavioral therapies or drugs that could help make us more likely to eat our veggies and less likely to bite our nails. Illustration by FOREAL.

SCIENTIFIC AMERICAN

June 2014 Volume 310, Number 6

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FEATURES

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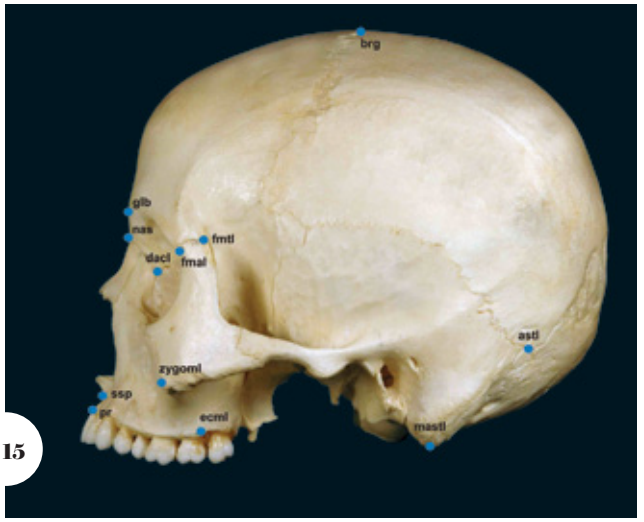

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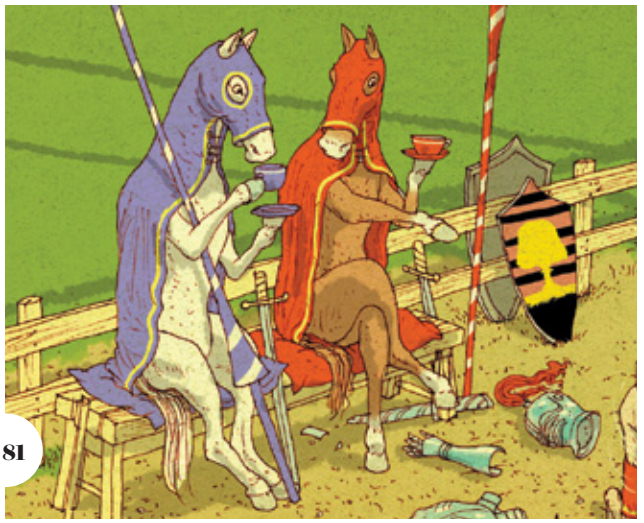

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SCIENTIFIC AMERICAN

DEPARTMENTS

ON THE WEB

The Beginning of World War I

The 1914 assassination of Archduke Franz Ferdinand helped to trigger the First World War. To mark the 100th anniversary in June, SCIENTIFIC AMERICAN is collecting 1,200 contemporary articles on the topic to show how the war shaped political, cultural and technological futures around the world.
Go to www.ScientificAmerican.com/jun2014/wwi

COURTESY OF ANN ROSS *North Carolina State University (skull)*

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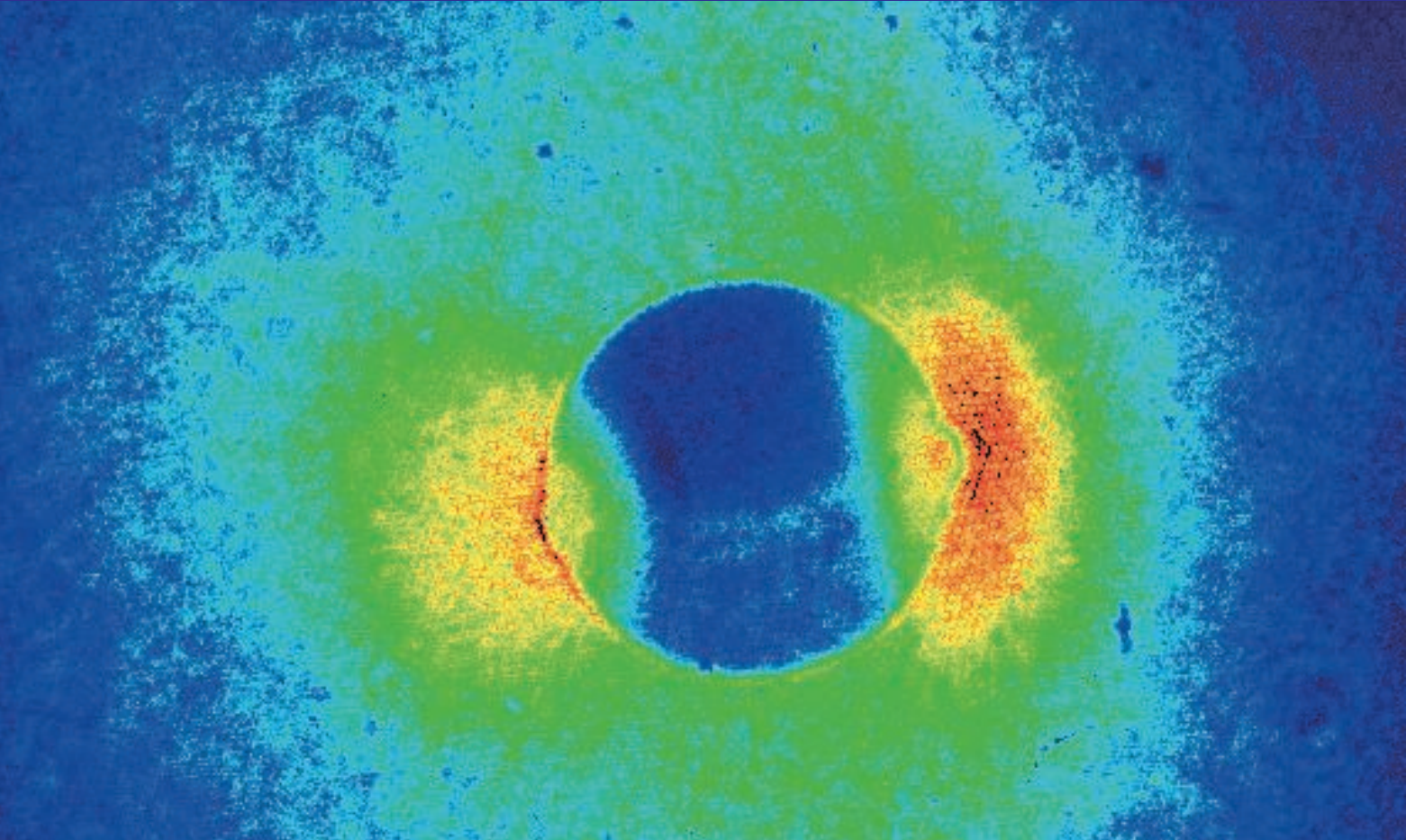

Photonics enables clean power and unlimited energy.

Harnessing the energy of the sun on earth will give us access to an unlimited source of clean power. To generate power using nuclear fusion energy, continuously fired fuel pellets can be ignited and burned using a high-power laser. Hamamatsu Photonics worked collaboratively with the Graduate School for the Creation of New Photonics Industries and with Toyota Motor Corporation to create the world's first technology that uses the fusion reaction of heavy hydrogen to generate a continuous stream of neutrons, by simultaneously irradiating flying pellets with two laser beams from two opposing directions. This achievement is significantly impacting humankind in our efforts to realize nuclear fusion generation early in the 21st century.

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

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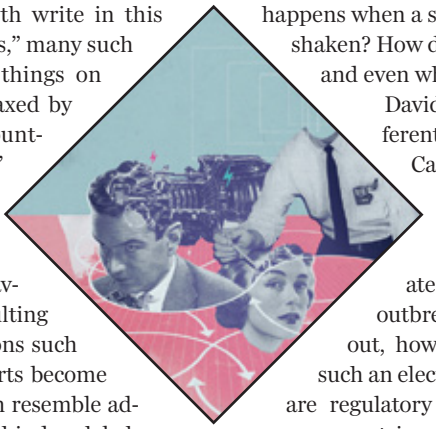
Mariette DiChristina is editor in chief of *Scientific American*. Follow her on Twitter @mdichristina

Creatures of Habit

ALTHOUGH WE HUMANS ARE CAPABLE OF CREATING amazing new innovations, most of our daily lives are shaped instead by routines. We get up, brush our teeth, dress, have that first cup of coffee, make the commute to work—and on, day after day. As Ann M. Graybiel and Kyle S. Smith write in this issue's cover story, "Good Habits, Bad Habits," many such activities "simply allow us to do certain things on autopilot so that our brains are not overtaxed by concentrating on each brushstroke and countless tiny adjustments of the steering wheel."



Some customs—taking a daily walk, for instance—are healthful. Others—having dessert after every meal—are not. Worse, the authors write, "The more routine a behavior becomes, the less we are aware of it," resulting in an insidious undercutting of our intentions such as happens when, say, those frequent desserts become extra pounds. In some ways, habits can even resemble addictions. What are the neural mechanisms behind such behavior, and why are these ingrained tendencies so hard to break? Recent work reveals the specific brain regions and connections necessary for forming habits. A better understanding of those circuits, researchers hope, will help us in learning how to amend them when needed. Turn to page 38.

With many research papers pointing out how often we are influenced, marionettelike, by automated processes like habits, many neuroscientists and philosophers argue that the conscious control we believe we have may be more illusion than reality. Azim F. Shariff and Kathleen D. Vohs probe that notion in their essay, "The World without Free Will," starting on page 76. What happens when a society's belief in the existence of free will is shaken? How do we then judge responsibility for crimes—and even whether they ought to be punished?

David J. Ecker discusses dealing with a very different kind of perpetrator in his article, "Germ Catcher," beginning on page 50. New biosensors are being developed that can identify viral, bacterial or fungal sources of infection. Connecting such sensors would create a dynamic network, enabling us to counter outbreaks effectively across the globe. As it turns out, however, the largest challenges to producing such an electronic shield are not technical. Instead they are regulatory and societal—requiring us to cooperate across countries without centralized health care systems. And, as we might be tempted to add at this point, to get past our current habits and routines.

As is the case so many times, a better understanding of ourselves and how we think, which we gain through the evidence-based process known as science, can help us create a more prosperous future. SA

Illustration by Marek Haiduk (mind circuits), Illustration by Nick Higgins (DiChristina)

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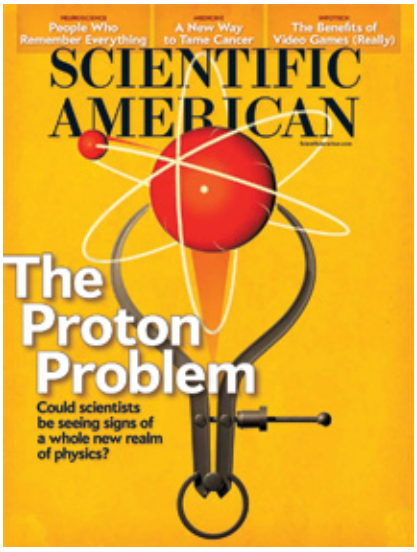

February 2014

PERCEPTIVE POULTRY

In "Brainy Bird," Carolynn "K-lynn" L. Smith and Sarah L. Zielinski discuss evidence that chickens are more intelligent than has been supposed.

Yet the complex behaviors that the authors present as evidence do not support the claim that chickens have advanced cognitive skills. They could just as easily be explained by the blind guidance of genes. For example, the absence of evidence for individual variation in the described chicken actions makes a stronger case for species-specific behavior through natural selection than for mammalian-level cognition.

But each species does deserve its own level of ethical treatment consistent with its cognitive abilities. There is no question that keeping animals cooped up is bad because it induces stress.

James Luce
Peralada, Spain

I would be curious to know if commercial broilers and egg layers would perform as well as the birds used in Smith's behavioral studies. Modern broilers appear to have significantly smaller normalized brain masses than lines that have not undergone such strong selection for meat production.

Carl J. Schmidt
Department of Animal and Food Sciences
University of Delaware

"Each species deserves its own level of ethical treatment consistent with its cognitive abilities."

JAMES LUCE *PERALADA, SPAIN*

Smith and Zielinski claim that the genetics of birds raised for their meat somehow naturally shortens their life span because if they were allowed to continue to live, they would develop a host of age-related diseases. This is false. If Cornish game hens are allowed to grow to maturity, they become healthy, huge chickens.

Russell R. Burton
San Antonio, Tex.

THE AUTHORS REPLY: In response to Luce: Whereas genetic programming or innate responses can explain some animal behaviors, the extent of individual flexibility exhibited by fowl in their calling to raise an alarm or indicate food refutes them. With alarm calls, for example, the behavior changes in response to moment-to-moment variation in the bird's context and audience—who is present, their relationship to the bird, the caller's safety, the individual's status within the group. All these things require mental architecture to take into consideration the aspects of the specific event and to select the appropriate action. An innate response is unlikely to be so versatile. We do, however, agree that higher cognitive function is not a requirement for an animal to deserve compassionate treatment.

Schmidt is absolutely correct about the reduction in brain mass in broilers. Layer hens appear to exhibit many of the same behaviors observed in the chicken strains used in the studies cited in the article. This question remains to be tested, however.

Burton is right about the life spans of Cornish game hens. That strain is, however, much smaller than other kinds of meat chicken, which do suffer major health-related issues as they grow.

PROTON SIZE

In "The Proton Radius Problem," Jan C. Bernauer and Randolf Pohl state that they have found wildly different values for the proton radius from two different experiments.

Is it possible that the measurements are different because the proton is not perfectly spherical? Perhaps the experiments might have exposed this.

Bob Drwal
South Barrington, Ill.

Could the close interaction of a muon passing the proton in muonic hydrogen cause a tidal wave at the surface of the proton, changing the form of the proton locally so that a lesser radius is measured?

Dirk Kronemeijer
Havixbeck, Germany

Is it possible that the central density of the muon wave function in muonic hydrogen is high enough to probe the quark structure of the proton?

Stanley Friesen
Frederick, Md.

To say that a proton has a clear-cut radius implies that it has a well-defined edge. But clearly, particles are not solid things with discrete edges.

Ed Miller
Oberlin, Ohio

THE AUTHORS REPLY: To first address Drwal's question: The proton does not have to possess spherical symmetry but could be, for example, a "prolate," a spheroid in which the polar axis is greater than the equatorial one. Both experiments average over all orientations, however, so the proton-charge radius measured in both is not affected by proton deformation.

The muon indeed changes the shape of the proton, as Kronemeijer suggests. This so-called proton polarizability expresses how easy it is to deform the proton. The radius result is corrected for such an effect. The effect's absolute size is still debated, but it seems unlikely that it can explain the discrepancy in our measurements.

Regarding Friesen's query: The muon wave function averages over the entire proton. Even in the scattering experiment, the momentum transfers are so small, and hence the wavelength so large, that one cannot resolve individual quarks.

Miller is correct. The proton is more of a

fuzzy ball, with an approximately exponentially decaying charge density. The quantity that is measured in both experiments is the square root of the average of the radius squared, weighted by the charge density. This definition is mathematically well defined and useful in theory. In practice, about two thirds of the proton's charge is contained in that radius.

FEATHERED FEEDING

"Living Claw to Mouth," by Jason G. Goldman [Advances], reports that a British study found that songbirds scout for food in the morning but do not eat it until the afternoon. American birds must have developed different eating habits than European ones. When we put out food on our deck just before dawn, it is gone within 10 minutes. Then it sits until almost the next dawn.

HERB STEIN
Washingtonville, N.Y.

GOLDMAN REPLIES: Most backyards are limited to a single feeder or perhaps a few feeders at a single location. But the study in question instead involved a large array of 101 feeders spaced widely apart across an entire forest, which provides a much more complete picture of bird behavior.

In addition, one of the most important aspects of the study was that it focused on a population of birds relatively free from human interference. Garden songbirds are able to rapidly adapt to changes in their environment caused by humans. If homeowners are providing food every day, then those birds can use a different foraging strategy than they would in a habitat where food sources are less predictable.

SUPERIOR METRICS

You should be ashamed to publish the "Politics of the Metric System," an excerpt of an 1864 article on then British resistance to the system, in the 50, 100 & 150 Years Ago column, compiled by Daniel C. Schlenoff.

More than two centuries after France introduced the system in 1799, almost the whole world uses it exclusively. That is, except for the U.S., Liberia and Myanmar (Burma)—and *Scientific American* itself!

HERZEL LAOR
Boulder, Colo.

LETTERS TO THE EDITOR

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Full Disclosure

Drug companies have begun to share their clinical trial data. The long-overdue shift heralds a new era in medicine

How well does a prescription drug work? It can be hard for even doctors to know. Pharmaceutical companies frequently withhold the results of negative or inconclusive trials. Without a full accounting, a physician who wants to counsel a patient about whether a drug works better than a sugar pill is frequently at a loss. Drug companies share only airbrushed versions of data on safety and usefulness.

As a consequence, regulators can approve drugs that have hidden health hazards. Clinical trials of GlaxoSmithKline's diabetes drug Avandia (rosiglitazone) and Merck's anti-inflammatory Vioxx (celecoxib) revealed an elevated cardiac risk from the drugs, but relevant findings were held back from regulators or never published. Far more drugs have gone to market with critical safety data kept secret. These scandals have tarnished the reputation of the pharmaceutical industry.

Such revelations have made the industry come to realize that greater transparency is inevitable. "The question is not *whether* but *how* these data should be broadly shared," noted an article in the *New England Journal of Medicine* last fall. The article had a co-author from the leading U.S. drug industry trade group.

Yet the challenge of how to share the data is not simple. A few manufacturers, including GlaxoSmithKline, Roche and Pfizer, have set up Web portals to open their files to outsiders with few, if any, restraints on access. Other companies worry that opening their doors too wide will compromise trade secrets, as well as the confidentiality of patient records.

Europe has recently taken the lead in adopting measures to ensure openness of data collected throughout drug trials. In early April the European Parliament voted to require that clinical trial results be published within a year of completion, whether or not the data are positive—a regulation that mirrors a similar effort being developed by the European Medicines Agency, an organization roughly equivalent to the U.S. Food and Drug Administration. (Physician and transparency advocate Ben Goldacre has pointed out that the vote is only a first step because it does not make public the data for already approved drugs.)

The FDA, meanwhile, has followed these proceedings intently as it contemplates requiring new levels of openness from pharmaceutical companies. As the agency deliberates, it should consider that the companies' poor track record is mirrored by its own. Since 2007 the FDA has required drugmakers to post some trial results in the government registry (ClinicalTrials.gov) within a year of a drug's approval, but the agency has failed to enforce this edict. A 2012 study showed that fewer than one in four approved drugs had results that were filed in time.

Fortunately, there are other ways to ensure that drug data get shared. The FDA should carefully consider a collaboration with the kind of independent institution that is already up and running at Yale University. In 2011 Yale's Open Data Access (YODA) Project reached an agreement with medical device maker Medtronic to act as an intermediary for releasing all data on clinical trials of a controversial bone-growth protein whose safety had been questioned. In an effort to defend its reputation, the company gave up any right to decide who would get the information. YODA then commissioned two systematic reviews of the protein, which conveyed mixed results that were then published. Following Medtronic's example, Johnson & Johnson pledged in January to make all its clinical trial data available for perusal by outsiders through YODA. Such early signs of successes might serve as the basis for devising a national system that replicates a YODA-like model for all U.S. drug trials, perhaps backed up by FDA-enforced penalties for companies that refuse to comply.

The benefits of this approach will assist not just independent evaluators trying to determine whether a pharmaceutical actually works. It will help drug companies do their job better. Large open data sets will improve the design of future clinical trials. Such an approach will also let pharmaceutical makers avoid committing tens of millions of dollars for late-stage studies that others have already found to be money sinks.

The most important reason for moving ahead has nothing to do with costs. An open data system—perhaps one like Yale's, backed with some regulatory clout—is the only way that physicians can weigh available evidence to make informed, timely decisions about what to tell their patients. SA

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Illustration by Bernard Lee

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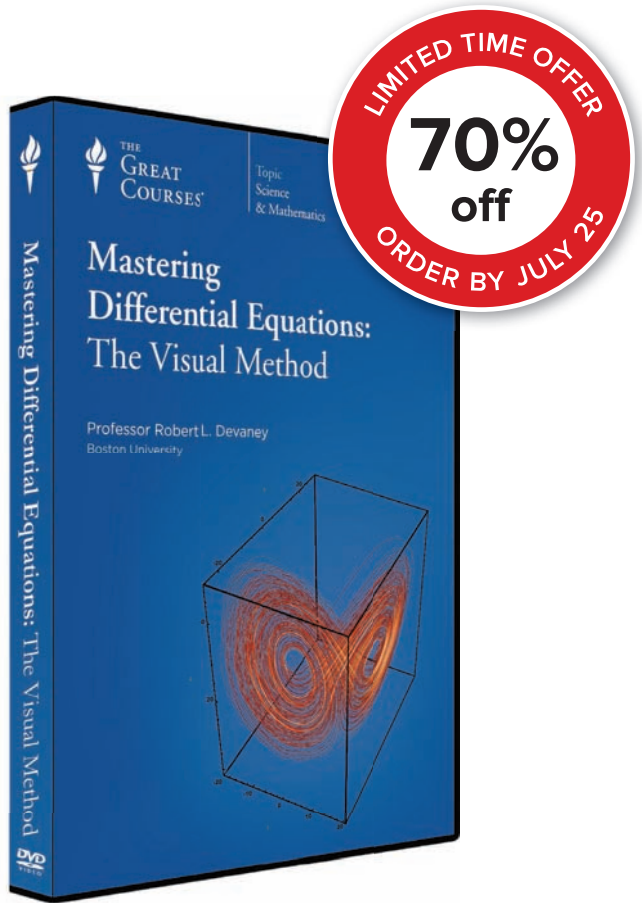

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Commentary on science in the news from the experts

Mary H. Schweitzer is a professor in the departments of marine, earth and atmospheric sciences and of biological sciences at North Carolina State University and curator of vertebrate paleontology at the North Carolina Museum of Natural Sciences.

FEATHERED DINOSAUR from Liaoning Province, China

Dinosaurs Are Important

Yesterday's big reptiles can help us figure out how the human era is shaping up

After more than 20 years as a professional paleontologist, I know how lucky I am to spend my days studying dinosaurs. In times when so many people can barely afford the basic necessities, how can I possibly justify using taxpayers' money to study animals that vanished millions of years ago? What can they teach us about today's world? Aren't they irrelevant to modern-day problems?

The truth is, paleontology is anything but irrelevant. The fossil record tells us that climate change is the planet's "normal" state. Does that mean the change we're seeing now is normal, or is the climate behaving in new ways because of human influence? How do we offset the damage we may have caused?

The best way to look ahead is to look behind, at those organisms, including dinosaurs, that survived extended climate change. The fossil record helps us compare today's climate changes and people's role in them with long-ago shifts before humans existed. And it has shown us five previous worldwide extinction events that occurred before the human era, enabling us to ask whether human activity is now causing a sixth global die-off. We could never consider such a question without knowledge of the distant past.

More than 99 percent of the species that have ever lived are extinct. Each taxon we recover represents a different set of evolutionary experiments with different outcomes, and most can be studied only via the fossil record. Dinosaurs, among the vertebrates with the most species, offer a particularly rich field. A single dinosaurian lineage—the extant birds, with roughly 10,000 species—far outnumbers the 5,500 or so species of living mammals.

Occupying a temporal span of more than 200 million years and a geographical range that includes every continent and virtually every niche, dinosaurs have much to teach us. No other terrestrial vertebrates have ever remotely approached the great size of the sauropods, nor have they achieved the food-processing efficiency of the hadrosaurs, which had vertically stacked teeth that were replaced as they wore out. And we can only speculate on the diversity of flight ability among extinct avian dinosaurs such as the enantiornithines and the enigmatic, four-winged microraptors, with flight feathers not only on their forelimbs but also on their legs. The fossil record exhibits for us what is *possible* for vertebrate organisms, both in niche occupation and in biomechanical and morphological adaptations to these niches.

There is another, no less important reason to study dinosaurs: they fascinate even nonscientists. We can use this fascination to encourage young people to enter the sciences, at a time when that is more important than ever.

Engaging future researchers isn't the only way paleontology might energize other sciences. We are just beginning to decode the molecular information hidden in the fossil record. It's tricky: molecules recovered from fossils inevitably have been modified from their living state. But techniques for cracking the code might be useful in medicine, for example.

Even now we are losing irreplaceable data. When fossils aren't recovered properly, their scientific value is diminished. It's a dilemma: for farmers in rural China or nomads in Mongolia—even for ranchers in the dry, bleak High Plains of the U.S.—fossil finds can help pay for their children's education, put food on the table or warm their homes in winter. But the fossil finders seldom know or follow proper recovery methods.

It's not their fault. To be sure, greedy middlemen and wealthy buyers are part of the problem. But so is ignorance. Scientists need to take a more active role in educating the public—explaining why proper recovery of fossil material is so important. And we need tougher laws to deter illegal trafficking.

Scientists have a responsibility to raise awareness of the value of fossils—not just as collectibles but for the lessons we have yet to learn from the creatures that once walked this planet. Only by understanding the geologic record of diversity, adaptation and climate variability can we hope to face the challenges ahead. SA

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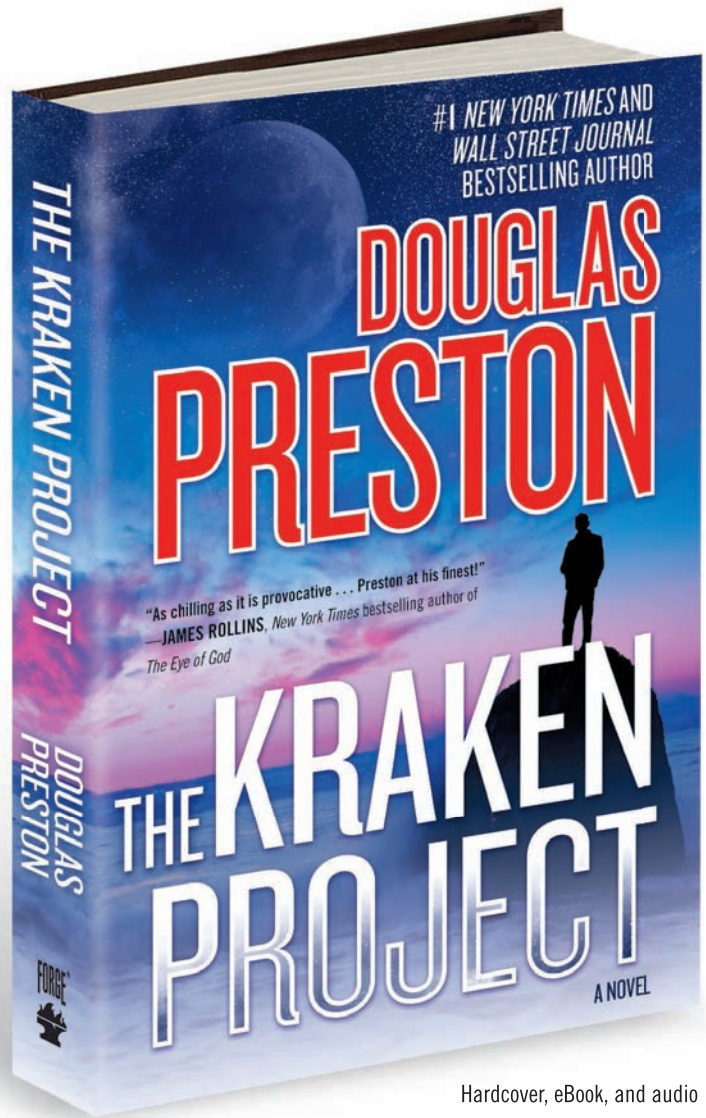
MICK ELLISON *American Museum of Natural History*

Artificial Intelligence is on the run in this thrilling new novel from *New York Times* bestselling author

DOUGLAS PRESTON



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NASA is building a probe to be splashed down in the Kraken Mare, the largest sea on Saturn's great moon, Titan. It's one of the most promising habitats for extraterrestrial life in the solar system, but the unpredictable surface requires the probe to contain artificial intelligence software. To this end, brilliant programmer Melissa Shepherd has developed "Dorothy," a self-modifying AI. When miscalculations lead to a catastrophe during testing, Dorothy flees into the internet.

Former CIA agent Wyman Ford is tapped to track down the rogue AI. But he and Shepherd aren't the only ones looking for the wayward software: a pair of Wall Street traders want to turn her into a high-speed trading bot.

Traumatized, angry, and relentlessly hunted, Dorothy has an extraordinary revelation—and devises a plan. As the pursuit of Dorothy converges on a deserted house on the coast of Northern California, Ford faces the ultimate question: is the AI bent on saving the world… or on wiping out the cancer that is humankind?

"Brilliant…full of huge ideas, but intensely human, too, and intensely suspenseful."

—LEE CHILD, *New York Times* bestselling author of the Jack Reacher novels on *Impact*

★ **"A very entertaining thriller…. His characters are so compelling, his storytelling so persuasive…. Bravo."**

—*BOOKLIST,* starred review

DOUGLAS PRESTON

is the author of *The Monster of Florence,* currently being developed as a film starring George Clooney, and the *New York Times* bestsellers *Impact, Tyrannosaur Canyon,* and *Blasphemy.* He is the co-author, with Lincoln Child, of the famed Pendergast series of novels, including *The Book of the Dead* and *The Wheel of Darkness,* as well as *The Relic,* which was made into a number one box office hit movie.

Deborah Feingold

ADVANCES

Dispatches from the frontiers of science, technology and medicine

ENVIRONMENT

Trees That Pollute

Some greenery makes smog levels worse

The next time you walk past a poplar or a black gum tree on a busy city street, think twice before taking a long, deep breath. Although these trees produce oxygen, they also release compounds that can react in the air to create lung-damaging ozone.

"It is kind of a surprise," says Galina Churkina, a senior fellow at the Institute for Advanced Sustainability Studies in Potsdam, Germany, who studies urban tree emissions. When certain trees dominate a street, they can raise the ozone level considerably. At ground level, ozone is an oxygen molecule that is linked to asthma, bronchitis and other respiratory illnesses.

Like vehicles and power plants, trees emit airborne chemicals called volatile organic compounds (VOCs), which in the presence of sunlight react with nitrogen oxides in vehicle fumes to form ozone, one of the components in smog that makes it a health threat. VOCs come out of tailpipes and smokestacks as a by-product of burning fossil fuels; the trees emit them in part to repel insects and to attract pollinators. Species such as birch, tulip and linden release very low levels of VOCs, but others such as black gum, poplar, oak and willow produce a lot, leading to ozone levels that can be eight times higher than those linked to the low-impact trees.

Churkina and her colleagues have not identified specific cities that contain too many of the top VOC emitters. That is up to urban planners. Because sunlight is needed to form ozone, and the reaction is more vigorous at higher temperatures, cold, cloudy cities have fewer worries than warm, sunny ones. Yet the problem could worsen because of climate change.

Does this mean cities should start cutting down the top emitters? No, Churkina says. Even the worst offenders are not a concern if they are scattered on city streets. Understanding, however, that a linden tree is better than a poplar can help metropolitan areas avoid problems. For example, "plant a million trees" projects are becoming popular as a way to store carbon dioxide, slow heat rise and soak up storm water. "We want them to be careful about choosing the best species," Churkina says. She will be meeting with Berlin officials this summer, and Boulder, Colo., is examining the issue.

Of course, there is another solution. Reduce car emissions, and cities won't have to worry about the trees.

—Mark Fischetti

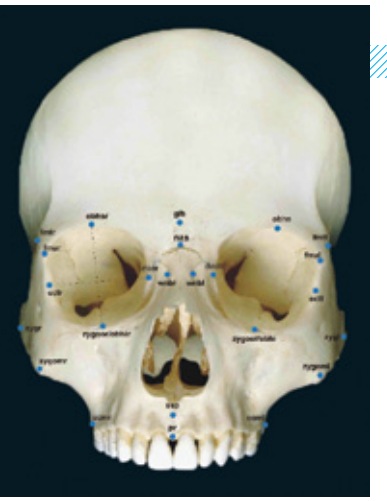
TOM NAGY *Gallery Stock*

FURTHER READINGS AND CITATIONS ScientificAmerican.com/jun2014/advances

FORENSICS

The Face behind the Skull

CT scans may soon link human remains to missing persons



COURTESY OF ANN ROSS *North Carolina State University*

You can tell a lot from a skull if you know what you're doing: an expert can suggest a skull's sex, age and ancestry just by looking at it. But such a subjective assessment would not hold water in a court of law, where it is essential to know how likely a skull belongs to a particular missing person. For that, you need numerical probabilities.

When an anthropologist wants to know if, say, a skull comes from a female in her 30s of Cuban descent, it would help to have a big digital database of skulls to query and analyze. Researchers at North Carolina State University have taken a few small steps toward such a tool. In 2009 forensic anthropologist Ann Ross developed software called 3D-ID that compares three-dimensional coordinates on a skull to a database of physical characteristics, such as the shape of the forehead. With numbers on its side, 3D-ID has consistently outperformed human experts and provides greater specificity. A skull's ancestry, for example, can be narrowed down from "Hispanic" to "Guatemalan."

Now Ross's goal is to make the database even more accurate. For that, she needs more skulls, and she thinks she has found the perfect source: computed tomography (CT) scans. Ross found that the technique provides the necessary measurements after scanning 48 skulls, results reported in the *Journal of Craniofacial Surgery* in January. In the future, living persons already undergoing CT scans for medical reasons could agree to add their scans to the database.

"We have a huge crisis in the U.S. of unidentified individuals, and sometimes we just have the skull," Ross says. In fact, up to 40,000 unidentified human remains exist in the U.S., and 3D-ID has already been used to help track down a handful of them. An expanded database with CT data could make a tremendous difference in tackling others. —*Tara Haelle*

BIG DATA

Twitter Opens Its Cage

A trove of billions of tweets will be a research boon and an ethical dilemma

Five hundred million tweets are broadcast worldwide every day on Twitter. With so many details about personal lives, the social media site is a data trove for scientists looking to find patterns in human behaviors, tease out risk factors for health conditions and track the spread of infectious diseases. By analyzing emotional cues found in the tweets of pregnant women, for instance, Microsoft researchers developed an algorithm that predicts those at risk for postpartum depression. And the U.S. Geological Survey uses Twitter to track the location of earthquakes as people tweet about tremors.

Until now, most interested scientists have been working with a limited number of tweets. Although a majority of tweets are public, if scientists want to freely search the lot, they do it through Twitter's application programming interface, which currently scours only 1 percent of the archive. But that is about to change: in February the company announced that it will make all its tweets, dating back to 2006, freely available to researchers. Now that everything is up for grabs, the use of Twitter as a research tool is likely to skyrocket. With more data points to mine, scientists can ask more complex and specific questions.

The announcement is exciting, but it also raises some thorny questions. Will Twitter retain any legal rights to scientific findings? Is the use of Twitter as a research tool ethical, given that its users do not intend to contribute to research?

To address these concerns, Caitlin Rivers and Bryan Lewis, computational epidemiologists at Virginia Tech, published guidelines for the ethical use of Twitter data in February. Among other things, they suggest that scientists never reveal screen names and make research objectives publicly available. For example, although it is considered ethical to collect information from public spaces—and Twitter is a public space—it would be unethical to share identifying details about a single user without his or her consent. Rivers and Lewis argue that it is crucial for scientists to consider and protect users' privacy as Twitter-based research projects multiply. With great data comes great responsibility.

—Melinda Wenner Moyer

Illustrations by Thomas Fuchs

YOU'VE REACHED THE AGE WHERE GIVING UP ISN'T WHO YOU ARE.

So if you're like millions of men who have some degree of erectile dysfunction (ED), talk to your doctor. Ask about VIAGRA (*sildenafil citrate*), and see if America's most prescribed ED treatment is right for you. 20 million men already have.

For more information go to viagra.com or call 1-888-484-2472 (1-888-4VIAGRA).

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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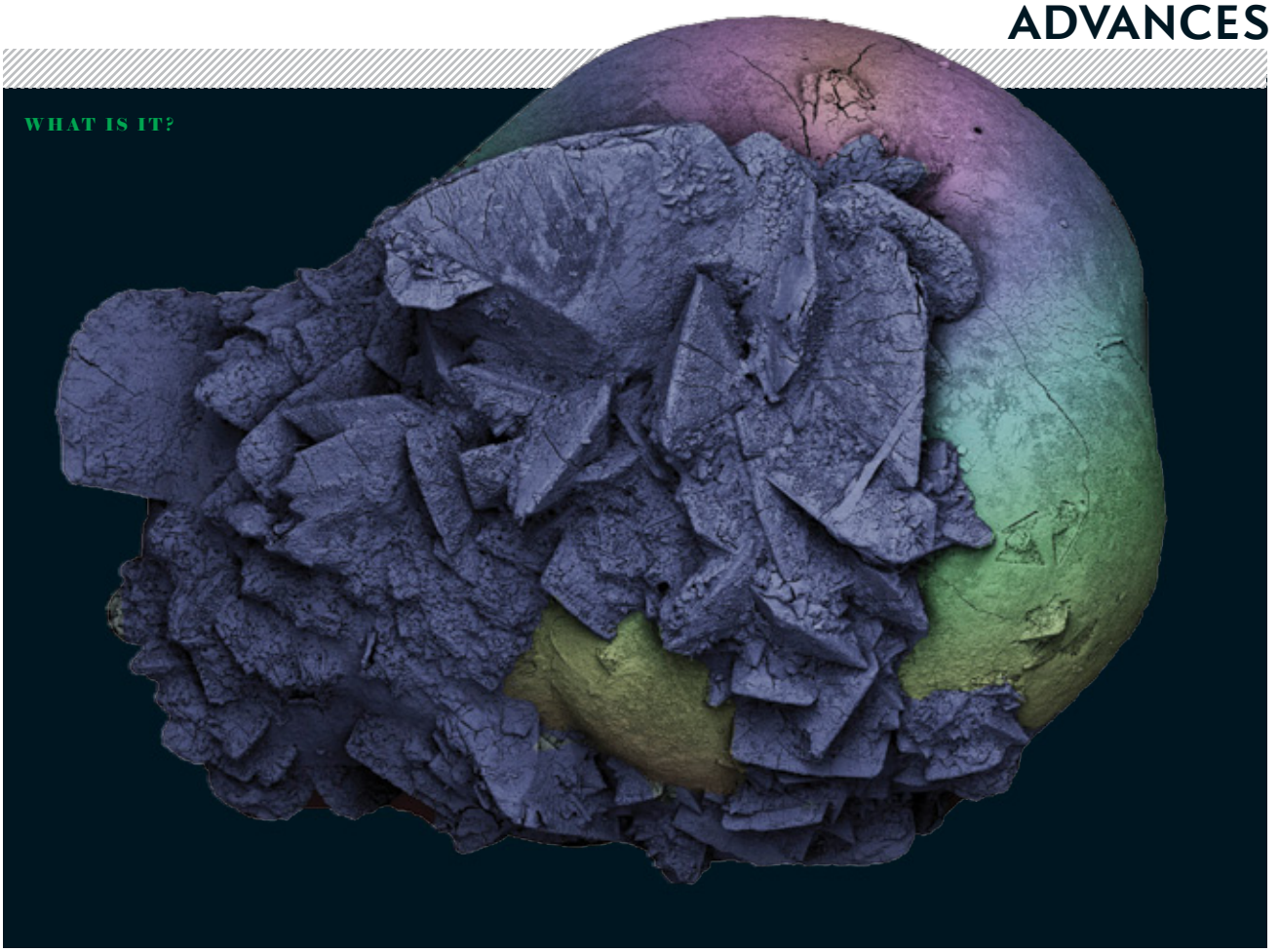


When the kidney does not properly eliminate salts and minerals, those waste products can grow into the small, agonizing pellets known as kidney stones. Roughly one in 11 Americans develops them—a rate that has doubled over the past two decades as a result, in part, of our obesity epidemic. About the size of a grape seed, this stone passed through the ureter of its owner naturally. The false-colored scanning electron microscope image (magnified 50×) depicts the stone in grisly detail, with smooth calcium oxalate monohydrate crystals overgrown with jagged dehydrate crystals.

Not all kidney stones escape easily: some grow so large that they block urinary flow and require medical intervention. The most common way to get rid of them is shock wave lithotripsy, a noninvasive technique in which high-frequency shock waves directed at the stone generate enough pressure to shatter it into tiny, sandlike fragments. This spring a team of urologists, engineers and mathematicians at Duke University improved on the technique. The researchers cut a small groove in the lens that focuses the shock waves and found that the simple adjustment optimizes wave shape so that the procedure is more accurate and minimizes damage to surrounding body tissues. It is a relatively cheap, straightforward innovation that may soon help treat millions of kidney stone patients worldwide. —*Annie Sneed*

DDG 1000: The Zumwalt-class guided-missile destroyer may be the future host of a rail gun.

BY THE NUMBERS

Mach 7

The speed at which an electromagnetic rail gun developed by the U.S. Navy shoots 23-pound projectiles. At that initial velocity, the projectiles could hurtle from Washington, D.C., to Philadelphia in three minutes. It is set to debut in 2016.

SOURCE: U.S. Navy

KEVIN MACKENZIE *Wellcome Images (top)*; COURTESY OF GENERAL DYNAMICS AND U.S. NAVY *(bottom)*

SPACE

Surf's Up on Titan

Waves on Saturn's largest moon indicate methane seas—a potential home to alternative forms of life

Saturn's moon Titan shares many of Earth's features, including clouds, rain and lakes. And now scientists know the two are similar in another way: they both have waves. Cameras on NASA's spacecraft Cassini recently saw what appear to be waves on one of Titan's largest methane lakes—a signal scientists have long searched for but never found.

"I was starting to despair that we were going to see them at all," says Jason Barnes, a physicist at the University of Idaho who presented the evidence in March at the 45th Lunar and Planetary Science Conference in The Woodlands, Tex. If confirmed, the discovery would mark the first time waves have been seen outside Earth.

Barnes and his team found patterns in the sunlight reflecting off a northern lake called Punga Mare that they interpret as two-centimeter-high waves. There is a different explanation, others caution: Punga Mare may be a mudflat instead of a deep lake, and a shallow film of liquid on top may be the cause of the unique light signature. "It's compelling, but it's not definitive," says Jonathan Lunine, a planetary scientist at Cornell University who was not involved in the study.

Waves on Titan would be noteworthy for several reasons. Such a finding would confirm that the lakes actually are deep reservoirs of methane and ethane, the dominant forms of liquid on that moon. If life on Titan exists, it would probably be primitive, so the best place to look for self-assembling structures, scientists say, is in large bodies of liquid—the kind that form waves.

True liquid bodies would also make a robotic spacecraft mission to explore Titan's habitability more feasible. After all, landing is easier in liquid than in a thicker substance or on solid ground.

By 2017 scientists should know for certain whether what they are seeing is indeed caused by waves. So far Cassini has been observing the moon during its northern winter, when weak winds are at work. As spring settles in over the next few years, bringing stronger winds to kick up seas, the probe should capture more definitive evidence of waves if they exist. Those waves will probably be larger than two centimeters.

—*Clara Moskowitz*

Just how deep are the seas on Titan?

COURTESY OF NASA/JPL/KARL KOFOED

COMMENT AT ScientificAmerican.com/jun2014

MEDICINE

Sugar Gut

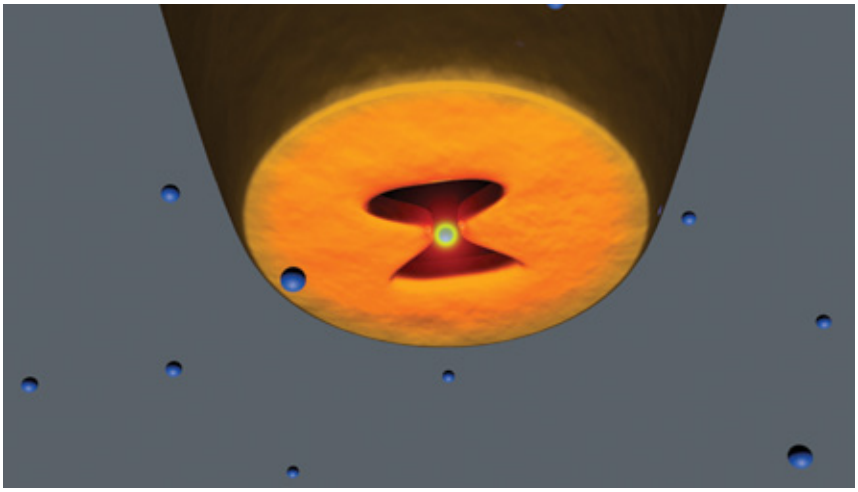
What good are sweet receptors in the intestines?

Three years ago researchers at the Monell Chemical Senses Center in Philadelphia made a shocking discovery: our guts can taste sugar. Just like the tongue, the intestines and pancreas have sweetness receptors that can sense glucose and fructose.

With that knowledge, scientists at Elcelyx Therapeutics, a pharmaceutical company in San Diego, developed a drug that targets the taste receptors. The drug, now in phase II clinical trials, is a modified version of metformin, the most commonly prescribed drug for treating type 2 diabetes. Usually metformin dissolves in the stomach and travels through the blood to the liver, which then talks with the pancreas. NewMet, on the other hand, is designed to dissolve only when it reaches the pH found in the gut. On release, the drug fills up the sweet receptors there, which send signals to the pancreas to produce insulin, a hormone that regulates blood glucose levels. "We're modulating a natural signal," says Alain Baron, president and CEO of Elcelyx.

Because of its direct route, NewMet is just as effective as metformin with half the typical dose, according to phase I results. The new pathway also reduces the amount of the drug that enters the bloodstream by 70 percent. That reduction is important because metformin can build up in the body with long-term use, and as a result, patients with kidney disease, up to 40 percent of people with type 2 diabetes, cannot take it. Their kidney is not able to filter the drug out of the blood, which can be deadly.

Baron thinks that other drugs could be modified to target the gut. A spin-off of Elcelyx is now working on a weight-loss drug, which would target the lower intestine and amplify the signals of fullness. —*Erin Biba*



MATERIALS SCIENCE

Particle Tweezers

Laser beams can pluck and manipulate objects as small as viruses

In the 1980s researchers at AT&T Bell Laboratories (now Bell Labs) created "optical tweezers" that could manipulate micron-size objects with focused laser beams, taking advantage of the gentle forces that light exerts on matter. Yet despite advancements made over the past 30 years, a problem has remained: as a result of the law of diffraction, which limits the degree to which light can be focused, most objects smaller than about 100 nanometers have evaded the tweezers.

It turns out that the law has a loophole, according to research recently described in *Nature Nanotechnology*. (*Scientific American* is part of Nature Publishing Group.) Diffraction applies to propagating light waves, but on the nanoscale, noble metals such as gold can convert light into evanescent fields, which are nonpropagating waves that quickly fade. Applying this phenomenon to a gold-plated optical cable, physicists at the Institute of Photonic Sciences near Barcelona were able to focus light at a fine enough scale to manipulate particles as small as 50 nanometers.

Previously researchers could work with particles of that size by attaching them to larger ones, but that method restricted movement. With the new tool, the physicists were able to pick up particles on their own and so move them freely in three dimensions.

"We have something that can be a universal tool of interest to scientists from many different fields—not just physicists," says photonics researcher Romain Quidant. Potential applications include building medical products with nanoscale exactness, manufacturing nanocrystal geometries for electronic devices and manipulating single molecules such as proteins. —*Rachel Nuwer*

FROM "THREE-DIMENSIONAL MANIPULATION WITH SCANNING NEAR-FIELD OPTICAL NANOTWEEZERS," BY J. BERTHELOT ET AL., IN *NATURE NANOTECHNOLOGY*, VOL. 9, APRIL 2014 (*artist's rendition*)

BY THE NUMBERS

50

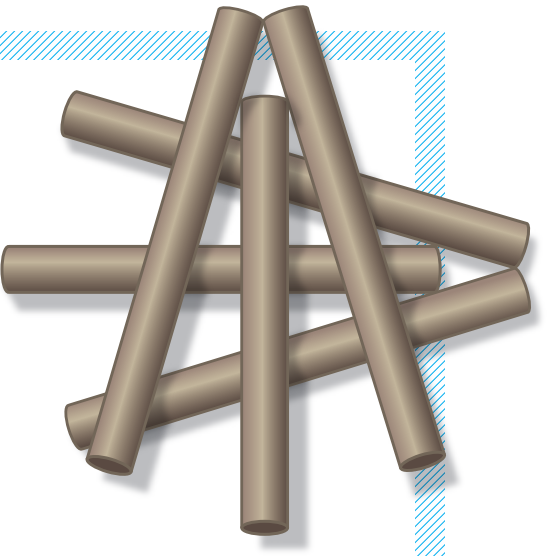
Distance in astronomical units from the sun that defines the edge of our solar system. One AU is about 93 million miles, the average distance between the sun and Earth.

SOURCE: NASA

MATHEMATICS

Meeting of the Puzzlers

The group that keeps Martin Gardner's magic alive



"The line between entertaining math and serious math is a blurry one," Martin Gardner wrote in the August 1998 issue of *Scientific American*. Gardner, who died in 2010, was this magazine's Mathematical Games columnist for a quarter of a century, until he retired in 1981. His fans have worked hard to maintain that blurriness, most recently in March at the 11th Gathering 4 Gardner, the biennial reunion dedicated to celebrating the polymath's contributions to mathematics and its relation to art, music, architecture and, well, fun.

Gardner loved recreational math, and his readers would take his observations and run with them, improving and generalizing to Gardner's delight. For example, he originally gave a solution in his column for the old challenge of arranging six cigarettes so that each one touches the others (*right*). His readers went on to find that seven cigarettes could also meet the requirements, and in 2013 mathematicians found that seven circular cylinders of infinite length could as well.

This year the meeting's attendants talked about at least 50 such problems, avoiding the cut-and-dried math education experience that is known to so many. Most of the 243 presentations were concerned with art or music: The beauty of stochastic geometry. Holographic visualizations. The relation of music to the Platonic solids. One presenter, cellist Philip Shepard, discoursed on string theory—the theory of stringed instruments in this case.

And magic made an appearance, of course. A well-known inventor of magic tricks, Gardner had shied away from performance. He did not, however, shy away from advocating awe, surprise and wonder in math—a talking point at the meeting—and wrote several essays on how a sense of wonder is the antidote to the hubris of the human condition. It is a testament to that enduring sense that so many people inspired by Gardner are compelled to seek one another out and puzzle over puzzles.

—Dana Richards

TECHNOLOGY

Data Mask

A phone that prevaricates

Local police confiscate a suspected drug dealer's phone—only to find that he has called his mother and no one else. Meanwhile a journalist's phone is examined by airport security. But when officials look to see what is on it, they find that she has spent all her time at the beach. The drug dealer and the journalist are free to go. Minutes later the names, numbers and GPS data that the police were looking for reappear.

A new programming technique could bring these scenarios to life. Computer scientist Karl-Johan Karlsson has reprogrammed a phone to lie. By modifying the operating system of an Android-based smartphone, he was able to put decoy data on it—innocent numbers, for example—so that the real data escape forensics. He presented the hack in January at the Hawaii International Conference on System Sciences.

Karlsson tested his hack on two forensics tools commonly used by police departments. Both can retrieve call logs, location data and even passwords. When he ran his modified system, the tools picked up the false information that he programmed into the phone and missed the real contents.

Even though his hack was successful, Karlsson says it is not going to stop a sophisticated analysis by the FBI or the NSA. Such a hack, however, could make it difficult to try some criminal cases. A phone that tells two stories complicates things.

Mikko Hypponen, a prominent computer-security expert, says Karlsson's modification is another stage in the arms race among spies, law enforcement and users. It also highlights the effort to find ways to protect legitimate needs for privacy. "This kind of tool," he says, "can be used for good or bad." *—Jesse Emspak*

WILDLIFE

Turtle Baby's First Steps

Tracking the transatlantic journey of young sea turtles reveals surprises

After baby loggerhead turtles hatch, they wait until dark and then dart from their sandy nests to the open ocean. A decade or so later they return to spend their teenage years near those same beaches. What the turtles do and where they go in those juvenile years has been a mystery for decades. Marine biologists call the period the "lost years."

Following the tiny turtles has proved to be difficult. Researchers tried attaching bulky radio tags, but the devices impeded the turtles' ability to move. The size of the tags shrank over time, yet the batteries remained stubbornly large. Then Kate Mansfield, a marine biologist at the University of Central Florida, got the idea to go solar.

She saw that other wildlife researchers were tracking birds with small solar panels. So her team decided to use similar tags with a matchbook-size panel, bringing the weight down to that of a couple of nickels. The researchers also figured out how to attach the tags securely without warping the turtles' shells, an idea that came from a team member's manicurist. She suggested acrylic lacquer as the base coat to hold silicone glue, which can grow with the turtles.

Mansfield's group tagged 17 turtles that ranged from three to nine months old. The scientists then plopped them—the biggest, seven inches long—off the coast of Florida and into the Gulf Stream, which is part of the North Atlantic Gyre, a system of currents that flows clockwise up the U.S. East Coast. Bryan Wallace, a marine biologist at Stratus Consulting and Duke University who was not involved in the work, said the study is likely to be remembered as a seminal paper in sea turtle biology. It was published in April in *Proceedings of the Royal Society B*.

"Based on long-standing hypotheses, we'd expect that the turtles would remain in the outer gyre currents and head toward the Azores," an archipelago off Portugal, Mansfield says. As the team tracked subjects over a few months, however, it found the turtles did not stick to this itinerary. Many of them swam into the center of the gyre, where seaweed accumulates. The turtles forage in the seaweed and use it for shelter.

The turtles also traveled faster than predicted, reaching the waters off North Carolina within three weeks. At that speed, they could easily reach the Azores in less than a year. Although that timeline agrees with estimates based on passive drifting, the turtles take many side trips, which means their actual speed of locomotion is impressive.

Another surprise: the tags' temperature sensors consistently read several degrees higher than the turtles' local water temperature, which suggests that the seaweed mats keep these cold-blooded reptiles warm, an important condition for growth.

—Beth Skwarecki

One turtle (*yellow path*) kept its tag for more than seven months.

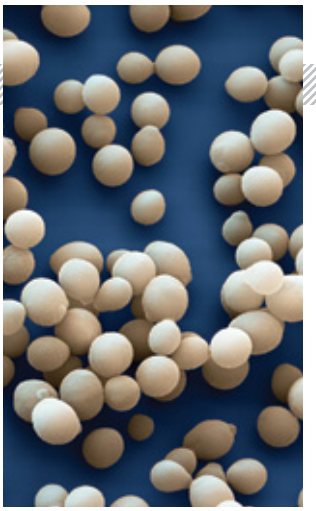
SOURCE: "FIRST SATELLITE TRACKS OF NEONATE SEA TURTLES REDEFINE THE 'LOST YEARS' OCEANIC NICHE" BY KATHERINE L. MANSFIELD ET AL., IN *PROCEEDINGS OF THE ROYAL SOCIETY B*, VOL. 281, NO. 1781; APRIL 22, 2014

Map by XNR Productions

SYNTHETIC BIOLOGY

DIY Yeast

An artificial version of the bug that makes bread



SCIENCE SOURCE

In March undergraduate students in Johns Hopkins University's Build a Genome course announced they had made a yeast chromosome from scratch—and history, too. It is the first time anyone has synthesized the chromosome of a complex organism, a landmark achievement in the field of synthetic biology. It is also a triumph for the movement known as DIY biology.

The target was chromosome 3, which controls the yeast's sexual reproduction and has 316,617 base pairs of the DNA alphabet—A for adenine, G for guanine, C for cytosine and T for thymine. To synthesize it, the students took a shortcut: they built only the sections considered essential or nonrepetitive. The resulting chromosome had a more manageable 272,871 base pairs. And as reported in *Science,* the yeast with the new genes thrived just as well as regular yeast did in terms of size and growth.

"They are going strong," says biologist Jef Boeke of New York University, who helped lead the research as part of the Synthetic Yeast 2.0 project—an effort to build a synthetic genome for yeast that would give scientists nearly complete control of it. Boeke and others plan to grow this batch for thousands of generations over the next several years to see how they evolve over time, which will give scientists a better understanding of fundamental biology, from the role of "junk DNA" to the absolute minimum of genetic code necessary for survival. "The questions are endless," Boeke says.

The current work is just 3 percent of the way toward creating an entirely synthetic yeast genome (there are 16 chromosomes in total) and will take many more years to finish. If finished, synthetic yeast could be second on the list of organisms with genomes built from scratch—the J. Craig Venter Institute built a bacterium's genome in 2010.

It could also be a breakthrough in humanity's millennia-long cohabitation with *Saccharomyces cerevisiae,* which is responsible for bread and wine. Yeasts today churn out human proteins for medicines, biofuels and other specialty products. Being able to fine-tune the microscopic fungus's genetics could lead to better beer or sustainable chemicals, according to Boeke. And after yeast? "The fruit fly? The worm? We're not sure what is next."

—David Biello

Megachile campanulae

ECOLOGY

Bee Resourceful

Urban-dwelling bees build homes from trash

Bowerbirds love discarded plastic. The males use colorful pieces to woo mates in an elaborate courtyard outside their nests. New research shows that another animal is putting our plastic waste to good use: two species of city-living bee have started building bits of plastic into their nests.

The bees that J. Scott MacIvor, an ecologist at York University, studies aren't social and don't build hives. They construct small nests in plant stems, tree holes and fence posts. To examine their nest-building habits in detail, MacIvor enlisted Toronto citizen scientists in the spring of 2012 to help place artificial nest boxes throughout the city.

When he checked them that fall, he found something unexpected: *Megachile rotundata*—one of the most commonly managed bees in the world—had incorporated pieces of plastic shopping bags into its nests in addition to the usual leaves. And *Megachile campanulae,* which typically seals the cells of its nest with plant and tree resins, had used plastic-based sealants, including caulk.

The findings, published in the journal *Ecosphere,* constitute the first scientific documentation of insects building nests with plastic. Bees routinely live inside plastic objects, such as straws, "but to actively gather plastic is novel," says John Ascher, a researcher at the American Museum of Natural History in New York City.

The study offers another example of how animals adapt to human-dominated environments. "There will always be those that have adaptive traits or enough flexibility in their behavior to persist in a disturbed landscape," MacIvor says. At least we hope so. —*Jason G. Goldman*

BY THE NUMBERS

80

Distance in AUs from the sun to a newly discovered object, most likely a dwarf planet. It is the most distant object ever observed that is beyond the edge of the solar system yet still orbits the sun.

SOURCE: "A Sedna-Like Body with a Perihelion of 80 Astronomical Units," by Chadwick A. Trujillo and Scott S. Sheppard, in *Nature,* Vol. 507; March 27, 2014

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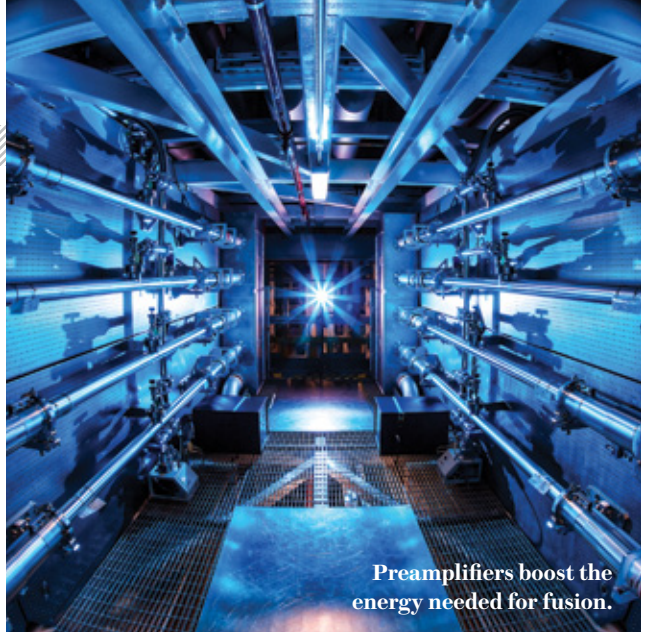
NUCLEAR PHYSICS

A Milestone on the Long and Winding Road to Fusion

A tiny fuel pellet gives more energy than it gets



Preamplifiers boost the energy needed for fusion.

COURTESY OF LAWRENCE LIVERMORE NATIONAL LABORATORY

Last September, under x-ray assault, the rapid implosion of a plastic shell into icy isotopes of hydrogen produced fusion at Lawrence Livermore National Laboratory's National Ignition Facility (NIF). This wasn't just a run-of-the-mill fusion reaction: it was the first one NIF has ever produced wherein the fuel released more energy than it absorbed.

The laboratory's 192 lasers have been pumping energy into a succession of tiny fuel pellets since 2010. In this instance, the scientists got the timing right. Instead of ramping up the lasers over the course of the blast, which lasts 20 trillionths of a second, Livermore physicist Omar Hurricane and his team started the blast at maximum intensity and then let it taper off. That change made the fuel in the two-millimeter pellet hotter sooner—reaching temperatures of about 50 million degrees Celsius and pressures of 150 billion Earth atmospheres. Such conditions enable fusion, and, in this case, the fusing fuel yielded nearly twice as much energy as the roughly 10,000 joules that triggered it.

The results were published in February in *Nature*.

"This is closer than anyone's gotten before" to self-sustaining energy, Hurricane says. Yet scientists still have a lot of work to do. Although the fuel pellet yielded 17,000 joules of energy, the entire fusion experiment fell far short of breaking even. The NIF experiment required more energy to run than it generated; feeding the lasers alone required a burst of about 500 trillion joules. Doing better than breaking even—or "ignition," as the NIF folks put it—will require even more extreme pressures and other conditions. A source of nearly unlimited, clean energy is still decades away.

—David Biello

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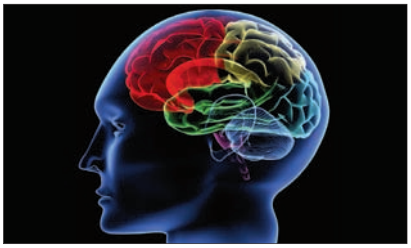

Brain Science

Speaker: Larry Cahill, Ph.D.

Brains "R" Us

How do we work? What makes us tick? For much (but not all) of human history people looked to the gooey, grey organ between your ears for answers. Learn how how our perception of the brain has evolved and how some of our most "modern" ideas about the brain aren't very modern at all.

Sex on the Brain

Overwhelmingly, brain science has ignored gender differences with findings in males assumed to apply equally to females. But it turns out that "sex matters" down to the level of single neurons, even to parts of neurons. Find out why there are entrenched biases against sex difference research in brain science, and why they are, finally, crumbling.

Emotional Memory

What makes the brain a brain (and not a spleen or a pancreas or a lung) is memory, and emotion is arguably the primary sculptor of memory. Studies of emotional memory consequently lie at the heart of brain science. Explore the most dominant theories of emotional memory, and discover how sex matters (yet again) to these theories.

When Brains Fail

The brain is the single most complicated system in the known universe. When human brains fail, they can fail spectacularly, sometimes failing in fascinating ways that challenge some of our most elementary assumptions about who we are. What have we learned about the human brain from studying brain disease? Find out with Dr. Cahill.

Planets

Speaker: David Stevenson, Ph.D.

Planetary Diversity

The Kepler spacecraft has found hundreds of planets and thousands of additional candidates. Exploration of our solar system leads to a view of planets that emphasizes diversity rather than similarity. With so many planets out there, yes, some must be like Earth, but are the most exciting prospects for planets and life forms very different from our home? Absorb the possibilities.

Origin of Earth & Moon

Four and a half billion years ago our own solar system developed from a disk of gas and dust. Get our current understanding of this process and how Earth emerged with the Moon, an atmosphere, oceans, a magnetic field, and conditions for life. Explore how the nature of Earth is inextricably linked to the existence of our satellite companion.

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Ice Worlds

There is more ice and liquid than rock in our solar system, including some exotic stuff: hot, dense soups of protons and oxygen ions deep under planetary surfaces; rivers and lakes of liquid hydrocarbons, and ice geysers. Find out the details as we explore the structure and dynamics of the large satellites and Pluto.

Jupiter!

Our solar system's largest planet, Jupiter, likely influenced Earth's formation and so is a key to understanding Earth. Delve into Jupiter's internal properties and interior structure, and family of satellites. Get an insider's scoop on the billion dollar Juno mission arriving at Jupiter in July 2016 and learn about Dr. Stevenson's Juno role studying Jupiter's gravity and magnetic fields.

Weather

Speaker: Robert G. Fovell, Ph.D.

How and Why Clouds Form

Clouds are key in the planetary energy balance and water cycle. Historically, they have signaled atmospheric processes to observers. Learn about clouds' characteristics, formation, and function, with details on precipitation, ice, and lightning. We'll look at clouds from all sides, identifying the many ways clouds are essential to Earth and the atmosphere.

How and Why the Winds Blow

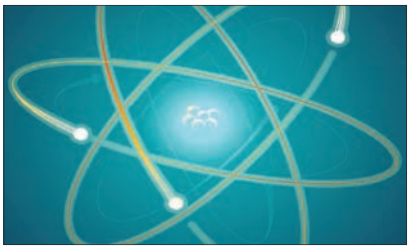
Delve into the role, causes and features of this invisible phenomenon. We'll look at the basics of atmospheric circulation and the complex interactions within the atmosphere that create wind. Learn about local winds (sea breezes), large-scale ones (fronts and cyclones) and legendary severe winds associated with mountains. Hone your knowledge of wind and its impacts.

Severe Storms

Storms impact our wellbeing, homes, cities, and economies. Learn about the causes, formation, and lifecycle of severe storms. Look at supercell thunderstorms and tornadoes, and the role of moisture and vertical wind shear in storms. From squall-lines, bow echoes, and flash flooding to hurricanes, get the latest need-to-know information on these forces of nature.

Understanding Extreme Weather

Synthesizing our knowledge from the three previous sessions, we'll apply these concepts to examples of extreme weather events from the recent past: 2013's devastating Colorado floods. The 2013 Oklahoma tornadoes. 2012's Hurricane Sandy. 1993's epic East Coast Snowstorm. 1991's "Perfect Storm."



Particle Physics

Speaker: James Gillies, Ph.D.

Hunting the Higgs Boson

Particle physics is the study of the smallest indivisible pieces of matter and the forces that act between them. Learn about the particle accelerators, detectors and computing that make this research possible at the Large Hadron Collider, and how hundreds of physicists teamed to hunt the long-sought Higgs boson.

Life after Higgs: What's Next?

Physicists at the Large Hadron Collider announced in 2012 they'd found *a* Higgs boson. But not *the* Higgs boson. What's the difference? Learn what the particular properties of the recently discovered particle could tell us about the nature of the universe, and why physicists don't know yet which Higgs boson they've found.

60 Years of Science for Peace

Sixty years ago, the idea of CERN, the European particle physics laboratory, was born. Hear the interwoven scientific and political stories of CERN's development and how particle physics has evolved from a regional to a global field, with the Large Hadron Collider as its frontier research tool.

Celebrating 25 years of the World Wide Web

"Vague, but exciting," were the words scrawled on Tim Berners-Lee's 1989 proposal for what became the World Wide Web. Hear the story of the Web's birth based on archival material and interviews with the major players, and learn how developments in physics and computing paralleled the development of the Web itself.

Astrobiology

Speaker: Peter Smith, Ph.D.

NASA's OSIRIS-Rex Mission

Learn about NASA's planned OSIRIS-REx mission to rendezvous with an asteroid and chip away samples to return home. Its target, the carbon-rich asteroid Bennu, should offer a peak at the types of organic materials and primitive minerals that existed on Earth when life was first forming.

The Earliest Life on Earth

Delve into the field of astrobiology, which investigates the origin of life on Earth and elsewhere. We'll probe the big questions: Was Earth seeded with life from space? Why is the backbone structure of DNA rarely found in nature? And what did the first microbes eat?

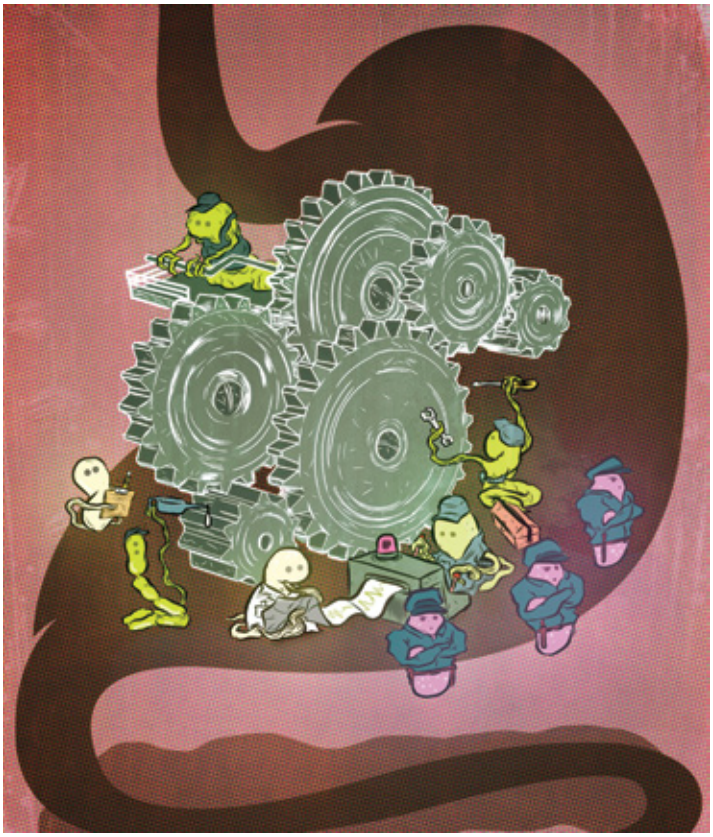
Life on Mars: What Do We Know?

Since the Viking missions of 1976, scientists have searched Mars for signs of life. From evidence of past water to questions of volcanism and methane gas, learn about the many signals that could tell us whether the Red Planet does, or ever did, host life.

Could Life Exist on Europa, Enceladus or Titan?

Some of the most intriguing potential sites for life in our solar system exist not on planets, but on moons with buried liquid oceans and lakes of methane and ethane full of organic materials. Learn why scientists are so interested in Saturn's moons Enceladus and Titan and Jupiter's moon Europa.

Claudia Wallis is a freelance writer and editor based in New York City and author of 40 *Time* magazine cover stories.



Gut Reactions

Intestinal bacteria may help determine whether we are lean or obese

For the 35 percent of American adults who do daily battle with obesity, the main causes of their condition are all too familiar: an unhealthy diet, a sedentary lifestyle and perhaps some unlucky genes. In recent years, however, researchers have become increasingly convinced that important hidden players literally lurk in human bowels: billions on billions of gut microbes.

Throughout our evolutionary history, the microscopic denizens of our intestines have helped us break down tough plant fibers in exchange for the privilege of living in such a nutritious broth. Yet their roles appear to extend beyond digestion. New evidence indicates that gut bacteria alter the way we store fat, how we balance levels of glucose in the blood, and how we respond to hormones that make us feel hungry or full. The wrong mix of microbes, it seems, can help set the stage for obesity and diabetes from the moment of birth.

Fortunately, researchers are beginning to understand the differences between the wrong mix and a healthy one, as well as the specific factors that shape those differences. They hope to learn how to cultivate this inner ecosystem in ways that could prevent—and possibly treat—obesity, which doctors define as having a particular ratio of height and weight, known as the body mass index, that is greater than 30. Imagine, for example, foods, baby formulas or supplements devised to promote virtuous microbes while suppressing the harmful types. "We need to think about designing foods from the inside out," suggests Jeffrey Gordon of Washington University in St. Louis. Keeping our gut microbes happy could be the elusive secret to weight control.

AN INNER RAIN FOREST

RESEARCHERS HAVE LONG KNOWN that the human body is home to all manner of microorganisms, but only in the past decade or so have they come to realize that these microbes outnumber our own cells 10 to one. Rapid gene-sequencing techniques have revealed that the biggest and most diverse metropolises of "microbiota" reside in the large intestine and mouth, although impressive communities also flourish in the genital tract and on our skin.

Each of us begins to assemble a unique congregation of microbes the moment we pass through the birth canal, acquiring our mother's bacteria first and continuing to gather new members from the environment throughout life. By studying the genes of these various microbes—collectively referred to as the microbiome—investigators have identified many of the most common residents, although these can vary greatly from person to person and among different human populations. In recent years researchers have begun the transition from mere census taking to determining the kind of jobs these minute inhabitants fill in the human body and the effect they have on our overall health.

An early hint that gut microbes might play a role in obesity came from studies comparing intestinal bacteria in obese and lean individuals. In studies of twins who were both lean or both obese, researchers found that the gut community in lean people was like a rain forest brimming with many species but that the community in obese people was less diverse—more like a nutrient-overloaded pond where relatively few species dominate. Lean individuals, for example, tended to have a wider variety of Bacteroidetes, a large tribe of microbes that specialize in breaking down bulky plant starches and fibers into shorter molecules that the body can use as a source of energy.

Documenting such differences does not mean the discrepancies are responsible for obesity, however. To demonstrate cause and effect, Gordon and his colleagues conducted an elegant series of experiments with so-called humanized mice, published last September in *Science*. First, they raised genetically identical baby rodents in a germ-free environment so that their bodies would be free of any bacteria. Then they populated their guts with intestinal microbes collected from obese women and their lean twin sisters (three pairs of fraternal female twins and one set of identical twins were used in the studies). The mice ate the same diet in equal amounts, yet the animals that received bacteria from an obese twin grew heavier and had more body fat than

Illustration by Rafa Alvarez

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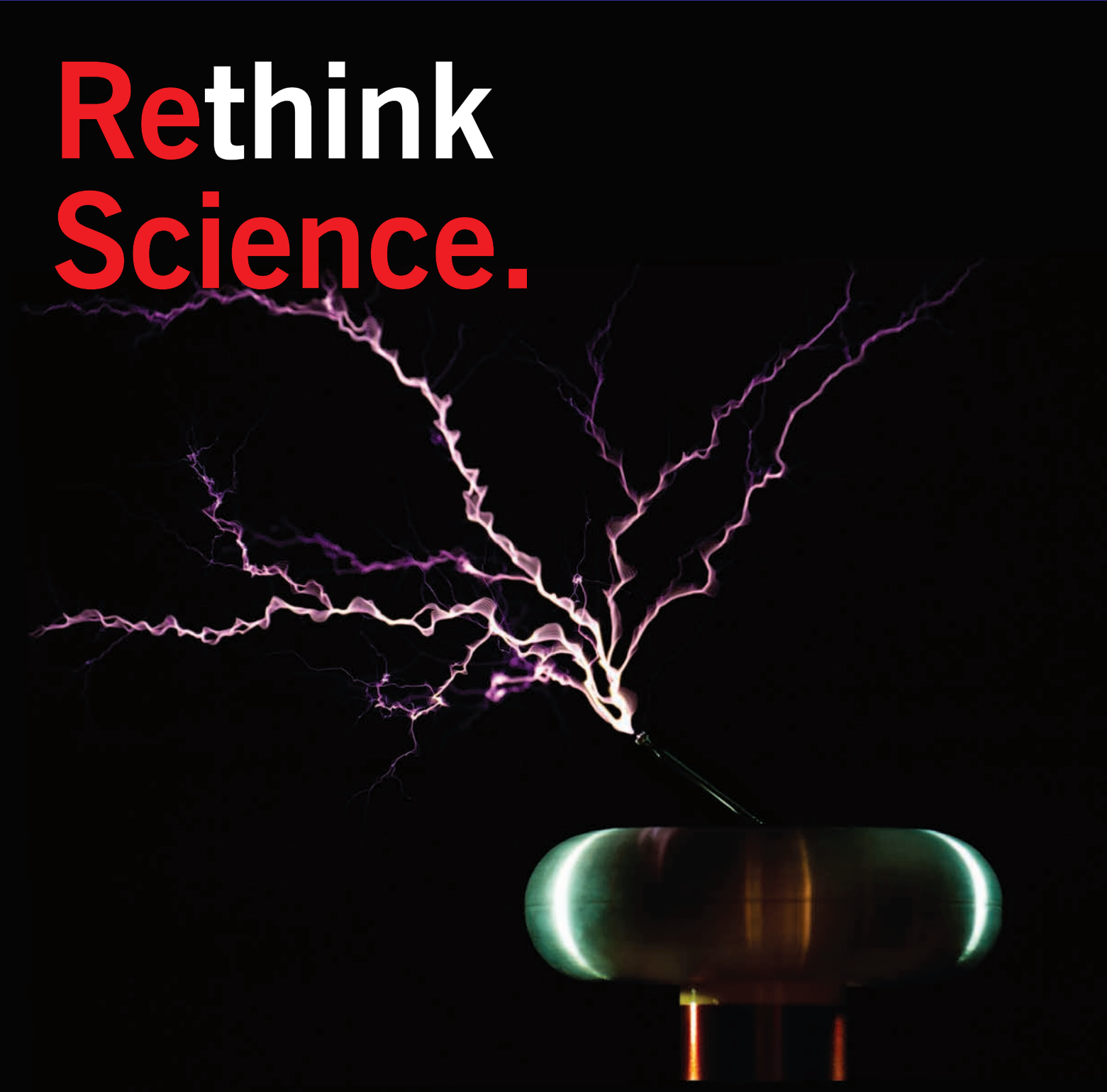

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mice with microbes from a thin twin. As expected, the fat mice also had a less diverse community of microbes in the gut.

Gordon's team then repeated the experiment with one small twist: after giving the baby mice microbes from their respective twins, they moved the animals into a shared cage. This time both groups remained lean. Studies showed that the mice carrying microbes from the obese human had picked up some of their lean roommates' gut bacteria—especially varieties of Bacteroidetes—probably by consuming their feces, a typical, if unappealing, mouse behavior. To further prove the point, the researchers transferred 54 varieties of bacteria from some lean mice to those with the obese-type community of germs and found that the animals that had been destined to become obese developed a healthy weight instead. Transferring just 39 strains did not do the trick. "Taken together, these experiments provide pretty compelling proof that there is a cause-and-effect relationship and that it was possible to prevent the development of obesity," Gordon says.

Gordon theorizes that the gut community in obese mice has certain "job vacancies" for microbes that perform key roles in maintaining a healthy body weight and normal metabolism. His studies, as well as those by other researchers, offer enticing clues about what those roles might be. Compared with the thin mice, for example, Gordon's fat mice had higher levels in their blood and muscles of substances known as branched-chain amino acids and acylcarnitines. Both these chemicals are typically elevated in people with obesity and type 2 diabetes.

Another job vacancy associated with obesity might be one normally filled by a stomach bacterium called *Helicobacter pylori*. Research by Martin Blaser of New York University suggests that it helps to regulate appetite by modulating levels of ghrelin—a hunger-stimulating hormone. *H. pylori* was once abundant in the American digestive tract but is now rare, thanks to more hygienic living conditions and the use of antibiotics, says Blaser, author of a new book entitled *Missing Microbes*.

Diet is an important factor in shaping the gut ecosystem. A diet of highly processed foods, for example, has been linked to a less diverse gut community in people. Gordon's team demonstrated the complex interaction among food, microbes and body weight by feeding their humanized mice a specially prepared unhealthy chow that was high in fat and low in fruits, vegetables and fiber (as opposed to the usual high-fiber, low-fat mouse kibble). Given this "Western diet," the mice with obese-type microbes proceeded to grow fat even when housed with lean cagemates. The unhealthy diet somehow prevented the virtuous bacteria from moving in and flourishing.

The interaction between diet and gut bacteria can predispose us to obesity from the day we are born, as can the mode by which we enter the world. Studies have shown that both formula-fed babies and infants delivered by cesarean section have a higher risk for obesity and diabetes than those who are breast-fed or delivered vaginally. Working together, Rob Knight of the University of Colorado Boulder and Maria Gloria Dominguez-Bello of N.Y.U. have found that as newborns traverse the birth canal, they swallow bacteria that will later help them digest milk. C-section babies skip this bacterial baptism. Babies raised on formula face a different disadvantage: they do not get substances in breast milk that nurture beneficial bacteria and limit colonization by harmful ones. According to a recent Canadian study, babies drinking formula have bacteria in their gut that are not seen in breast-fed babies until solid foods are introduced. Their presence before the gut and immune system are mature, says Dominguez-Bello, may be one reason these babies are more susceptible to allergies, asthma, eczema and celiac disease, as well as obesity.

A new appreciation for the impact of gut microbes on body weight has intensified concerns about the profligate use of antibiotics in children. Blaser has shown that when young mice are given low doses of antibiotics, similar to what farmers give livestock, they develop about 15 percent more body fat than mice that are not given such drugs. Antibiotics may annihilate some of the bacteria that help us maintain a healthy body weight. "Antibiotics are like a fire in the forest," Dominguez-Bello says. "The baby is forming a forest. If you have a fire in a forest that is new, you get extinction." When Laurie Cox, a graduate student in Blaser's laboratory, combined a high-fat diet with the antibiotics, the mice became obese. "There's a synergy," Blaser explains. He notes that antibiotic use varies greatly from state to state in the U.S., as does the prevalence of obesity, and intriguingly, the two maps line up—with both rates highest in parts of the South.

BEYOND PROBIOTICS

MANY SCIENTISTS who work on the microbiome think their research will inspire a new generation of tools to treat and prevent obesity. Still, researchers are quick to point out that this is a young field with far more questions than answers. "Data from human studies are a lot messier than the mouse data," observes Claire Fraser of the University of Maryland, who is studying obesity and gut microbes in the Old Order Amish population. Even in a homogeneous population such as the Amish, she says, there is vast individual variation that makes it difficult to isolate the role of microbiota in a complex disease like obesity.

Even so, a number of scientists are actively developing potential treatments. Dominguez-Bello, for example, is conducting a clinical trial in Puerto Rico in which babies born by cesarean section are immediately swabbed with a gauze cloth laced with the mother's vaginal fluids and resident microbes. She will track the weight and overall health of the infants in her study, comparing them with C-section babies who did not receive the gauze treatment.

A group in Amsterdam, meanwhile, is investigating whether transferring feces from lean to overweight people will lead to weight loss. U.S. researchers tend to view such "fecal transplants" as imprecise and risky. A more promising approach, says Robert Karp, who oversees National Institutes of Health grants related to obesity and the microbiome, is to identify the precise strains of bacteria associated with leanness, determine their roles and develop treatments accordingly. Gordon has proposed enriching foods with beneficial bacteria and any nutrients needed to establish them in the gut—a science-based version of today's probiotic yogurts. No one in the field believes that probiotics alone will win the war on obesity, but it seems that, along with exercising and eating right, we need to enlist our inner microbial army. SA

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

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

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

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

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

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

While taking ELIQUIS:

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

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

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

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

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

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

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

What is ELIQUIS?

ELIQUIS is a prescription medicine used to:

- reduce the risk of stroke and blood clots in people who have atrial fibrillation.
- reduce the risk of forming a blood clot in the legs and lungs of people who have just had hip or knee replacement surgery.

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

Who should not take ELIQUIS (apixaban)?

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?

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 (apixaban). Refill your prescription before you run out.** When leaving the hospital following hip or knee replacement, be sure that you will have ELIQUIS available to avoid missing any doses. **If you are taking ELIQUIS for atrial fibrillation, stopping ELIQUIS may increase your risk of having a stroke.**

What are the possible side effects of ELIQUIS?

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

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

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

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

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

Manufactured by:
Bristol-Myers Squibb Company
Princeton, New Jersey 08543 USA

Marketed by:
Bristol-Myers Squibb Company
Princeton, New Jersey 08543 USA
and
Pfizer Inc
New York, New York 10017 USA

Bristol-Myers Squibb | Pfizer

Bristol-Myers Squibb | PATIENT ASSISTANCE FOUNDATION

This independent, non-profit organization provides assistance to qualifying patients with financial hardship who generally have no prescription insurance. Contact 1-800-736-0003 or visit www.bmspaf.org for more information.

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

Smart Watches Flunk Out

You can now control your phone from your wrist. But why would you ever want to?

Electronics companies sometimes seem like a pack of overcaffeinated lemmings. They all bolt as a herd, en masse, without realizing that nobody is leading them.

That's why the industry keeps spending so many billions on tech products that nobody buys. We were supposed to want to surf the Web on our TV sets. We were supposed to want our refrigerators connected to the Internet. Apparently "if you build it, they will come" doesn't always apply to gadgets.

Which brings us to smartwatches.

You can't blame the tech companies for thinking of smartwatches. The march of progress has always meant smaller and smaller machines. We can now cram storage, processors, sensors and wireless features into a matchbook-sized package. Wouldn't it be cool to strap it onto your wrist?

Well, yes and no.

First of all, miniaturization hasn't marched on enough. Smartwatches are still too bulky; the Samsung Galaxy Gear watches, versions 1 and 2, are so chunky, they make you stand lopsided.

That's a particular problem in watches because they are supposed to be fashion. They're on your body for looks. The first smartwatches seem to miss that point.

The second problem is that most smart watches depend on a companion smartphone. It's the phone that receives your text messages, calls and e-mails and sends them to your wrist.

On one hand, you can see who's trying to reach you without having to extract your phone from your pocket or purse. And you feel the watch's vibration, so you don't miss the incoming communication in a noisy place.

But Samsung's Gear watches work only with certain Samsung phone models; Apple's rumored smartwatch will, of course, work only with an iPhone. And watches are fashion, remember? Without freedom of choice, you don't have much range of expression. So there goes fashion.

The biggest problem, though, is that these first smartwatches don't know what they want to be. We know that putting a computer on your wrist is possible—but nobody's convincingly answered the question, "Why should I?"

What problems do a smartwatch solve that haven't already been solved by the smartphone? The notification-of-calls-and-texts thing: yes, that's useful.

The apps thing: On the Pebble watch—compatible with iPhone and Android—as well as on Sony's and Samsung's watches, you can install tiny apps. They're stripped-down versions of the apps you can already get on your phone. Not convincing.

The making-calls-on-your-wrist thing: I'm not so sure. If you're going to hold your wrist up to your ear to talk, why not just hold your phone? The usual answer is, "Because the watch lets you have both hands free while you're driving." But as you know, you shouldn't be making calls at all while you're driving.

The taking-pictures-with-a-hidden-lens-on-the-wristband thing: Does the world really need another way to be a creep?

Here's one thing that really does make tremendous sense: fitness tracking. All those Fitbit and Jawbone UP bands measure your activity and sleep in truly enlightening, habit-changing ways. Those aren't watches—they're glorified pedometers—but they really work, and they're popular.

That, surely, is why Samsung's new Gear Fit watch includes fitness monitors and why Apple has been hiring engineers from Nike.

In other words, lest you think I'm just a knee-jerk crab apple, I do believe that smartwatches are coming. Google has announced an Android operating system just for watches, and Apple entering the field will trigger a gigantic wave of competitors. Somebody will figure out what is genuinely useful about having a screen on your wrist—and make sure that it's small and good-looking enough that you'd want to wear it.

And that should be enough to tide us over—until we implant our computers inside our heads. SA

SCIENTIFIC AMERICAN ONLINE
What the perfect smartwatch would be: ScientificAmerican.com/jun2014/pogue

Illustration by Lily Padula

BEHAVIORAL SCIENCE

GOOD HABITS, BAD HABITS

Researchers are pinpointing the brain circuits that can help us form good habits and break bad ones

By Ann M. Graybiel and Kyle S. Smith

IN BRIEF

As we repeat a behavior, it becomes laid down in special habit circuits involving the brain's striatum. The circuits treat the habit as a single "chunk," or unit, of automatic activity.

Another brain region, the neocortex, monitors the habit, however. Tweaking the neocortex in laboratory rats with light signals can interrupt a habit and even prevent one from forming.

By learning more about how these brain structures operate, researchers could find drugs, behavioral therapies and simple tricks to help us control habits, good and bad.

Illustration by Marek Haiduk

Ann M. Graybiel is an Institute Professor at the Massachusetts Institute of Technology and an investigator at the McGovern Institute for Brain Research at M.I.T.

Kyle S. Smith is an assistant professor of psychological and brain sciences at Dartmouth College.

EVERY DAY WE ALL ENGAGE IN A SURPRISING NUMBER OF HABITUAL BEHAVIORS. MANY OF THEM, FROM brushing our teeth to driving a familiar route, simply allow us to do certain things on autopilot so that our brains are not overtaxed by concentrating on each brushstroke and countless tiny adjustments of the steering wheel. Other habits, such as jogging, may help keep us healthy. Regularly popping treats from the candy dish may not. And habits that wander into the territory of compulsions or addictions, such as overeating or smoking, can threaten our existence.

Even though habits are a big part of our lives, scientists have had a hard time pinning down how the brain converts a new behavior into a routine. Without that knowledge, specialists have had difficulty helping people break bad habits, whether with medicines or other therapies.

New techniques are finally allowing neuroscientists to decipher the neural mechanisms that underlie our rituals, including defining our so-called habit circuits—the brain regions and connections responsible for creating and maintaining our routines. The insights from this work are helping neuroscientists to figure out how the brain builds good habits and why all of us seem to struggle with breaking habits that we do not particularly care for, as well as those we are told to stop by doctors or loved ones. The research suggests that by deliberately conditioning our brain, we might be able to control habits, good and bad. That promise springs from one of several surprises: that even when it seems we are acting automatically, part of our brain is dutifully monitoring our behavior.

WHAT IS A HABIT, REALLY?

HABITS SEEM TO STAND OUT as clear-cut actions, but neurologically, they fall along a continuum of human behavior.

At one end of that continuum are behaviors that can be done automatically enough to let us free up brain space for different pursuits. Others can command a lot of our time and energy. Our habits emerge naturally as we explore our physical and social environments and our inner feelings. We try out behaviors in particular contexts, find which ones seem beneficial and not too costly, and then commit to those, forming our routines.

We all begin this process when we are very young. Yet it comes with a trade-off that can work against us. The more routine a behavior becomes, the less we are aware of it. We lose the fully alert surveillance of that behavior. Did I actually turn off the stove before I left the house? Did I lock the door? This loss of surveillance not only can interfere with our daily functioning, it also can allow bad habits to creep up on us. Many people who gain weight, just a couple of pounds at a time, suddenly realize that they have been going to the snack aisle or the doughnut shop more and more frequently, scarcely thinking about it as they do.

This insidious failure to check our actions also means that habits can become akin to addictions. Witness computer gaming, Internet gambling, and constant texting and tweeting—and of course alcohol and drug use. A repetitive, addiction-driven pattern of behavior can take over part of what had been deliberate choice. Neuroscientists are still grappling with whether addictions are like normal habits, only more so, although they certainly can be thought of as extreme examples at the other end of the continuum. So can certain neuropsychiatric conditions such as obsessive-compulsive disorder—in which thoughts or actions become all-consuming—and some forms of depression, in which negative thoughts may run in a continuous loop. And extreme forms of habit may be involved in autism and schizophrenia, in which repetitive, overly focused behaviors are a problem.

DELIBERATE BEHAVIOR BECOMES ROUTINE

ALTHOUGH HABITS FALL ALONG different parts of the behavior spectrum, they share certain core features. Once they form, for example, they are stubborn. Tell yourself to "stop doing that," and most of the time the lecture fails! Part of the reason may be that this critique usually happens too late, after the behavior plays out and its consequences are being felt.

This stubbornness, in particular, has been a clue to uncovering the brain circuitry responsible for habit formation and maintenance. Habits become so ingrained that we perform them even when we do not want to, in part because of what are called "reinforcement contingencies." Say you do A, and then you are rewarded somehow. But if you do B, then you are not rewarded or are even punished. These consequences of our actions—the contingencies—push our future behavior one way or another.

Signals discovered in the brain seem to correspond to this rein-

forcement-related learning, as shown in studies originally conducted by Wolfram Schultz and Ranulfo Romo, both then at the University of Fribourg in Switzerland, and today modeled by computational scientists. Particularly important are "reward-prediction error signals," which, after the fact, indicate the mind's assessment of how accurate a prediction about a future reinforcement actually turned out to be. Somehow the brain computes these evaluations, which sculpt our expectations and add or subtract value from particular courses of action. By monitoring our actions internally and adding a positive or negative weight to them, the brain reinforces specific behaviors, shifting actions from deliberate to habitual—even when we know we should not gamble or overeat.

We and others wondered what goes on in the brain's wiring to cause this shift and whether we could interrupt it. In the Graybiel lab at the Massachusetts Institute of Technology, our group began experiments to decipher which brain pathways were involved and how their activity might change as habits formed.

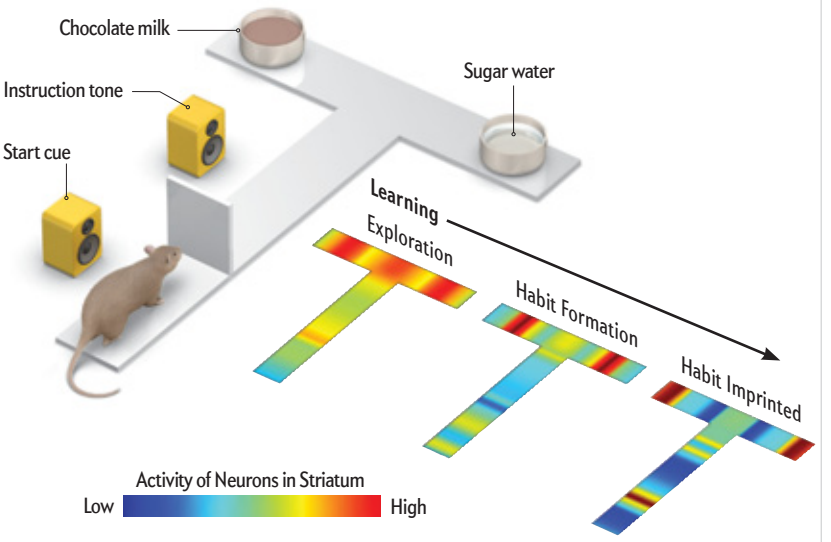
First, we needed an experimental test for determining whether a behavior is a habit. British psychologist Anthony Dickinson had devised one in the 1980s that is still widely used. He and his colleagues taught lab rats in a test box to press a lever to receive a food treat as a reward.

When the animals had learned this task well and were back in their cages, the experimenters "devalued" the reward, either by letting the rats eat the reward to the point of oversatiation or by giving them a drug that produced mild nausea after the reward was eaten. Later on, they brought the rats back to the experimental box and gave them the choice of pressing the lever or not. If a rat pressed the lever even though the reward was now sickening, Dickinson considered the behavior to be a habit. But if a rat was "mindful"—if we can speak of mindfulness in a rat—then it did not press the lever, as though it realized that the reward was now unpleasant; it had not formed a habit. The test gave scientists a way to monitor whether or not a shift from purposeful to habitual behavior had occurred.

THE EXPERIMENT

Acting without Thinking

Tests on rats revealed that the brain treats a habit as a single unit of behavior. The rats learned to run down a T-maze and turn left or right toward a reward, depending on an instruction sound. During early runs (*first colored T*), activity in the brain's striatum was high (*yellow* and *red*) most of the time. As a habit formed (*second T*), activity quieted (*green* and *blue*) except when the rat had to decide to turn or to drink. Once a habit set in (*third T*), activity was high only at the start and finish, marking one unit of behavior.



IMPRINTING A HABIT ON THE BRAIN

BY USING VARIATIONS of this basic test, researchers, including Bernard Balleine of the University of Sydney and Simon Killcross of the University of New South Wales in Australia, have found clues suggesting that different brain circuits take the lead as deliberate actions become habitual. New evidence from experiments on rats, as well as on humans and monkeys, now points to multiple circuits that interconnect the neocortex—regarded as the crowning glory of our mammalian brain—and the striatum, at the center of the more primitive basal ganglia, which sit at the core of our brain [*see box on next page*]. These circuits become more or less engaged as we act deliberately or habitually.

We taught rats and mice to perform simple behaviors. In one task, they learned to run down a T-shaped maze once they heard a click. Depending on an audio "instruction" cue that then sounded as they ran, they would turn left or right toward the top of the T and run to that end to receive one kind of reward or another. Our goal was to understand how the brain judges the pros and cons of behaving in a particular way and then stamps a sequence of behavior as a "keeper"—a habit. Our rats certainly did develop habits! Even when a reward had become distasteful, the rats would run to it when the instruction tone sounded.

To figure out how the brain stamps a behavior as one to make a habit, the M.I.T. lab began recording the electrical activity of small collections of neurons (brain cells) in the striatum. What our group found surprised us. When the rats were first learning the maze, neurons in the motor-control part of the striatum were active the whole time the rats were running. But as their behavior became more habitual, neuronal activity began to pile up at the beginning and end of the runs and quieted down during most of the time in between. It was as though the entire behavior had become packaged, with the striatal cells noting the beginning and end of each run [*see box above*]. This was an unusual pattern; what seemed to be happening was that the striatal cells were malleable and could help package movements together while leaving relatively few "expert cells" to handle the details of the behavior.

COURTESY OF ANN M. GRAYBIEL (*heat maps*)

Illustrations by AXS Biomedical Animation Studio

The future, just a bit ahead of schedule.

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To this day, nothing can replicate the feeling you get when driving a Porsche. No other combination of sound, feel, sight and soul will connect in quite the same way. Nothing else is simultaneously as recognizable yet breathtakingly novel.

Keeping it this way requires vigilance. So we remember to honor the past but charge fearlessly into the future. We cast a skeptical eye at the word “impossible.” And we fiercely resist dilution at every step.

Otherwise, a Porsche could become interchangeable with, dare we say it, some other car. Which is the moment a Porsche ceases to be a Porsche.

Porsche. There is no substitute.

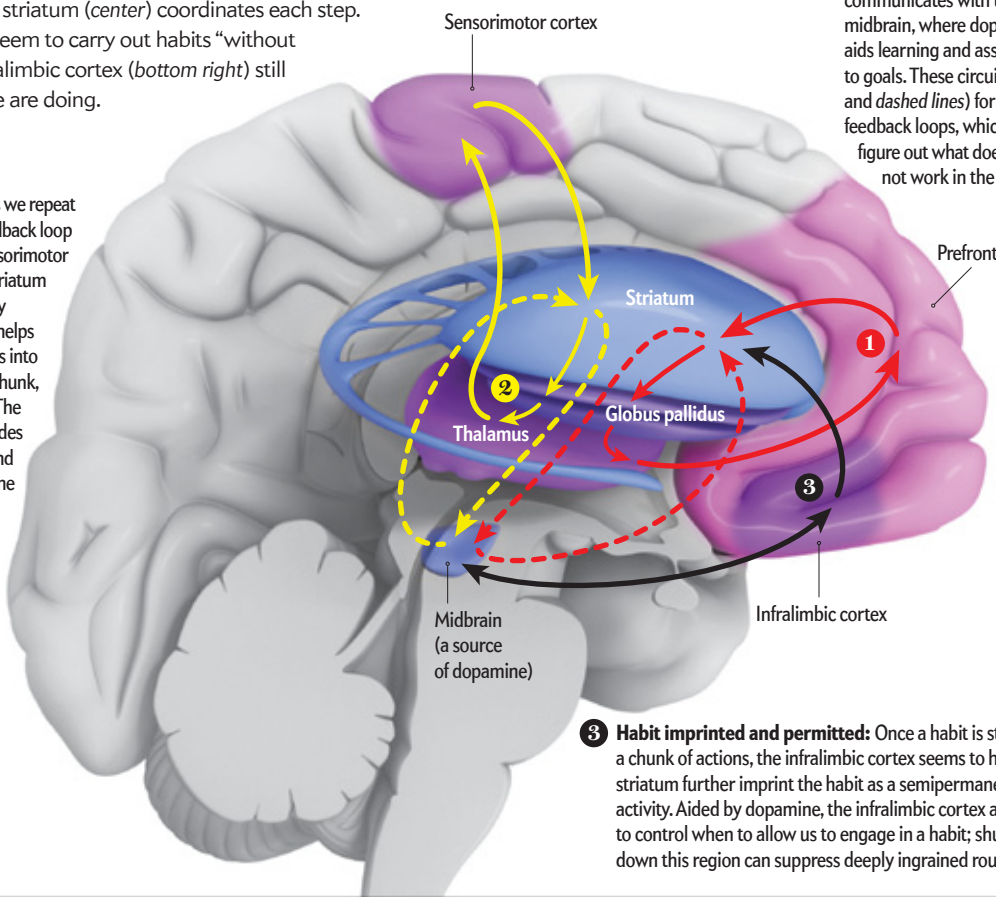
PORSCHE

How Habits Form

We use three steps to learn and lock in habits: explore a new behavior, form a habit, then imprint it into the brain (*colored numbers*). Although scientists have not refined all the details, the striatum (*center*) coordinates each step. Even though we seem to carry out habits "without thinking," the infralimbic cortex (*bottom right*) still monitors what we are doing.

1 New behavior explored: The prefrontal cortex communicates with the striatum, and the striatum communicates with the midbrain, where dopamine aids learning and assigns value to goals. These circuits (*solid* and *dashed lines*) form positive feedback loops, which help us figure out what does and does not work in the behavior.

2 Habit forms: As we repeat a behavior, a feedback loop between the sensorimotor cortex and the striatum becomes strongly engaged, which helps us stamp routines into a single unit, or chunk, of brain activity. The chunk partly resides in the striatum and relies on dopamine input from the midbrain.



3 Habit imprinted and permitted: Once a habit is stored as a chunk of actions, the infralimbic cortex seems to help the striatum further imprint the habit as a semipermanent brain activity. Aided by dopamine, the infralimbic cortex also seems to control when to allow us to engage in a habit; shutting down this region can suppress deeply ingrained routines.

This pattern reminded us of the way the brain lays down memories. We all know how helpful it is to remember a string of numbers as larger units instead of one by one—such as thinking of a phone number as "555-1212" instead of "5-5-5-1-2-1-2." The late American psychologist George A. Miller coined the term "chunking" to refer to this packaging of items into a memory unit. The neural activity we observed at the beginning and end of a run seemed similar. It is as though the striatum sets up boundary markers for chunks of behavior—habits—that the internal evaluation process has decided should be stored. If true, this maneuver would mean that the striatum essentially helps us combine a sequence of actions into a single unit. You see the candy dish, and you automatically reach for it, take a treat and eat it "without thinking."

Researchers have also identified a "deliberation circuit," which involves another part of the striatum and is active when choices are not made on autopilot and instead require some decision making.

To understand the interplay between these deliberation and habit circuits, our group's Catherine Thorn recorded signals in both circuits simultaneously. As the animals learned a task, activity in the deliberation part of the striatum became strong during the middle of the runs, especially when the rats had to decide which way to turn at the top of the T, based on the instruction tone. This pattern was almost the exact opposite of the chunking pattern that we had seen in the habit striatum. And yet the activity did recede as the behavior became fully habitual. The pattern means that as we learn habits—at least as rats do—habit-related circuits gain strength, but changes in related circuits occur, too.

Because the striatum works together with a habit-related part of the neocortex at the front of the brain known as the infralimbic cortex, we then recorded activity in that region. This was an eye-opener as well. Even though we saw the beginning-and-end pile-up of activity in the habit striatum, during the initial learning period we saw very little change in the infralimbic cortex. It was not until the animals had been trained for a long time and the habit became fixed that the infralimbic activity changed. Strikingly, when it did, a chunking pattern then developed there, too. It was as though the infralimbic cortex was the wise one, waiting

SCIENTIFIC AMERICAN ONLINE For insight about whether obsession is a habit, see ScientificAmerican.com/jun2014/graybiel

until the striatal evaluation system had fully decided that the behavior was a keeper before committing the larger brain to it.

STOP THAT!

WE DECIDED TO TEST whether the infralimbic cortex has online control over whether a habit can be expressed by using a new technique called optogenetics. With this technique, we could place light-sensitive molecules in a tiny region of the brain, and then, by shining light on the region, we could turn the neurons in that region on or off. We experimented with turning off the infralimbic cortex in rats that had fully acquired the maze habit and had formed the chunking pattern. When we turned off the neocortex just for a few seconds while the rats were running, we totally blocked the habit.

The habit could be blocked rapidly, sometimes immediately, and the habit blockade endured even after the light was turned off. The rats did not stop running in the maze, however. It was just the habitual runs to the devalued reward that were gone. The animals still ran just fine to reach the good reward on the other side of the maze. In fact, as we repeated the test, the rats developed a new habit: running to the good-reward side of the maze no matter what cue they were given.

When we then inhibited the same tiny piece of infralimbic cortex, we blocked the new habit—and the old habit instantly reappeared. This return of the old habit happened in a matter of seconds and lasted for as many runs as we tested, without our having to turn off the infralimbic cortex again.

Many people know the feeling of having worked hard to break a habit only to have it come back, full-blown, after a stressful time or after one relapse. When Russian scientist Ivan Pavlov studied this phenomenon in dogs many years ago, he concluded that animals never forget deeply conditioned behaviors such as habits. The most they can do is suppress them. We are finding the same stubbornness of habits in our rats. Yet remarkably, we can toggle the habits on and off by manipulating a tiny part of the neocortex during the actual behavior. We do not know how far this control could reach. For example, if we taught the rats three different habits in a row, then blocked the third one, would the second habit appear? And if we then blocked the second one, would the first one appear?

A key question was whether we could prevent a habit from forming in the first place. We trained rats just enough to have them reach the correct end of the T but not enough for the behavior to settle in as a habit. We then continued the training, but during each run we used optogenetics to inhibit the infralimbic cortex. The rats continued running well in the maze, but they never acquired the habit, despite many days of overtraining that usually would have made the habit permanent. A group of control rats that underwent the same training without the optogenetic interruption did form the habits normally.

BREAKING BAD HABITS

OUR EXPERIMENTS OFFER some curious lessons. First, no wonder habits can be so difficult to break—they become laid down and marked as seemingly standardized chunks of neural activity, a process involving the work of multiple brain circuits.

Yet surprisingly, even though habits seem nearly automatic, they are actually under continual control by at least one part of the neocortex, and this region has to be online for the habit to be enacted. It is as though the habits are there, ready to be reeled off, if the neocortex determines that the circumstances are right. Even if we are not conscious of monitoring our habitual behaviors—after all, that is a large part of their value to us—we have circuits that actively keep track of them on a moment-to-moment basis. We may reach out for the candy dish without "thinking," but a surveillance system in the brain is at work, like a flight-monitoring system in an airliner.

So how close are we to helping people clinically? It will likely be a long time before anyone can flip a switch to zap away our pesky habits. The experimental methods that we and others are using cannot yet be translated directly to people. But neuroscience is changing at lightning speed, and those of us in the field are closing in on something truly important: the rules that habits work by. If we can fully understand how habits are made and broken, we can better understand our idiosyncratic behaviors and how to train them.

It is also possible that our expanding knowledge could even help people at the severe end of the habit spectrum, providing clues for how to treat obsessive-compulsive disorder, Tourette's syndrome, fear or post-traumatic stress disorder.

Drug treatments and other emerging therapies could possibly do the trick to help with such harmful habits. But we are also impressed by how the lessons we have learned from this brain research support behavioral therapy strategies, which are often suggested for helping us to establish healthy habits and weed out unhealthy ones. If you want to condition yourself to jog in the morning, then perhaps you should put out the running shoes the night before, where you cannot miss them when you wake up next day. This visual cue mimics the audio cue we used to train the rats—and it could be especially effective if you reward yourself after the jog. Do this on enough mornings, and your brain might develop the chunking pattern that you want. Alternatively, if you want to forgo the candy dish, you could remove it from the living room or office—eliminating the cue.

Changing habits might never be easy. As Mark Twain said, "Habit is habit, and not to be flung out the window by any man, but coaxed downstairs one step at a time." Our experiments, however, lead us to an optimistic point of view: by learning more about how our brains establish and maintain routines, we hope we can figure out how people can coax themselves out of undesirable habits and into the ones they want. SA

MORE TO EXPLORE

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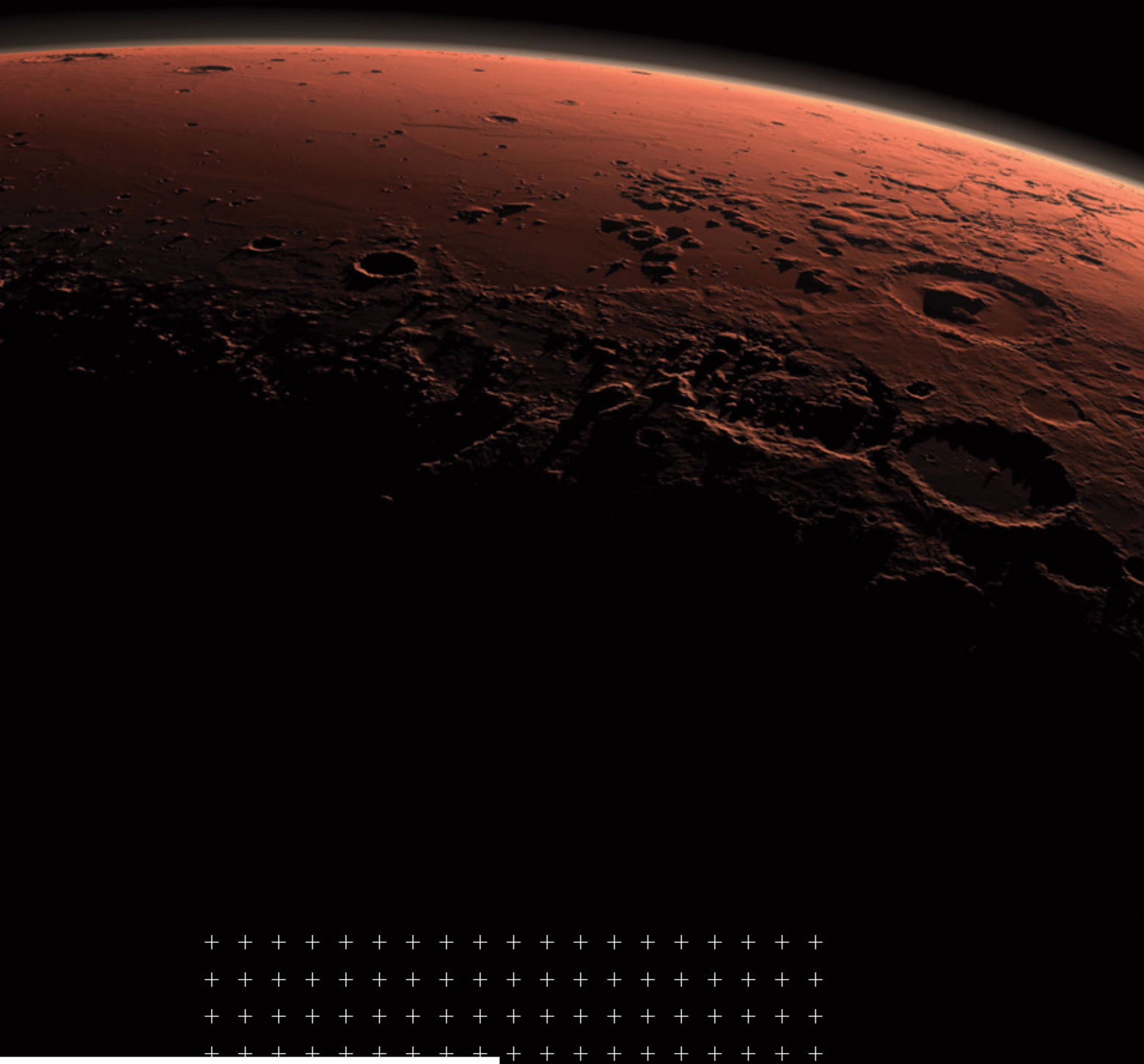
Experiments now under development could finally answer one of the



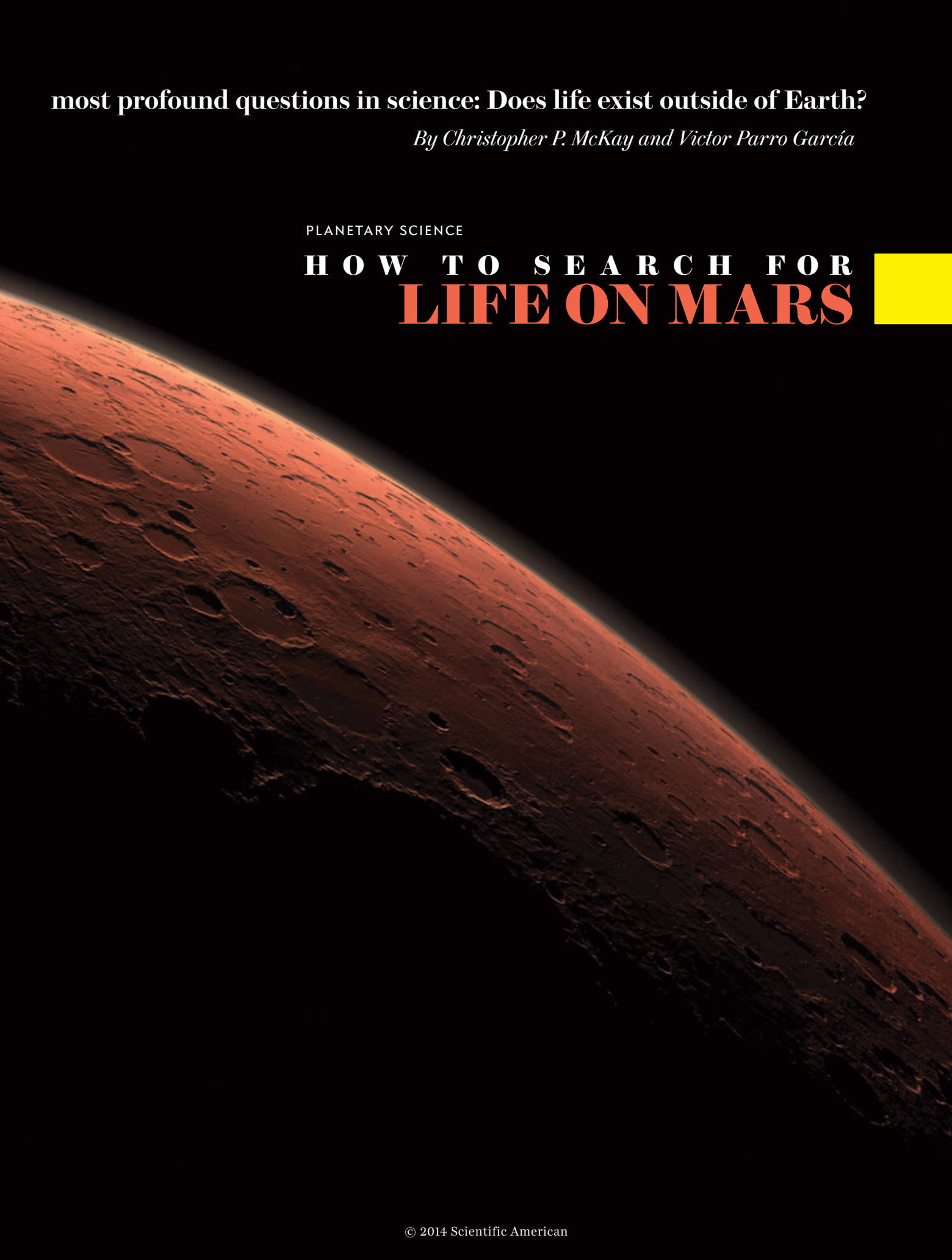
GALE CRATER—seen to the left of center in this composite image, distinguished by the mountain inside—once held liquid water. Earlier this year the Curiosity rover found evidence of organic molecules on its plains.

most profound questions in science: Does life exist outside of Earth?

By Christopher P. McKay and Victor Parro García

PLANETARY SCIENCE

HOW TO SEARCH FOR LIFE ON MARS



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Victor Parro García is a scientist at the Center for Astrobiology in Spain.

Astronomers have learned a great many things about Mars since the first probes landed there nearly four decades ago.

We know that liquid water once flowed across its surface and that Mars and Earth were similar in their early history. When life on Earth arose, some 3.5 billion years ago, Mars was warmer than it is today and had liquid oceans, an active magnetic field and a thicker atmosphere. Given the similarity between the two planets, it seems reasonable to think that whatever steps led to life on Earth could also have occurred on Mars.

In fact, for all we know, microscopic life might still exist on the Red Planet. Every mission to our neighbor in the past 35 years has examined its geology, not its biology. Only the twin Viking 1 and 2 spacecraft, which touched down in 1976, conducted the first and thus far only search for life on another world. Each spacecraft carried four experiments relevant to the search, and each experiment returned ambiguous data. The Viking missions gave us puzzles, not answers. Yet we now know that Viking's methods would not have been able to find life on Mars even if it were there—which means the question of whether the planet harbors life remains open.

Fortunately, in the intervening decades microbiologists have developed a cornucopia of tools for detecting microorganisms. These tools are now unexceptional here on Earth. But if applied by one of the several missions soon expected to head for Mars, they could deliver a first: a definitive answer as to whether our closest neighbor also pulses with life.

THE FIRST SEARCH

THE VIKING EXPERIMENTS looked for life using standard search techniques of the time. In the initial experiment, the lander took a scoop of Martian soil and added carbon compounds as food for any microorganisms that might be in the soil. If microbes did exist in the soil, we might expect them to consume the food and release carbon dioxide.

In fact, the Viking missions did see this behavior. On its own, the test would seem to indicate that microorganisms were present in the Martian soil. When combined with the results of the other experiments, however, researchers could not be sure.

The second experiment looked for evidence of photosynthesis but returned inconclusive results. A third experiment added water into a soil sample. If life were present, the moist soil might have produced carbon dioxide. Instead it produced oxygen. This was very strange, as no known soil on Earth does this. Scientists concluded that the oxygen came from a chemical reaction.

In the final experiment, the landers searched for organic compounds in the soil. Organics are carbon-containing compounds that form the building blocks of life. If any life existed on Mars, we would expect to find these compounds. Yet organics alone would not provide definitive evidence of life, because we also expect meteorites to continuously deposit organic com-

IN BRIEF

No mission to Mars has searched for life since the Viking program in the 1970s. Those missions did not find convincing evidence for life, and we now know that their experiments were doomed to fail. **A modern search for life** on Mars could employ biological tests that we commonly use on Earth. **Such experiments** could be included on a number of missions that are scheduled to travel to Mars by the end of this decade.

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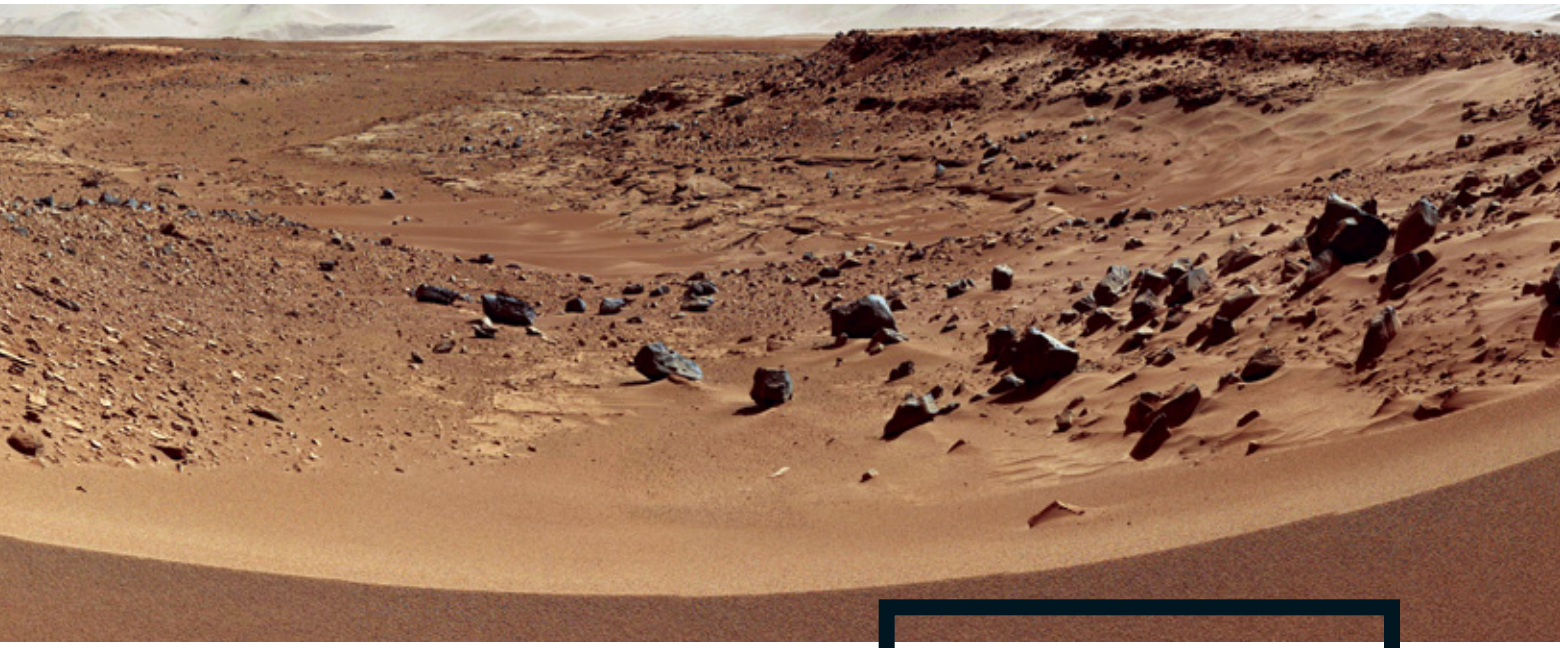


DRY NOW, Gale Crater once held a freshwater lake that could have supported life. The Curiosity rover's successor will be able to carry experiments that could determine whether traces of life still exist.

pounds on Mars. Puzzlingly, the experiment found no evidence of organics whatsoever.

Taken together, the findings left investigators stumped. Most scientists believed that chemical reactions were responsible for the results in the last two experiments, but chemistry could not quite explain the first. A small but vocal minority of Mars scientists held that the first experiment did, in fact, find evidence of life. But most everyone else concluded that Mars was barren.

In 2008, 32 years after Viking landed, the solution to these puzzles began to emerge when NASA's Phoenix lander touched down in the northern polar region of Mars. To everyone's surprise, Phoenix detected perchlorate, a rare molecule on Earth that features four oxygen atoms connected to a chlorine ion, which are connected to a magnesium or calcium ion. When perchlorate salts reach 350 degrees Celsius, they decompose, releasing reactive oxygen and chlorine. Perchlorates are so reactive that they are used in many rocket fuels.

This finding made investigators see that the perchlorates could well have obliterated signs of life in the soil. Viking's organic search experiment first heated the soil sample to 500 degrees C so that it might vaporize any organic molecules and detect them in gaseous form. But in 2010 a team led by Rafael Navarro-González of the National Autonomous University of Mexico, which included one of us (McKay), showed that perchlorate would have completely destroyed any carbon compounds in the soil during the heating process.

Perchlorate also illuminates the puzzles of the first and third experiments. In the first experiment, adding food to the soil generated carbon dioxide. But perchlorate produces bleachlike compounds when exposed to cosmic rays. These compounds can decompose organic molecules (such as those found in the added food), producing carbon dioxide in the process. In the third experiment, oxygen emerged from moistened soil. The perchlorate bleach production also forms oxygen, yet the oxygen remains initially trapped in the soil. It is released only later, once the soil is wetted, as happened on Viking. Two mysteries solved.

Yet hope for the discovery of life is not lost. The Curiosity rover landed on Mars in 2012 and has been taking samples of the soil ever since. Earlier this year the Sample Analysis at Mars (SAM) instrument team (which includes McKay), led by Paul Mahaffy of the NASA Goddard Space Flight Center, reported that the experiment found carbon compounds in ancient mudstone sediments on the bottom of Gale Crater, even in the presence of perchlorate. Organics exist on Mars—Viking was just unable to find them. Could the same be true for life itself?

MODERN APPROACHES

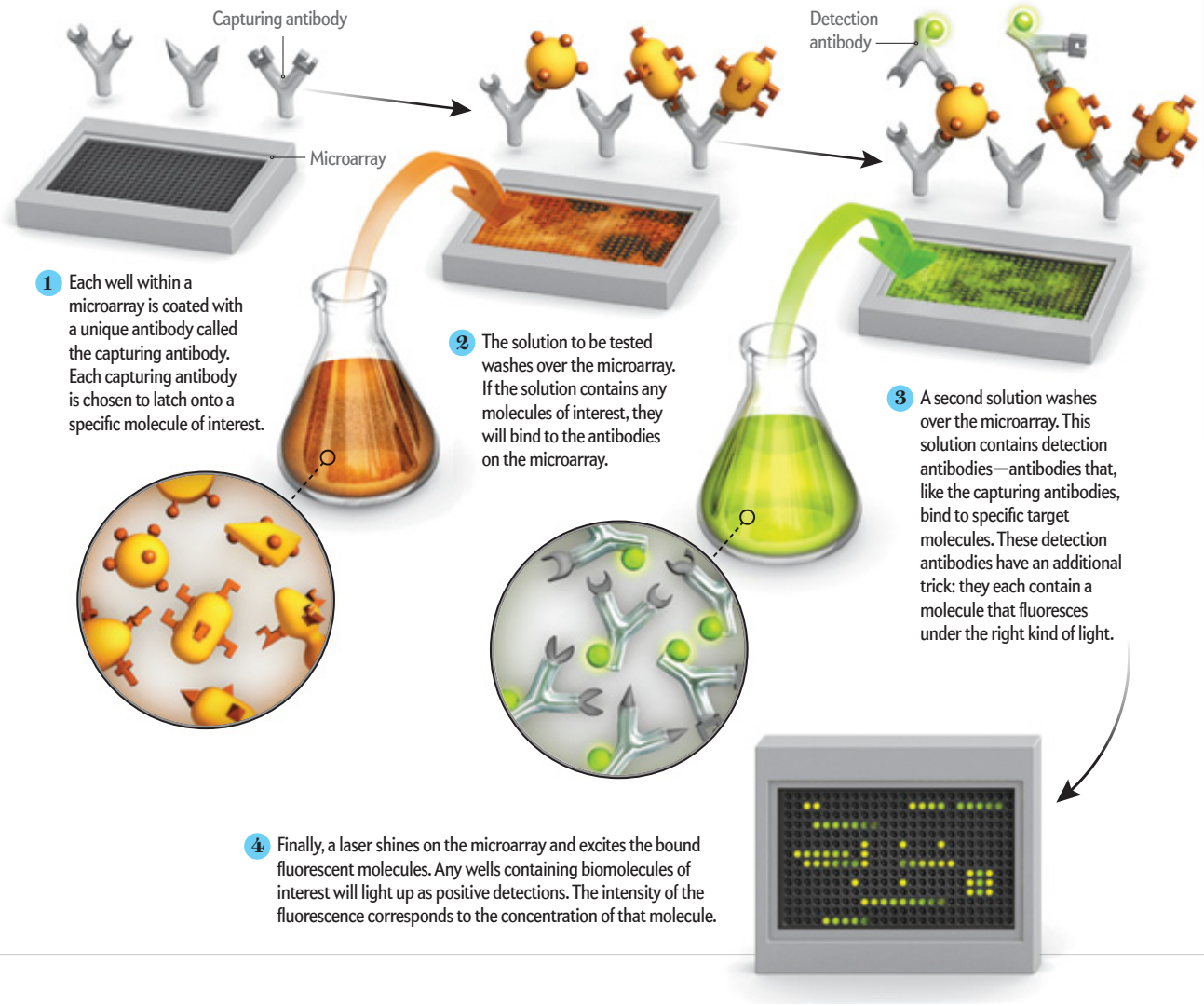
IN THE 40 YEARS since the Viking landers were built, microbiology technology has changed dramatically. The Viking missions used culture-based methods, in which microorganisms grow in petri dishes. But these are no longer considered definitive, and we now know that only a small fraction of soil microbes can be cultured. Scientists have developed vastly more sensitive techniques that directly detect the biomolecules in microbial lifeforms. These new methods provide the basis for a novel way to search for evidence of life on Mars.

The most widely known method is DNA detection and sequencing. No longer is it necessary to culture an organism so that it will replicate sufficiently to provide enough DNA for sequencing. Several teams are working on ways to incorporate DNA-extraction technologies into instruments suitable for upcoming Mars missions.

One drawback of relying on DNA detection to reveal life on Mars is that although DNA is common to all life on Earth, it may

The Martian Protein Detector

Immunoassay tests exploit the Velcro-like nature of antibodies—Y-shaped proteins found in the immune system—to act as precise detectors of foreign molecules. A single immunoassay test can detect hundreds of biological molecules (such as proteins), as well as molecule fragments. These tests are being optimized to search for evidence of life on Mars.



not occur in alien life. Or if it is present, it may be so different that DNA detectors built to find Earth biology will miss it.

Fortunately, Mars could harbor other signs of life. Among these biomarkers are proteins and polysaccharides. Proteins are long, linear chains composed of various mixtures of the 20 different kinds of amino acids used by life. Amino acids are present in meteorites and are likely to have been a common component of the prebiotic environment on any world. Polysaccharides are long chains of sugars constructed by enzymes (biological catalysts), which themselves are proteins.

Detecting molecules as complex as a protein or a polysaccharide would be strong evidence of life, widely defined: a biological system that encodes information and uses this information to build complex molecules. These complex molecules would stand out against any background of simple prebiotic molecules like a skyscraper would stand out against a field of boulders.

One of us (Parro García) has been developing an instrument for detecting such complex molecules on Mars. It is based on a technique—immunoassay testing—already in use for simultaneously detecting hundreds of different types of proteins, polysaccharides and other biomolecules (including DNA itself).

Immunoassay tests employ antibodies—Y-shaped proteins—each of which binds to just one type of biomolecule [*see box above*]. In an immunoassay test, a solution that might contain substances of interest is poured over a large array of antibodies, each one designed to bind to a specific target. If the sample solution contains a biomolecule that links to an antibody in the array, the antibody will capture and, by binding, identify it.

One nice feature of immunoassays is that antibodies can detect molecules that are smaller and less complex than full proteins are.

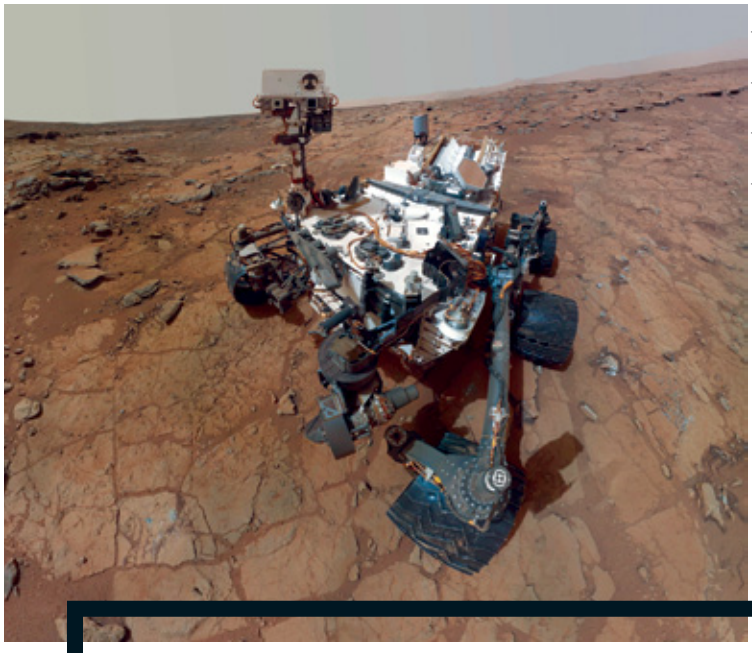
SCIENTIFIC AMERICAN ONLINE How to land safely on Mars—watch a video at ScientificAmerican.com/jun2014/mars

Illustration by Emily Cooper

The test can thus search for molecules that are life-related but of lesser complexity, such as fragments of proteins that have broken into bits. Finding these bits would also imply that life exists.

All of Earth's organisms collectively contain many millions of different proteins. With so many to choose from, how do we pick the few hundred that a single immunoassay test could search for? The short answer is that we can't know for sure. But we can make educated guesses based on two strategies: First, we could search for proteins that would be useful or essential to survival on Mars. For example, we might search for enzymes that consume perchlorate, cold-adapted enzymes that would allow a microorganism to survive Mars's frigid temperatures or enzymes that would repair damage to DNA caused by Mars's strong ionizing radiation. Second, we could target molecules that are ubiquitous throughout the microbial world, such as peptidoglycan, which is a universal component of all bacterial cell walls, or adenosine triphosphate (ATP), which is used by all living organisms on Earth to transport chemical energy for metabolic activity.

Even if Mars's harsh environment has destroyed large molecules such as DNA and proteins, we might still find evidence for life in the debris. The key will be searching for patterns. Many types of molecules are chemically equivalent to one another but may have opposite "chirality"—their bonds may twist to the left or the right. Life on Earth is dominated by left-handed amino acids. If an experiment detects amino acids and finds a particular set that has a dominant left- or right-handed chirality, this would be compelling evidence for the presence of life. Interestingly, if that chirality were right-handed—the opposite of Earth proteins—it would be evidence that the life-forms on Mars evolved independently from Earth life.



CURIOSITY SELF-PORTRAIT shows where it first drilled into the soil. Any microbes would have to live far below the surface.

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MISSION PLANNING

VIKING CARRIED THREE biology experiments; we might imagine a mission to Mars that also carries three biomarker search instruments—perhaps a DNA detector, an immunoassay microchip, and an instrument to detect and characterize amino acids. The technology is nearly ready. The next task is to pick a target—the location that holds the best chance of harboring biomarkers.

Ice and salt are friends to biomarkers, protecting them from damage and decay. The enemies? Ionizing radiation and heat. Fortunately, the low temperatures on Mars make thermal decay negligible even over the age of the planet. Ionizing radiation, however, could completely destroy biomarkers that are within the first meter or so of the surface over a few billion years. The promising targets, then, are icy sites that may have harbored recent life—such as the Phoenix landing site near Mars's north pole—or sites where erosion has recently exposed the ancient material. In either case, one would want to drill down to extract samples from a meter or more below the surface.

The missions to Mars that are now being planned could conduct this search. The European ExoMars mission, slated for 2018, should be able to carry a drill. NASA recently announced plans to launch another copy of the Curiosity rover in 2020. ExoMars and the new Curiosity could search the dry equatorial regions of Mars for biomarkers in salt and sedimentary deposits. (Neither rover can function in the polar regions.)

As for a polar search, NASA is studying an inexpensive lander called Icebreaker that could do the job. Equipped with a one-meter drill and an immunoassay instrument, it could search the water-rich northern permafrost of Mars for biomarkers in the ice-cemented ground.

Any one of these missions would be a worthy candidate to lead the next era of Mars exploration. The past few decades of research have left no doubt that Mars once harbored liquid water. The time has now come to test whether that once watery planet provided a home to any life-forms. If we find biological molecules on Mars—and especially if those molecules indicate that Martian life arose independently of Earth life—we will gain a profound insight into life beyond our home. Just as we know there are many stars and many planets, we will know that there are many biologies. We will know the universe is alive with diversity. SA

MORE TO EXPLORE

Signs of Life Detector (SOLID) experiment: http://auditore.cab.inta-csic.es/solid/en
NASA's Mars Exploration Program: http://mars.jpl.NASA.gov

FROM OUR ARCHIVES

The Search for Life on Mars. Norman H. Horowitz; November 1977.
The Red Planet's Watery Past. Jim Bell; December 2006.
Digging Mars. Peter H. Smith; November 2011.
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EPIDEMIOLOGY

GERM C

Machines that can quickly identify virtually any bacterium, virus or fungus are being developed for hospitals. Networking the devices could allow health authorities to save lives by spotting disease outbreaks earlier than ever before

By David J. Ecker

Illustration by I Love Dust

ATCHER

David J. Ecker is a scientist and inventor at Ibis Biosciences, an Abbott company.

I ONCE WALKED THROUGH AN OLD GRAVEYARD near Philadelphia and noticed the years of births and deaths carved on the headstones. It reminded me that up until the early 1900s, most people died before their 50th birthday. The primary causes of these deaths were infectious diseases such as smallpox, influenza and pneumonia.

Today contagious illnesses kill more rarely in developed nations, where improvements in sanitation, nutrition and vaccines and the introduction of antibiotics have virtually eliminated premature deaths from such afflictions. Yet we are perilously close to returning to an era of untimely deaths from these illnesses because many microorganisms are becoming resistant to existing drugs and because the pharmaceutical industry is not developing enough replacements.

Overprescription of antibiotics is one of the most important contributors to this problem and occurs for understandable reasons. Current diagnostic tools typically cannot quickly determine whether any of a wide range of bacteria—the only organisms susceptible to antibiotics—are making someone sick. In most cases, old-fashioned culturing methods that take several days to complete are required to identify specific bacterial strains. Delaying treatment could prove deadly, and so physicians may try to cover all likely possibilities by prescribing powerful so-called broad-spectrum antibiotics that can dispatch many kinds of germs. At times, however, the drugs kill off susceptible bacteria but leave some that are resistant to that particular medication. These antibiotic-resistant bugs then multiply unchecked by their now absent competitors and can silently spread to other people until finding the right conditions to sicken someone else. Such treatment practices help to safeguard many patients' health today, but they also unavoidably guarantee the emergence of more drug-resistant bacteria tomorrow.

Solutions to this paradox may be at hand. New molecular biosensors are being developed that will allow physicians to quickly determine whether a patient is suffering from a bacterial or other kind of infection and which species is responsible. A key time-saving feature of these devices will be that they look for almost all pathogens at once, instead of testing for individual microorganisms, one at a time. Furthermore, clinicians who suspect that bacteria are at work will not have to guess which species might be present. My research at Ibis Biosciences, which is now a part of Abbott, provides the foundation for one such device. Other bioengineers are racing to develop similar products at other companies.

These rapid diagnostic machines are on track to become commercially available in hospitals and clinics in the next few years. With a little bit of forethought and planning, however, we can greatly magnify their benefit by joining them together in a nationwide or even global network of interconnected devices that would provide the first broad-based, real-time early-warning system for outbreaks of new diseases, foodborne illnesses, global pandemics and, potentially, attacks from bioterrorists.

TIME FOR AN UPGRADE

CURRENT METHODS for diagnosing infectious disease are based on culture techniques that date back more than 150 years to Louis Pasteur. Clinicians collect a sample of a patient's tissue—blood, mucus or urine, for example—and transfer it to a nutrient-rich culture bottle or onto a plate containing agar, a gelatin-like seaweed extract that allows pathogens to grow. After a day or two, the individual microbes will multiply so much that laboratory technicians can identify them. Seeing whether—and how quickly—these cultures fail and die when grown in the presence of various drugs also gives an idea of their sensitivity to different medications. Even if this approach were less time-consuming, however, it would not be ideal for making treatment decisions, because many pathogens—for example, those that need special media or growth environments—can be tricky to culture. Sometimes it is impossible to culture bacteria from patients because they might have already been treated with an antibiotic before the specimen was taken for culture.

I first became interested in the problem of infectious disease diagnosis and tracking while working for the Defense Advanced

IN BRIEF

New biosensors are being developed that can identify the viral, bacterial or fungal origin of disease or infection within a few hours of testing a sample from a patient.
Individuals would receive the right treatment sooner, and doctors would be more likely to prescribe antibiotics only when they were truly necessary.
Connecting as few as 200 of these biosensors together into a network could offer the U.S. early warnings of emerging epidemics or bioterrorism attacks.
The greatest obstacles to creating such a network are mostly political and regulatory challenges—not technical ones.

HOW IT WORKS

Instant Biosensor

Sophisticated devices that employ a combination of biological, physical and mathematical tools (*shown below*) are being developed that can identify any of more than 1,000 pathogens that cause human illness. A network of such biosensors distributed across a country or region could provide early warnings of disease outbreaks or biological attacks and identify the most effective treatments.

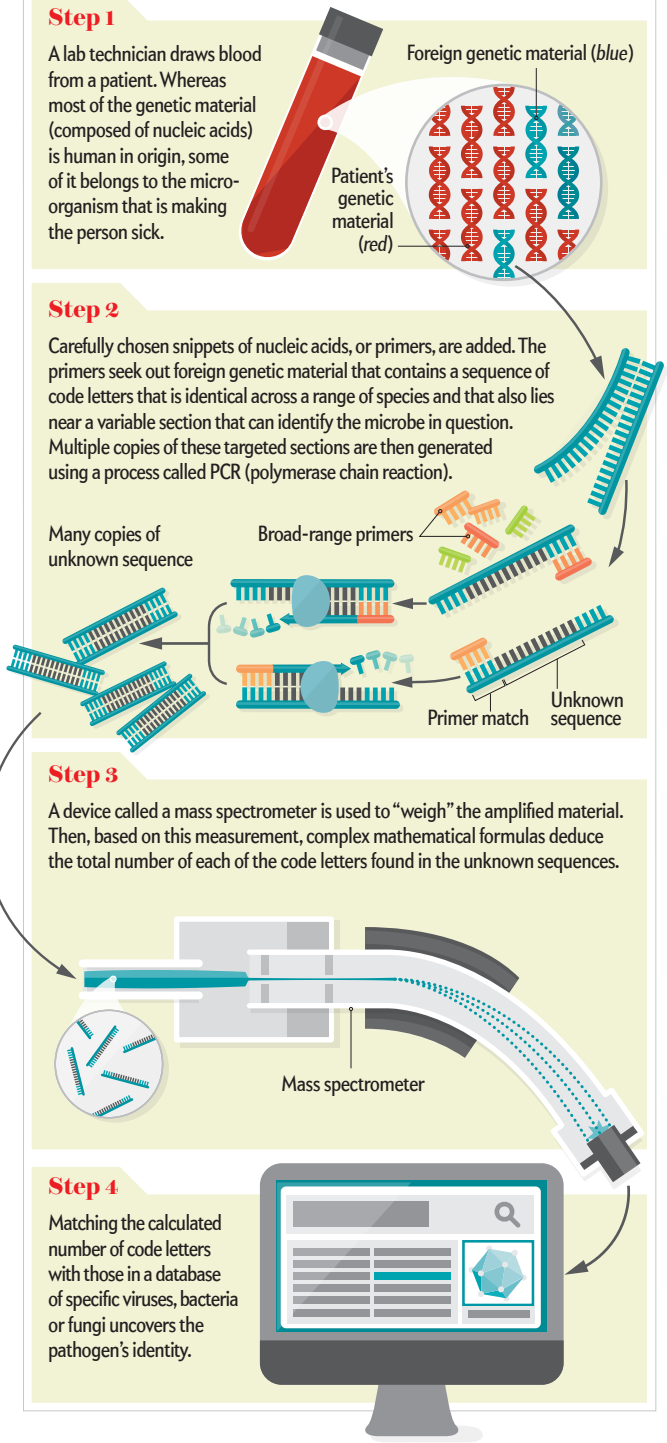

Illustration by Lucy Reading-Ikkanda

Research Projects Agency on new approaches to discovering antibiotics. Our goal was to pick through thousands of compounds to find a few that disabled many different kinds of bacteria by gumming up a specific stretch of RNA—a molecule that is central to the machinery of all living cells—that they shared.

My colleagues and I used devices called mass spectrometers to determine whether the potential drugs had attached themselves to the bacterial RNA. Mass spectrometers are essentially scales that weigh molecules very accurately. (Formally speaking, they determine their mass.) Because we knew the weight of the bacterial RNA in question, we could deduce the weight of any compound that was stuck to it in the same way you might weigh a dog by holding it while standing on a bathroom scale and then subtracting your own weight. Knowing the compound's weight in turn gave us its identity because each compound had its own unique mass.

We soon realized that this same technology could allow us to distinguish among bacteria, viruses, fungi and parasites by weighing some of the organism's RNA or DNA, which is a closely related type of nucleic acid. Each strand of these molecules is made up of subunits, or nucleotides, that are often referred to by the letters that distinguish their nitrogen-containing sections—A (adenine), C (cytosine), G (guanine) and either U (uracil), in the case of RNA, or T (thymine), in the case of DNA. Practically by definition, some portion of those nucleic acids will be unique to different pathogens. Because the molecular weights of the various nucleotides (A, T, C, G and U) significantly differ from one another, we can determine the numbers of each nucleotide present in a particular strand based solely on its mass spectrometry reading. For example, any DNA strand that weighs 38,765.05 daltons (daltons are the standard unit of atomic measurement), as determined by a mass spectrometer, must contain 43 adenine, 28 guanine, 19 cytosine and 35 thymine subunits; that combination is the only one to give precisely that result without having to resort to fractions of a nucleotide, which do not exist in nature. And that information, in turn, tells you what species of microorganism is present.

The method is similar to one you might use to calculate the numbers of unblemished coins in a jar containing only U.S. quarters (which weigh 5.670 grams apiece when brand-new) and nickels (which weigh 5.000 grams apiece). If the total collection weighs 64.69 grams, it must consist of seven quarters and five nickels ($64.69 = 5.67q + 5n$, where q and n can only be positive integers or zero). Any other number of quarters would require fractional nickels.

The process for identifying pathogens requires an ability to distinguish the culprit's DNA or RNA from the patient's own in a specimen being tested. Usually the amount of foreign material is too scant to allow for meaningful measurements unless additional copies are made. Instead of having to wait until more microbes can be grown in culture, however, we use a technique called PCR (for polymerase chain reaction, named after enzymes that can duplicate nucleic acids) to make copies—or amplify—the DNA or RNA present in a sample from a patient. PCR has been used for a long time to detect pathogens, but it has been limited to detecting one or just a few pathogens at a time. My colleagues and I decided to use PCR in a way that, when coupled with mass spectrometry, enables detection of very broad groups of organisms at the same time.

MAPPING OF CHOLERA CASES (*black shading*) **in 1854 London led a physician named John Snow to the source of the illness: a public pump delivering water contaminated by feces (*added red mark*). Similar mapping is done today to pinpoint the origin of disease outbreaks and bioterror attacks. The author's proposed network of pathogen sensors would identify the sources of outbreaks much more quickly and easily than is currently possible.**

The key element is limiting the amount of nucleic acid we have to generate to get definitive results. We achieve that aim by being very picky about the segments of DNA or RNA that we amplify. We make sure to select fragments that contain sequences of letters that are identical, or conserved, across broad groups of organisms—such as all organisms that can be tinted with a so-called Gram stain versus those that cannot—and that are adjacent to regions unique to a particular species such as *Staphylococcus aureus*. Targeting multiple carefully chosen sequences allows us to identify precise categories and subcategories of organisms without having to lengthen the process unnecessarily. So after extracting the microorganism's RNA or DNA, we add primers (short pieces of DNA that mimic a living cell's natural mechanism to initiate the process of copying nucleotides) to the sample, which will then pick out the desired segments for further processing. After that process is complete, we measure the segments in the mass spectrometer, which gives us a distinct series of numbers that we can cross-reference to a master database we have collected of the more than 1,000 organisms known to cause disease in humans.

Together the hardware and software constitute a universal pathogen detector capable of identifying the type of organism responsible for a person's illness, as well as some of its unique identifying characteristics, in just a few hours.

A prototype of the machine that I helped to create was put to the test under real-world conditions in 2009, when a nine-year-old girl and a 10-year-old boy with flulike symptoms showed up at two different locations in southern California. Clinicians swabbed the children's throats and subjected the samples to standard rapid screening tests for flu. The results suggested that influenza virus was responsible for the youngsters' illnesses but were unable to say which of the then known strains of virus was responsible.

The samples were sent to the nearby Naval Health Research Center in San Diego, which was running numerous tests of the prototype device. The instrument correctly determined that the two children had been infected with the same viral strain, which had never been seen before. The device also pinpointed the virus's recent origin in pigs because the count of the RNA letters most closely matched strains of influenza from pigs in the database. Furthermore, the mass spectrometer's count of the letters, or fingerprint, of the two first cases matched later samples of what was soon referred to as the swine flu virus—now known as pandemic (H1N1) 2009 virus. No one can say whether the early warning saved any lives, but it certainly did not hurt, and having technology in routine use that called out a strain of virus as new and unique would undoubtedly have value for identifying new outbreaks.

As important as it was to quickly identify the new flu virus in 2009, universal pathogen detectors are expected to really shine in situations where clinicians have no clue what is making their patients ill. The devices can also help when selecting drugs. Notably the same mass spectrometric profile that reveals the strain of a bacterium provides clues to its susceptibility to various antibiotics, allowing doctors to prescribe the correct antibiotics right away and only when they are truly needed. Patients should benefit from faster recovery time, even for resistant strains, because they receive the optimal therapy sooner.

BEYOND SINGLE PATIENTS

MOVING FROM INDIVIDUAL to societal benefits, clinicians will quickly be able to determine if several people in one area have been infected by the same organism—for example, *Salmonella,* which is a common cause of food poisoning. You might expect that once public health investigators have such information, they would conduct an old-fashioned, shoe-leather epidemiological investigation, interviewing patients and tracing their recent movements to determine whether they all have something in common—such as having been a patron at a particular restaurant or eating the same specific salad ingredient. The results from such investigations, which follow the same basic format as John Snow used in 1854 to trace the cause of a cholera epidemic in London to a shared water pump, can take weeks to months to complete—which explains why only the most severe outbreaks are usually investigated or solved.

There is a better way, however—and the key to achieving it is probably sitting in your pocket or purse right now. Most people today carry a mobile phone, which maintains geolocation data as part of the operating software or in one of the ancillary applications. In addition, service providers collect all types of cell-tower information that can triangulate a person's whereabouts at any

JOHN SNOW, 1854

SCIENTIFIC AMERICAN ONLINE Learn more about Threat Net at ScientificAmerican.com/jun2014/ecker-threat-net

given time. If patients infected with an organism of public health importance were to volunteer to share their recent travel history from their cell phone, epidemiologists could rapidly determine whether several patients sickened with the same organisms had visited the same location within a specific time window.

The same right to privacy that must be respected in current epidemiological investigations would need to be preserved in a cell-based system as well. The biggest difference: the answers would come a lot faster. Properly coordinated, the data from a well-designed network of universal pathogen detectors would do more than allow essentially instantaneous identification of such public health threats as an epidemic outbreak, a bioterror attack or a potentially life-threatening contamination of the food supply. In addition, public health experts would know right away where an infection might have originated and whether the event was contained to a single city or had already spread to multiple cities. Results could be quickly reported to individual patients or health authorities as needed, and doctors could expedite sharing information about effective treatments.

Building such a network—I call it "Threat Net"—would finally bring medical diagnostics and epidemiology out of the 19th century and squarely into the 21st.

HOW BIG A NETWORK?

BECAUSE THE SPREAD of infection can be represented as a social network, we can determine mathematically how many pathogen detectors should be connected to one another for the entire enterprise to function as an effective early-warning system across a country or region. One of the easiest ways to approach the problem is to use a mathematical model called a Monte Carlo simulation, in which a computer runs the same scenario under multiple conditions to determine a range of probable outcomes. (Investment firms use similar calculations all the time to estimate the size of a person's nest egg at retirement, under several potential market conditions.) Given known national epidemiological data on infection rates, where and how symptomatic people seek health care, how often diagnostic tests are ordered and the incubation times of a wide range of infecting organisms, I ran the numbers thousands of times to determine the size at which the network would begin providing an early alert about a national outbreak of a public health–relevant organism.

The results were remarkable. Linking 200 carefully chosen hospitals across the nation to the network would be sufficient to cover the entire U.S. metropolitan population. Each urban area the size of Washington, D.C., or San Diego would need about five hospitals with universal biosensors on the network; there would be a 95 percent probability of immediately detecting a public health–relevant infectious agent, such as bird flu, anthrax, plague or a foodborne pathogen if only seven patients sought care in an emergency department.

This unexpectedly low number of networked machines, or nodes, is driven by a phenomenon that I refer to as "the funnel effect." Most sick people stay home to nurse themselves. But the sickest individuals will manage to get themselves to a hospital (the first funnel), where trained physicians (the second funnel) will decide which of them needs to be tested. In other words, we do not have to put biosensors where the people are—which would require more devices; enough of the "right" people will bring, or funnel, themselves to the biosensors.

When I conducted computer simulations of the most common public health–relevant infectious diseases and compared the performance of Threat Net in identifying new outbreaks with the best possible performance of the current system, Threat Net was far superior. It identified the leading edge of the outbreak, several days to weeks before the current system. In a real-world context, having even a few days' advance notice of an outbreak could mean the difference between life and death for thousands of people, as hospitals prepare for an influx of patients, health authorities release stockpiles of medications or investigators determine the source of a malevolent attack.

WHAT'S NEXT?

BY MY CALCULATIONS, it would cost about $40 million to establish a network of 200 hospitals (assuming the hospitals buy their own biosensors) and then about $15 million a year to maintain the network. In contrast, a 2012 study of the 14 most common causes of severe foodborne illness put the direct costs of treatment and missed work at $14 billion a year. In the U.S., it would probably make the most sense for the Centers for Disease Control and Prevention to run the network—given its current expertise and mission for tracking outbreaks.

No one has ever developed an epidemiological surveillance system as sophisticated as Threat Net. Given past experience, designing the hardware and software will probably be the easiest part. Many regulatory, legal and turf issues must also be addressed. But the greatest obstacle is that no single stakeholder has the mandate, incentive or opportunity to launch such an undertaking—even though everybody's global interest would be served. The level of cooperation needed from physicians, nurses, hospital administrators, public health experts and privacy advocates may be especially hard to achieve in countries with decentralized and mostly private health care systems.

A society-wide integrated approach to infectious disease diagnosis will be more effective and substantially less expensive than the current approach to public health and medical countermeasures for the detection of pandemic agents and biothreats. The concept of piggybacking real-time public health surveillance onto next-generation diagnostic technology, in combination with modern network and communications technology, has great potential to improve patient care, spare antimicrobial use, and provide alerts that would enable earlier containment of outbreaks or bioterror attacks. What remains to be seen is whether we are wise enough to combine our efforts to produce a smarter health surveillance system. SA

MORE TO EXPLORE

Ibis T5000: A Universal Biosensor Approach for Microbiology. David J. Ecker et al. in *Nature Reviews Microbiology*, Vol. 6, pages 553–558; July 2008.

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scientificamerican.com/magazine/sa

Summon the Rain

PUFFY CLOUDS CONTAIN A BREATHTAKING AMOUNT OF WATER. The volume of even a small one can top 750 cubic kilometers, and if you figure a half gram of water per cubic meter, those wispy balls of atmospheric fluff start looking like flying lakes.

Now imagine you are a farmer watching them glide over drought-parched fields, carrying more than enough water to save your crops and pull you out of debt yet yielding only a few tantalizing drops before disappearing over the horizon. It is that maddening condition that leads people worldwide to spend millions of dollars every year trying to control the rain.

In the U.S., the desire to wring more moisture from the sky is growing particularly intense in

Governments and farmers worldwide spend millions every year trying to control the weather. New science suggests they might be on to something

By Dan Baum

CLOUD SEEDERS of the West Texas Weather Modification Association fire silver iodide flares in an effort to wet the parched fields below.

this fourth year of severe drought. Over much of the Great Plains and the Southwest, rainfall since 2010 has been off by anywhere from a third to two thirds, with corn, wheat and soybean prices jumping by as much as a quarter. California, the source of much of the nation's fruits and vegetables, has yet to emerge from a three-year drought that has left reservoirs half-dry and snowpack dangerously low. In February, the National Weather Service gave the state a one-in-1,000 chance of recovering anytime soon. Almond farmers were bulldozing their trees for want of moisture, and even drinking water was threatened.

Worldwide, millions people are living in extreme drought, with 168 countries undergoing some

level of desertification. Australia recently spent nine years in a drought they named the Big Dry. Turkey has been experiencing its worst drought in a decade. Brazil, China, and countries throughout the Middle East and South Asia have all recently faced drastic water shortages. And if the United Nations' World Meteorological Organization is correct, climate change is going to make things worse. Although only about 0.04 percent of the world's freshwater is floating in the atmosphere at any one time, it is the water we can get our hands on—if we are lucky. Or smart.

Dan Baum is author, most recently, of *Gun Guys: A Road Trip*. A former staff writer for the *New Yorker*, he has written from five continents.

A few visionaries are experimenting with zapping the atmosphere with ions to squeeze more moisture out it, but the primary method of increasing rainfall is infusing, or "seeding," clouds with chemicals. In 2012 nationwide a dozen operators in nine states ran cloud-seeding operations over more than 83,000 square miles. The Chinese government, for its part, deploys a "weather army" of 48,000 people armed with 50 airplanes, 7,000 rocket launchers and 7,000 cannons to coax more rain from the heavens.

The principle is simple. Clouds that could produce rain contain micron-size droplets of water whose temperature is below freezing but that have not yet turned to ice because they lack nuclei around which to form—say, dust particles of precisely the right size. The droplets are too light to counter the updrafts keeping them aloft. Provide suitable nuclei, though, and the droplets coalesce into pellets of ice. As they fall through the warm atmosphere, they turn to nourishing rain. Bernard Vonnegut, an atmospheric scientist at the General Electric Research Laboratory in Schenectady, N.Y., invented the technique in 1946, shortly after his little brother, Kurt, was released from the German POW camp that he would later immortalize in the novel *Slaughterhouse-Five*.

The chemical that Vonnegut used to seed clouds was silver iodide, whose molecular structure mimics that of ice crystals. In a cold cloud, it tricks the water into sticking to it. Silver iodide works in theory, and it even works in practice; pilots say they can see clouds change as the chemical hits them. But the question that has hung over cloud seeding for half a century is: Would that seeded cloud have rained anyway? There is no way to run a perfect controlled experiment. These are clouds we are talking about, and while a regiment of scientists today call themselves "cloud physicists," clouds are the very definition of ephemeral. Each one is as unique as a snowflake and as skittish as a flame.

What we know about clouds is dwarfed by what we do not. Predicting what they will do is hard enough. Determining with certainty what they might have done under different circumstances is impossible. As recently as 2003, the National Research Council was skeptical. "There is ample evidence that 'seeding' a cloud with a chemical agent … can modify the cloud's development and precipitation," read a summary of one of its reports. "However, scientists are still unable to confirm that these induced changes result in verifiable, repeatable changes in rainfall, hail fall, and snowfall on the ground."

In the decade since the National Research Council's report, though, a fleet of new NASA weather satellites, advances in radar and the exponential growth of computing power have combined to let scientists say with considerable certainty—for the first time—that, yes, under the right circumstances and in limited ways, cloud seeding works.

ACCUMULATING EVIDENCE

"WATER IS AN EMOTIONAL THING. Drought is emotional," Roelof Bruintjes said when I visited him at his sparsely furnished lair

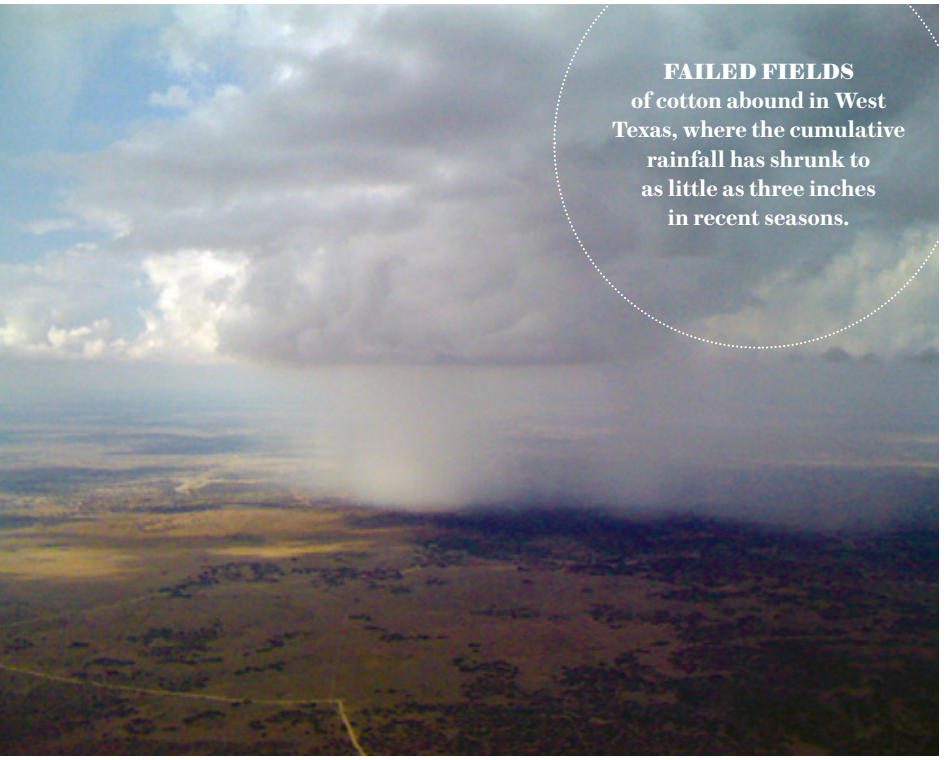
IN BRIEF

Cloud seeding is an industry worth many millions of dollars, but controlled experiments to verify its efficacy have long been nearly impossible to conduct.

New satellite and radar evidence and more powerful computer models have lent qualified credibility to the practice of silver iodide cloud seeding.

Meanwhile, as humans adjust to a warming world, new, highly dubious forms of weather control such as atmospheric ionization continue to arrive.

PRECEDING PAGES AND OPPOSITE PAGE: COURTESY OF FIL FILBURN *West Texas Weather Modification Association*; THIS PAGE: BEN DEPP *Redux Pictures*



FAILED FIELDS of cotton abound in West Texas, where the cumulative rainfall has shrunk to as little as three inches in recent seasons.

in one of the austere modern buildings that houses the National Center for Atmospheric Research (NCAR). Bruintjes, a courtly, elegant, Dutch-born cloud physicist, has been studying weather modification for decades and is only now starting to feel confident about its usefulness. "Farmers look up and see all this water passing overhead, and their fields are drying out, and they want the government to get them that water."

It is hard to think of another scientific endeavor in which the fundamental technology has not changed in 70 years. Most cloud seeders are still putting plain-old silver iodide in clouds. What has changed, especially in the past 10 years, is the technology for evaluating its efficacy. In the 1980s came Doppler radar, particularly a version called 88D, which allowed scientists to see concentrations of water inside a cloud for the first time. This is the machine that throws those green splotches across the weather maps we see on television. "But even that is imprecise," Bruintjes said. "Ten hailstones can show up as 1,000 raindrops." The big advances since 2000, he explained, include dual-polarization radar, which emits wave signals on both the x and y axes, slicing into a cloud with amazing precision. "With dual-polarization radar, you can determine if it's hail or rain, and you can see the size and shape of the raindrop," Bruintjes said. "It's really remarkable."

Along with better data came increases in the power of computers to analyze the data and, more important, the ability to create virtual models to see what clouds would have done had they not been seeded. In October 2012 the NCAR switched on its Yellowstone supercomputer, a behemoth capable of 1.5 quadrillion calculations a second—180 times more powerful than the Bluesky supercomputer that the NCAR unveiled in 2002. Yellowstone lets Bruintjes and his colleagues assemble real-world data from the National Weather Service and a fleet of new NASA satellites—all of which are quite coarse—and create a numerical simulation of the cloud that is vastly finer. The computer can divide an area as big as 15 square miles into grid points as close together as 300 feet and carve up six hours of data into "time steps" of less than a second. This level of granularity delivers what Bart Geerts, a Belgian-born professor of atmospheric sciences at the University of Wyoming, called "the best representation of the atmosphere that we've ever had." The computer is powerful enough, he said, to let scientists create a virtual sky: "There are a lot of idealized simulations—what-if simulations. You create a cloud, and you insert virtual silver iodide nuclei and see what happens."

Only in the past year or so has Bruintjes been willing to be this declarative. "The evidence is strong," he said, "that under certain conditions, we can increase rainfall by 10 to 15 percent."

TRUE BELIEVERS

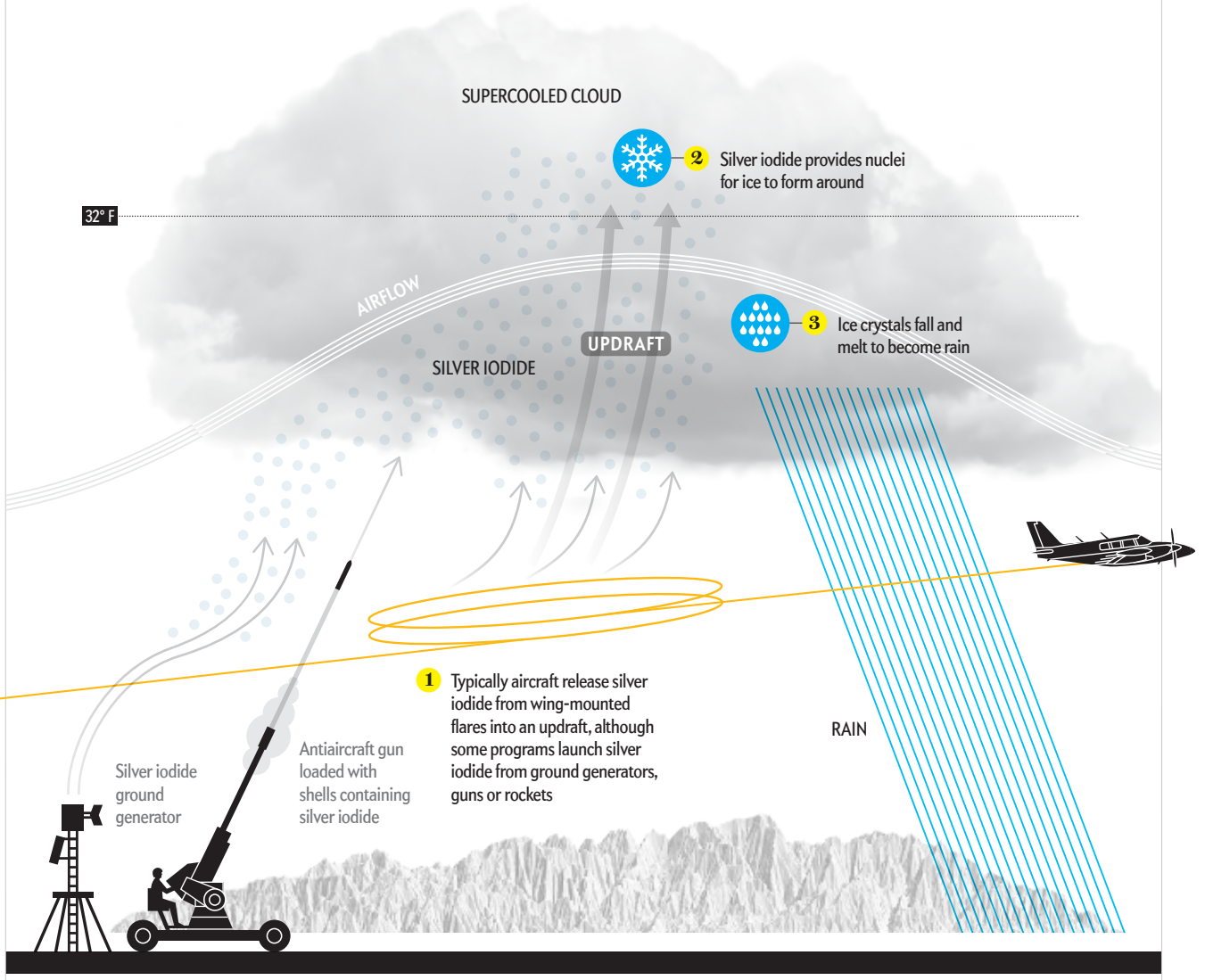
AMONG THE MOST ENTHUSIASTIC BELIEVERS in cloud seeding are West Texans, which is no surprise, given the seemingly perpetual drought under which they labor and the gigantic fires that sweep across their flat prairies, summer after summer. The West Texas Weather Modification Association has, since its founding in 1997, been charged with increasing rainfall over 6.4 million acres of southwestern Texas that lie within a zone that was getting only half its normal rainfall last summer. It is not doing research the way Bruintjes and Geerts are; it gets paid to put water on the ground.

The city of San Angelo and the water-conservation districts of seven counties pool $359,000 a year to support the association's effort, based partly on faith and partly on data, to squeeze a little more moisture out of the big, stubborn sky. It costs Texas and these farmers and ranchers, in other words, 4.4 cents an acre a year to gamble on the chance of making their fields a bit wetter. The dryland farmers want rain to fall directly on their crops. Irrigators and municipalities are eager to replenish the aquifers underneath the hardpan soil. What their money buys is the use of four single-engine airplanes, the part-time services of six retired military pilots at $75 an hour and a one-room office at the edge of San Angelo's sun-blasted airport. They also engage the full-time services of Jonathan Jennings, a 28-year-old meteorologist with a strong build and clipped-down hair who, at a time in which universities are churning out meteorologists, feels lucky to have a job. We met at the spare, unadorned office where he was keeping an eye on the computer monitor that feeds him 24 hours a day of data from Thunderstorm Identification Tracking Analysis and Nowcasting (TITAN), an NCAR program.

To me, the sky looked relentlessly cloudless, but Jennings was enthused about a couple of small, gray radar shadows he

How to Make it Rain

Clouds produce rain when tiny droplets of supercooled water collide with dust particles of precisely the right size, forming ice pellets that fall toward the ground and melt along the way. The most widely practiced rainmaking method involves injecting clouds with particles of silver iodide, "seeds" around which ice particles can form—but new, highly suspect rainmaking schemes emerge all the time.



Another Approach: Ion Generation

Electrified towers send ionized particles skyward to seed water droplets. No scientist interviewed for this article put much faith in it, yet ion-generation projects are going forward in Abu Dhabi and elsewhere.

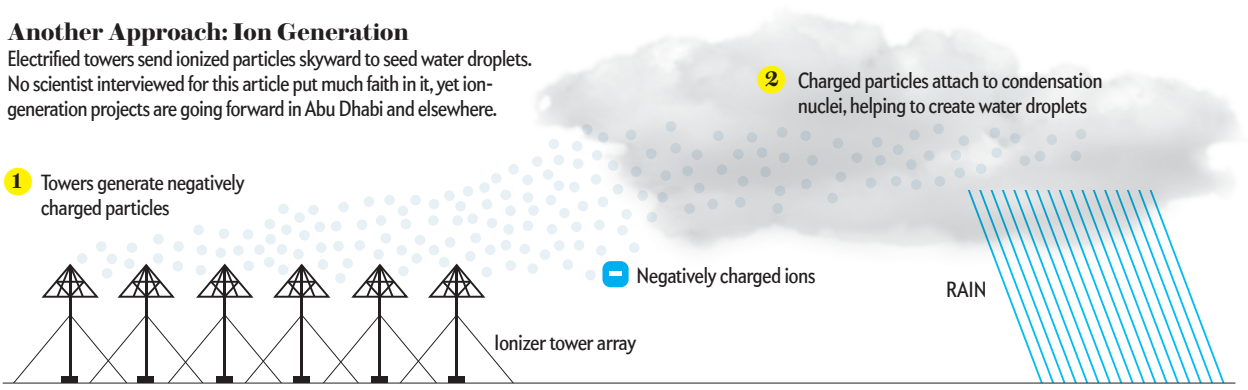


Illustration by John Grimwade

was watching over Crockett County; to him, they looked promising. Just outside the door sat one of Jennings's planes, an ordinary Piper Comanche, a low-wing four-seater that is a favorite of cloud seeders because its airframe is strong enough to withstand flying close to thunderstorms. The tips and trailing edges of its wings bristled with red-topped white tubes, each about a foot long and an inch around—the flares that apply the silver iodide to the clouds. Each was filled with Gilsonite, a type of flammable asphalt, mixed with 5.2 grams of silver iodate. When a pilot fires one, it burns hot and bright, transforming the iodate and leaving a trail of smoke containing iodide.

It was a hot, quiet day, occasional puffs of breeze stirring dust on the airstrip. I told Jennings I was a little disappointed. I had been expecting a scene from the Battle of Britain, with pilots hunkered in a ready room, drinking coffee and waiting to scramble while big, black thunderheads played the role of the German bombers. Jennings laughed. "You're not far off," he said, "though we no longer keep the pilots hanging around."

"The evidence is strong," NCAR's Roelof Bruintjes said, "that under certain conditions, we can increase rainfall by 10 to 15 percent."

Every morning at about seven, Jennings e-mails his members and pilots a weather forecast assessing the likelihood of what he calls "operations." Then he runs errands and goes to the gym, using his smartphone the whole time to monitor weather maps. Usually by around two in the afternoon, he knows if he is going to run seeding operations, and he will call the pilots to give them a heads-up. "When it's go time, we need to get them from phone call into the air in 30 minutes."

Once the pilots have scrambled, things move swiftly, with Jennings watching his computer and acting as air-traffic control. "What I have to do is get them to the favorable part of the storm," he said, which is the "inflow," the tube of warm, moist air that rises into the storm and acts as its fuel. "Most of my pilots are experienced enough to know where the inflow is." Sometimes you can even see it: ghostly tendrils of moisture rushing skyward. Pilots target the inflow because they cannot fly into the cloud. The wind shears inside could tear the plane to pieces, and Federal Aviation Administration rules forbid flying into thunderheads. And they no longer fly over the clouds because they discovered three drawbacks to doing so: it takes a lot of fuel to climb that high; the turbulence up there is brutal; and the chemical does not get deposited in the most efficient delivery zone—the inflow.

Instead Jennings's pilot circles the sweet spot, firing as many flares as he thinks necessary, letting the inflow carry the silver-laden smoke into the cloud. Sometimes one shot will do it; sometimes it takes as many as 50. Giving a cloud a silver lining takes 10 to 15 minutes. "The supercold water is about 2,000 feet inside the cloud," Jennings said. The inflow carries the silver iodide up to precisely where it needs to go, causing the first ice crystals to form. "Once you trigger that reaction, the cloud naturally starts to create ice crystals. They start hitting each other and fracturing." Each time an ice crystal fractures, it can pick up more moisture to carry earthward.

Jennings is experimenting with a new kind of flare that uses calcium chloride—salt—instead of silver iodide. Salt does not raise environmental concerns, it is cheaper than silver iodide (whose price is pegged to the price of mined silver and is now astronomical), and it works on warmer clouds and at lower relative humidity. In addition, some clouds seem to respond better to calcium chloride, Jennings said. On a few occasions, his pilots have deployed both. When that happens, so much rain pours out that "it's like dragging a knife along the underside of a cloud," he noted. For him, there is nothing mystical about it. He does not have to count on long-term measurements and comparisons of what might have happened without his pilots: he sees the clouds respond instantly to their work.

"Look at this," Jennings said and started playing the radar feed from April 28 on his computer. As we watched, tiny dots of yellow and pink—rain—twinkled in a few gray blotches. "When I saw that, I sent up the aircraft." We followed the planes' flight paths inching across the screen. Within minutes of them reaching their targets, the yellow and pink dots swelled monstrously, smearing into a long line of boiling color. Cloud seeding not only creates droplets, Jennings explained, it can also lift clouds into a tall vertical structure that makes them "stronger," as in better at producing rain. "We created a mesoscale squall line, an area of very strong convergence," he said. "That gives more lift, which in turn gives more rain." Of course, I responded, that might have happened anyway, without the seeding. He was ready for me: "The city of Sonora was predicted to have no rain that night and instead had an inch and a half."

Vail, the Colorado ski resort, has been having the clouds above it seeded since 1975. Western Weather Consultants, a private contractor, operates 22 silver iodide generators on mountaintops in a 30-mile ring around the resort. When conditions are right, the generators, which are much less expensive to buy and operate than aircraft, are ignited to burn acetone permeated with silver iodide. The smoke rises into the clouds, and, the company says, as much as 35 percent more snow falls on the slopes than outside the target area. "Vail figures that cloud seeding for snow costs about 5 percent of what making snow costs," Larry Hjermstad of Western Weather Consultants told me when I phoned him about it. Besides the generators at Vail, his company has 50 more operating up and down the continental divide for ski areas, municipalities and the states of the Colorado River basin. The regional drought that started three years ago has increased interest in cloud seeding, Hjermstad added, and with

climate change and a rising population in the West, "we think of this as a long-term solution to a recurring problem."

A DUBIOUS HISTORY

THE REPUTATION OF CLOUD SEEDING has not been helped over the years by the endless string of hucksters who tried to squeeze rain out of clouds and money out of suckers. As James Rodger Fleming of Colby College recounts in his dense and hilarious 2010 book, *Fixing the Sky: The Checkered History of Weather and Climate Control,* literature is full of weather changers, going back to the Bible and advancing forward through Jules Verne and, yes, Kurt Vonnegut. Serious "scientific" efforts to make rain go back to the mid-19th century, with people trying everything from cannon fire to forest fires to tickling clouds into raining. As recently as 1894, Nebraskans tried ending a hideous drought by touching off eight kegs of gunpowder at the Hastings fairgrounds. Typical of the science's ambiguity, a light sprinkle fell—not enough to do any good but just enough to encourage people to continue trying.

"We think of this as a long-term solution to a recurring problem," said Larry Hjermstad of Western Weather Consultants.

The federal government's scientific establishment used to be a devout believer; the National Science Foundation and the National Oceanic and Atmospheric Administration lavishly funded weather-modification experiments for 40 years, even in the face of setbacks. In 1962, for example, the government launched Project Stormfury: seeding hurricanes to reduce their intensity. A year later Category 4 Hurricane Flora killed thousands of people in Cuba, and Fidel Castro, still smarting from the previous year's missile crisis, accused the U.S. of manipulating the storm. But the government stuck with Stormfury for two more decades before conceding that seeding had no effect on hurricanes.

Just enough evidence trickled in, during the 1960s, to sustain belief that perhaps cloud seeding increases rain. The U.S. even employed it as a weapon in the Vietnam War. From 1967 to 1972, the air force seeded clouds over Laos in the hopes of slowing down North Vietnam's transport of men and materiel along the Ho Chi Minh trail, and it claimed to have increased rainfall by 30 percent. Although it was never clear why dropping rain on the enemy was more offensive than dropping napalm or high-explosive bombs, the revelation of "Operation Motorpool" in 1973 shocked the nation and the world. Cloud seeding began taking on malevolent connotations, and by 1977 the U.S. was compelled to sign an international treaty banning the manipulation of weather for military purposes.

Cloud seeding has proved contentious in other ways. On June 9, 1972, during a prolonged cloud-seeding experiment in South Dakota, a flash flood killed 256 people in Rapid City, and the ensuing lawsuit put the cloud seeders in the awkward position of arguing, essentially, the ineffectuality of their own undertaking. The case was dismissed on a legal technicality before the court could determine causality. Before and since Rapid City, farmers have been known to complain that seeding interfered with water that would have dropped on their farms had the clouds been left alone, and other, lesser floods have since been blamed on seeding. Cloud seeding's effectiveness has never been adjudicated, but the recurring incidents tarnish its reputation.

Then, of course, cloud seeders have had to contend with those who believe that they are interfering with God's plan; with those who think it is a capitalist plot to privatize the weather; and with those who are convinced that cloud seeding, crop dusting and even the contrails of high-flying jetliners are part of a "diabolical chemtrail genocide aerosol spraying operation" run by the government. One Web site, AboveTopSecret.com, describes how "Cloud Seeding Will Kill Us All."

Some of the paranoia derives from the fact that silver iodide, a chemical used to develop photographs, is indeed toxic, especially to fish, and it is not just conspiracy theorists who worry about slinging the chemical around the atmosphere. Mainstream environmental groups have questioned the safety of cloud seeding since the 1970s, especially in light of seeding's dubious effectiveness. Francis Mangels, a former wildlife biologist for the U.S. Forest Service in California's Shasta-Trinity National Forest, has been fighting cloud seeding for years. "Silver iodide is an aquatic insect poison," Mangels told a reporter in 2010. "Cloud seeding has never been adequately shown to work; it fails 95 percent of the time, and it's poison. Doesn't that say it all?"

Not quite. The truth is that, though toxic, silver iodide is applied in such tiny quantities as to be all but impossible to measure in the environment. The kind of clouds that are ripe for seeding generally contain between 10,000 and 30,000 kilotons of water, so the 40-odd grams of silver iodide used in a typical seeding is infinitesimal. Altogether cloud seeding worldwide annually constitutes about a tenth of a percent of the total silver that human activity in the U.S. adds to the biosphere. The cloud-seeding industry continues to argue that the silver iodide it uses is not detectable above background levels in either soil or groundwater and that it poses no threat to either humans or fish, although that does not mean it can expect the issue to go away anytime soon.

Scientists believe that it was the combination of controversy and uncertain results that led the federal government to pull out of weather-modification research in the 1980s. Bill Woodley, a retired meteorologist now on the board of the *Journal of Weather Modification,* recalled running a promising cloud-seeding ex-

SCIENTIFIC AMERICAN ONLINE Explore a gallery of weather-control schemes at ScientificAmerican.com/jun2014/rain

periment in Florida in the 1970s that suddenly lost its funding. Although he and his colleagues seemed to have increased rainfall in their 13,000-square-kilometer area by about 15 percent, they had predicted more. "Some people in the media said, 'Well, then, it was a failure.' We tried to say, 'No, we learned a lot,' and put in for funding for a confirmatory phase," but NOAA pulled the plug, Woodley asserted. "People were saying, 'If it isn't obvious and provable, we don't need the grief.'"

To scientists, promising but ambiguous data are an argument for more intense investigation, not less. "A reasonable scientist would say, 'It's clear [cloud seeding] works under some circumstances, but how often do those circumstances occur in an area that makes economic sense, and how do you quantify it on the ground?" recounted Dan Breed, another NCAR meteorologist. To government officials making funding decisions in a highly charged political environment, though, conflicting data have been an excuse to withdraw from an increasingly controversial enterprise. "At a certain point, the [federal] government said, 'To hell with it; it's not worth it,' and got out of funding research altogether" in the early 1980s, said Joseph Golden, who once chaired NOAA's now defunct Atmospheric Modification Program and who today works with the Utah-based Weather Modification Association, a consortium of 18 Western cloud-seeding projects. Golden is a jolly and ruddy man in his 60s. When we met for coffee in Boulder, Colo., he was ready to talk for hours about the fecklessness of the federal research establishment. "We need to have a neutral evaluator [of the data]. That would be the government. But there is no federal presence in supporting research because it is controversial." So for the past 20 years, scientists studying weather modification in the U.S. have done so without federal funding.

Those keeping track of the ways that the Chinese are surpassing Americans can add public support for cloud seeding to the list. The Chinese government's weather army has a goal of squeezing 3 to 5 percent more rain out of the sky during this decade. They claim to have generated almost 500 billion tons of rain that otherwise would not have fallen. Thailand has been seeding clouds since the 1960s—using a method patented by King Bhumibol Adulyadej himself called "super sandwich," which calls for simultaneously seeding both warm and cold clouds floating by at different levels. (It is hard to find reliable information about the program's effectiveness, though, because it is a crime to say anything negative about the king in Thailand.)

Malaysia aggressively seeded clouds this year to make rain, which seems to have also fallen on neighboring Singapore. This year Indonesia, which experimented two years ago with cloud seeding to reduce haze from forest fires, seeded clouds to divert flooding rains from Jakarta. Russia is a big believer in the technology and deployed it to wash radioactive particles out of the air after the Chernobyl nuclear meltdown in 1986. In all, 50 countries participate in cloud seeding, most of them with the assistance of Bruintjes and his colleagues at the NCAR.

ENHANCING THE RAIN

AIRPLANES, to say nothing of rocket launchers and antiaircraft guns, are blunt instruments. They are expensive to operate and maintain, they pollute, and the whole cloud-seeding process can seem hopelessly 20th century. So it is no surprise that people are searching for cleaner, more advanced ways of generating rain. The current fad is for ionizing the atmosphere; in the laboratory, filling the air with charged particles causes moisture to clump and fall. A project in Abu Dhabi fields antennas that look like gigantic umbrella frames, and the project's scientists claim to be yielding results, as do others in Australia, whose antennas look like Brobdingnagian jungle gyms. Not a single scientist interviewed for this story had much faith in either the theory or the practice of making rain by ionizing the atmosphere, though. Bruintjes went so far as to call it "fraud." Even one of the first scientists to experiment with the technique, Arquimedes Ruiz-Colombié, who in the 2000s ran an experiment in Laredo, Tex., that attempted to make rain with an ionization antenna the size of a circus tent, found no proof that it produced rain.

Ruiz-Colombié is a large, jovial 61-year-old who began his career in Cuba before being imprisoned and then expelled for political activity in the 1990s. Now an instructor at Texas Tech University, he works with Jennings at the San Angelo seeding project. While Jennings and I were talking, he came thundering into the office. He told me emphatically that despite what I might have heard, his ionization experiment was not a failure. It just had different results than anticipated. "We found no signal for increased rain—that's true," he said. "But what we did find is that downwind of the tower, the concentration of aerosols [airborne particles] was less. They stick together and fall to the ground. So ionization cleans the environment." As for the Abu Dhabi and Australia rainmaking experiments, Ruiz-Colombié was "very skeptical. But I have an open mind," he said. "Show me the data."

With Ruiz-Colombié nodding modestly beside him, Jennings explained that as much as anything, Ruiz-Colombié's meticulous data collection, mathematical work and modeling of cloud behavior have demonstrated the validity of cloud seeding. They handed me a 10-year analysis of the efforts of their parent organization, a statewide weather-modification association that covers 35 counties. The 3,100 seeded clouds in the study grew larger and lived longer than unseeded clouds outside the target area—and they dumped a total of 3.4 million more acre-feet of water, almost 12 percent more than the unseeded clouds.

"Understand something, please, because this is what you call the bottom line," Ruiz-Colombié said, sitting forward and holding up a finger. "We cannot 'make' it rain. If there are no clouds or not the right clouds, we cannot make something out of nothing. What we do is *enhance* rain."

"Right," Jennings chimed in. "Think of pulling a sponge out of a bucket of water. You can hold it up and let it drip, or you can squeeze it. What we do is squeeze." SA

MORE TO EXPLORE

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FROM OUR ARCHIVES

Cloud Seeding. Bernard Vonnegut; January 1952.

scientificamerican.com/magazine/sa

CHILD HOSPITALIZED with malaria is one of 200 million people a year who contract the parasite, most of them in Africa, where the current gold standard treatments are often prohibitively expensive.

MEDICINE

SEEDS OF A CURE

Desperate to develop new drugs for malaria and other ailments, researchers are running clinical trials with traditional herbal medicines—and generating promising leads

By Brendan Borrell

Brendan Borrell, based in New York City, writes frequently for *Scientific American* and reported on herbal medicines as an Alicia Patterson fellow.

THE TALL FULANI WOMAN CARRIED HERSELF INTO THE TRADITIONAL HEALER'S hut with the bearing of a princess. Like other members of this nomadic cow-herding tribe in southern Mali, she wore a long, flowing blue dress, painted her lips with indigo and henna, and adorned her earlobes with magnificent gold crescents. Once inside, however, the old healer watched her poise wither away. She was weak from recent childbirth, the palms of her hands were pale with anemia and her forehead was hot to the touch. The woman was so terribly exhausted that she nodded off just recounting her woes. "*Soumaya,*" the healer proclaimed. Malaria.

With that folk diagnosis in hand, the two Western doctors observing her visit—Bertrand Graz of the University of Lausanne in Switzerland and Merlin Willcox of the University of Oxford—got to work. The woman signed an informed-consent form, provided her medical history, and allowed the researchers to take a prick of her blood for parasite counts and other analyses. She would be taking part in a remarkable study to measure the cure rate of an herbal tea prepared with the leaves of a canary yellow poppy. By the time of her follow-up, three days later, she was well on her way to recovery.

Although many U.S. Food and Drug Administration–approved drugs have their origins in the natural world, running a clinical trial with a traditional herbal medicine falls outside mainstream practice. The conventional approach to natural drug discovery involves isolating pure compounds from plants, fungi and bacteria, screening and optimizing promising leads in the laboratory, evaluating their safety in animals and, only then, proceeding through clinical trials in humans. Yet few would quibble with the observation that the conventional approach is broken: 95 percent of experimental drugs fail in clinical trials. After too many failures, pharmaceutical companies have largely turned away from natural products. But the alternative—testing vast libraries of synthetic compounds in tiny vials—has not fared much better.

Against this backdrop, Graz and Willcox are attempting to turn the paradigm for natural products discovery upside down: starting with human studies and only isolating active compounds later. The scientists make careful observations of patients already using a variety of traditional herbal remedies to identify the most promising one, then conduct a clinical trial of that remedy. Finally, they identify the active compound, which becomes the starting point for drug development. Their approach, called reverse pharmacology, was inspired by the efforts of Indian scientists hunting for new drugs from ancient Ayurvedic medicine. The beauty of it is that even if a manufactured drug never emerges, the researchers can advise traditional healers and the communities they serve about which herbs work and which do not. And they can carry out this research with a budget suited to the developing world because the early stages require little more than a pen and paper. Their studies of a type of poppy in Mali are exhibit A for the potential success of this approach and have inspired some unexpected players in global health to take a second look at herbal medicines.

LEGACY OF FAILURE

A NUMBER OF HIGH-PROFILE DRUGS available today, including aspirin and codeine, grew out of the study of plants used by humans—ethnobotany, as it is known—yet such success stories have become vanishingly rare. The problem is that there has never been a clear path to gauge the potential of a plant before millions of dollars are invested in drug development. For its part, ethnobotany has always been more descriptive than analytic. Anthropologists might spend time with a shaman in the Amazon, documenting his or her plants and methods, but they have rarely remained in the field to evaluate the efficacy of these concoctions.

Nor has simply collecting and testing every species in sight panned out. An isolated chemical that shows promise in rats or petri dishes is not necessarily safe or effective in humans. The opposite is also true. Some plant compounds may have entirely unknown mechanisms of actions that standard lab tests might miss. One high-profile attempt at such bioprospecting came from Merck, which partnered with Costa Rica's National Biodiversity

IN BRIEF

Conventional methods of drug discovery, which involve testing compounds in vitro and then in animals before evaluating them in humans, have yielded few commercially available drugs in recent decades. **Some researchers** are thus taking a radically different approach in which they study patients who are already being treated with traditional herbal remedies and then analyze the most promising of these natural products in the laboratory.

PRECEDING PAGES: ANDREA BOLOGNESI (*boy*); MARY E. EATON *National Geographic* (*poppy*)

CHILD WITH MALARIA receives tea made from the Mexican prickly poppy during a trial of the herb in Mali (*left*), where traditional healers have long used the plant to treat the disease (*right*).

Institute in the 1990s to take stock of every palm or weevil they could find in the country's national parks and evaluate its pharmaceutical potential. The project was abandoned six years ago without a single blockbuster success. In essence, big pharma's chemists decided they preferred working with compounds they could synthesize on their own, and their lawyers, no doubt, found it easier to lay claim to them with patents. Today these companies evaluate millions of these compounds for hints of biological activity through an automated process called high-throughput screening.

Of course, identifying a biologically active compound is only the first step. In the U.S., the journey from drug discovery to regulatory approval takes 12 years and costs up to $800 million. High-profile flops, such as Sanofi-Aventis's weight-loss drug Acomplia or Pfizer's cholesterol drug Torcetrapib, both of which failed only in the final stages of costly clinical trials, have demonstrated that this model is failing for the developed world. It has had even worse consequences when it comes to neglected diseases in the developing world, where most of the population cannot afford medications that are, by and large, manufactured abroad.

The lack of effective new drugs and the prohibitive cost of existing drugs are particularly troubling where malaria is concerned. Every year this mosquito-borne parasite infects 200 million people in tropical countries, killing half a million. Malaria has evolved resistance to just about everything researchers have thrown at it. In Africa, where 85 percent of the world's malaria cases occur, the current gold standard treatments, artemisinin-combination therapies (ACTs), are subsidized and theoretically available at government clinics and village shops. Yet poor roads and the availability of other, substandard medications make the drug combination's efficacy look a lot better on paper than on the ground. In one recent survey in Mali, 87 percent of children who came down with malaria were initially treated at home, and one quarter received traditional medicines alone. Taking those factors into consideration, some researchers think traditional practices deserve a closer look. But time is running out. Traditional medicine in Africa and other regions is threatened by both modernization and intense competition from Chinese herbal manufacturers, which have outposts in far-flung villages. "If we don't study it now," Graz says, "it may well vanish in large parts of the world within a single generation."

FLOWER POWER

THE IDEA FOR REVERSE PHARMACOLOGY evolved gradually, by trial and error, as Graz and Willcox homed in on and began testing the magical poppy from Mali. Graz is a committed defender of observational studies, in which investigators make inferences about the effect of a treatment based on observation. This type of study contrasts with randomized clinical trials, which randomly assign patients to a treatment group and a control group. Graz recognizes that a randomized controlled trial is the only way to truly tell if a drug works. Yet such trials are often conducted under unrealistic conditions and with only a subset of the patient population, he notes. Although observational studies are not experiments, by documenting and analyzing patient outcomes at clinics, they give researchers a better idea of what works in the real world.

Such a counterintuitive take is what brought Graz to Mali in December 2002. He planned to a run a type of observational trial he invented called the Retrospective Treatment Outcome study, or RTO, with the help of Drissa Diallo, director of the department of traditional medicine at Mali's National Institute of Research in

COURTESY OF MERLIN WILLCOX

Public Health. Over many months, their team visited households in which a family member had recently been sick with malaria. Graz tallied 66 plants that families said they used alone or in combination to treat the illness. "The failure rate was high," Graz notes. But there was a bright spot in the data. Of the 952 patients they tracked, 30 used tea made from the leaves of *Argemone mexicana,* a poppy native to Mexico that came to Africa in the 1800s. Everyone who took it reported complete recovery. The study was like high-throughput screening but with humans, which made a promising lead all the more significant.

Graz contacted Willcox with the news. Willcox had run several clinical trials on antimalarial herbs, with mixed results. The two had previously agreed that if Graz were to identify a plant that seemed to work in the RTO, Willcox would come down to run a cohort study, which follows a group of patients over time, and, they hoped, later a clinical trial. When Graz arrived at an Internet café in the city of Sikasso in southeastern Mali to begin his background research on the poppy, however, he made a disturbing discovery. He found a paper entitled "*Argemone mexicana* Poisoning: Autopsy Findings in Two Cases." In 1998 more than 3,000 people fell ill in Delhi, India, and more than 65 died as their bodies swelled from a buildup of lymph. They had all eaten mustard seed oil adulterated with *A. mexicana,* which contains the poison sanguinarine.

Graz and Willcox were spooked. Could their promising natural remedy for malaria kill patients instead of curing them? Many effective drugs can be deadly at the wrong dosages, yet that did not seem to be happening in Mali. The researchers tried to determine the lethal dose of the *Argemone* tea by subjecting mice to increasing amounts of it, but the mice suffered no ill effects. Eventually they determined that sanguinarine occurs only in the poppy's seeds, not the leaves that go into the healer's tea.

The researchers could now proceed with their studies with a clear conscience. And in September 2004 Willcox arrived in the Malian village of Missidougou. Chief Tiemoko Bengaly, a traditional healer whose grandfather had taught him to use *A. mexicana,* was happy to take part in a study of the plant's effectiveness. In contrast with Graz's retrospective study, which looked back in time, Willcox's prospective study would follow patients forward, allowing for more exacting observations and lab tests.

On one of the healer's mud-brick, straw-roofed buildings, Willcox installed a gleaming solar panel and a car battery to run microscopes, centrifuges and an electrocardiography machine. He cautioned Bengaly to shake out the poppy seeds before preparing the tea but otherwise allowed the healer to follow his own time-tested recipe: boiling the leaves for three hours in a black cauldron, over a wood fire. It was the height of the rainy season, and nearly 100 patients were clamoring to be examined on the first day.

Early on, Bengaly prescribed a single dose of tea for three days, but Willcox noticed that patients were not recovering. When he asked if that was normal, Bengaly said that he thought that dose was more "scientific." Puzzled and concerned, Willcox asked what the usual dose was. Bengaly did not have one. He usually gave patients dried plants and told them to drink as much as possible for about a week. Implementing this higher dose, Willcox now saw results. Parasite counts dropped from around 30,000 per microliter of blood to less than 2,000. After two weeks, 89 percent of adult patients had no fever. The poppy seemed to be working.

To prove that the plant was effective against malaria, Graz and Willcox needed to bring this unorthodox drug-discovery process full circle with a randomized controlled trial. Back in Missidougou, the researchers enrolled 301 patients with malaria in the trial. They randomly assigned patients to be treated with a standardized dose of *A. mexicana* tea or with artemisinin-combination therapy and followed them for 28 days. The study, published in 2010, found that 89 percent of patients taking the poppy recovered, compared with 95 percent of patients taking ACT. The full cost of the *A. mexicana* trial, which was paid for by the Swiss Agency for Development and Cooperation, came to $500,000. Willcox and Graz estimate that using the herbal medicine instead of ACT could yield a cost savings of 75 percent.

QUININE OBTAINED from the bark of the cinchona tree has been used to treat malaria for hundreds of years.

The evidence from this relatively early stage study is so compelling that Graz and Willcox argue that *A. mexicana* tea should be recommended in Mali and other remote regions where it can be cultivated for adults with malaria that is not life-threatening. This approach could help prevent malaria from developing resistance to modern drugs and reserve scarce medicines for the most serious cases, which can lead to brain damage or death.

Reverse pharmacology dovetails with conventional drug discovery in the next phase of the process, as scientists isolate active compounds from *A. mexicana,* improve their chemical characteristics, and test these pharmaceuticals in rodents and humans in more recognizable clinical trials. Yet in contrast with the conventional model of discovery, in which chemical leads are so plentiful that they are abandoned at the first signs of trouble, reverse pharmacology has the potential to bring leads to the table that have proved to be highly effective and safe. In fact, under the conventional model, *Argemone* would have already been shelved. That is because the poppy compound that shows the greatest antimalarial activity in vitro, berberine, failed to fight the parasite in mice and humans. Why the whole plant is so effective remains a mystery, one that Graz and Willcox hope to crack with further study.

GETTY IMAGES

SCIENTIFIC AMERICAN ONLINE View a slide show of Borrell's photographs from his reporting trip to Uganda at ScientificAmerican.com/jun2014/reverse-pharmacology

PROMISE AND PERIL

THE REVERSE PHARMACOLOGY approach is particularly well suited to finding new drugs for acute diseases such as malaria that can be easily monitored, but it is hardly restricted to such remedies. About a decade ago in India, a consortium of universities, research institutes and pharmaceutical companies began using a reverse pharmacology approach to identify potential drugs for arthritis, diabetes and hepatitis from traditional Ayurvedic medicine. Following nationwide surveys of Ayurvedic physicians, Arvind Chopra of the Center for Rheumatic Diseases in Pune, India, and his colleagues came up with a short list of promising herbs for arthritis and began observational studies in clinics alongside animal pharmacology studies. In August 2013 they published the results of their double-blind randomized controlled trial of 440 patients in *Rheumatology,* showing that a combination of four herbal extracts performed as well as celecoxib (Pfizer's Celebrex) in reducing knee pain and improving knee function.

Meanwhile Willcox and Graz have been spreading the word about reverse pharmacology, training African scientists in several countries who would like to study herbs that boost lactation in women or improve symptoms associated with HIV infection. Last December, Graz traveled to the Pacific island group of Palau, ranked as the seventh most obese nation in the world, to identify traditional medicines that are effective against diabetes and hypertension. His RTO of 30 plants revealed that *Morinda citrifolia,* a tree in the coffee family, was associated with weight loss and that *Phaleria nisidai* was associated with lower blood glucose levels. A clinical trial of *P. nisidai* is now in the works. Success against diabetes, which afflicts tens of millions of people in the developed world, could reinvigorate the hunt for natural products by pharmaceutical companies.

Not everyone is convinced this new strategy for developing drugs is appropriate. Take, for example, Nicholas White, now at Oxford, who knows firsthand about the importance of traditional medicines. In 1979 he found an obscure article in a Chinese journal about an herb called *quinghao—Artemisia annua*—which had been used for more than 2,200 years to treat malaria. Working in the lab, he identified the active compound as artemisinin and ran it through the standard gauntlet of safety trials before progressing to successful human clinical trials in the 1990s. It was, in other words, a success under the conventional model of drug discovery, which is why he is so skeptical of reverse pharmacology. "It seems a bit naive," he observes. Making basic observations of healers is one thing, but running a clinical trial is potentially unethical. "Malaria is a life-threatening infection: Is it right to give a person a bark or a toad?" he says.

Willcox and Graz are used to hearing such challenges. During a presentation Willcox gave at a meeting of the Royal Society of Tropical Medicine and Hygiene in Liverpool, an audience member pointed out that their clinical trial would not pass muster under the guidelines followed by British ethical review boards, which require Western doctors to provide a Western standard of care. Others have suggested that all the money and effort spent on the research should have gone toward administering conventional drugs. "That money would have lasted two years, and after that, what?" Willcox demands. One reason why Diallo initiated the collaboration is because Mali already has a system of approving "improved herbal medicines" and sought to expand the list and beef up the evidence for it. A Malian ethical review board approved the study, and the National Institute of Research in Public Health is now honing a standardized *A. mexicana* syrup that can be manufactured and distributed locally.

Willcox and Graz have also found an unlikely ally in the Geneva-based Medicines for Malaria Venture. "It's been an interesting journey," admits chief science officer Timothy Wells. The only organization focused on research into malaria treatments (as opposed to vaccines), it is staffed by veterans of the pharmaceutical industry, and it funds projects that follow the conventional model of drug discovery. Several years ago it paid Novartis, GlaxoSmithKline and other drugmakers to test more than six million proprietary compounds in their libraries for antimalarial activity. They came back with 25,000 hits. The study raised the bar as to how potent a compound should be to warrant further investigation, but it has not necessarily brought researchers that much closer to a novel antimalarial agent.

When Wells saw the clinical trial data for *A. mexicana,* he was floored. "It's not as a good as ACT," he says, "but the point is that it has not been optimized." Derivatives of artemisinin, for instance, have been designed to be more soluble, and quinine drugs used today have gone through several iterations to enhance their efficacy. To move things in that direction, Medicines for Malaria Venture is now funding the next phase of the research on *A. mexicana* to identify the active compounds in the drugs and measure their metabolism in the body. The organization funded a search for active compounds in another antimalarial herb, which showed promise in a clinical trial in the Democratic Republic of Congo.

CROSSING BORDERS

IN JANUARY 2013 WILLCOX traveled to Missidougou to pay his respects to the family of the healer Tiemoko Bengaly, who had died the previous year. It was the week that the French military began air strikes against Islamist militants in the north, and the turmoil underscored just how important it is for Africans to have local sources of medicine. In 2010 the Global Fund to Fight AIDS, Tuberculosis and Malaria terminated $18 million in malaria grants over charges of corruption, and in 2012 the fund announced it was shuttering the Affordable Medicines Facility, which has provided subsidies to importers to help get reliable drugs into village shops.

Willcox and Graz had plans to measure the public health impact of their *A. mexicana* recommendations, but the tenuous political situation put them on hold. Willcox dared to stay in the country only for a week. One morning he looked out of the car he was riding in and saw those yellow flowers rustling in a fallow field. "It's a stopgap insurance policy," Willcox says, "something to fall back on when you haven't got anything else." SA

MORE TO EXPLORE

***Argemone mexicana* Decoction versus Artesunate-Amodiaquine for the Management of Malaria in Mali: Policy and Public-Health Implications.** Bertrand Graz et al. in *Transactions of the Royal Society of Tropical Medicine and Hygiene,* Vol. 104, No. 1, pages 33–41; January 2010.

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FROM OUR ARCHIVES

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scientificamerican.com/magazine/sa

ECONOMICS

The Ponzi ECONOMY

Many ordinary business practices resemble the infamous con game

By Kaushik Basu

IN BRIEF

Con artistry of the kind in which the scammer robs Peter to pay Paul has likely been a fixture of economic activity at least since the Dickensian world of the 19th century.

A new look at Ponzis reveals that they are a more ubiquitous feature of modern economies than had been previously believed—and that financial regulators are ill equipped to deal with them.

Boom-and-bust activity of financial bubbles takes on a Ponzi-like quality. Meanwhile ordinary business practices—awarding of stock options—may be used to camouflage a pyramid scheme.

ISTOCKPHOTO (*decorative graphics*)

Illustration by Adam Simpson

Kaushik Basu is senior vice president and chief economist of the World Bank and a professor of economics at Cornell University. Besides his work on Ponzi schemes, he has conducted wide-ranging research in many fields, including studies on the law and economics of bribery.

THE PONZI SCHEME HAS BEEN A RECURRING FIXTURE OF ECONOMIC LIFE in rich and poor nations at least since the 19th century, creating a few millionaires and ruining the lives of millions. Yet most people have only a vague idea of what they are, which may explain why so many continue to fall for their strange and almost mystical allure. This topic, of course, has acquired a certain urgency because of the recent global financial crisis and headlines about the Bernard Madoff scandal, the biggest ever Ponzi scam, which occurred at the height of the turmoil.

Anyone who followed the Madoff debacle probably thinks about Ponzis as being deliberately concocted frauds. Instead of using investor money to fund a productive business venture, the con artist channels the proceeds from new investors to pay interest to earlier ones. But economists have started to realize that this type of behavior can also occur spontaneously, even unconsciously, simply by having one expectation feed on another, creating a frenzy of speculation, an inflating economic bubble that is doomed to eventually crash.

Scholars of financial markets and behavioral economists have come to realize that Ponzi-like behavior may be endemic to the ebb and flow of global financial markets, as if they were natural phenomena akin to ocean tides or a lunar eclipse. No Madoff-like villain is required.

Ponzis, in fact, can wear many different disguises, which makes them difficult to detect and isolate so that clear regulatory or legal action can be taken. My own research has focused on a difficult-to-discern means of manipulating a business's operations to keep it afloat, at least for a time—"a camouflaged Ponzi" that breaks no laws but can wreak economic havoc.

Interest in Ponzis has grown, not only because of tabloid headlines but because new research has found that they can be explained partially through scientific analysis that reveals their underlying mathematical structure and partially by the psychology of the con artist that appeals to our innate ingenuousness. This research is important because it raises hope that we will be able to detect malignant financial products early, before thousands are drawn to their strange attraction, bringing financial ruin and profound emotional distress.

THE BASIC CON

THE PONZI SCHEME is actually older than Carlo ("Charles") Ponzi himself (1882–1949). Ponzi pioneered his scam in New England in 1920, but it was probably common before, as illustrated by Charles Dickens's unscrupulous fictional characters, drawn from investment scams in Victorian-era London—and in truth, some form of "rob Peter to pay Paul" arrangement has probably existed for as long as large human settlements have.

As Madoff demonstrated so well, the basic Ponzi is a get-rich-quick scheme that, with a dash of marketing wizardry, can be made to flourish—that is, until the ruse collapses. In the classic Ponzi, the con artist might promise a phenomenal return of 10 percent each month to persuade someone to put in $100. The next month two people invest $100 apiece, and $10

gets returned to the original investor while the Ponzi entrepreneur keeps $190. In this fashion, the pyramiding of the investments continues to grow. Starting from the $100 brought in the first month, and by doubling the number of investors every month, income in the 10th month will reach $46,090. This is why people who run successful Ponzis amass enormous wealth. The catch is that there is no graceful way to stop—the entire thing collapses when new investment dries up.

What makes a Ponzi so compelling, though, is that there is no well-defined point at which the crash occurs. If there were a given implosion point, then Ponzis would not be as pernicious. No one would invest one month before the crash, and knowing this, no one would invest two months before the crash, and so on. According to this relentless logic, known as backward induction, the scam would be unlikely to take off in the first place.

The absence of a defined implosion point gives rise to an important psychological conundrum. A Ponzi may ultimately be deemed a collective folly. Yet, for a given individual, investing in one is not intrinsically irrational, because it can take some time before the tenuous structure comes toppling down.

NATURAL PONZIS

FINANCIAL BUBBLES are a relative newcomer to the motley collection of Ponzis. The recognition of their status as Ponzis came about because it became clear that the psychology of an investor is the same, whether or not money is going to a realtor, a stockbroker or a fast-talking con artist. In all cases, it is the sustained rise in prices—or, more precisely, the expectations of an upswing—that keeps the process going. This is what led economics Nobel laureate Robert J. Shiller of Yale University to call it a "naturally occurring Ponzi"—that is, a bubble that forms not in response to a manipulator's baton but to natural market forces, with one person's expectations stoking the next person's.

We have seen this happen in the housing market and, through the ages, in the markets for gold, whereby you want to buy a good only because others have the same motivation, and so the prices will rise. Recently gold prices crashed—a result of herd behavior that gave rise to a natural Ponzi. Prices had risen sharply from 2009 to 2011 because investors thought the injection of liquidity by central banks to counter the financial crisis would cause gold prices to continue to go up, driving some people to off-load cash for gold as the former's value decreased. A flood of funds arrived to take advantage of the expected upswing in the market. The price of an ounce of gold rose from around $900 to $1,800 during these two years. In April 2013 a minor correction occurred, which fueled a panic to sell the metal that led to a major crash. Over two days prices collapsed more than they had in 30 years, baffling speculators and analysts.

Just as Ponzis can form naturally without orchestration, bubbles and subsequent crashes that seem natural can also be engineered. One of the most famous in the history of finance happened when John Law's "Mississippi Company" in France began supplying inflated returns in the early part of the 18th century from earnings of enterprises in the French colony of Louisiana. The scam drew in ever more investors until a run on a bank affiliated with Law's company brought the elaborate deception crashing down.

HIDDEN SCAMS

SOME FINANCIAL DEALINGS that do not look outwardly like Ponzis may actually reveal themselves to be "camouflaged" instances of a pyramid scheme. They are perfectly legal, and they often arise when businesses manipulate their operations to stay afloat when times are tough. A camouflaged Ponzi poses a challenge to regulators because it comes intertwined with perfectly legitimate activities. Using regulation too bluntly to excise them can damage the surrounding healthy tissues, and leaving them unchecked is to risk the growth of malignancy. Further, these camouflaged pyramid schemes can take different forms.

One illustration is when companies and governments indulge, from time to time, in what is called loan juggling—a practice that by itself is not harmful. A company may not wish to liquidate a portion of an asset, which could entail high costs to pay back a lender. So the borrower—whether an individual, a company or a nation—performs a kind of juggling act, borrowing from one lender to pay back the first. If in doing so, the capacity to pay back a loan diminishes or an expected high return does not materialize, these events can precipitate a crash.

The early 1980s debt crisis in Peru, in which the government took out new

Carlo Ponzi:

Special Assistant to the Warden

Carlo Pietro Giovanni Guglielmo Tebaldo Ponzi was born March 3, 1882, in Lugo, Italy. After squandering years at a university in Rome, which he treated as "a paid vacation," he migrated to the U.S., landing in Boston in late 1903. His lack of scruples and high-level intelligence quickly became evident—the former when he landed in a Canadian prison for forging a signature and the latter when he wrote to his beloved mother from prison, explaining his new address as part of his wonderful job as "special assistant" to a prison warden.

Returning to Boston after his release, Ponzi went on to create one ingenious financial scheme after another to lure the vulnerable middle classes and give financial fraud a high profile. The crash of one of his big schemes not only ruined many families but brought down six Boston banks. In and out of prison, he was finally deported to Italy, and from there he immigrated to Brazil. Broken in spirit and health and nearly blind, he died in poverty in Rio de Janeiro on January 18, 1949. —*K.B.*

GETTY IMAGES

loans to pay back preexisting ones, is considered by some economists to be a form of loan juggling. The government's expectations that the economy would improve and that it would be able to pay back the interest and principal owed never materialized. Those hopes were dashed by a major earthquake, a subsequent decline in potato and sugar exports, and a generalized debt crisis throughout Latin America, all of which translated into falling gross domestic product.

Many forms of legitimate business activity can also camouflage a Ponzi. Consider the widespread and perfectly legal practice of giving stock options to employees. It can generate profits even though the company's practices may create low-cost products of trifling value.

An iconic example would be a Silicon Valley start-up that hires highly skilled graduates by offering a starting package with low wages, below the prevailing market rate, while adding in stock options that carry the promise of large future returns. The paltry wages guarantee that the company can still make a profit even if it charges customers cut-rate prices for its products. The owner, meanwhile, keeps a part of the difference between the low-cost goods and the even more menial wages while giving away the rest as supplementary earnings to senior employees.

As the firm grows by employing more workers, the entrepreneur can earn a very high profit, even though, like all Ponzis, this one will eventually crash and leave the employees without jobs or in possession of worthless options.

A simplified example illustrates how this process works—and how it can take on the attributes of a Ponzi. A start-up offers workers a low wage, less, in fact, than the dollar value of what a worker produces. Hence, with each worker, the firm generates some profit. What makes people want to work for this firm, despite low wages, is the allure of stock options that the firm gives to its employees. Thus, in the first quarter of the start-up's operations, the company employs one worker and offers options equivalent to one half of all profits for that period on. In the next quarter, the firm doubles the size of the workforce by employing one new worker—and offers the new hire options that total one fourth of the profit from that period on. In the third period, the company again doubles its staff complement by hiring two new employees, furnishing an options package equal to one eighth of all profits for that period on, which means that each new hire is offered one sixteenth of all profits. And so on in every future quarter.

This plan will ensure that a company's profits will double each quarter. Because employees get a fixed share of profits, earnings from their options will also double each period. And the entrepreneur's income comes from the difference in the value of the goods produced by the workers and the low wages because the entrepreneur gets to keep a part of this difference while giving away the rest to employees as returns on their stock options.

The exponential growth of the value of the stock options makes a job at this company alluring even though these highly trained professionals would not have found the job attractive otherwise, given the low pay. Ultimately, however, a camouflaged Ponzi will crash and will drive the firm into bankruptcy because growing a business in this fashion requires an inexorable expansion of the workforce, an impossibility in a world with a finite population.

One case of a camouflaged Ponzi gone wrong involved the Brazilian oil firm OGX, run by the colorful former billionaire Eike Batista. The rise of OGX was nothing short of spectacular, and so was its demise. When it collapsed in October 2013, it was the largest corporate default in Latin American history. A strategy that OGX used was to poach talented employees from other companies by giving them lavish stock options. This parceling of options continued for a while, with debt building up like an inverted pyramid. And then the company imploded, leaving employees and investors broke.

Again the regulatory challenge comes from the fact that a camouflaged Ponzi can alter its character en route, ultimately rendering the venture fully legitimate. Endowed with the right economic climate and a modicum of luck, a company that indulges in such practices may end up innovating and creating

Robbing Harsha to Pay Gobar

A short story, "Rnam Krttva" ("By Debt If Need Be"), by a well-known mid-20th-century Bengali writer, Shibram Chakraborty, effectively describes the basis of the Ponzi scheme. The narrator tells of how one Wednesday morning, desperately in need of 500 rupees, he targets his gullible school friend Harshabardhan and musters up the courage to visit him. He persuades him to part with the money with the promise that it will be returned on Saturday. When Saturday arrives, he is of course again in trouble. Luckily, he remembers his other naive childhood friend, Gobardhan, and soon manages to flatter him and receive a loan for 500 rupees, with the promise that this sum will be returned on Wednesday. He returns the 500 to Harshabardhan, but on Wednesday he has to pay Gobardhan, and he is back again at Harsha's. Reminding Harsha how he is a man of his word, he borrows 500 rupees once again and repays Gobar. And soon this becomes a weekly event.

Life trundles on for the narrator—from Saturday to Wednesday and Wednesday to Saturday. Then calamity seems to be literally around the corner, when the narrator sees Gobar and Harsha walking in his direction from two sides of a crossroad. He feels dizzy but recovers just in time to say how delighted he is to meet his two best friends together. After some casual conversation, he tells them he has a plan, which, he assures them, will leave their lives unchanged but save him a lot of unnecessary hassle. "Every Wednesday," he tells Harsha, "please give 500 to Gobar, and every Saturday," he turns to Gobar, "give 500 to Harsha. Remember you must never stop." And while the nonplussed friends try to figure this out, the narrator bids them good-bye and takes his leave. —*K.B.*

English translation of "Rnam Krttva" in An Economist's Miscellany, *by Kaushik Basu (Oxford University Press, 2011)*

SCIENTIFIC AMERICAN ONLINE Watch a talk about Carlo Ponzi at ScientificAmerican.com/jun2014/ponzis

more valuable products, thereby making the hiring of more workers possible even without the awarding of stock options. It can then slow down its expansion and gradually become viable, without the need for endless growth and distribution of more options. This is what makes regulation so hard. Overzealousness can kill legitimate businesses and dampen the willingness to launch new ones. On the other hand, a lack of regulation can give rise to pyramid schemes and scams that can do great damage.

TOO BIG TO FAIL

THE IMPOSING CHALLENGE in considering a set of regulations comes from the existence of activities that blend legitimate and fraudulent finance. If someone scams an investor by pretending that money is being invested productively—and current gains are being matched only by the eventual losses of future investors—the con man can face criminal fraud charges. As with other Ponzis, however, it is possible to run these operations openly and still attract money from the unwitting.

It is a telling commentary on economic orthodoxy that a whole subdiscipline—behavioral economics—and a raft of lab experiments are needed to show that humans often fail to behave with the rationality expected of them.

Part of the problem arises as well from basic human irrationality. It is a telling commentary on economic orthodoxy that it needed a whole subdiscipline—behavioral economics—and a raft of lab experiments to recognize that humans are often not rational beings. And along with that recognition has come the need to design laws to protect the vulnerable.

Thanks to years of accumulated data and analyses, many laws now try to prevent Ponzis that are outright scams targeted at the unsuspecting. In the U.S., the Securities and Exchange Commission is charged with shutting down fraudulent Ponzis. Increasingly sophisticated laws, such as the Dodd-Frank act that was passed by Congress in 2010, are meant to tackle the myriad forms that these pyramid schemes take. The spate of Ponzi-like schemes also led to recent discussions in India to amend the 1992 Securities and Exchange Board of India Act to make it more effective in controlling financial scams.

One major difficulty in regulating Ponzis, legal or not, has to do with the idiosyncrasies of government policy. Many governments, especially in industrial economies, have made it a point to step in and rescue very large corporations when they are about to fail. This practice of "too big to fail" (ubiquitous enough to have acquired the unpleasant acronym "TBTF") can attract investors to a firm running a Ponzi in the belief that once the company becomes sufficiently large, the government will step in with taxpayer money at the time of collapse, thereby protecting investors fully or at least in part.

The rationale for TBTF hinges on the belief that if a big investment company goes bust, the collateral damage for ordinary citizens will be so large that the government needs to save the company. It has now become evident, however, that a well-meaning TBTF policy—or, for that matter, one that is ill meaning but well disguised—can exacerbate a crisis by assuring financial honchos that if they make a profit, it will be theirs to keep, and if they experience a loss, it will be for taxpayers to bear. This clearly played a role in the recent global financial crisis.

This situation led to reckless risk taking and irresponsible financial ventures. It is clear that what we need is a policy that may, on special occasions, entail government intervention to save a private company from ruin, but it must not save the people who run the company and make the decisions. With this realization, many nations are trying to create guidelines to ring-fence financial companies to ensure that taxpayer money will not have to be spent to save large corporations from collapse.

Among other new ideas prompted by the past decade of scams and financial crises is a system of prescription for financial products. As in the case of a physician who writes a script for a dangerous drug, this system will entail having a financial professional sign off on a new financial product, perhaps a complex home mortgage, as safe for the buyer before someone can sign to take delivery. Even if companies adopt these measures, the reality is that Ponzis and concomitant financial bubbles will remain a sometimes toxic by-product in any national economy. Every new regulation will be met by another ingeniously concocted financial product that will attempt to separate people from their money and a corresponding need for yet another response from regulators. SA

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COGNITIVE SCIENCE

the world without free will

What happens to a society that believes people have no conscious control over their actions?

By Azim F. Shariff and Kathleen D. Vohs

IN BRIEF

In the past decade an increasing number of neuroscientists and philosophers have argued that free will does not exist. Rather we are pushed around by our unconscious minds, with the illusion of conscious control.

In parallel, recent studies suggest that the more people doubt free will, the less they support criminal punishment and the less ethically they behave toward one another.

But science-informed doubt of free will could actually help us improve our legal system by focusing less on doling out jail time solely for the sake of retribution and more on discouraging further crime.

Illustration by Kyle Bean

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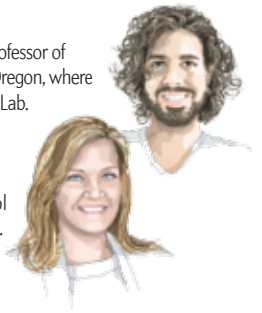

IN JULY 2008 RETIRED STEELWORKER BRIAN THOMAS AND HIS WIFE, CHRISTINE, DROVE their camper van to a small seaside village in Wales. Disturbed by men on motorbikes performing loud stunts, the couple relocated to the parking lot of a nearby inn. Later that night Thomas dreamed that one of the bikers had broken into the van. As he slept, he confused his wife with the imaginary biker and strangled her to death. That is how he told the story, anyway.

The next year a jury had to decide whether Thomas was guilty of murder. He had been prone to sleepwalking since childhood, the jury learned. An expert psychiatrist explained that Thomas was not aware of what he was doing when he choked his wife and that he had not consciously chosen to attack her. Thomas went free.

Such cases force people to consider what it means to have free will. During sleepwalking the brain clearly can direct people's actions without engaging their full conscious cooperation. Recently an increasing number of philosophers and neuroscientists have argued that—based on a current understanding of the human brain—we are all in a way sleepwalking all the time. Instead of being the intentional authors of our lives, we are simply pushed around by past events and by the behind-the-scenes machinations of our unconscious minds. Even when we are wide awake, free will is just an illusion.

Philosophers with this viewpoint argue that all organisms are bound by the physical laws of a universe wherein every action is the result of previous events. Human beings are organisms. Thus, human behavior results from a complex sequence of cause and effect that is completely out of our control. The universe simply does not allow for free will. Recent neuroscience studies have added fuel to that notion by suggesting that the experience of conscious choice is the *outcome* of the underlying neural processes that produce human action, not the cause of them. Our brains decide everything we do without "our" help—it just feels like we have a say.

Not everyone agrees, of course, and debates over the existence of free will continue to rage. The two of us, however, are intrigued by a related question of equal importance: What happens when people's belief in free will—justified or not—is shaken? What does a post–free will society, or rather a post–belief in free will society, look like? Our research into this issue offers inklings of an answer, some of which are disturbing. In particular, we see signs that a lack of belief in free will may end up tearing social organization apart.

EXONERATION FOR CRIMINALS

SOME OF OUR EXPERIMENTS have, however, hinted at a more benign outcome, implying that a society that abandoned its belief in free will would be less punitive than our world is today. In survey research, we found that the more people doubt free will, the less they favor "retributive" punishment—punishment meted out not primarily to deter future crime but rather to make individuals suffer for their transgressions. Yet what people believed about free will did not diminish support for "consequentialist" punishment, which abandons the notion of comeuppance and focuses instead on the most effective ways to discourage crime and rehabilitate perpetrators. In effect, free will skeptics treat people who break the law as they would viruses, raging floods or other natural phenomena: they want to protect themselves against further harm but have no desire to seek vengeance.

A subsequent investigation reached a similar conclusion. Half of our participants read a book excerpt arguing that a rational view of human beings leaves no room for free will. The other half read a passage from the same book that was unrelated to free will. As we expected, the first group became more doubtful of free will's existence. All the participants subsequently read a story about a hypothetical man convicted for killing someone in a bar fight. The story made it clear that imprisonment would not help reform him. Those who had been exposed to arguments against free will recommended half as much time in prison as did volunteers in the other group.

In follow-up experiments, we discovered that it was not even necessary to explicitly mention free will to change the way people think about it and, consequently, how they decide appropriate punishment for a crime. After reading glossy popular science magazine articles describing the neural mechanisms that underlie human actions—with no overt mention of free will—people viewed an imaginary criminal as less culpable than did volunteers who were not exposed to such materials. Participants who read about brain science also recommended about half the prison time for murder. Learning about the brain in a college class appears to have similar effects. A recent experiment by Lisa G. Aspinwall of the University of Utah and her colleagues adds to this line of evidence. They showed that when a mental disorder of a supposed criminal is explained in scientific language as something that essentially takes over a person's brain, judges are especially likely to give a supposed criminal a shorter prison sentence.

PRECEDING PAGES: MITCH PAYNE (*photograph*)

SCIENTIFIC AMERICAN ONLINE Read more about the neuroscience of free will at ScientificAmerican.com/jun2014/free-will

SOCIAL DISORDER

ALTHOUGH INCREASED LENIENCY as a result of doubting free will might be a good thing in many instances, completely abandoning criminal punishment would be disastrous. Such punishment is vital to a well-functioning society. Experimental research by Bettina Rockenbach of the University of Cologne in Germany has shown that although few people like the abstract idea of belonging to a group that punishes its members for wrongdoing, in practice they overwhelmingly prefer it. Rockenbach and her colleagues asked volunteers to play cooperative games and gave them the choice between joining a group that either could or could not punish its members for failing to help out. Initially only a third of the participants chose to join the group that could penalize its members, but after 30 rounds nearly all of them had switched over to the punishing group. Why? Because these experiments confirmed what human societies have found over and over again throughout history: when laws are not established and enforced, people have little motivation to work together for a greater good. Instead they put themselves above everyone else and shirk all responsibility, lying, cheating and stealing their way to societal collapse.

Free will skepticism can be dangerous even to a society that has laws, however. Some of our research reveals that such doubt, which weakens a sense of accountability for one's actions, encourages people to abandon existing rules. In studies conducted with Jonathan W. Schooler of the University of California, Santa Barbara, participants who read an anti–free will passage cheated on an academic test—electing to peek at the answers—50 percent more than participants who read a neutral passage. Moreover, in another study where participants were paid for each test question they answered correctly, those who read anti–free will statements claimed they had answered more questions correctly, and accepted payment accordingly, than did other participants.

Equally disturbing for social cohesion, diminished belief in free will also seems to release urges to harm others. One of the admittedly odd ways that psychologists measure aggression in the laboratory is by giving people the opportunity to add hot sauce or salsa to a snack that they know will be served to someone who hates spicy food. Roy F. Baumeister of Florida State University and his colleagues asked a group of volunteers to read arguments for or against the existence of free will before preparing plates of tortilla chips and clearly labeled hot salsa for another volunteer who had rebuffed each group member earlier, refusing to work together with that person. This same aloof individual, the subjects knew full well, was not a fan of spiciness, and the person would have to eat everything that was handed out. Those who had read texts doubting free will's existence used nearly double the amount of salsa.

Neuroscience has revealed that at least one way skepticism about free will erodes ethical behavior is by weakening willpower. Before people make a motion—such as reaching for a cup—a particular pattern of electrical activity known as readiness potential occurs in the brain's motor cortex, which helps to regulate movement. By placing electrodes on the scalp, Davide Rigoni of the University of Padua in Italy and his colleagues showed that diminishing people's belief in free will decreased this electrical activity. In a follow-up study, people whose free will beliefs had been weakened were less able to inhibit impulsive reactions during a computerized test of willpower. The less we believe in free will, it seems, the less strength we have to restrain ourselves from the urge to lie, cheat, steal and feed hot sauce to rude people.

NEW JUSTICE

IF NEUROSCIENCE RESEARCH CONTINUES to degrade people's belief that they have free will, how will society change?

We see three possibilities. History is replete with examples of moral norms evolving with new knowledge of the world. In his recent book *The Better Angels of Our Nature,* Harvard University psychologist Steven Pinker documents a "humanitarian revolution" over the past 300 years in which previously institutionalized practices such as slavery and cruel and unusual punishment became widely reviled as morally abhorrent. Pinker credits the change, in part, to the expanded knowledge of different cultures and human behavior afforded by the Enlightenment's massive increase in literacy, learning and information exchange.

New research unveiling the biological machinery behind human thought and action may prompt a similarly dramatic change in moral views. This is the first possibility. As they have before, changes in moral sentiments may actually help improve the U.S.'s penal system. Currently, criminal punishment is driven primarily by eye-for-an-eye retribution—the kind of punishment favored by people who believe in free will—and, perhaps as a result, is woefully ineffective at deterring future crime. Society should stop punishing people solely for the sake of seeing them suffer and instead focus on the most effective ways to prevent criminal activity and turn past lawbreakers into productive citizens—strategies that become more appealing when people question the reality of free will. Though uncomfortable at times, doubting free will may end up as a kind of growing pain for our society, aligning our moral intuitions and legal institutions with new scientific knowledge and making us stronger than before.

It may not happen that way, though. As our research has suggested, the more people doubt free will, the more lenient they become toward those accused of crimes and the more willing they are to break the rules themselves and harm others to get what they want. Thus, the second possibility is that newfound skepticism of free will may end up threatening the humanitarian revolution, potentially culminating in anarchy.

More likely is the third possibility. In the 18th century Voltaire famously asserted that if God did not exist, we would need to invent him because the idea of God is so vital to keeping law and order in society. Given that a belief in free will restrains people from engaging in the kind of wrongdoing that could unravel an ordered society, the parallel is obvious. What will our society do if it finds itself without the concept of free will? It may well reinvent it. SA

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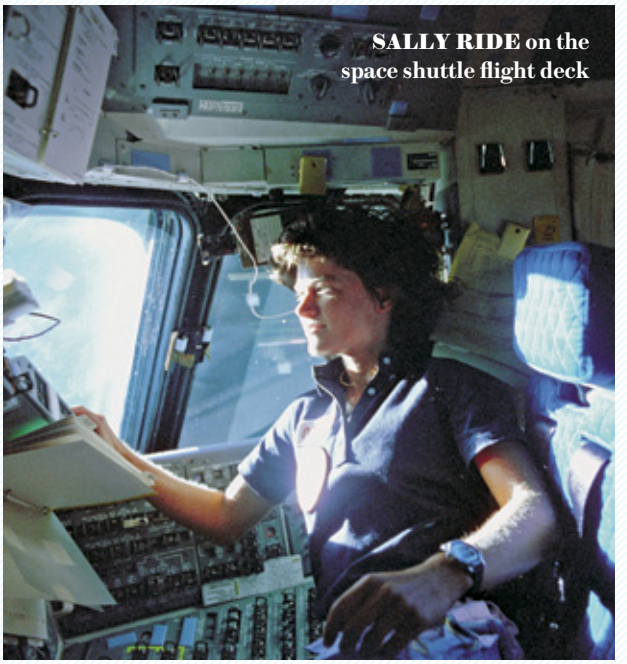
scientificamerican.com/magazine/sa

MORE TO EXPLORE For more recommendations and an interview with author Lynn Sherr, go to **ScientificAmerican.com/jun2014/recommended**

Sally Ride: America's First Woman in Space

by Lynn Sherr. Simon & Schuster, 2014 ($28)

Based on exclusive interviews with Sally Ride's friends and family, including her partner, Tam O'Shaughnessy, this biography tells the fullest life story yet of America's first female astronaut. Sherr, a longtime journalist who covered the space shuttle program for *ABC News,* was also a close friend of Ride's. Sherr admits, however, that parts of the astronaut's history—including her long-term relationship with O'Shaughnessy—came as a surprise after Ride's death because Ride was fiercely private, keeping even friends "from knowing her completely." Sherr tells of an astronaut who was "at heart, a scientist" and who devoted her post-NASA years to inspiring children, especially girls, to pursue science. "NASA was her launchpad, not her apogee," Sherr writes, "and no challenge matched the thrill of sensing the neurons firing to make new connections in a young girl's brain."



SALLY RIDE on the space shuttle flight deck

NASA/GETTY IMAGES

Virtual Unreality: Just Because the Internet Told You, How Do You Know It's True?

by Charles Seife. Viking, 2014 ($26.95)

Modern technology, especially the World Wide Web, has profoundly altered how people find and interpret information, journalist Seife argues, and even how we interact with the world around us. "We now live in a world where the real and the virtual can no longer be disentangled," he writes, illustrating his case with stories of Web hoaxes and viral falsehoods that have fooled experts, journalists and the public alike.

In 2011, for example, the *New York Times,* the *Guardian,* CNN and many other media outlets reported that Syrian-American blogger Amina Arraf had been abducted in Damascus. Shortly thereafter, however, it became clear that Arraf was a fabrication by a man in Scotland, who had created her story and blog remotely. Through such anecdotes, Seife demonstrates how easy it is for fallacies to become accepted truths online. But rather than writing a Luddite screed, he aims to "act as a guide for the skeptic, a handbook for those who wish to understand how digital information is affecting us."

Deep: Freediving, Renegade Science, and What the Ocean Tells Us about Ourselves

by James Nestor. Houghton Mifflin Harcourt, 2014 ($27)

Initially a skeptic, journalist Nestor quickly became enthralled by the extreme sport of freediving, whereby humans plunge hundreds of feet into the sea without the aid of oxygen or sophisticated equipment. The result of his investigation into freediving, among the most dangerous adventure sports in the world, is this mediation on humans' relationship to the ocean, "the last truly quiet place on Earth." Nestor meets a diversity of freedivers who are drawn to the sea for many reasons—some for the glory of record breaking, some for the escape they find in the depths, and a surprising number of maverick scientists who freedive "because it's the most direct and intimate way to connect with the ocean."

Brian Cox's Wonders of Life

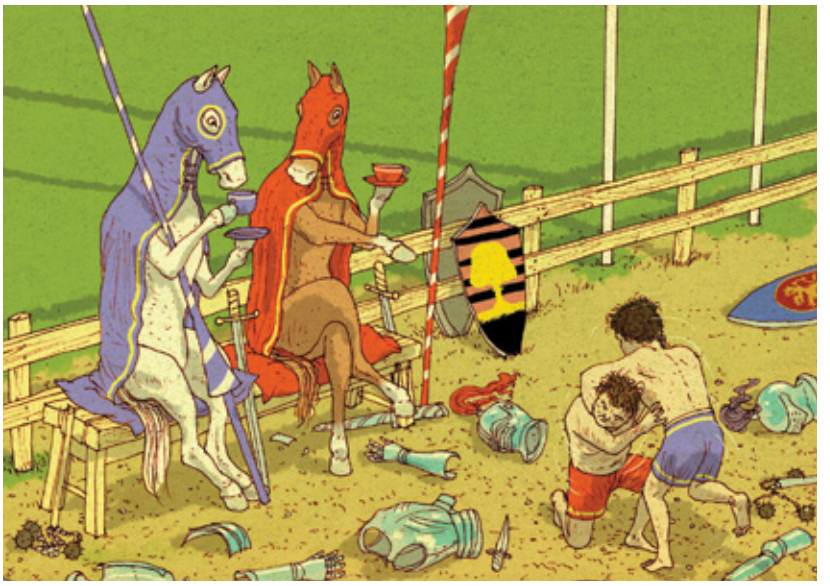
For iPhone and iPad. HarperCollins, 2014 ($6.99)

This BBC science documentary turned app engages the eyes, ears and mind on an interactive tour of our planet's impressive biological diversity and complexity. The app opens with a bird's-eye view of the globe. With a swipe of your fingers, go from Africa to North America to Australasia, where you can zoom in to examine unique local organisms. Cox, a winning tour guide, even takes you through the bodies of the creatures you select. With the help of an array of audio, visuals, video and text, you can, for instance, dive into a kangaroo's ear, climb inside a gigantic termite mound or stare down the jaws of a great white shark. *—Annie Sneed*

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

Nuclear Nada

Does deterrence prohibit the total abolishment of nuclear weapons?



When I was in elementary school in the early 1960s, we were periodically put through "duck and cover" drills under the risibly ridiculous fantasy that our flimsy wooden desks would protect us from a thermonuclear detonation over Los Angeles. When I was an undergraduate at Pepperdine University in 1974, the father of the hydrogen bomb, Edward Teller, spoke at our campus about the effectiveness of mutual assured destruction (MAD) to deter war. He said that by stockpiling many weapons neither side has anything to gain by initiating a first strike because of the retaliatory capability of both to send the other back to the Paleolithic.

So far MAD has worked. But as Eric Schlosser reveals in his riveting 2013 book *Command and Control,* there have been dozens of close calls, from the Cuban missile crisis to the Titan II missile explosion in Damascus, Ark. And popular films such as Stanley Kubrick's 1964 *Dr. Strangelove* have played out how it could all go terribly wrong, as when General Jack D. Ripper becomes unhinged at the thought of a "Communist conspiracy to sap and impurify all of our precious bodily fluids" and orders a nuclear first strike against the Soviet Union.

A deterrence strategy like MAD is not a long-term sustainable solution because of escalation, accidents and crazies, and efforts have been made over the past two decades to reduce the world's stockpiles, from a peak of around 70,000 in 1986 to about 17,300 today, only 4,200 of which are operationally active nuclear warheads. Can we get to "nuclear zero"?

The original cold warrior himself, Ronald Reagan, thought we could. He considered nuclear weapons to be "totally irrational, totally inhumane, good for nothing but killing, possibly destructive of life on earth and civilization." Also calling for "a world free of nuclear weapons" are such cold warriors as former secretaries of state Henry Kissinger and George Shultz, former secretary of defense William Perry and former senator Sam Nunn of Georgia in, of all places, the *Wall Street Journal*. The movement Global Zero has charted a path to reach that goal by 2030. General James E. Cartwright, formerly vice chairman of the Joint Chiefs of Staff, says that the U.S. and Russia could reduce their nuclear arsenals to 900 weapons each and still maintain a deterrence peace until, later, they reach zero through diplomatic means. It's worth noting that 185 of the world's 194 countries (95 percent) are doing just fine without nuclear weapons, and more nations have started and abandoned nuclear weapons programs than started and completed them. This is encouraging, but is it fail-safe?

To find out, I audited a class called Perspectives on War and Peace at Claremont Graduate University, taught by political scientist Jacek Kugler. His answer is no, for these reasons: One, some states that have nukes, such as North Korea, are unpredictable. Two, rogue states want nukes. Three, states waging conventional wars might escalate to using nukes. Four, if terrorists get nukes, they'll use them. Five, the taboo against *using* nuclear weapons has not yet expanded into a taboo against *owning* them, and so the danger of accidents or unhinged leaders remains. And six, the nuclear genie of how to make an atomic bomb is out of the bottle, which means other nations or terrorists can obtain them and destabilize deterrence.

Kugler thinks we can have "regional zero"—nuclear-free zones such as Latin America and Australia—provided the largest nuclear powers (the U.S., Russia, China and the European Union) agree to provide a secure response, which none can veto, to any preemptive use of nuclear weapons by rogue states. Even then, nonstate entities such as terrorist groups may be able to purchase fissile material on the black market, and if they do there is nothing to deter them because many look forward to a martyr's death.

With the ongoing terrorist threat and the lack of trust between nuclear nations (Russia comes to mind), nuclear zero is not yet in the cards. But if we continue to reduce the size of the global stockpile, reinforce the "no first use" policy, amp up the taboo against owning nukes, guard all fissile material, increase economic interdependency and spread democracy, we can inch our way to global security. SA

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Illustration by Izhar Cohen

The ongoing search for fundamental farces

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

Being Driven Up the Wall

Young physicists find the specs to keep a race car off the beaten track

Any kid who ever clutched the wheel of a parked car and vocalized engine noises such as "vroom, vroom, bbbbbbb, nehnehnehnehneh, vroooom" has thought about this basic physics question: If I went fast enough, could I drive along the racetrack's wall without falling?

In the spring of 1978 I actually went to the Indianapolis 500. And my biggest question was whether I could negotiate the incredibly slippery bathroom floors without falling. When you have hundreds of thousands of inebriates assembled before 10 in the morning, the bathroom floors will be slippery, trust me. As the great sportswriter Dan Jenkins described the Indy atmosphere in his 1991 semiautobiographical novel *You Gotta Play Hurt,* "There were cars and people as far as we could see, and the infield was already running with rivers of vomit, beer, grease, and smoke." To be fair, the bathrooms were not all that greasy.

My second biggest question was whether some part of one of the vehicles was about to fly off into the stands and turn my obituary into a sidebar of the race coverage. But I digress.

The short answer to the driving-up-the-wall problem is, of course, that a car of the right mass moving at sufficient speed on a curved vertical surface could stay up there. Then again, Jenkins noted that "the wall had won more Indy 500s than A. J. Foyt, Wilbur Shaw, and all of the Unsers combined." Therefore, professional drivers usually try very hard to avoid contact with the wall.

Nevertheless, four intrepid physics students at the University of Leicester in England crunched the numbers in the university's 2013 *Journal of Physics Special Topics.* (The publication gives Leicester's future physicists a place to ponder issues such as the "implications of our moon being made of cheese," specifically Wensleydale. The upshot of that dire dairy debate: a cheese moon of the same volume would be less dense, thus imparting smaller gravitational forces and weakening the earth's tides. Hey, they said these topics were special.)

For the vertical-driving analysis, the students model their track on the Indy speedway. And as do all great physicists, they include some simplifying assumptions: "The track is circular rather than oval, [and] the vehicle is already traveling at a given speed on the vertical banking." (Vertical banking also describes how your financial institution's service fees send you up a wall.)

At this point, the sideways driver is at the mercy of four forces: static friction between the tires and the surface; the normal force (basically the force with which the surface pushes back at an object, insisting on annoying the surface with its presence); gravity; and the "downward force" (also sideways in this case) of the car, which should have aerodynamic qualities that make it stick more to the wall the faster it goes.

And we're talking really, really fast. "The cars were whining by so fast," Jenkins wrote, "we couldn't make out the decals." At my Indy 500, I sat between the third and fourth turns, a short and therefore slow section of the track, and the cars were indeed still going so fast that even Rick Mears's were smears. As were the decals of Al Unser, Sr., the eventual winner.

The Leicester kids consider two vehicles, an Audi TT road car with a mass of 1,390 kilograms and an open-wheeled Penske-Reynard-Honda racing car, at 700 kg. ("It's impossible to escape the Penske logo at Indy," Jenkins wrote. "You see it in your sleep.") And at a dawdling 150 miles per hour, the Penskemobile will stick to that wall like an ExxonMobil ad on a driver's fire-resistant uniform. Although the heavier Audi will drop and roll.

The young physicists conclude, "Given the right vehicle, the vertically banked race track would be feasible. However, it is unlikely to ever become a reality as such a track would likely be both hugely expensive and very dangerous in the event of a crash." Jenkins also considered a hypothetical: "I [offered] a suggestion on how to make automobile racing more interesting and prove who the best driver was, really. Two-way traffic." SA

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Illustration by Matt Collins

Rare African Emerald Find Shocks Colombian Cartel

U.S. jeweler seizes more than 10,000 carats and makes history by releasing the One-Carat Pride of Zambia Emerald Ring for UNDER $100!

LUSAKA, ZAMBIA - A recent find of high quality emeralds in this African republic has thrown the luxury gem world into tumult. For hundreds of years, Colombians have controlled the high-end emerald market and sent prices soaring to over $15,000 per carat for top graded stones. But the history-making discovery of Zambian emeralds has revealed a green gemstone with mesmerizing clarity that simply changes everything.

This important find led Stauer, a major gem dealer and importer, to bid on over 10,000 carats. Stauer designed a classic 1-ctw ring for people who love the gem but don't love outrageously priced luxury. Because of their timely buy, Stauer is releasing this exclusive, natural emerald ring—aka ***"The Pride of Zambia"***—to the public for under $100!

Discover a Different Kind of Emerald

"For the price, these natural gemstones were the most magnificent emeralds that I've seen in 30 years," said Michael Bisceglia at Stauer. "The value of Colombian stones can't compare."

Industry experts back him up. Lab tests prove that Zambian emeralds are less porous and brittle than their Colombian brothers. And gem cutters have found Zambians so brilliant that they lend themselves more to high-luster cuts than traditional emerald designs.

Unfortunately, the window on this exciting emerald opportunity is closing fast. Not long after Stauer acquired their cache, a recent auction saw Zambian emerald prices hit a new record high. The time to act on this great gem value is now, before it's too late. Please call our U.S.-based client service team at 1-888-277-8375 or visit us online at www.stauer.com.

Emerald Is THE Gem of 2014

The rise of emeralds is more than just a passing trend. An article in the *Financial Times of London* from June of this year pointed to the reason. In "Emeralds: Shades of Green Start to Outshine Diamonds," the newspaper reported that emerald demand is soaring worldwide even as diamond demand softens. Rarity is key as fine emeralds are much rarer than diamonds.

"With wealthy Russian and Chinese demand for emeralds way up, we expect prices to continue to rise quickly," Bisceglia said. "That's why we're so happy to have found these beautiful stones at this price."

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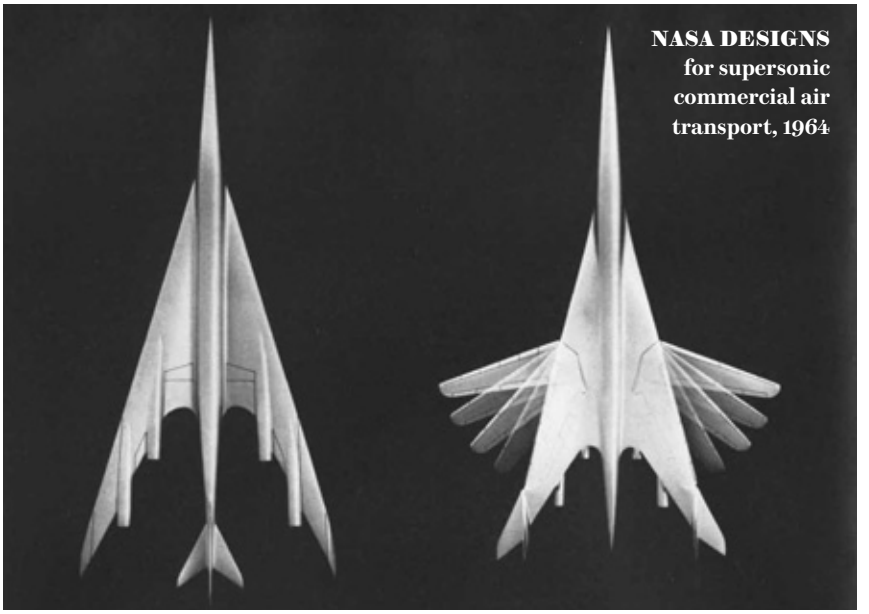
June 1964

Supersonic Transport

"In the years since the flight of the X-I, aeronautical engineers have almost continuously examined the practicability of commercial aircraft that would fly faster than the speed of sound. Such examinations have become more pertinent in recent years with the successful employment by airlines of high-speed subsonic jet transports. These studies reflect the traditional evolution of air transportation toward higher cruising speeds. Anyone who has considered this long-term trend has wondered if it would be finally halted at velocities approaching the speed of sound. There now appears to be no valid technical or economic reason why the trend should not continue well into the range of supersonic speeds [*see photograph*]."

Within five years the Russian Tupolev Tu-144 and the Concorde had made their first flights.



NASA DESIGNS for supersonic commercial air transport, 1964

June 1914

Editors' note: The assassination of Archduke Franz Ferdinand, heir to the Austrian throne, 100 years ago on June 28, 1914, was not covered in these pages. SCIENTIFIC AMERICAN began reporting on the "Great War," or World War I, after the European political crisis of July escalated into a military conflagration in August. Look for coverage of the war in upcoming issues.

Tango Foot

"Housemaid's knee, miner's elbow and similar ailments have now a formidable rival in 'tango foot.' In the *Medical Record,* Dr. Gustav F. Boehme, Jr., states that he has recently been consulted by a number of dancers who complained of 'pain in the front of the foot.' In every instance, he found the same symptom, and on investigation, discovered the cause—the modern dance. Says the doctor: 'The latter-day dances, especially the tango and the maxixe, and to some extent the complicated figures of the hesitation waltz, call for great flexibility of the ankle, throughout the various intricate steps.'"

Skype Preview?

"A very ingenious apparatus has just been introduced from Germany, which is designed to transmit writing, drawing, and the like over a telephone or telegraph line to an instrument which makes a perfect reproduction of the original. Telautographs have long been in use, but this apparatus differs from others in that the writing at the receiving end is done by a pencil of light which travels over a sensitized sheet of paper. The message is thus photographically reproduced, automatically, in the machine, in a few seconds."

Superconductors

"For many years the laboratory of Prof. Kammerlingh Onnes at Leyden has been the center from which some of the most important advances in low temperature research have been announced. Of late, attention has been centered on the remarkable influence of temperature on the electrical resistance of metals. This resistance is found to become practically zero before the absolute zero of temperature is reached. The question arises, What happens to an electric current once started in a conductor of zero resistance? Does the current continue to flow indefinitely?"

For an exploration of electrical science in 1914, see ScientificAmerican.com/jun2014/electricity

June 1864

Deep-Sea Research

"In making the soundings for the Atlantic telegraph between Newfoundland and Ireland, a small tube with a valve was fitted to the end of the line, so as to bring up a little of the sediment from the bottom of the sea, and when this was dried it was found to be a dust so fine that on rubbing it between the fingers it would disappear in the cracks of the skin. Under a microscope each particle was seen to be a shell—the home of a sentient being. When these shells are highly magnified, little holes are discovered in them through which delicate filaments protruded that were the animal's organs of locomotion. As these filaments branch out like the roots of a tree, the animal is called a rhizopod, from two Greek words which signify 'root-footed.'"

SCIENTIFIC AMERICAN, VOL. 210, NO. 6; JUNE 1964

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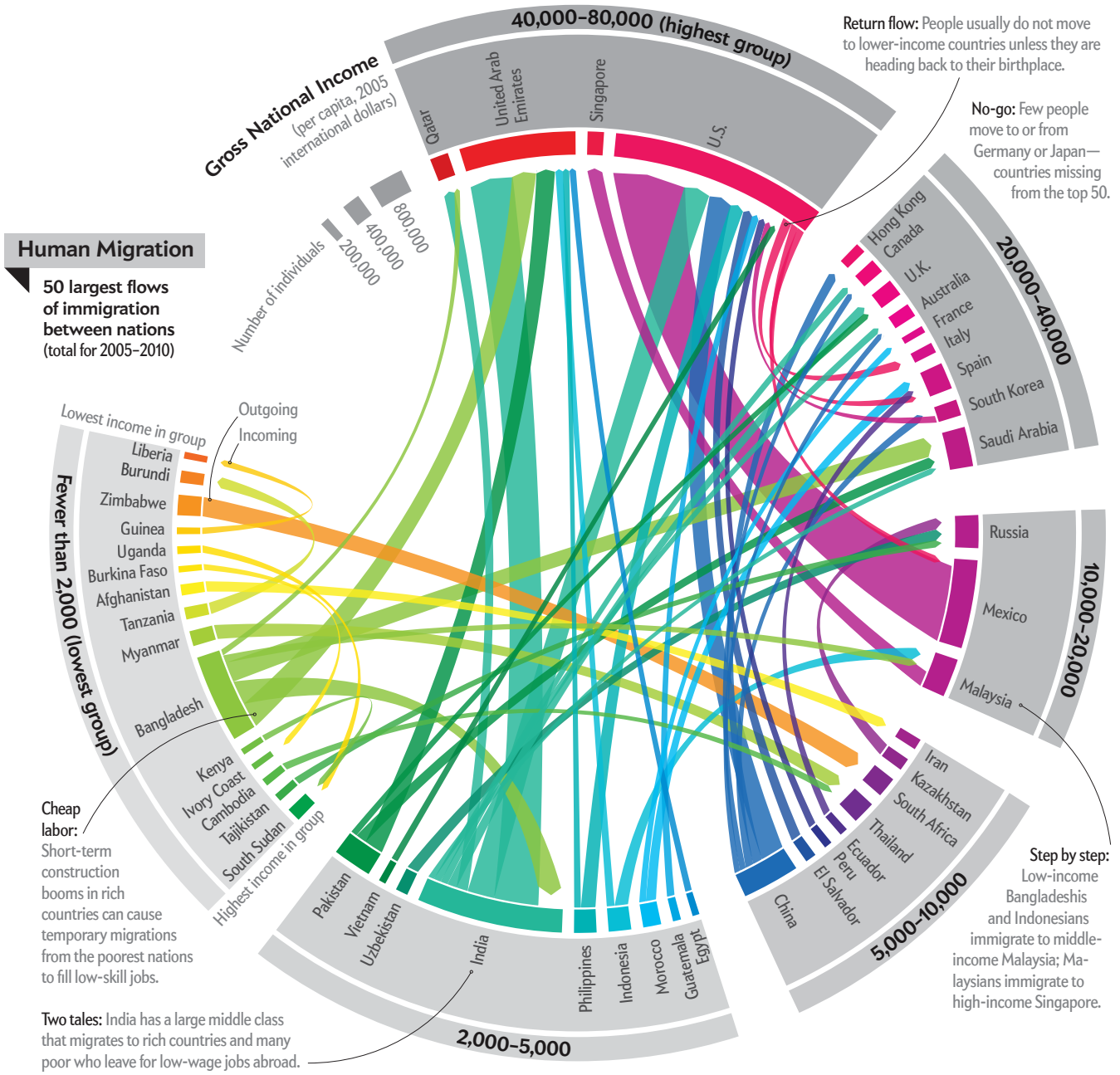


The Not So Wretched Masses

Immigrants go gradually up the wealth ladder

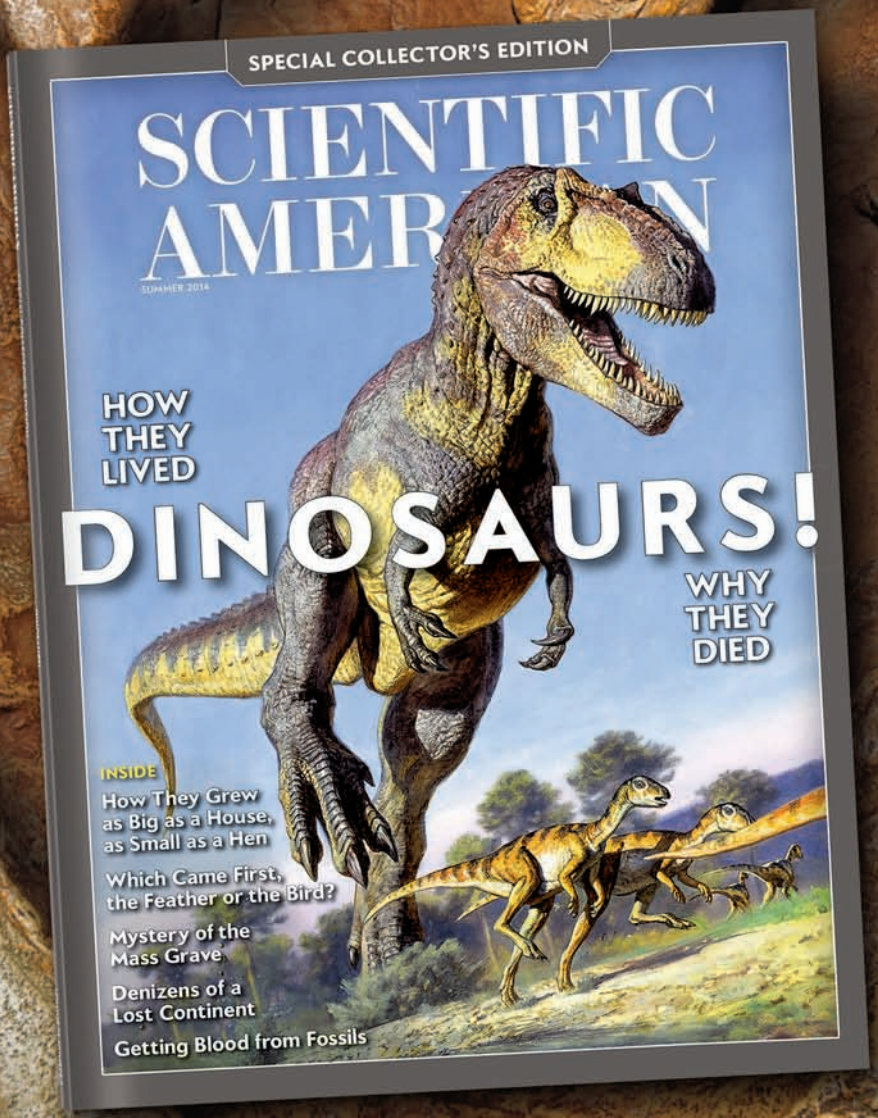
Immigration is often tied in the popular imagination to poverty—"the wretched refuse of your teeming shore," as poet Emma Lazarus wrote in 1883 to honor the Statue of Liberty. Data, however, show this notion to be a caricature. In this plot of the 50 largest migration flows, few of the poorest people leave home, and when they do they usually go to middle-income nations. Research suggests that is because they do not have the resources or education to survive in the richest countries. "Just like climbing a ladder, you have to take steps to get from the bottom to the top," says Nikola Sander, who, with one of her colleagues at the Vienna Institute of Demography in Austria, found the trends using United Nations data. The largest migrations are from middle-income countries (*2,000–20,000 segments of circle*) to high-income countries—with a few exceptions (*noted on graphic*).

—Mark Fischetti

SCIENTIFIC AMERICAN ONLINE
For an interactive graphic of human migration flows between world regions, see ScientificAmerican.com/jun2014/graphic-science

SOURCES: "QUANTIFYING GLOBAL INTERNATIONAL MIGRATION FLOWS," BY GUY J. ABEL AND NIKOLA SANDER, IN *SCIENCE*, VOL. 343; MARCH 28, 2014; "THE GLOBAL FLOW OF PEOPLE," BY NIKOLA SANDER, GUY J. ABEL AND RAMON BAUER *www.global-migration.info*

Graphic by Nikola Sander



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