PUBLIC HEALTH
The War on Ebola

PLANETARY SCIENCE
Oceans from the Skies

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Electric Cures

Bioelectronic medicine could create an "off switch" for arthritis, diabetes, even cancer

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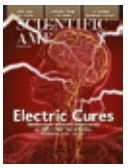

An overactive immune system can produce an inflammatory reaction that affects organs throughout the body. When the nervous system senses excessive inflammation, it tries to activate an immunological "off switch," sometimes with limited effectiveness. Medical implants that enhance the anti-inflammatory process may help fight rheumatoid arthritis and other diseases. Image by Bryan Christie.

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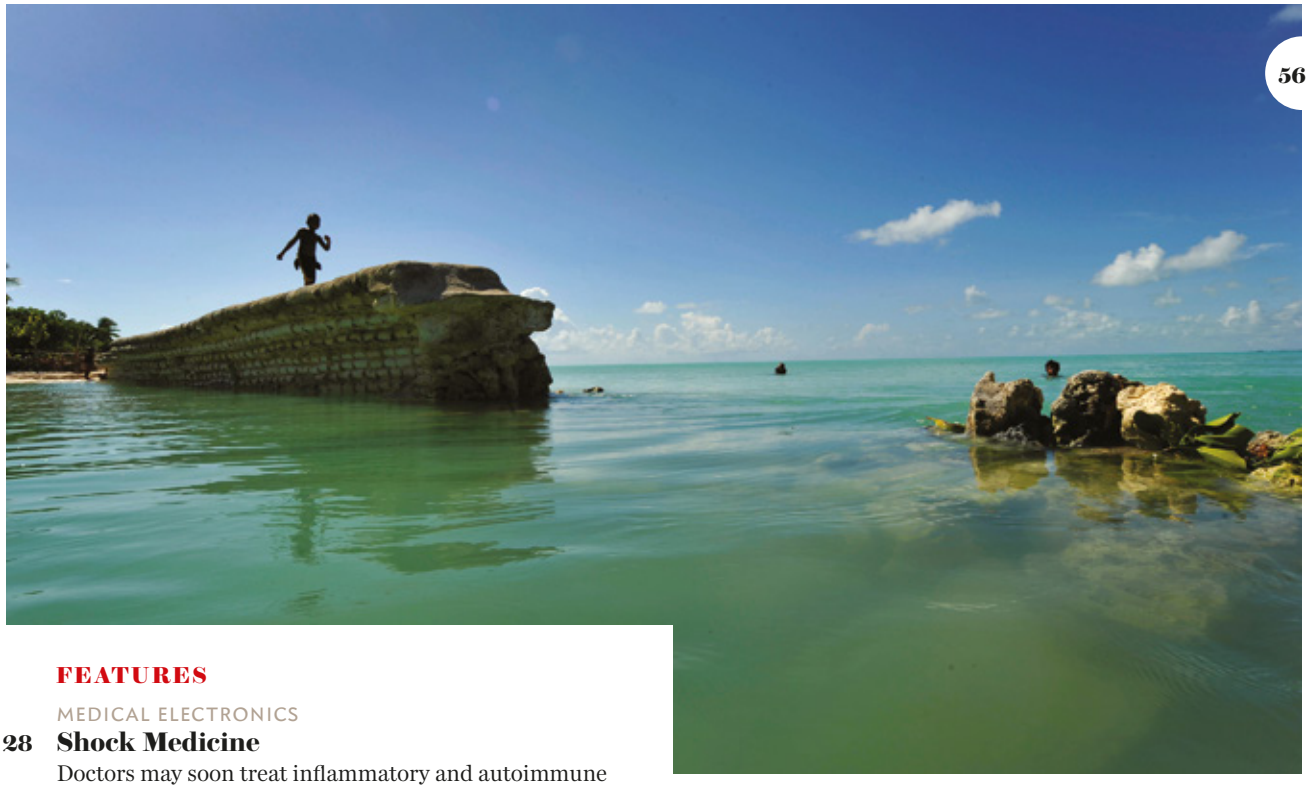

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JUSTIN McMANUS Getty Images (broken seawall on Tarawa atoll, Republic of Kiribati)

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Consumer Electronics In-Depth Report
Scientific American looks at the latest trends in flexible device screens, automotive gadgets and voice recognition, with reporting from the International Consumer Electronics Show. *Go to www.ScientificAmerican.com/mar2015/consumer-electronics*

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

The Battle Within and Without for Healthier Lives

I DON'T OFTEN GET TO REPORT AND WRITE my own stories anymore. But I do deeply enjoy the privilege, as editor in chief, of seeing our crackerjack team of journalists and scientists identify large themes in the evolving flow of science as it is being applied to discovery and to solving society's pressing challenges; scientists, of course, serve both as protagonists in our feature articles and as authors.

In this issue, for instance, let us look together at our species' continuing efforts to manipulate our own body's inner mechanisms to treat diseases and generally improve public health. Take "Shock Medicine," the cover article by brain surgeon and neuroscientist Kevin J. Tracey, starting on page 28. He describes fascinating work in the field of bioelectronic medicine for harnessing the body's natural reflexes, rather than using drugs, to treat a variety of inflammatory and autoimmune conditions. "By precisely targeting the biological processes underlying disease, this nerve-stimulating technology should help avoid the troublesome side effects of many drugs," Tracey writes. The diseases may include, among others, rheumatoid arthritis, multiple sclerosis, diabetes and perhaps even cancer.

An inner (and outer) battle of another kind is involved in the fight against Ebola, which exploded onto global headlines last year, infecting 21,000 people and killing more than 8,500 by mid-January. Journalist Helen Branswell reveals the vicious and unusual one-two punch that the small group of Ebola virus species uses to blow past the immune system. Our counterattack, accelerated by the large number of patients as global attention and funding have focused on this lethal virus, involves efforts in public health as well as the rapid development of new vaccines. Turn to page 48.

Unseen invaders also play a far milder—indeed, a beneficial—role in our microbiome, the community of microorganisms inside each of us that exceeds the number our own body's cells by 10 times. "Innovations in the Microbiome," a special report with our sister publication *Nature*, starting on page S1, takes us on a tour of how these microbes aid digestion, train the immune system and produce anti-inflammatory compounds that help to keep pathogens away. Last, as always, I find myself looking forward to seeing what basic research will turn up next time. SA

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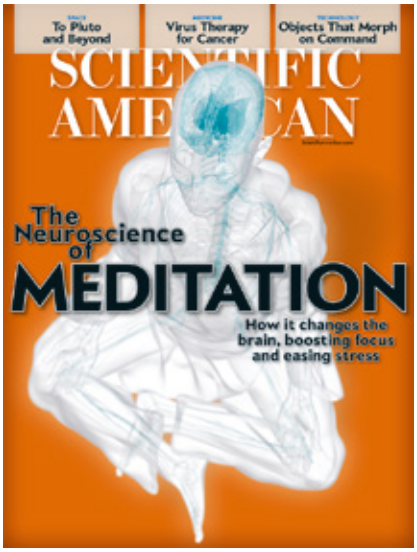

November 2014

ROOFTOP SOLAR

In "Solar Wars," David Biello discusses the impact of the rooftop solar energy "boom" in the U.S., including electric utilities' worries about lost revenue.

He omits the question of the future stability of large-scale power systems, which will be radically affected by increasing local energy generation. New types of load imply a greater risk of feedback-induced oscillatory behavior.

Ensuring the stability of the grid while creating a system that can deal with two-way local power flows and less predictable generation requires effective technical coordination across multiple parties. A one-system approach rather than one that looks at only parts of the power network system in isolation would seem necessary.

Hubert Montagu-Pollock
University of Lancaster, England

The article had one important fact missing: a household solar power system that is connected to the electrical utility network cannot serve as backup source of power if the utility service fails unless the homeowner has arranged for battery backup.

John O. Stoner, Jr.
Tucson, Ariz.

Using solar power panels for air conditioning, as Doug Cox is described as doing in the article, is hardly making "the bucolic lifestyle of the suburbs sustainable." Apart from the required regular maintenance, the panels had to be constructed (using petroleum products), assembled on a line and transported to his house. Dumping any environmental benefits gained from using solar panels back into air-conditioning seems perverse.

Richard Knijnenburg
via e-mail

"Land mines could be equipped with kill switches that would be activated remotely or even automatically after a given period of time."

Clement H. Kreider, Jr.
via e-mail

KILL SWITCHES

In "The Case for Kill Switches" [Forum], Jonathan Zittrain argues that implementing ways to remotely disable military weapons if they fall into the wrong hands deserves serious consideration.

One of the most valuable uses for such kill switches in weaponry would be in land mines. It is well known that leftover mines remain hazardous for years to innocent civilians, animals and vehicles. To the extent that the military insists that these mines are an essential weapon, they could be equipped with kill switches that would be activated remotely or even automatically after a given period of time.

Clement H. Kreider, Jr.
via e-mail

Kill switches should become a compulsory but secret add-on for all weapons. Once everybody has become dependent on their imaginative and efficient ways of carnage … hit the kill switch.

Karl Aeberli
Hemhofen, Germany

MEDITATION STUDIES

"Mind of the Meditator," by Matthieu Ricard, Antoine Lutz and Richard J. Davidson, really captured my interest because I have been a member of a Zen sangha for about five years now.

But I was disappointed that the question of selection bias in the meditation studies the authors refer to was not discussed. It appears to me that most, if not all, of the subjects observed in most of the studies had been regular meditators or at least would have shown a positive disposition toward meditation. So, the question arises: To what degree are identified differences in brain structure, brain dynamics, behavior and temperament that correlate with varying levels of "meditation practice" a cause and to what degree an effect?

Jim Gerofsky
Montclair, N.J.

CANCER THERAPY

"Virus Therapy for Cancer," by Douglas J. Mahoney, David F. Stojdl and Gordon Laird, describes research on using engineered viruses to infect and destroy human cancers. According to the authors, one of the reasons that such viruses are effective is that they damage the tumor cells' camouflage from the immune system, allowing it to do its work and finish the job.

I have thought that if I were unlucky enough to have an incurable cancer, I would ask for a graft of a tumor, as similar as possible to mine, from another person. My body would start to reject the grafted tumor because it was foreign but in the process might notice the damaged cells were also cancerous. Once my immune system was primed in this way, it might move on to start destroying my own cancer cells. Is there any mileage in this idea?

John Hobson
Devizes, England

MAHONEY REPLIES: What you have described is similar to an approach called allogeneic cancer cell vaccination, in which cancer cells from one patient are irradiated with ultraviolet light (to kill them) and then grafted into another patient in an attempt to elicit an antitumor immune response. It has shown some promise in clinical trials and—like other cancer vaccines—will almost certainly benefit by rational combination with some of the new immune-targeting drugs recently approved by the U.S. Food and Drug Administration.

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DRUG-ABUSING DOCTORS

In "Do No Harm—And No Drugs" [Science Agenda], the editors argue that random drug testing should be mandatory among health care workers, citing the substance abuse rates of physicians.

Perhaps the reason drug abuse is prevalent among physicians is that drugs are perceived as performance enhancers: no doctor wants to be seen as drowsy or moody.

I worked in the construction business for years, and we never used drug tests. A supervisor can tell when an employee has a hangover, is lacking sleep or has cut a board short, but a drug test cannot. Drug tests do not test for impairment and cannot substitute for proper supervision.

PETER WILSON
Phoenix, Ariz.

METRIC OF MORTALITY

There is an interesting slipup in "Killer Chairs," by James Levine [The Science of Health]. The article states that "when you combine all causes of death and compare any group of sitters with those who are more active, sitters have a 50 percent greater likelihood of dying." The active group members have a 100 percent chance of dying during their lifetime, so this would mean that the sitters have a 150 percent chance of dying.

Obviously, that is nonsense, so there must have been some time factor omitted.

JOHN SHONLE
Amherst, N.H.

THE EDITORS REPLY: Indeed, that sentence should have mentioned a time period. The overall differences in mortality between sitters and more active people were observed after both groups had been followed for about 8.5 years.

ERRATA

"Inside the Audience Studio," by Katharine Gammon [Advances], incorrectly refers to McMaster University as being in Toronto. It is in Hamilton, Ontario.

"The Evolution of Architecture," by Rob Dunn, incorrectly refers to Jesse N. Weber and Hopi E. Hoekstra as creating a backcross of hybrid mice with oldfield mice. The hybrid mice were crossed with deer mice.

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An Unhealthy Work Ethic

When employers forbid paid time off for illness, infectious workers spread disease and hurt business

A round of high fives after a successful sales call this month could be the start of something big: big numbers of salespeople calling in sick with the flu, passed from palm to palm to nose. In a restaurant break room, a sneeze from one employee can trigger weeks of sniffles and fever among co-workers. These daily run-ins on the job sideline a lot of us, particularly at this time of year. But those who are passing germs around are often doing so because they do not have paid sick leave.

Data published in 2013 by the U.S. Centers for Disease Control and Prevention indicate that one in five restaurant workers clocked in even when they were suffering from diarrhea and vomiting, the two main symptoms of norovirus. That formidable group of nausea-inducing viruses causes about half of all foodborne illnesses in the U.S. Bringing those harmful microbes into the workplace puts customers at risk. Employees also infect other staff members and force their bosses to scramble with a costly deluge of absences. When swine flu broke out in a 2009 pandemic, eight million infected American adults still went to work. Those employees may have caused another seven million flu infections, according to estimates by the Institute for Women's Policy Research. Together, that adds up to one out of every four people who caught the disease that flu season.

Many of these workers cannot afford to stay home. Roughly 75 percent of part-time workers in the U.S. and 25 percent of full-time employees have no paid sick days. It is time for that to change. We need laws that increase the number of people who can take time to see a doctor or stay home with the flu without having to sacrifice a day's wages.

Pushing employees with the flu or a stomach bug to drag themselves into the office means more absences, not fewer. Workers who are not able to take paid time off to see a doctor are more likely to take six or more sick days a year than are those who can take time off, according to a 2005 Commonwealth Fund report. Overall, workers who are ill while on the job account for anywhere between 18 to 60 percent of workforce productivity losses, according to a 2004 review of estimates in the *Journal of Occupational and Environmental Medicine*. CDC data also show that employees without sick leave are more likely to get injured on the job and are less likely to get preventive health screening for cancer.

Experience suggests that paid sick leave does not hurt the bottom line. Sixteen U.S. cities and the states of Connecticut, Massachusetts and California have passed regulations that typically allow workers to earn one hour of paid sick leave for every 30 hours on the job. A 2013 audit by the city of Washington, D.C., found no evidence that its five-year-old paid sick leave law had prompted businesses to leave the area or discouraged new companies from coming in. On the West coast, San Francisco continued to outperform nearby Bay Area cities in job growth after it implemented a paid sick leave law in 2007. There are expenses: employers have to bear a small increase in base pay for employees who use leave, for instance. But productivity and public health benefits outweigh these costs.

Many opponents of laws to require more paid sick leave say that healthy workers will abuse the benefit, resulting in mass absences. But a study of Connecticut's experience by the Center for Economic and Policy Research shows this fear is unfounded. Still, the specter of empty workplaces has helped kill many proposals for minimum numbers of sick days. States and municipalities should follow the science, not the specters, and act now to require paid sick leave. It would be good for all of us. SA

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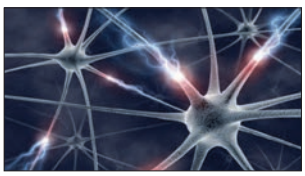

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Karl Frederick Rauscher is ambassador at large and chief architect of cyberspace policy at IEEE. He is a Bell Labs Fellow and former Distinguished Fellow and chief technology officer at the EastWest Institute.

A Matter of Trust

American tech companies, ensnared by the NSA controversy, must act boldly to restore the world's confidence

Last November in the town of Wuzhen, China hosted its first large international summit on Internet governance and cybersecurity. Many felt the step was long overdue. After all, China has the world's largest population of Web users—more than 600 million and climbing. Internet players of this stature have a responsibility to shoulder some of the burden of leadership. Right?

Apparently not everyone thinks so. One of the major stories surrounding the event was the lack of senior U.S. government presence. While China hosted at the minister and vice minister levels, only a handful of relatively junior (though quite competent) representatives from the American government attended. It was a politically oriented event, and the Chinese perceived the U.S. absence as a snub and a sign of lack of respect.

The list of possible reasons for the U.S. government's minimal participation is long: the unresolved issue of Chinese hacking of U.S. interests, disapproval of Chinese Internet censorship, lingering embarrassment from the Edward Snowden revelations. But the event's themes—Internet governance and cybersecurity—are central agenda issues for American political leaders. The former topic is on the front burner for the U.S. Congress, and the latter is a staple of the ongoing dialogue between President Barack Obama and President Xi Jinping of China.

One U.S. group was well represented in Wuzhen: technology companies. The reason is simple: there is a lot at stake. Trust in American technology is eroding, not only in China but also in economic powerhouses such as Germany, where the government recently ended a contract with a major U.S. network operator over security concerns, and Brazil, where there are plans under way to build a new undersea cable to Europe and deliberately avoid U.S. technology companies.

It is easy to see why this trust has eroded. Before the Snowden revelations, Chinese security experts *suspected* that U.S. technology might have ulterior purposes (that is, spying). In their calculations, those suspicions have now become certainties. A former U.S. spy chief went on record to explain that it is not good national security policy to buy critical-infrastructure technology from a potential adversary. We should not be surprised if China's Ministry of Industry and Information Technology takes a page from U.S. national security strategy and builds out the world's largest national Internet infrastructure with systems it knows it can trust—systems that will not necessarily come from U.S. companies.

American corporations facing the blacklist in China and elsewhere have a few options. The easiest is to stay the course, but that plan has a very real risk of ending badly. Likewise, marginal efforts to restore confidence will almost certainly fall short. The best option is to commit to building bona fide trust. A report prepared by experts from the U.S. and China and presented at the 2013 cybersecurity summit held by the EastWest Institute, IEEE and Stanford University explains how this could be done. The detailed list of recommendations is long, but the key step American companies would have to take is to state, in clear and certain terms, that they are *commercial* entities and are not part of any country's national security apparatus. These assertions could be backed by severe contractual penalties should products or services be found to violate the level of commercial purity claimed. This would be a simple and practical enough commitment—with enough skin in the game to be a game changer.

A likely collateral benefit is that American firms would have a business imperative to build more secure products. It is possible that the U.S. government could still covertly compromise products made by an American company, but because doing so would jeopardize the very health and survival of a domestic business, it should be less likely. In any case, American companies might not have much choice. Given the U.S. government's reluctance to engage, tech companies need to be prepared to go it alone. SA

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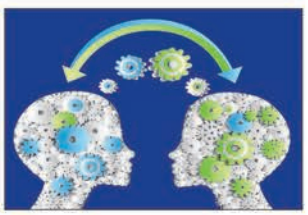

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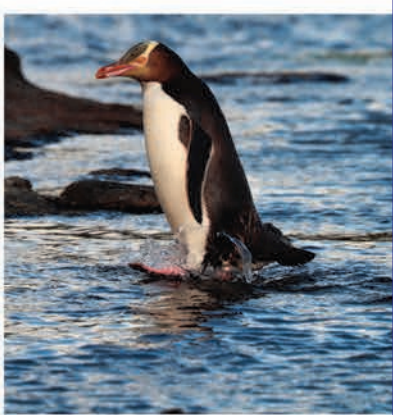

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The human papillomavirus (*shown stained below*).

HEALTH

Cancer Goes Viral

HPV-positive throat and tongue cancers are taking off in men

A vaccine to protect against the most dangerous strains of human papillomavirus (HPV), which cause almost all cervical cancers, as well as many cases of other cancers and genital warts in both sexes, won the approval of the U.S. Food and Drug Administration nearly nine years ago. The Centers for Disease Control and Prevention now recommends that all boys and girls aged 11 or 12 receive the shots. Vaccination campaigns, aimed largely at girls and women, have fallen short of expectations. By 2013 just over half of U.S. females aged 13 to 17 had received at least one dose of either the Gardasil or Cervarix vaccine. For males, that figure was a disappointing 35 percent. Now head and neck cancers associated with the virus are on the rise, leading some experts to recommend that a gender-neutral or male-centric approach might be more effective.

HPV is the most prevalent sexually transmitted disease in the U.S. and worldwide, infecting just about all men and women at some point in their lives. Although most people clear the virus naturally, persistent infections with some strains can lead to cancer—usually cervical or oropharyngeal (affecting the back of the throat, tonsils and back of the tongue). HPV-associated cancers make up 3.3 percent of all cancer cases among women and 2 percent of all such cases among men annually in the latest available figures, yet the incidence of virally instigated oropharyngeal and anal cancers is increasing.

Ohio State University medical oncologist and epidemiologist Maura Gillison has studied men with oropharyngeal cancer in three different decades. She and other colleagues first noticed an odd shift in patient profiles in

Continued on page 12

KWANGSHIN KIM *Science Source (HPV)*; SCIENCE SOURCE *(head)*

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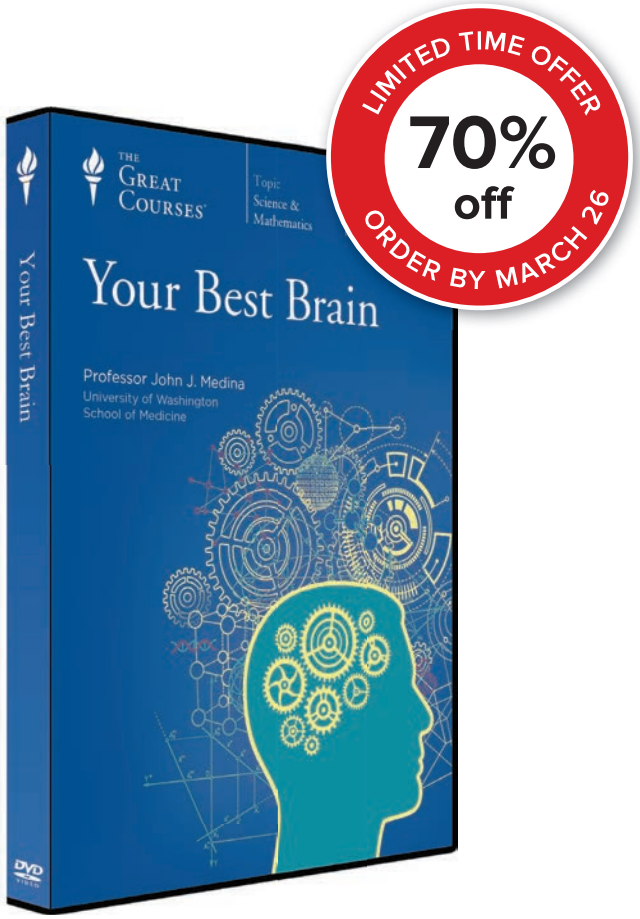

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the late 1990s: younger men were showing up in her clinic, often with no significant history of smoking or heavy drinking, which are risk factors for head and neck cancers. She later found that whereas from 1984 to 1989 in the U.S. only 16 percent of oropharyngeal cancers tested positive for HPV, by 2005 that figure had skyrocketed to 73 percent. By 2020 experts project that such cancer diagnoses will exceed those for cervical cancer in the U.S., shifting the burden of HPV-associated cancers from women to men. Gillison reported these findings in October 2014 at the annual ScienceWriters meeting.

Based on these data, Gillison thinks that the female-centric approach to HPV-related cancers in the U.S. should switch to focus on both men and women. Nobel laureate Harald zur Hausen, who discovered 30 years ago that HPV causes cervical cancer, has gone further, saying that males should get the vaccine if only one sex were the focus. The vaccine is currently voluntary in most U.S. states, and only a smattering of vaccination coverage campaigns exist, such as those launched by the New York City Department of Health and the Minnesota Department of Health in the past year. Public health messages and even research literature often fail to mention male vaccination prominently or at all. Unfounded fear of vaccines and claims that the HPV shots would provoke early teen sexuality have hindered efforts to vaccinate broadly in much of the U.S.

No data exist to prove that the vaccines protect against HPV-positive oropharyngeal cancer. But such coverage is probable given that the same strains that cause most cervical, vaginal and vulval cancers also cause most head and neck cancers. If a shift in public health policy were to result in an increase in male vaccinations, experts say, at the very least rates of females' HPV-associated cancers would decrease as a result of fewer infections acquired from men. And the rise in HPV-associated cancers in men would most likely decelerate, plateau or even reverse. A win for all of us.

—Robin Lloyd

BY THE NUMBERS

Poison Control

28.5% ***The drop in telephone calls*** placed to the U.S.'s 55 poison-control centers between 2009 and 2013, according to the most recent report by the American Association of Poison Control Centers. The organization says the steady decline could be the result of the falling U.S. birthrate or growing preference for text messages over phone calls. It might also suggest that more Americans are instead searching the Internet for health advice—even in emergencies. Staffers still field about three million calls a year, picking up the phone every 14 seconds on average. In 2013, 1,218 people with cases logged at poison-control centers died from direct exposure to a poison or drug. *—Amy Nordrum*

The five substances that generated the most calls in 2013 were:

PAIN RELIEVERS
11.5%

COSMETICS/ PERSONAL CARE PRODUCTS
7.7%

HOUSEHOLD CLEANERS
7.6%

SEDATIVES/HYPNOTICS/ ANTIPSYCHOTICS
5.9%

ANTIDEPRESSANTS
4.2%

MATERIALS SCIENCE

Rubbery Glass

A new concoction exhibits both hardness and elasticity

Glass is strong—until it shatters. If it could stretch more like a rubber band, glass could be used in shatter-proof windows and flexible electronic displays or fashioned into mechanical sensors that could operate at the high temperatures encountered in such fields as aeronautics. Materials scientists led by Seiji Inaba of the Tokyo Institute of Technology have created the first such elastic glass.

Glass is typically made up of phosphorus- or silicon-based molecules tightly bound to one another in orderly but noncrystalline three-dimensional structures. Inaba and his colleagues designed their glass so its molecular structure would instead resemble chains of rubbery materials; its relatively long chains of phosphorus oxide are weakly connected to one another. After the scientists stretched this glass at high temperatures, its fibers shrank by about 35 percent—demonstrating elasticity, a behavior not seen in glasses before. The stretchy glass was described online last December in *Nature Materials*. (*Scientific American* is part of Nature Publishing Group.)

Inaba, who now works at Asahi Glass in Yokohama, says he still has work to do. So far the glass contracts well at 220 to 250 degrees Celsius, but ultimately designers want such performance closer to room temperature. Michael Demkowicz, a materials scientist at the Massachusetts Institute of Technology, notes that engineers could use Inaba's recipe to modify a glass that is, say, already known as a good conductor and make it elastic, too. Maybe someday soon a dropped phone or wineglass will be a far less shattering experience. *—Katherine Bourzac*

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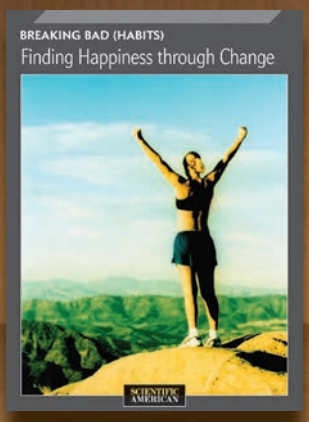

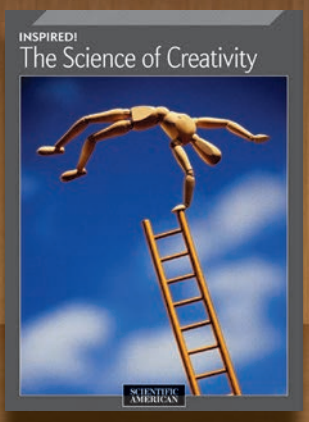

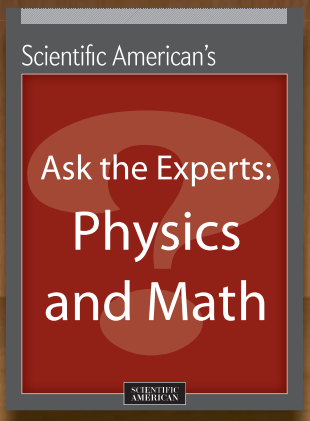

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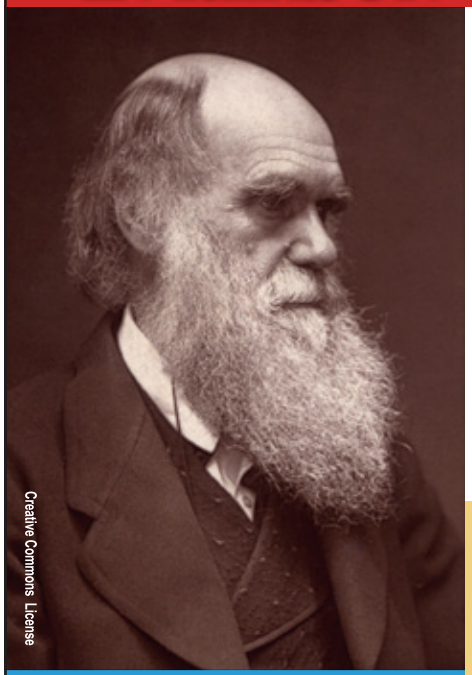

CHARLES DARWIN

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ANIMAL BEHAVIOR

The Bird with a Breadbox

Spotted nutcrackers take perishability into account when storing food for later

Every year around the end of winter, baby spotted nutcrackers peck their way out of their shells, ready to learn as much as they can from their parents about how to live as a bird—such as how to bury seeds throughout the year for later consumption. Spotted nutcrackers are fairly unique, even among seed-caching birds, because they rely on the seeds from just one kind of tree: the Swiss stone pine trees of the Carpathian Mountains and the Alps. Reciprocally, the tree relies on them for sowing seeds.

The problem for the birds is that these seeds are available for harvest only between August and October. If the nutcrackers are not careful, the seeds they bury could easily germinate and become saplings, making the deposit useless as a meal weeks or months later. Thus, spotted nutcrackers have a clever greengrocer system, according to a new study: they choose food-hiding places that maximize the shelf life of seeds, where perishability is lowest.

Most caching birds choose their hiding spots carefully, but no one has known exactly how. The prevailing hypothesis has been that the birds decide in favor of sites that minimize the likelihood that other animals will discover their caches and pilfer them. Eike Lena Neuschulz, a postdoctoral researcher at the LOEWE Biodiversity and Climate Research Center in Frankfurt, Germany, recently tested that assumption. She and her colleagues randomly cached 900 stone pine seeds at sites within one of five microhabitats in the eastern Swiss Alps, such as under snow, beneath a tree or near shrubs. Then the researchers spent nearly 400 hours watching spotted nutcrackers hide their own caches.

By comparing their experimental caches with those of the birds, Neuschulz discov-

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ered that the nutcrackers explicitly chose to hide seeds in the areas that were least likely to sprout a tree—sites that lacked the requisite soil moisture or were heavily shaded. The team also found that all caches

The nutcrackers explicitly chose to hide seeds in the areas that were least likely to sprout a tree.

were equally likely to be pilfered, no matter their surroundings, according to results published in January in the *Journal of Animal Ecology*.

"The Swiss stone pine can [live] more than 500 years," Neuschulz says, "so it doesn't need a lot of successful germination events to maintain population viability." That life cycle explains how these evergreens evolved to rely on birds that attempt to hide the seeds where they are least likely to result in a new tree. Just a few germinated seeds each season spread out over multiple centuries can yield quite a lot of offspring. Meanwhile the spotted nutcrackers have learned to use nature as a breadbox, keeping their food from spoiling.

—*Jason G. Goldman*

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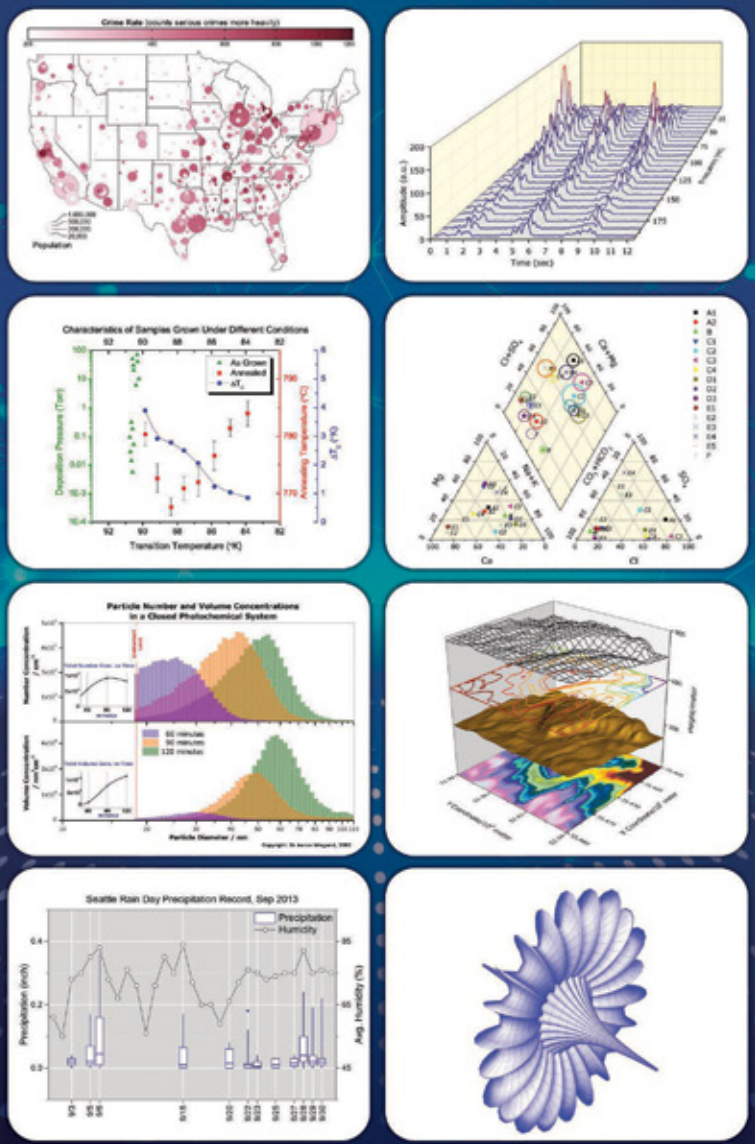

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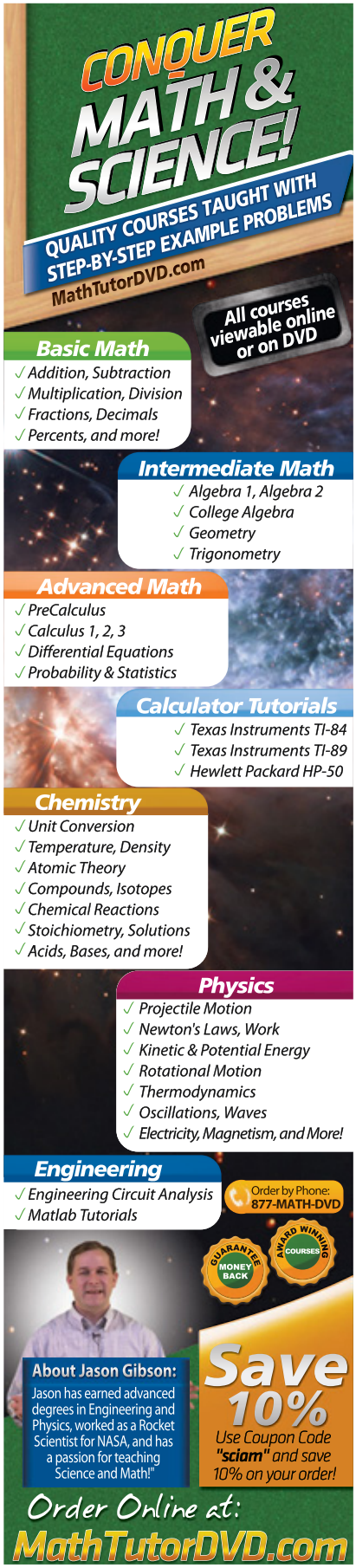

ENERGY

Nuclear Letdown

A falloff in construction of new nuclear power plants in the U.S. will make climate change requirements harder to meet

The U.S.'s nuclear reactor fleet dipped below 100 for the first time in decades, when, at the tail end of 2014, Vermont Yankee shuttered its operations. The 604-megawatt power plant's termination did not come as a surprise: it had logged a slew of safety issues in recent years, including burst pipes, leaks and misplaced fuel rods. Nevertheless, it provided up to 4 percent of New England's power and one third of Vermont's. Its owner, Entergy, just did not have enough money to make the necessary upgrades, especially at a time of low electricity prices. The loss means more natural gas will be burned to meet New England's electricity needs, which undermines U.S. policy to move away from reliance on fossil fuels and control climate change.

This year is expected to be a bad one for the nuclear energy industry in the U.S., with several reactors, including a handful in Illinois and New York, at risk of shutting down. Yet the dwindling number still produce roughly 70 percent of the electricity in the country that does not exacerbate global warming.

The International Energy Agency's most recent blueprint for holding global warming to two degrees Celsius requires an expansion of nuclear power in every region of the world by 2040. Yet only 14 countries plan to build new reactors, and only China intends to build a significant number. Four advanced nuclear plants are under construction in the U.S., but with ongoing shutdowns, the fleet—once the largest in the world—now seems doomed to fade away, done in by cheap natural gas and policies that favor renewable resources such as wind energy.

Without nuclear power, the Obama administration's Clean Power Plan, which would set limits on carbon dioxide emissions from all power plants, will become more costly to implement. And if states cannot meet the plan's requirements, the U.S.'s promise to China to cut greenhouse gas emissions by as much as 28 percent by 2025 may fall through.

The paucity of replacement reactors also presses the U.S. to depend on nuclear power plants built with designs from the 1950s that have known flaws. In fact, the U.S. still has 23 reactors with the same design that melted down after the 2011 earthquake and subsequent tsunami in Fukushima, Japan. These reactors are aging, too: components face a daily load of high temperatures, pressures, vibration and bombarding neutrons, which can render thick steel walls so brittle that cracks form at welds and joints.

New, safer reactor designs or the massive scale-up of wind, solar and, particularly, geothermal power—because of its ability to produce electricity at all times, as does fission or coal burning—could ultimately replace aging reactors. But swapping nuclear with natural gas is no way to help combat climate change.

—David Biello

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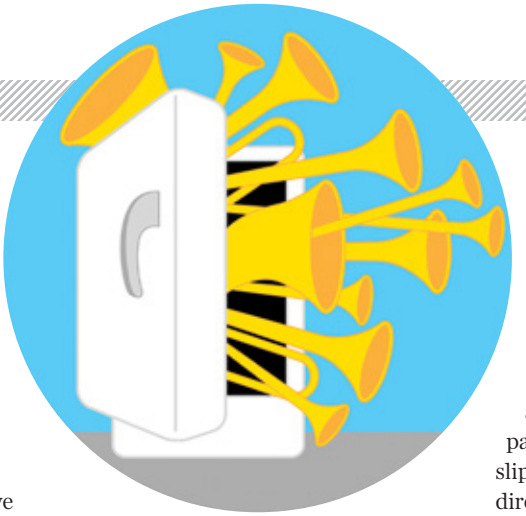
ACOUSTICS

Din for Dinner

Fridge noises become less mysterious, still annoy



The buzzing. The whirring. The high-pitched ringing. Refrigerators could drive a person a bit mad, and they do: more than half of people who have a fridge are annoyed by its racket, according to a study by Korean engineers presented in 2006. One particularly irksome noise is unique to no-frost fridges: a popping sound that bursts into the room in spats when the home appliance's compressor revs up. Researchers were uncertain as to the cause of these sounds, so mechanical engineers from MEF University and Istanbul Technical University, both in Turkey, launched a study to zero in on the audibles' origins. First, they built their own stripped-down fridge as a testing rig. It contained only the necessary parts, including a compressor, fan, heater, evaporator and cooling pipes. With vibration sensors and microphones taped to the various parts, the team ran the components separately or in combination in different scenarios. They observed that the popping, or "cracking," noises took place most frequently—and were loudest—when the heater was running, during the fridge's defrost stage. No-frost fridges cycle between warming and cooling phases to prevent ice buildup. The team published its results in the March issue of *Applied Acoustics*.

More specifically, these bursts most likely occur during rapid temperature changes that cause contraction and expansion of metal and other materials in the heating panel that touch. It is called the "stick-slip" phenomenon, says David Bowen, director of the noise and vibration group at Acentech, an acoustics consulting firm in Cambridge, Mass. The ultimate culprit is friction: the parts "stick" to one another because of static friction but then suddenly "slip" by one another, which causes the panel to vibrate and radiate sound.

The authors note that there are ways to reduce the popping, such as lowering the heating rate. Ultimately the bursts probably get past quality-assurance inspections because such sounds are difficult to quantify and qualify, Bowen says: "It's a that-really-bothers-me type of noise." —*Amber Williams*

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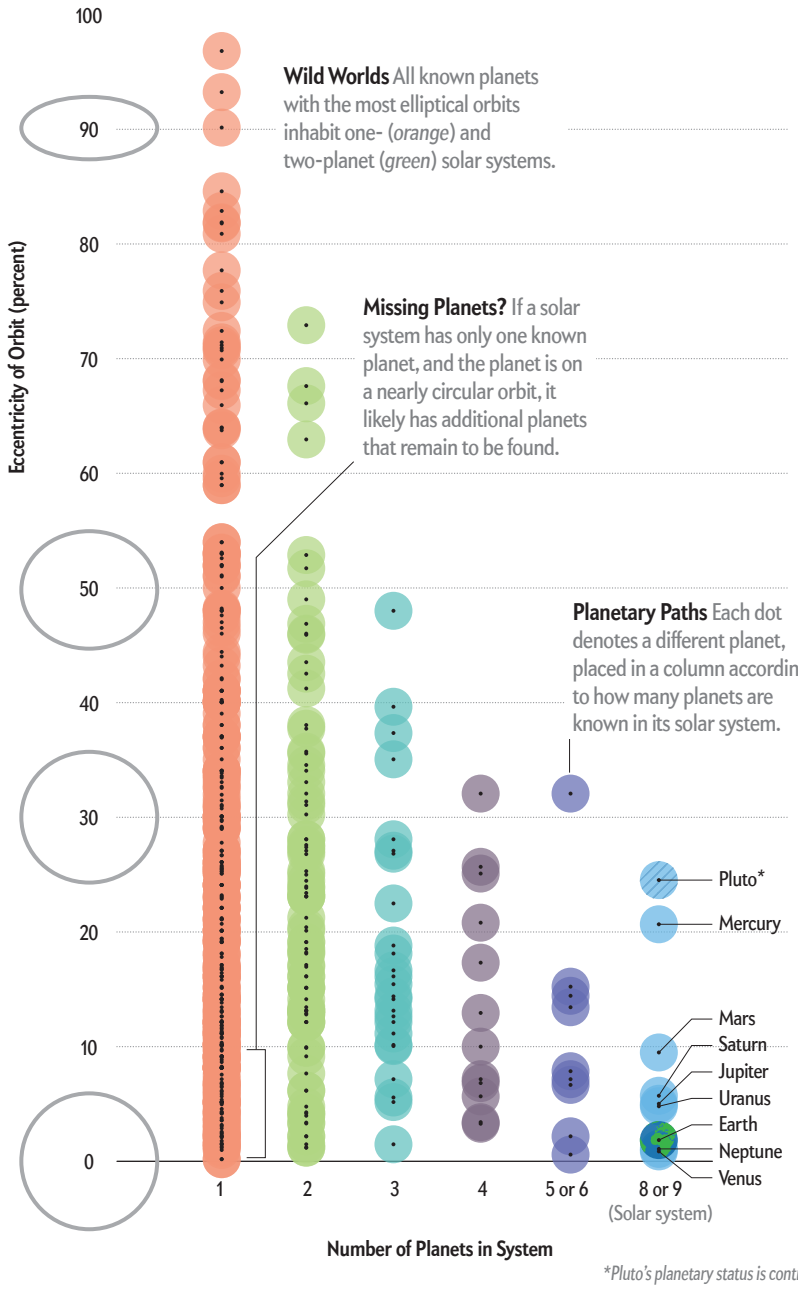
ASTRONOMY

Circle of Life

Which solar systems are more likely to harbor extraterrestrials? Those with lots of planets that make circular orbits

If intelligent life is out there, it probably resides in a solar system with many planets. The more planets a star has, a recent study found, the more circular the orbits tend to be. Because planets on circular orbits do not move toward or away from their star, their climates may be stable enough to foster advanced life.

Our own solar system fits that pattern. The sun has eight or nine planets



*Pluto's planetary status is controversial.

SOURCE: "EXOPLANET ORBITAL ECCENTRICITY: MULTIPLICITY RELATION AND THE SOLAR SYSTEM," BY MARY ANNE LIMBACH AND EDWIN L. TURNER, IN *PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES USA*, VOL. 112, NO. 1; JANUARY 6, 2015

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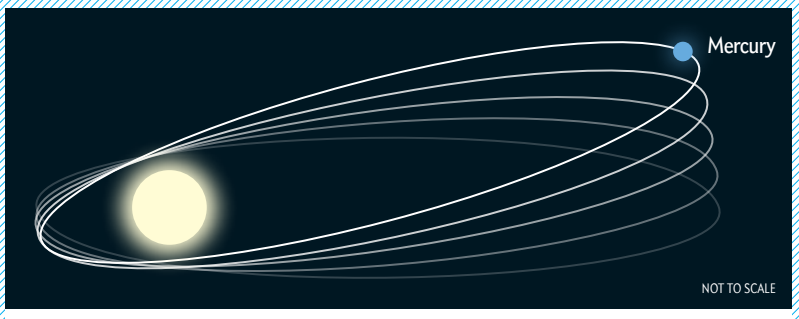
(depending on how you count), and most of them have fairly circular paths. Earth's orbit, for example, has an eccentricity of just 1.7 percent. (Eccentricity ranges from 0 percent for a perfect circle to nearly 100 percent for extreme ellipses.) Mercury and Pluto pursue oval-shaped orbits, with eccentricities of 21 and 25 percent, respectively, but even Pluto—whose planetary status is controversial—seems tame when compared with many of the planets orbiting other stars, where eccentricities can exceed 60, 70, even 80 percent.

As far as we know, such wild worlds exist only in solar systems with one or two planets, say astronomers Mary Anne Limbach and Edwin L. Turner of Princeton University, who conducted the study. In contrast, solar systems with four or more planets feature moderately round orbits. The conclusions, based on 403 planets with previously measured orbital eccentricities in hundreds of solar systems, appeared in January in the *Proceedings of the National Academy of Sciences USA*.

Illustration by Jason Mischka



ELLIPTICITY IN HISTORY

Like any planet on an elliptical path, Mercury comes closest to the sun once every orbital period, but the position of the closest point changes faster than Newton's law of gravity predicted—convincing some 19th-century astronomers that a planet they named Vulcan was pulling Mercury off course. In fact, its proximity to the sun accentuates the (then unknown) effects of general relativity, which helped to confirm Einstein's theory. *—K.C.*

Jack Lissauer, a planetary scientist at the NASA Ames Research Center, notes that the newfound correlation makes sense because planets on circular orbits do not interfere much with one another. A planet on an elongated path, on the other hand, can "mess up the orbits of the other planets and kick them out [of the system]," Limbach says.

These planetary road hogs do not make good abodes themselves. When near their sun, they fry; when far away, they freeze. Thus, intelligent beings are more likely to prosper on planets with circular orbits. Such beings would see many other worlds orbiting their star, just as we do—and may even bicker over which ones are truly planets. *—Ken Croswell*

SOURCE: UNDERSTANDING SCIENCE: http://undsci.berkeley.edu/article/howscienceworks_11

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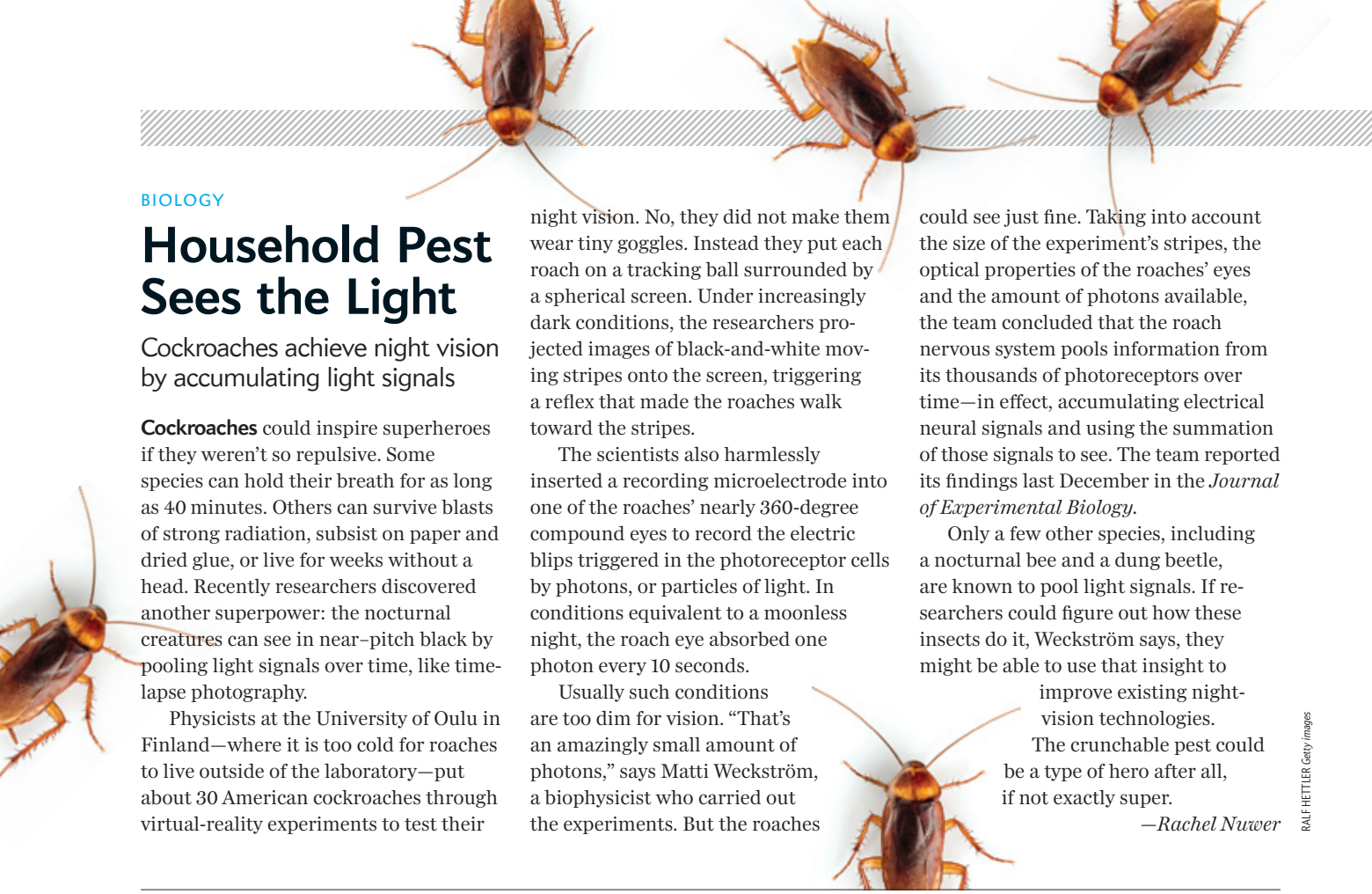

RALF HETTLER Getty Images

BIOLOGY

Household Pest Sees the Light

Cockroaches achieve night vision by accumulating light signals

Cockroaches could inspire superheroes if they weren't so repulsive. Some species can hold their breath for as long as 40 minutes. Others can survive blasts of strong radiation, subsist on paper and dried glue, or live for weeks without a head. Recently researchers discovered another superpower: the nocturnal creatures can see in near–pitch black by pooling light signals over time, like time-lapse photography.

Physicists at the University of Oulu in Finland—where it is too cold for roaches to live outside of the laboratory—put about 30 American cockroaches through virtual-reality experiments to test their night vision. No, they did not make them wear tiny goggles. Instead they put each roach on a tracking ball surrounded by a spherical screen. Under increasingly dark conditions, the researchers projected images of black-and-white moving stripes onto the screen, triggering a reflex that made the roaches walk toward the stripes.

The scientists also harmlessly inserted a recording microelectrode into one of the roaches' nearly 360-degree compound eyes to record the electric blips triggered in the photoreceptor cells by photons, or particles of light. In conditions equivalent to a moonless night, the roach eye absorbed one photon every 10 seconds.

Usually such conditions are too dim for vision. "That's an amazingly small amount of photons," says Matti Weckström, a biophysicist who carried out the experiments. But the roaches could see just fine. Taking into account the size of the experiment's stripes, the optical properties of the roaches' eyes and the amount of photons available, the team concluded that the roach nervous system pools information from its thousands of photoreceptors over time—in effect, accumulating electrical neural signals and using the summation of those signals to see. The team reported its findings last December in the *Journal of Experimental Biology*.

Only a few other species, including a nocturnal bee and a dung beetle, are known to pool light signals. If researchers could figure out how these insects do it, Weckström says, they might be able to use that insight to improve existing night-vision technologies.

The crunchable pest could be a type of hero after all, if not exactly super.

—*Rachel Nuwer*

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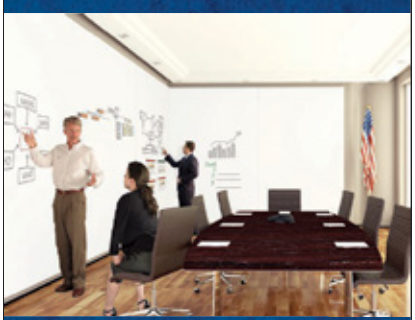

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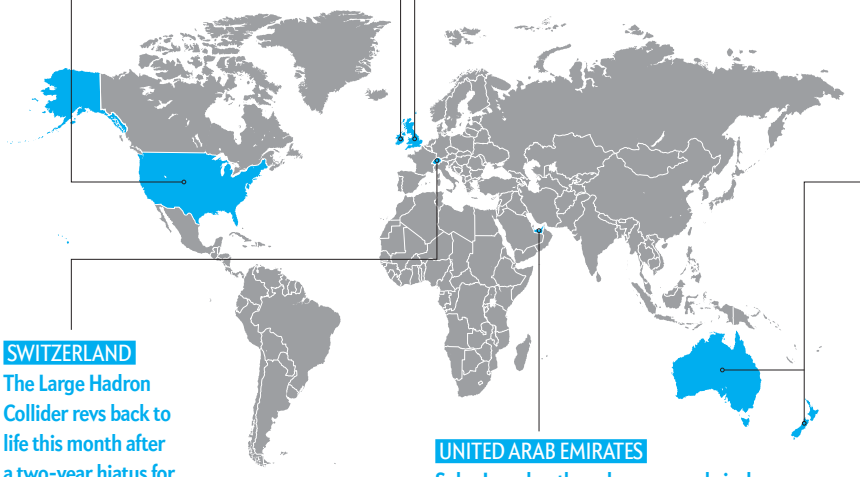
IN THE NEWS

Quick Hits

IRELAND
Every household—2.2 million in all—will receive its own seven-digit postal code this spring. Until now, many addresses were specified with just a name and neighborhood, which mixed up deliveries and misrouted ambulances.

U.K.
Archaeologists will reinter the skeleton of Richard III—discovered underneath a parking lot in 2012—at Leicester Cathedral this month. After two years of study, they concluded that the king had a rich diet, endured a roundworm infection and probably died in battle from head wounds.

U.S.
Ground was broken in California on a years-in-the-making high-speed train, which will carry passengers between San Francisco and Los Angeles in about 2.5 hours—half the time it takes by car. Estimated completion date: 2029.



AUSTRALIA AND NEW ZEALAND
Netflix comes to residents of the Land Down Under this spring.

SWITZERLAND
The Large Hadron Collider revs back to life this month after a two-year hiatus for repairs and upgrades.

UNITED ARAB EMIRATES
Solar Impulse, the solar-powered airplane that flew across the U.S. in 2013, will take off from Abu Dhabi early this month in an attempt to circumnavigate the world.

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PHYSIOLOGY

Nature vs. Nurture vs. NASA

The space agency sends a twin into orbit for a "natural" experiment

As of March, if retired astronaut Mark Kelly wants to talk with his identical twin, he will have to make a long, long-distance call—to the International Space Station (ISS). His brother, Scott Kelly, age 51, chose the same profession and will be living there as part of a yearlong study of space travel's effect on human health. The Kellys' clonal DNA provides a unique opportunity to observe changes in genetic expression in a zero-gravity environment and compare them with a simultaneous quasi-control case on Earth. NASA scientists will also compare fluid flow in the twins' brains, the composition of their microbiomes, and rates of decay of their telomeres—the protective caps on the ends of chromosomes that signal cellular aging.

Repeat fliers Scott and Mark Kelly are among more than 200 humans to have floated around all day on the ISS. Ever since the station's first crew arrived in November 2000, researchers have monitored how astronauts there respond to long-term spaceflight. Michael Barratt, who spent 199 days in space in 2009, says "it feels like you're hanging upside down." He adds: "We train really hard so we know every task—especially in the first couple of weeks so you rely on your training and checklist even if you're not feeling very well." NASA scientists already know a great deal about how an extended celestial sleepover affects the body in space and will monitor the twins for such symptoms, too. —*Amy Nordrum*

"It would be nice to learn that there are no genetic effects of long-term space flight, but I somewhat doubt that to be the case."
—SCOTT KELLY

COURTESY OF NASA (*space suit*); COURTESY OF ROBERT MARKOWITZ NASA (*Kelly*)

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Celestial Influence

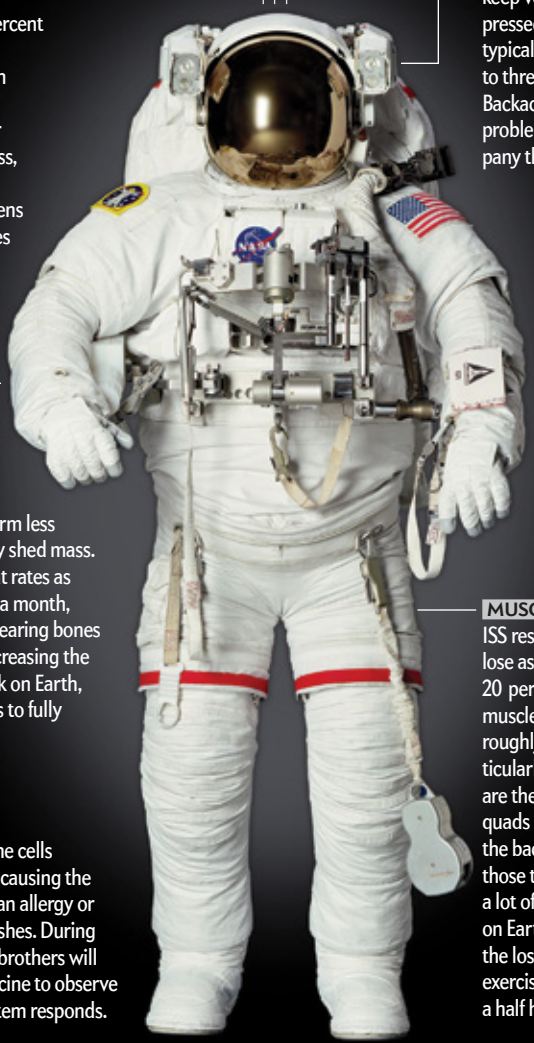
How living in zero gravity changes the human body

SICKNESS
Most astronauts initially experience headaches, lethargy or motion sickness in zero gravity. These symptoms disappear after a few days when the body's sensory systems adapt.

BLOOD FLOW
At liftoff, blood rushes to the head. The upward flow continues in space because of low or zero gravity. In time, about 10 percent of the fluids found in the lower half of an Earth-bound body (one to two liters) will float to the head. Pressurized pants combat this "puffy face–bird leg" effect.

EYES
A survey revealed that 29 percent of shuttle astronauts and 60 percent of station astronauts reported worse vision while in flight. Many became farsighted or experienced blurriness, possibly because the shape of the eye flattens with pressure changes in the skull.

SPINE
Without gravity to keep vertebrae compressed, astronauts typically become two to three inches taller. Backaches and nerve problems can accompany the new height.



BONE*
In space, bones perform less support work, so they shed mass. Bone loss can occur at rates as fast as 1 to 2 percent a month, particularly in load-bearing bones such as the pelvis, increasing the risk for fractures. Back on Earth, it can take three years to fully restore bone density.

MUSCLES*
ISS residents can lose as much as 20 percent of their muscle mass in roughly a week. Particularly vulnerable are the calf muscles, quads and muscles in the back and neck—those that support a lot of weight back on Earth. To combat the loss, astronauts exercise for two and a half hours a day.

IMMUNE SYSTEM
Some types of immune cells become more active, causing the body to overreact to an allergy or develop persistent rashes. During their study, the Kelly brothers will each receive a flu vaccine to observe how the immune system responds.

*These are homeostatic adaptations—the body's quest to find a new equilibrium. Such changes present a problem only for space travelers returning to Earth.

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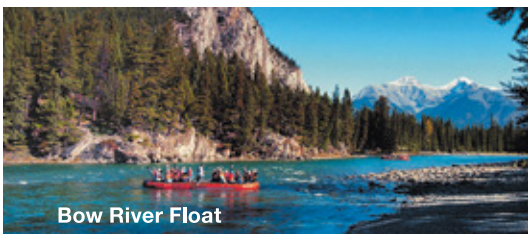

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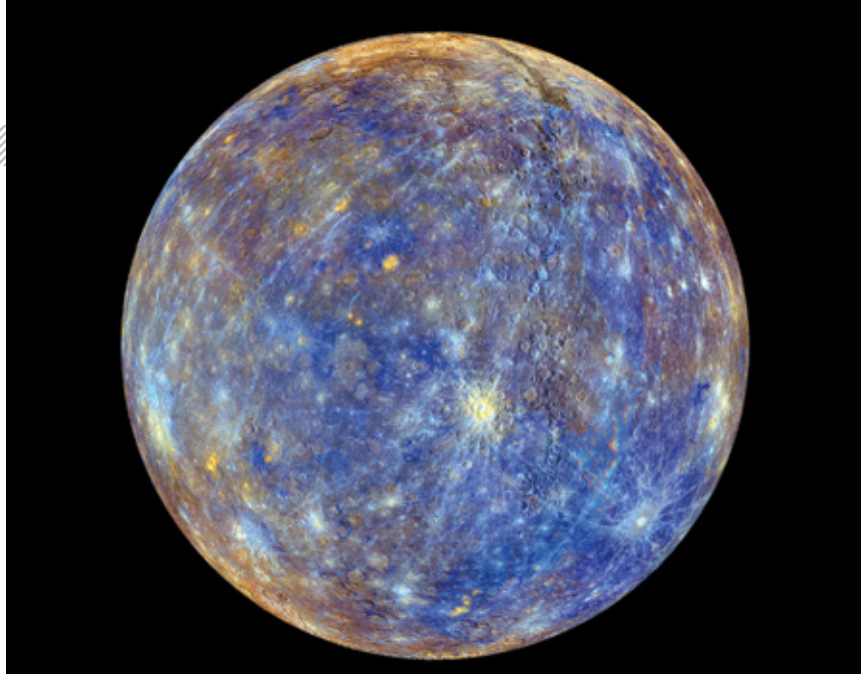
SPACE

Ode to the Messenger

NASA's Mercury orbiter completes its four-year mission

The first mission to orbit Mercury is nearing its end. Since arriving at the innermost planet in March 2011, the Messenger spacecraft has "rewritten the entire textbook on Mercury and the implications for the formation and evolution of the inner solar system," says its principal investigator Sean Solomon of Columbia University. The probe was due to run out of fuel at the end of March, which would have initiated its gradual fall to the planet's surface. Recently, however, engineers found a way to squeeze a few more weeks' worth of propellant from its stores of helium, potentially pushing Messenger's demise into mid-April. The reprieve should allow sufficient extended time for measurements of Mercury's surface from within 15 kilometers—closer than ever before. Although the official mission will be over soon, astronomers now have more than 10 terabytes of data to keep them busy unspooling the mysteries of Mercury for years to come. —*Clara Moskowitz*



Messenger is the only craft to have completely mapped the surface of Mercury (*above*). Color-enhanced, this image represents chemical and mineral variations across the planet: tan areas are lava-formed plains, and blue regions show material that reflects little light.

What We've Learned about Mercury

WEIRD MAGNETIC FIELD

In the 1970s Mariner 10's flyby revealed that Mercury has a magnetic field. Yet Messenger's observations showed that, strangely, the field is not centered inside the planet but instead is offset toward its north pole. Theorists have yet to explain what causes the asymmetry.

VOLCANISM

Messenger settled a long-running debate about whether volcanism is prevalent on Mercury. Previous imagery showed plains that could have resulted either from volcanic activity or from asteroid collisions. New data from Messenger indicated that these areas best match expectations for dried lava flows and that, in fact, volcanic material covers most of the planet's surface.

SURPRISING FORMATION HISTORY

Before Messenger, researchers thought Mercury had experienced periods of superhigh temperatures—up to 10,000 kelvins—during its early history, perhaps caused by an asteroid impact. Messenger detected surface metals that would have vaporized at such high temperatures, contradicting this theory.

MYSTERIOUS "HOLLOWS"

Messenger revealed enigmatic flat and shallow bright spots littering Mercury's surface. Scientists dubbed them "hollows," which appear to be unique to the planet. Experts' best guess is that these features form when volatile material from the surface is lost to space, perhaps through interactions with the solar wind of particles blown off the sun.

Mission Timeline

- **JULY 1999** — NASA approves Messenger mission
- **AUGUST 3, 2004** — Messenger launches
- **OCTOBER 2006** — First Venus flyby
- **JANUARY 2008** — First Mercury flyby
- **MARCH 2011** — Spacecraft enters Mercury orbit
- **MARCH–APRIL 2015** — Mission ends

BY THE NUMBERS

8.6
Mercury days Messenger has orbited the planet

1,504
Earth days Messenger has orbited the planet

4,105
Orbits of Mercury completed

258,095
Photographs returned to Earth

8.7 billion
Total miles traveled

COURTESY OF NASA, JOHNS HOPKINS UNIVERSITY APPLIED PHYSICS LABORATORY AND CARNEGIE INSTITUTION OF WASHINGTON

COMMENT AT ScientificAmerican.com/mar2015

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Claudia Wallis is an award-winning science journalist whose work has appeared in *Time* magazine, *Fortune*, the *New York Times* and numerous other publications.

The Coming Revolution in Knee Repair

New techniques in orthopedic surgery aim to unleash the body's own healing power

If you look very carefully at the C-curved squiggle taking shape on a 3-D printer at Columbia University Medical Center, you just might spot the future of knee repair. Layer by layer, the machine's tiny needle squirts out a bead of white polymer, matching a virtual blueprint of a meniscus—the semicircular band of tough, fibrous cartilage that serves as the knee's shock absorber. A bioprinter in the laboratory of Jeremy Mao can churn out three menisci in just under 16 minutes.

These particular parts are destined for sheep, the test animal for a new method of correcting a torn meniscus, one of the most common of all human joint injuries. Surgeons will substitute the manufactured part for a sheep's own damaged meniscus to serve as a scaffold for healing. Once the device is in place, specialized proteins embedded in it will attract stem cells that will rebuild the meniscus as the polymer breaks down. A study published in December 2014 found it took just four to six weeks to restore a sheep's meniscus using this method. If successfully developed for humans, the new approach would be far superior to what physicians can offer today, which in most cases is simply to remove the ripped tissue if it is causing pain or disrupting knee function. "What we are shooting for is true joint regeneration," Mao explains.

The sheep experiment is part of a broader trend in orthopedic surgery to find ways to trick the body into healing joints in ways that are more functional and durable than current surgical interventions. Although modern orthopedic surgery does a good job of getting people back on their feet and, in the case of professional athletes, performing at exalted levels, it does not restore an injured knee to its original condition and generally fails to stop—or even exacerbates—the long-term deterioration of the joint.

For reasons that are not entirely clear, damage to the key stabilizing structures of the knee joint often triggers a degenerative process that leads to the worn-out cartilage and chronic pain of osteoarthritis. The goal of next-generation treatment is to return the knee to its full function in as natural a way as possible, which may also slow or stop the runaway cycle that leads to arthritis. "It's repair and regeneration, rather than removal

Illustration by Logan Faerber

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and replacement," says orthopedic surgeon Martha M. Murray, who heads the Sports Medicine Research Laboratory at Boston Children's Hospital.

The need is huge. Every year an estimated 5.5 million people in the U.S. visit orthopedic surgeons for a knee problem. About a million undergo outpatient knee surgery, and that figure does not include another 700,000 annually who have reached the end of the line with one or both of their own knees and wind up with artificial replacements.

WHY CAN'T THESE JOINTS JUST HEAL?

MUCH OF THE NEW THINKING about joint repair is rooted in research into the perplexing question of why connective tissues in the joints—tendons, ligaments and cartilage—do not necessarily heal the way other tissues do. A big part of the problem in many of these structures is a relatively poor blood supply; blood contains cells and proteins that are essential to healing.

Tendons, the flexible ropes of fibrous tissue that connect muscles to bone, and ligaments, the slightly stretchy bands that link bone to bone, are less well nourished by blood vessels than are most other tissues. As for cartilage—such as the supersmooth white material on the end of bones (think chicken legs) that helps joints glide—most of it has no blood supply. "So cartilage has virtually no capacity to heal," says Scott Rodeo, an orthopedic surgeon and researcher at the Sports Medicine and Shoulder Service at the Hospital for Special Surgery in New York City and a team physician for the New York Giants.

Although surgeons can sometimes stitch together a torn meniscus—especially if the tear is in the outer region, which has its own supply of blood vessels—most of the time they can do little more than cut away the frayed pieces—a procedure that a major study in 2013 found was of questionable, long-term value. Nor can surgeons sew up a tear in the anterior cruciate ligament (ACL), located in the middle of the knee and the site of many sports injuries. Instead they remove the torn ligament and replace it with a graft from a cadaver or from the patient's own body.

In addition to a paltry blood supply, the ACL's central location in the joint capsule, which is filled with a lubricant called synovial fluid, is another reason the band will not heal on its own. Wound repair normally begins with bleeding and the formation of a blood clot. Cells in the clot called platelets release certain proteins that promote healing, whereas the sticky clot itself serves as a temporary scaffold for reconstruction with new cells. In joints, however, synovial fluid dissolves clots, "so there's never that early bridge that gives healing a place to happen," says Murray of Boston Children's Hospital. This is why a tear in the ACL does not heal, but a rip in the nearby medial collateral ligament, which runs along the side of the knee beyond the synovial fluid, slowly knits itself together.

SECRETS OF SELF-REPAIR

ORTHOPEDIC SURGEONS have long made attempts to lure the body into doing a better job of healing cartilage, ligaments and tendons. In recent years they have turned to what they call "biologics"—substances made from the patient's own blood and other tissues. One of the most popular is called platelet-enriched plasma (PRP), which was first used by oral surgeons to help regenerate bone and soft tissue in the jaw.

PRP is simple to produce and deploy: extract some blood from the patient, spin it in a centrifuge to concentrate the platelets, and then inject the resulting fluid into an injured joint or use it in combination with surgery. PRP is replete with growth factors and other substances that promote healing. Studies have so far shown that it can help heal inflamed tendons, such as "tennis elbow," and relieve pain in an arthritic joint, but whether it can effectively address the wide variety of problems for which it is used is not yet clear.

A newer biologic is made of bone marrow instead of blood and is richer in stem cells than PRP. It, too, is extracted from the patient (through a thin needle in the hip, under local anesthesia) and concentrated using a centrifuge. Bone marrow aspirate concentrate, or BMAC, can be turned into a dense clot that serves as a blood-red spackle that surgeons use to fill gaps in cartilage and to surround and nurture grafted tissue. Veterinarian Lisa Fortier of Cornell University developed the stuff to help racehorses get back on track after a cartilage injury. It offers what she calls "the trilogy of tissue repair": a thick clot that serves as a short-term scaffold, stem cells to generate new tissue and growth factors to guide that regeneration. Studies in both humans and horses show that cartilage healed with BMAC has a more normal structure than cartilage repaired in other ways.

Because PRP and BMAC come from the patient and go right back into the patient, they did not need to be approved by the Food and Drug Administration, and their use has spread rapidly without a lot of testing. "They are hard to study," Rodeo notes, because they vary from person to person, making results uneven. With additional research, he predicts, "we will probably turn to a more refined approach—where we'll identify the factors in bone marrow aspirate and PRP that we want to keep and factors we want to take out" and modify accordingly.

Although the biologics appear to promote healing, they cannot generate a sturdy enough scaffold to repair a torn meniscus or ACL. That is why researchers are trying out 3-D printing and other innovations. At Boston Children's Hospital, Murray is testing a small cylinder of spongelike material—made of proteins such as collagen that are found in connective tissue—as a scaffold for repairing a torn ACL. The sponge is soaked in the patient's blood and then sutured between the two torn ends of the ligament, creating a temporary bridge for healing, much the way a blood clot would. It has worked so well in pigs that Murray and her associates have received FDA approval to try it in humans this year. One especially hopeful finding in pigs: those treated with the new technique developed far less arthritis than those given traditional ACL reconstruction.

Despite the promise of these and other regenerative techniques on the horizon, it is, of course, always a good idea to try to avoid surgery by protecting your knees as best you can. But for those unfortunate enough to damage this complex joint, the future is looking stronger and a lot less painful. SA

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

Is E-mail Dead?

With the rise of rapid-fire messaging, the digital letter seems to be crawling toward the fate of snail mail

If your in-box is currently reporting unread messages in the hundreds or thousands, you might have a hard time believing the news: e-mail is on the decline.

The total volume of e-mail has dropped about 10 percent since 2010.

The word "e-mail" itself tells you about its origins: it was modeled on written letters. To this day, a lot of e-mail begins with a salutation. Maybe it's "Hey" instead of "Dear Casey," but it's there.

And because there was so much overhead involved with sending a letter—folding, enveloping, addressing, stamping, mailing—few bothered to send only a few pithy words. The effort seemed to justify a longer message.

Once heralded as the death of the personal human touch, e-mail has now taken over the letter's place as a ubiquitous form of communication—both business and personal. But is its day in the digital sun coming to a close?

At first blush, that might seem to be the case. The incoming generation, after all, doesn't do e-mail. Oh, they might have an account. They use it only as we would a fax machine: as a means to communicate with old-school folks like their parents or to fulfill the sign-up requirements of Web sites. They rarely check it, though. As of just a few years ago, among 25- to 35-year-olds, e-mail had already dropped 18 percent—and among teenagers, it was down about 60 percent. A Microsoft human resources guy recently told me that lately, applications from recent college graduates leave the "e-mail address" field blank. It's considered too unwieldy, uncool, not immediate enough.

Today's instant electronic memos—such as texting and Facebook and Twitter messages—are more direct, more concentrated, more efficient. They dispense with the salutation and the signoff; we already know the "to" and "from."

Many corporations are moving to messaging networks for exactly that reason: more signal, less noise. And less time.

This trend is further evidence that store-and-forward systems such as e-mail and voicemail are outdated. Instead of my leaving you a lengthy message that you pick up later, I can now send you an unobtrusive, easily consumed message that you can read—and respond to—on the go.

The decline of e-mail corresponds neatly to the dawn of the mobile era. Let's face it: e-mail has historically been an *activity*. You sit down to do it. You fill up a block of time. And long missives are clumsy on a phone.

Illustration by Kyle Stecker

But instantaneous written messages are different. These are neatly tailored to fit in just about any time: before a movie, in a taxi, waiting for lunch. And because these notes are invariably brief, they're a natural for smartphone typing.

With these formats, you also have control over who can correspond with you, which you usually don't in e-mail. And especially on Facebook, instant messaging can take on the character of a chat room, where several people can carry on at once.

As a bonus, none of these channels have been overrun by spam, and advertisers have yet to blast us that way.

Does this mean e-mail is on its way to the dustbin of digital history? Was it just a transitional technology—from postal mail to the new, rapid-fire communication channels?

Not necessarily. E-mail still has certain advantages. Whereas tweets and texts feel ephemeral—you read them, then they're gone, into an endless string—e-mail still feels like something you *have,* that you can file, search and return to later. It's easy to imagine that it will continue to feel more appropriate for formal communications: agreements, important news, longer explanations.

So, no, e-mail won't go away completely. Remember, we've been through a transition like this not so long ago: when e-mail was on the rise, people said that postal mail was dead. That's not how it works. Postal mail found its (smaller) niche, and so will e-mail. Technology rarely replaces an institution completely; it just adds new avenues.

E-mail down, messaging up. Now go clean out your in-box. SA

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Pros and cons of e-mail alternatives: ScientificAmerican.com/mar2015/pogue

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MEDICAL ELECTRONICS

SHOCK MEDICINE

Stimulation of the nervous system could replace drugs for inflammatory and autoimmune conditions

By Kevin J. Tracey

IN BRIEF

Exposure to heat, pressure, light or chemicals sets in motion a process to ensure that bodily organs do not overreact to these stresses.

Nerve signals that link the brain and the rest of the body inhibit the making of immune molecules that cause inflammation.

Electrical stimulation of neural pathways with an implanted medical device may assist the body in suppressing inflammation.

Bioelectronic medicine is the name of the new discipline that uses electrical stimulation to treat inflammation and other disorders.

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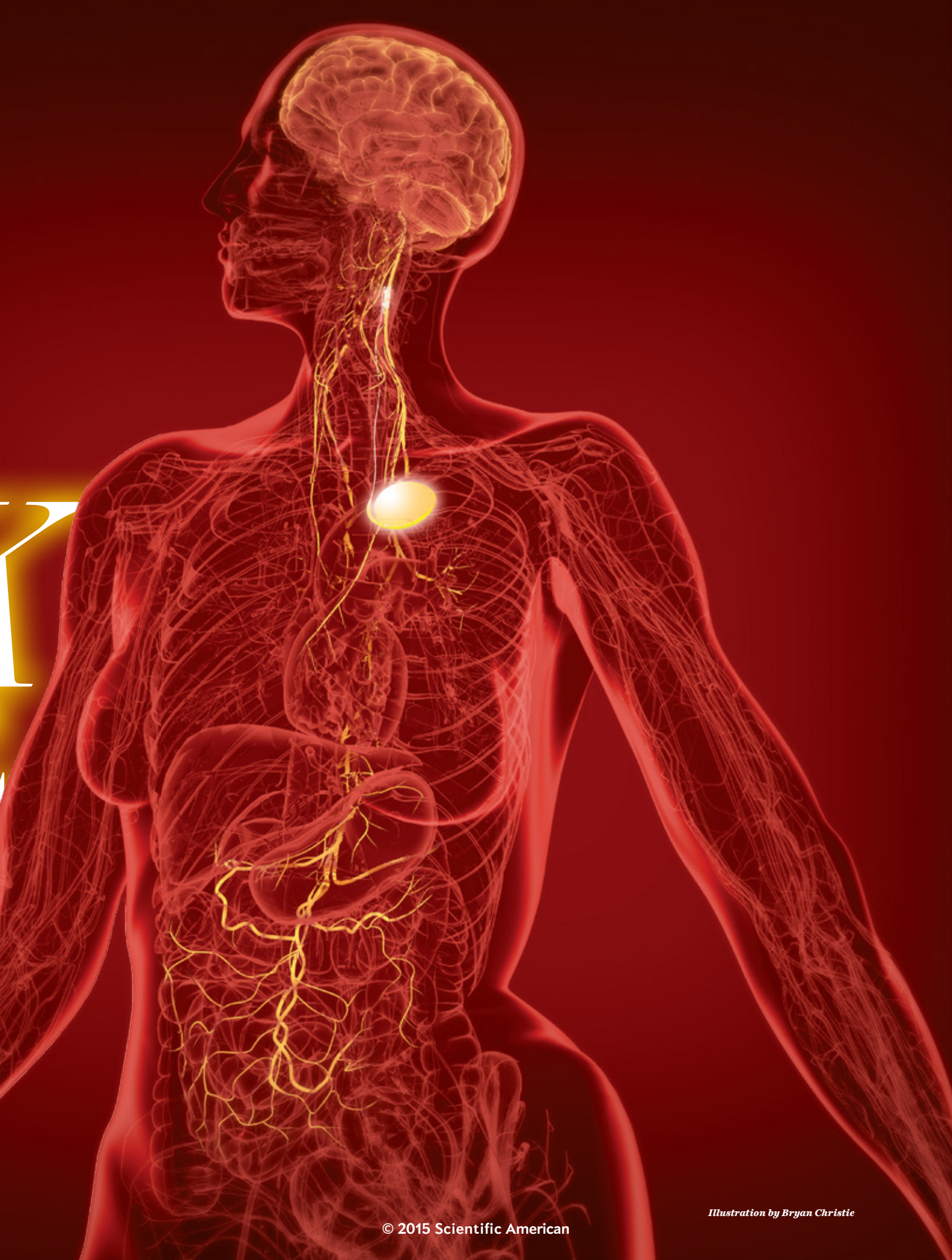

Illustration by Bryan Christie

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I am a brain surgeon who is fascinated by inflammation. Along with my laboratory colleagues, I examine molecules that cause inflammation so that we can discover methods for alleviating the pain, swelling and tissue damage that is a consequence of many diseases.

Some of this work has already benefited patients. In 1987 I published the results of an experiment that targeted an inflammatory molecule called tumor necrosis factor, or TNF, to rescue lab baboons from the consequences of lethal infection—a study that contributed to the discovery of a new class of drugs for inflammatory, autoimmune and other diseases that disrupt the normal functioning of the body's immunological defenses.

As a neurosurgeon, I am also intensely interested in the workings of the brain. A surprising discovery we made in the late 1990s, again involving TNF, merged insights from neuroscience and immunology. We inadvertently discovered that neurological reflexes—predictable responses to certain sensory stimuli—block the production of TNF. This insight culminated in an invention I devised to treat inflammation using small, electrical nerve stimulators implanted in patients.

The use of nerve-stimulating electronic devices to treat inflammation and reverse disability is laying the foundation for a new discipline called bioelectronic medicine. It is being tested in clinical studies of patients with rheumatoid arthritis and other diseases. It is based on a deceptively simple concept of harnessing the body's natural reflexes to develop an array of effective, safe and economical alternatives to many pills and injectable drugs. By precisely targeting the biological processes underlying disease, this nerve-stimulating technology should help avoid the troublesome side effects of many drugs.

THE REFLEX CIRCUIT

HEAT, TOUCH, PRESSURE, LIGHT and the presence of specific molecules generate an electrical signal in nerve cells called sensory neurons. This electrical information is transmitted to "interneurons," another type of nerve cell in the central nervous system that passes the incoming impulse along to motor neurons, which complete the third and final stage in the simple reflex circuit. The subsequent firing of the motor neuron sends electrical signals back to the body's muscles and organs, triggering behaviors ranging from the withdrawal of a finger from a hot plate to the dilation of an airway during a three-mile run.

Simple reflex circuits harmonize the activity of individual organs, so that you do not have to consciously plan the minute actions that keep your body functioning efficiently. When you leap from a chair and run up the stairs to answer the ring of a telephone, you do not have to think about coordinating your respiration, heart rate and blood pressure. Reflexes take care of all the essentials, matching organ function to the body's needs, whether resting comfortably or running at full speed.

Charles Scott Sherrington (1857–1952), the Nobel Prize–winning British physiologist, proposed that simple reflexes made up of neural circuits are the basic building blocks of the nervous system. The combined output of millions of nerve signals that control reflexes directs the functioning of the body's organs. But Sherrington did not address one lingering question: How do the electrical signals that course through motor neurons actually control organ function? The answer is relatively simple. In effect, they produce "drugs." Neurons transmit information along nerve fibers, or axons, the long, wirelike extensions that terminate in the organ being regulated. At the very end of the axon lies the "synapse," a word coined by Sherrington. The motor neuron's axon on one side of the synapse does not physically touch the nerve or organ cells on the opposite side of the narrow gap called the synaptic cleft. Instead the arrival of the electrical signals at the end of the axon stimulates release of neurotransmitters that diffuse across the synaptic cleft and bind to receptors, docking sites on the target nerve or organ cells. Chemical neurotransmitter molecules latch on to receptors at the other side of this cleft to alter the behavior of the targeted cells, changing their function. It turns out that many drugs work in a similar manner.

The pharmaceutical industry invests billions of dollars to design, synthesize and develop new chemicals as experimental drugs that, like neurotransmitters, are nothing more than molecules that interact with receptors. Many blockbuster drugs

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selectively bind to specific receptors that modify metabolic activity and turn on genes in selected cells. But drugs can have dangerous side effects. Once swallowed or injected, pharmaceuticals travel throughout the body, where they may produce undesired consequences when interacting with cells that are not their intended targets.

Using a device to send signals down a nerve to stimulate production of druglike neurotransmitters offers a distinct advantage. The body's self-made drugs deliver chemicals to specific tissues in precise, nontoxic amounts at just the right time, diminishing the occurrence of side effects.

AN ACCIDENTAL DISCOVERY

BY THE LATE 1990S a new class of pharmaceutical called monoclonal antibodies were being used to treat patients with rheumatoid arthritis, inflammatory bowel disease and other disorders. Monoclonal antibodies, which my colleagues and I helped to pioneer, can alleviate the pain, swelling, tissue destruction, and other symptoms of inflammation caused by the overproduction of TNF and other molecules. For many patients, it offers their only chance for a normal life. But success has come with soaring costs. Drug bills range from $15,000 to $30,000 annually for a single patient, even though anti-TNF is ineffective in up to 50 percent of patients. Perhaps most worrisome to patients and their caregivers, these drugs can cause dangerous, even lethal, side effects.

In my lab, now at the Feinstein Institute for Medical Research in Manhasset, N.Y., I was working with my colleagues on an alternative approach to block TNF, a molecule we had developed and named CNI-1493. My original hypothesis was that injecting this experimental drug directly into the brain would prevent TNF production during a cerebral infarction, or stroke. Although this proved to be true, I was entirely unprepared to find that administering tiny quantities of CNI-1493 into the brain also blocked TNF production in organs *throughout the body*. At first not believing the results, we repeated the experiments many times. In each instance, we confirmed that vanishingly small quantities of CNI-1493 in the brain, concentrations too low to saturate the body's organs, somehow blocked TNF outside the brain. For months we discussed these findings in weekly lab meetings, never getting any closer to understanding how the drug worked.

Initially we reasoned that perhaps CNI-1493 activated the brain's pituitary gland at the base of the brain to stimulate production of hormones, including steroids—or glucocorticoids—that in turn inhibited TNF production in distant organs. Alas, after surgically removing the pituitary gland in rats and repeating the experiments, we found that CNI-1493 injected into the brain still inhibited TNF. This result meant that the pituitary gland did not convey the signal that turned off TNF production in the body. Searching for another explanation, we began to consider the improbable possibility that motor neurons exiting the brain carried electrical signals to inhibit TNF in the rest of the body.

To test the hypothesis, we relied on the established practice in neuroscience that links a particular brain area to certain behaviors. Much of what is known about neural control of behavior originated in early studies of stroke patients with localized brain damage. Paul Broca (1824–1880) observed that damage to a small region in the left posterior frontal cortex resulted in an inability to speak while preserving language comprehension, a condition called expressive aphasia. Similarly, Carl Wernicke (1848–1905) noted that stroke damage in a nearby area—the left posterior, superior temporal gyrus—produced sensory aphasia, an incapacity to either understand or produce meaningful speech. The insight that discrete brain regions control specific behaviors led us to postulate that cutting the individual circuits connecting the brain and organs could reveal the identity of specific nerves controlling TNF. We were perplexed about where to begin because there are millions of such connections between the brain and the organs.

While contemplating a plan of attack, we came across a seminal paper by Linda Watkins of the University of Colorado Boulder that demonstrated that the vagus nerve has a major role in transmitting sensory information from the body's organs into the base of the brain. In her experiments with rats, Watkins administered a signaling molecule called interleukin-1, or IL-1, that causes inflammation and fever. When injected into the abdomen, IL-1 increased body temperature. But when she cut the vagus nerve and repeated the experiment, no fever occurred. She concluded that the nerve transmitted information to the brain about the presence of IL-1 and that these neural signals controlled the onset of fever.

How do electrical nerve signals control organ function? The answer is relatively simple. They make and deliver drugs.

Working independently at Japan's Niigata University School of Medicine, Akira Niijima also had been injecting IL-1 in rats. He discovered that IL-1 administration to the animals spurred electrical activity in the vagus nerve traveling to the brain. Reviewing these data, I hypothesized that they might hold the key to identifying a reflex circuit for the immune system.

Considering the consequences of vagus nerve signals stimulated by IL-1, I reasoned that there would be a corresponding motor signal returning to organs outside the brain to regulate the inflammatory process. I proposed that a simple reflex control mechanism would shut down inflammation and fever to minimize possible damage to tissues. The process could be carried out if signals from inflammatory molecules in tissues not only traveled up the vagus nerve to the brain but also returned through the nerve to the original tissues, directing them to turn off the production of TNF and other inflammatory molecules, collectively known as cytokines.

Abiding by Sherrington's idea that a simple reflex begins with sensory input traveling along a nerve, I proposed that the TNF "off" signal from the vagus nerve completes a reflex nerve circuit between the brain and the immune system. This idea

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had potentially profound implications for understanding the body's defense mechanisms against infection and injury. I theorized that reflex neural circuits controlling immunity would maintain health-promoting processes—as opposed to disease-triggering inflammation—by preventing the toxic release of TNF and other inflammatory signaling molecules. I became immediately concerned, though, that someone else must have already thought of this seemingly obvious biological mechanism.

Searching the published literature turned up evidence that the major organs of the immune system, including the thymus, spleen, liver, lymph nodes and lungs, are all innervated with connections that descend from the brain. But none of this work identified research on reflex circuits controlling immunity. In fact, the antithesis had become medical dogma. Decades of immunology studies had focused on the role of the immune system in protecting the body independent of the nervous system. Immunity, in these accounts, centered on the workings of lymphocytes, monocytes, macrophages and other white blood cells, but not neurons.

The inflammatory reflex, which keeps the immune system from becoming overactive or underactive, is the name I gave the circuit that prevents toxicity and tissue damage. When the inflammatory reflex did not function well, the presence of cytokines would lead to the complications that occur in autoimmune diseases, such as rheumatoid arthritis. It seemed like a good theory, but experimental evidence was needed.

Testing this idea required a painstaking process of surgically dividing the vagus nerve at various points along its route from the brain to the body's organs. The nerve originates in the brain stem (at about the level of the ear in humans) and travels as paired left-and-right bundles of nerve fibers, descending through the neck, crossing the thorax, and coursing throughout the abdomen. Along its wandering path, it connects directly or indirectly to most of the body's organs. Working in anesthetized rats, we cut the vagus nerve in the neck, injected CNI-1493 into the brain, and then measured TNF in the brain, spleen and other organs. Convincing results emerged: an intact vagus nerve was required for CNI-1493 in the brain to switch off TNF production by immune cells in various organs. Mapping farther downstream, we selectively cut the vagus nerve at points along its route from the neck to the abdominal organs. The TNF off switch functioned only when the vagus nerve was intact in its entire trajectory beginning in the brain stem and proceeding through the neck, thorax and abdomen and into the spleen.

Proof that vagus nerve transmission provides the TNF off signal to the spleen came using a handheld nerve-stimulating electrode I acquired from the North Shore University Hospital's neurosurgery operating room. I had often used it to identify the facial nerve while removing a brain tumor to spare damage to the nerve. Resembling a flashlight that doctors carry in their shirt pockets, the battery-operated device has a small wire extending from the tip, near where a lightbulb would be in a flashlight. When placed onto a nerve, the tip delivers an electrical charge that stimulates the nerve to fire action potentials, the transmission of electrical information along the nerve fibers.

When I applied the tip of the nerve stimulator to the vagus nerve of anesthetized rats, TNF production in various organs was blocked. Here was

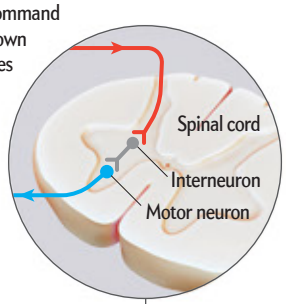
A PATH TO NEW THERAPIES

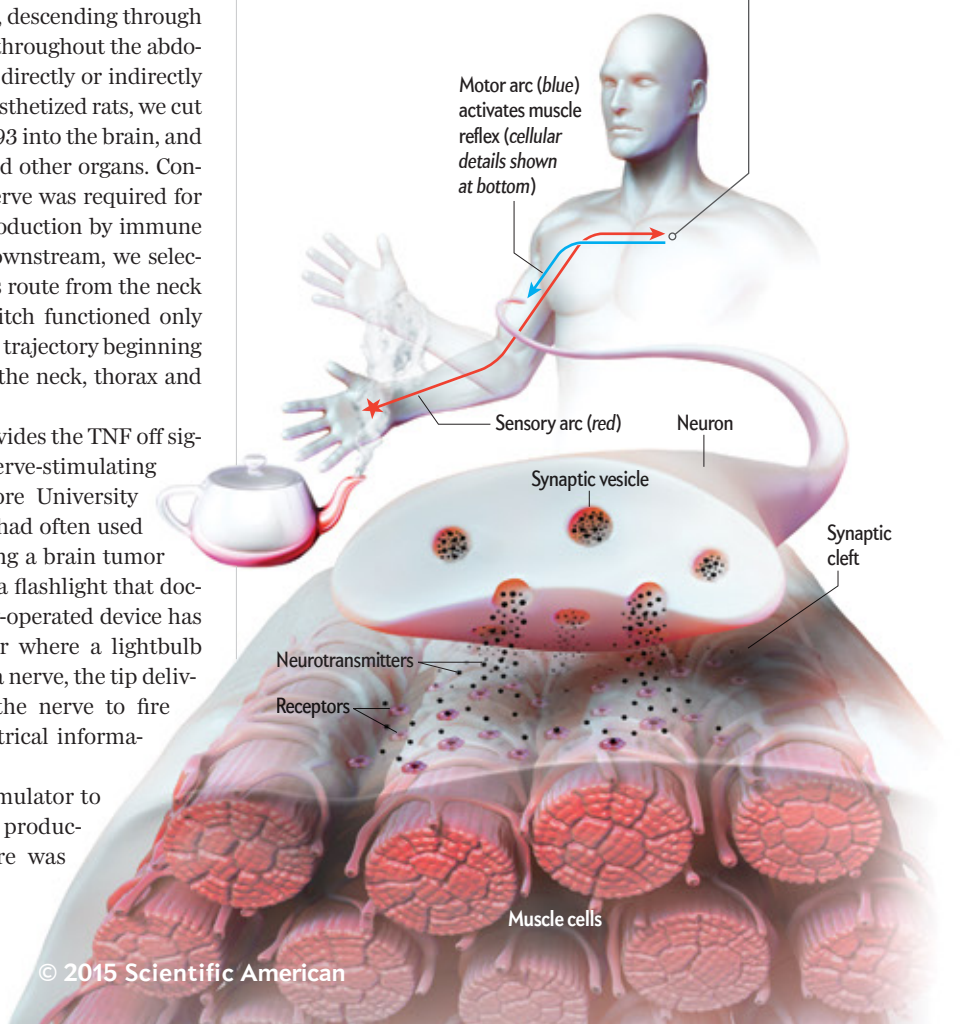
Reflexes and Inflammation

The nervous system receives inputs from throughout the body that it processes to enable various organs to function smoothly. Sudden exposure to a flame from a hot stove causes a reflex that makes a hand recoil. Reflexes also quell inflammation, opening the possibility for new therapies that forgo anti-inflammatory drugs.

Basics: Reflexes Ensure That We Don't Kill Ourselves

When a hand grazes a cloud of hot steam from a teapot, the inadvertent slip intiates a set of events—a reflex—in nerves and muscles. A nerve cell in the hand sends an electrical signal up a nerve pathway—known as a sensory arc. It goes up the arm to the spinal cord, where an interneuron relays it to a motor neuron. The motor neuron issues a command that travels in the reverse direction down the long nerve extension that branches off from the cell body of the neuron and terminates in the arm. Vesicles at the nerve ending then release neurotransmitters. These chemicals cross the synaptic cleft before interacting with receptors that prompt muscle cells to contract and withdraw the hand.





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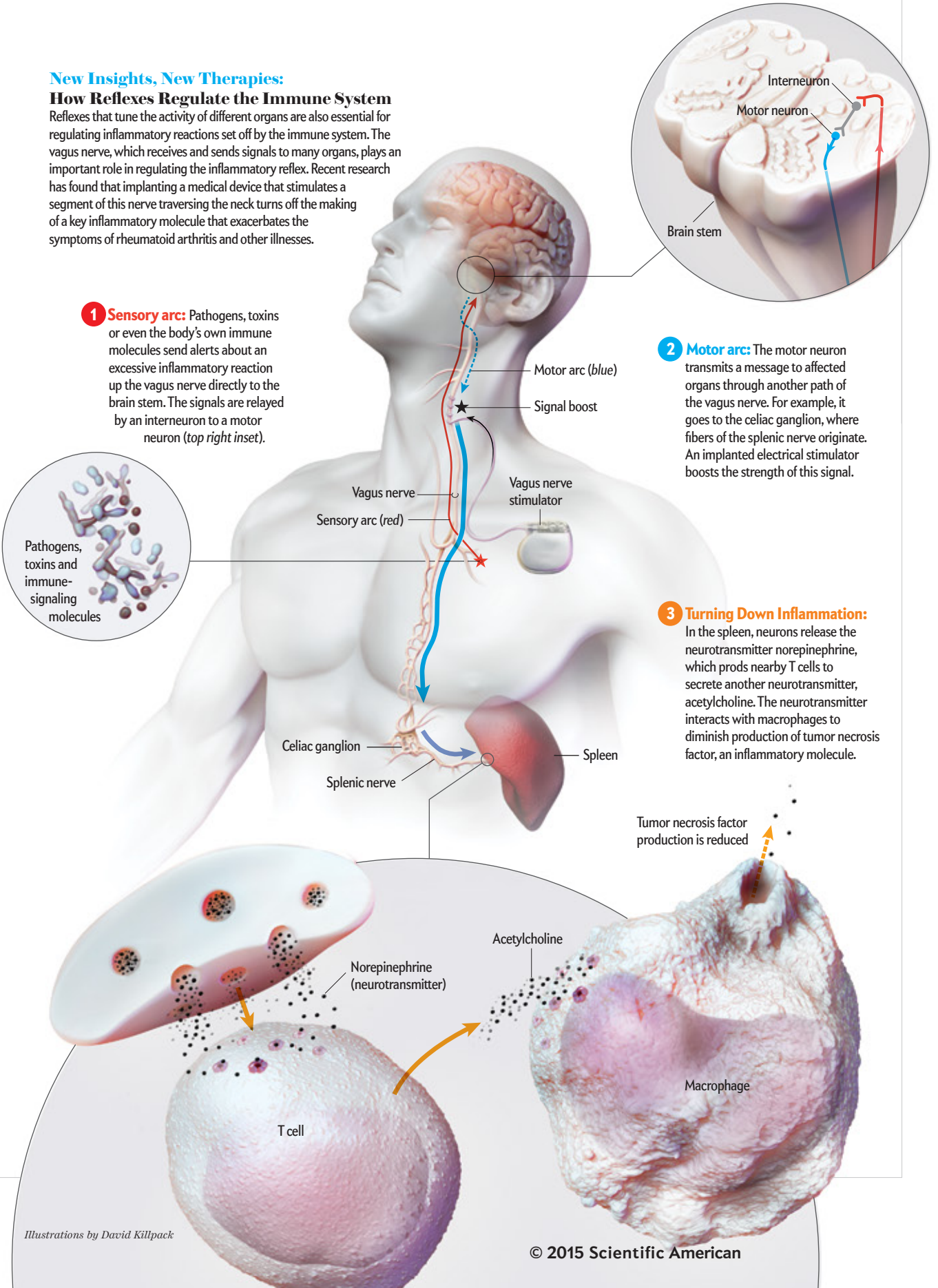
New Insights, New Therapies:

How Reflexes Regulate the Immune System

Reflexes that tune the activity of different organs are also essential for regulating inflammatory reactions set off by the immune system. The vagus nerve, which receives and sends signals to many organs, plays an important role in regulating the inflammatory reflex. Recent research has found that implanting a medical device that stimulates a segment of this nerve traversing the neck turns off the making of a key inflammatory molecule that exacerbates the symptoms of rheumatoid arthritis and other illnesses.



Illustrations by David Killpack

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proof that electrical transmissions carried in the vagus nerve regulated TNF production by the immune system. This experiment inspired us to consider that treating inflammatory diseases using a bioelectronic device might be possible. At lunchtime, on the back of a napkin, I drew a sketch showing a pacemaker connected to an electrode placed on the vagus nerve in the chest of a patient with rheumatoid arthritis or another inflammatory disease. Usually I save things. I have accumulated more old junk than most, dating all the way back to a paper I wrote about Louis Pasteur in eighth grade. But somehow I lost that napkin. Too bad because today it would be a nice memento.

More than a decade of work by dozens of colleagues in my lab and by many others in research institutions around the world has laid out the physiology and molecular biology of the inflammatory reflex. The vagus nerve—the central focus of most of this research—sends signals from the brain to the spleen, liver, gastrointestinal tract, heart and other organs. Many of these studies have examined the spleen as a target because it is a major site for production of TNF. Along this pathway, action potentials descend down the vagus nerve to the upper abdomen, terminating in the celiac ganglion, a group of nerve cells that send their fibers to the spleen. These fibers deep within the spleen release a signaling molecule, norepinephrine, that then binds to immune system cells called T lymphocytes. Norepinephrine attaches to receptors on T cells, which trigger production of another neurotransmitter, acetylcholine, that binds to receptors on immune cells called macrophages, which produce TNF in the spleen. Acetylcholine docking onto the receptor—abbreviated α7 nAChR—causes macrophages to shut down TNF production by inhibiting two molecular pathways.

One pathway controls the activity of a protein, NF-κB, that instructs genes in the nucleus of the macrophage to initiate the making of TNF. The other pathway governs the release of IL-1 and other inflammatory molecules. Future research will examine other organs reached by the vagus nerve and investigate other nerves that interact with the immune system.

Defining the anatomical and molecular basis of these pathways demonstrates that an immune response can be controlled by the nervous system. When infection or injury creates a biochemical imbalance, these changes are relayed to motor neurons in the brain, which return signals to the affected tissues to regulate the release of TNF, IL-1 and other molecules into the tissues and the bloodstream that produce inflammatory reactions throughout the body.

The development of new techniques to observe and control these pathways is proceeding rapidly. Today we measure cytokines to monitor the course of inflammation. In the future, we will decipher the electrical signals carried in the nerves as a method to diagnose, monitor and control inflammatory disease.

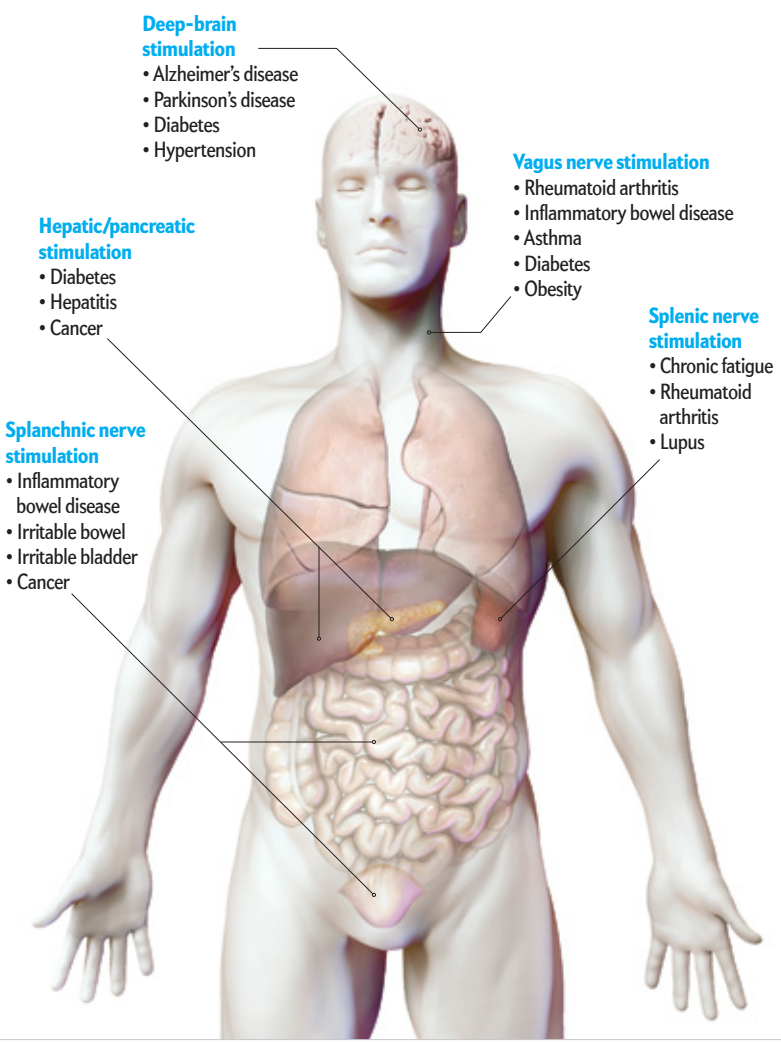
As we have shown, neural circuits that regulate immune responses can be mapped by cutting and stimulating nerves and by looking at pathways that activate genes and immune molecules. Results so far suggest these approaches will help treat disorders that include rheumatoid arthritis, inflammatory bowel disease, multiple sclerosis and perhaps even diabetes and cancer.

In 2011 in Mostar, Bosnia and Herzegovina, 13 years after sketching on a nap-

TARGETS AND DISEASES

Where to Zap

Bioelectronic medicine holds promise for using electrical stimulation technologies to treat a variety of diseases—and may become an alternative to some pharmaceuticals. Vagus nerve stimulation—the topic of this article—is only one of these techniques. Deep-brain stimulation is already helping patients with Parkinson's disease. Other therapies, such as splenic nerve stimulation, are being investigated but have not reached clinical trials.



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kin, I met the first rheumatoid arthritis patient treated with a vagus nerve stimulator—a more sophisticated version of the simple handheld device that I had used in my lab. A middle-aged father of young children, he told me that his hands, feet and knees hurt so much that he spent days at a time lying on the couch, unable to work, play with his children or enjoy life. Without access to expensive anti-TNF drug therapy in his country, he had tried and failed therapy with steroids, methotrexate and other anti-inflammatory drugs. He consented to participate in a clinical trial led by Paul-Peter Tak, a leading rheumatologist at the Academic Medical Center at the University of Amsterdam and GlaxoSmithKline. Neurosurgeons implanted a vagus nerve stimulator just underneath his collarbone—and the man went home hoping for the best. Within days he was improving. Within weeks he was nearly pain-free. He began playing Ping-Pong, soon advancing his sporting activities to include tennis, at which point he injured his knee. The clinical team cautioned him against further strenuous exertion—this advice to the same person who could barely move a few weeks before. Now, nearly four years after surgery, he remains in remission, free of dangerous medications, which in the case of steroids can include lowered resistance to infection, diabetes and hypertension.

His case was presented at the November 2012 meeting of the American College of Rheumatology in Washington, D.C., by Tak and his colleague Frieda Koopman of the Academic Medical Center, along with Ralph Zitnik of SetPoint Medical, a company I co-founded to develop nerve stimulation to regulate the inflammatory reflex. Of the eight patients with long-standing, disabling, rheumatoid arthritis, he and five others benefited significantly after surgical implantation of a vagus nerve stimulator. As of this writing, additional studies are under way to assess vagus nerve stimulation in inflammatory bowel disease as a supplement to drug therapies. If successful, the potential for bioelectronic medicine to replace some drugs will be realized.

Progress in the field continues. In mid-January the Food and Drug Administration approved a device that stimulates the vagus nerve to induce a feeling of satiety in obese patients. Prospects for bioelectronic medicine were discussed at the first Bioelectronic Medicine Summit in 2013, a meeting hosted by GSK to begin charting a research road map for the field. GSK announced a $1-million innovation prize, beyond the $50 million the company had committed to support research on individual projects. In addition, the National Institutes of Health recently announced a $248-million program over seven years called SPARC—Stimulating Peripheral Activity to Relieve Conditions—to advance biolectronic technologies, and DARPA has launched ElectRx—Electrical Prescriptions—to fund work on techniques to promote health by harnessing the body's nerves.

Our original approach of inspecting the molecular mechanisms underlying the inflammatory reflex is now being widely applied to other diseases of the immune, cardiovascular, respiratory, gastrointestinal, neuroendocrine and renal systems. The broadening knowledge of specific neural circuits enabled by ever finer electrodes and molecular tools will shape our ability to stimulate small nerve fibers or even single axons.

The question might arise about whether the field of bioelectronic medicine presents a threat to the drug industry. I believe that bioelectronic devices will replace some drugs and supplement others. Antibiotics and other anti-infection agents, however, are here to stay. But I expect that drug companies will continue to increase their investments in bioelectronic medicine.

MIND OVER IMMUNITY

MOST PEOPLE DO NOT THINK much about reflexes. But they are everywhere. Primitive animals, such as worms that lack brains or consciousness, rely on reflexes to find food and mates, avoid predators, and develop defensive responses to infection and injury. Consider *Caenorhabditis elegans,* an evolutionarily ancient roundworm that feeds on soil bacteria for sustenance. On occasion, it encounters pathogenic bacteria, a potentially lethal event that activates a series of defensive countermeasures within the worm's immune system. Evolution favors species that present a coordinated, protective response to a threat from infection or injury with minimal collateral damage and side effects, and the worm has evolved an elegant system to do so. Of the 302 neurons that constitute the worm's simple nervous system, a select few are sensitive to the presence of pathogens. These same neurons trigger a reflex circuit that controls the activity of the worm's immune system, preventing the immune response from becoming toxic for the worm itself.

In higher vertebrates, the two biological systems that learn from experience to defend an organism are the nervous and immune systems. Discovery of the inflammatory reflex revealed that these two systems intersect in simple, precise reflex circuits to maintain immunological homeostasis. Like the lowly roundworm, we do not have to be conscious of these mechanisms to be the beneficiaries of their amazingly protective functions.

We have arrived at a unique juncture in the history of medicine. Simple reflexes are distributed across the entire nervous system. Trillions of synapses in the human nervous system connect one neuron with another. Today our research tools are sensitive enough to detect specific circuits that control the immune system and might be harnessed for therapy. In the early 20th century Sherrington ascribed the dominance of the human race as the most successful animal species on earth to the capacity of the higher-order areas of the human brain to master its primitive reflexes, noting that "reflex-arcs are controllable by mechanisms to whose activity consciousness is adjunct." Back then, he could not have envisioned the advent of technologies to control reflexes to keep the inflammatory processes of the immune system in proper balance. But that time has come. SA

DISCLOSURE OF COMMERCIAL TIES: Kevin J. Tracey co-founded and serves as a consultant to SetPoint Medical. The Feinstein Institute for Medical Research has applied for patents related to work summarized here. Tracey has received grants from GSK.

MORE TO EXPLORE

The Inflammatory Reflex. Kevin J. Tracey in *Nature,* Vol. 420, pages 853–859; December 19, 2002.

Reflex Principles of Immunological Homeostasis. Ulf Andersson and Kevin J. Tracey in *Annual Review of Immunology,* Vol. 30, pages 313–335; April 2012.

Invasion of the Body Hackers. Michael Behar in *New York Times Magazine;* May 25, 2014.

FROM OUR ARCHIVES

Treating Depression at the Source. Andres M. Lozano and Helen S. Mayberg; February 2014.

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PLANETARY SCIENCE

Oceans FROM THE Skies

New evidence is rekindling the debate over whether comets, asteroids or other things entirely were the source of our planet's seas

By David Jewitt and Edward D. Young

Illustration by Ron Miller

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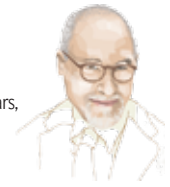
David Jewitt traces his interest in astronomy to age seven, when he was astonished by a spectacular meteor shower over London. He is a member of the National Academy of Sciences and a professor at the University of California, Los Angeles. Jewitt drinks a lot of water (but only in the form of coffee).

Edward D. Young is a professor of geochemistry and cosmochemistry and a member of the Institute for Planets and Exoplanets at the University of California, Los Angeles. He searches for clues to the origins of the solar system by studying the chemistry of meteorites, the interstellar medium and other stars, using sophisticated laboratory instruments and the world's largest telescopes.



STANDING ON THE SEASHORE, WATCHING WAVES ROLL IN FROM OVER THE HORIZON—it is easy to see the ocean as something timeless. Our ancient ancestors certainly did. In numerous creation myths, a watery abyss was present before the emergence of land and even light. Today we realize that Earth's global ocean has not been around forever. Its water—as well as every drop of rain, every gust of humid air and every sip from your cup—is a memory from eons ago, when the seas literally fell from the sky.

All the water in our solar system can be traced to the giant primordial cloud of gas and dust that collapsed to form the sun and planets more than four and a half billion years ago. The cloud was rich with hydrogen and oxygen, the two atomic ingredients for water, H_2O. That enrichment is no surprise because hydrogen and oxygen are also the first and third most abundant elements in the universe (chemically inert helium is the second). Most of the gas was sopped up by the sun and the gas-giant planets, which formed earlier than the rocky planets. Much of the remaining oxygen bonded with other atoms, such as carbon and magnesium, but the hydrogen and oxygen left over were sufficient to produce several times more water than rock in our solar system.

And yet this is not what we see. Earth and its neighbors Mercury, Venus and Mars are rocky, not water worlds. Their relative lack of water is a product of where and how they were born. As the cloud that would become our solar system collapsed, its angular momentum flattened the material into a whirling disk, in which all the planets formed. The formation of rocky worlds is thought to be a progressive, step-by-step process where smaller objects in the disk collide and stick together to form larger ones: microscopic grains become pebbles, which become boulders, which become kilometer-scale planetary building blocks called planetesimals. Many of the planetesimals left over from planet formation then became the objects that we know today as asteroids and comets.

In the disk's inner regions near the sun, intense frictional heating of the gas and more sunlight probably cooked off hydrogen and other light elements, leaving only relatively dry material from which to form planets. As dry, rocky bodies were growing rapidly near the sun, farther out, somewhere in the vicinity of what is now the asteroid belt and Jupiter, temperatures in the disk were low enough to allow water and other volatiles to form ices. Astronomers call this transition point the "snow line," and conventional wisdom holds that most of Earth's water came from beyond it, in showers of icy asteroids and comets that were perhaps flung down into the inner solar system by the outer giant planets during the last gasps of planet formation.

Recently further evidence of snow lines and late-stage planetesimal collisions has emerged from observations of other stars in the midst of forming planets. Looking into the depths of interstellar space, we can see the same primordial processes that took place here in our own solar system unfolding far away, before our telescopic eyes. Even so, many aspects of the grand tale of our ocean's formation remain mysterious and are subjects of intensive ongoing research. As timeless and ineffable as

IN BRIEF

Intense heat and light near the young sun largely confined water to the outer solar system during planet formation, leading to relatively dry inner worlds.
Earth's water probably arrived late in the planet's development, via showers of asteroids or comets. But the data in hand leave room for alternative ideas.
Exactly how our water got here could remain an unsolved mystery for some time, pending the questions of when and if we will commence more robust exploration of the rest of the solar system.
A one-size-fits-all solution for the source of Earth's water may never be found.

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Earth's oceans may seem, new evidence is bringing us closer to answering exactly how and when they formed and whether it was mostly comets, asteroids or some entirely different delivery mechanism that brought all that water to our once dry planet.

AN OCEAN PLANET DRIER THAN A BONE

AS VIEWED FROM SPACE, planet Earth might instead be "planet Ocean." Water covers more than two thirds of the surface and makes up more than two thirds of the typical earthling. The oceans, which have an average depth of four kilometers, hold enough water to fill a sphere more than 1,300 kilometers across. Yet many people are surprised to learn that all this ocean water constitutes only about 0.02 percent of the mass of Earth. Put another way, if our planet was a 300,000-kilogram Boeing 777, then all the water in the oceans would have the mass of a single passenger. Freshwater locked up in polar ice caps, clouds, rivers, lakes, soil and Earth's biota contributes only a tiny fraction to this total.

More water may lurk deep underneath our feet, in the planet's rocky mantle, which extends more than 3,000 kilometers from the crust down to the cusp of the liquid-iron core. Water there is not in liquid form. Instead it is bound into the molecular structure of "hydrated" rocks and minerals that have been dragged below the crust by tectonic processes. Some of this rock-locked moisture can escape from the mantle back to the surface through volcanoes, but a larger fraction is buried. Deeper still lies Earth's hefty nickel-iron core. Weighing in at about 30 percent of the planet's mass, the core potentially holds even more water than the mantle in the form of hydrogen that would otherwise bond with oxygen outside of the immense heat and pressure.

No one knows just how much water our planet's interior holds. That uncertainty stems from a lack of direct samples, as well as a poor understanding of how efficiently water is transported to and from the surface. A reasonable guess is that the mantle alone contains at least another ocean's worth of water, effectively doubling Earth's total aquatic inventory. Even so, adding that water to the surface ocean accounts for only 0.04 percent of the planet's mass, equivalent to two passengers on a fully loaded 777. As strange as it may seem, in actuality, Earth is some 100 times drier than old bone, which contains only a tiny amount of water. Nevertheless, the question of how the water that we do possess got here demands an answer.

If Earth was a fully loaded Boeing 777, then its ocean would have the mass of a single passenger. As strange as it may seem, proportionally our planet is some 100 times drier than old bone.

COMETS OR ASTEROIDS?

SINCE THE EARLY EARTH is generally thought to have been even drier than our planet is today, researchers investigating the origin of the world's water have focused on the relatively late stages of Earth's formation, after the moon came into being.

The freshly formed Earth, like the sun's other rocky planets, must have had at least a partly molten surface for, at minimum, tens of millions of years after its birth. That melting would have occurred from the immense energy pumped into our planet by infalling swarms of mountain-size planetesimals. Although there is geochemical evidence that Earth's magma ocean contained some water, hot molten rock is not very good at holding water, so much of the moisture from the proto-Earth and from the planetesimals would have been liberated as ionized gas and steam. Some of that material was lost to space, but some of it could also have fallen back to Earth to once again become locked in rock before being subsumed deep into the mantle.

Later, other huge impacts would have further altered the inventory of water at and near the terrestrial surface. In particular, Earth seems to have collided with a Mars-size body approximately 4.5 billion years ago, ejecting a plume of material that cooled and coalesced to become the moon. The energy of this global-scale impact would have swept away much of the atmosphere, flash-boiled any watery oceans and produced an ocean of magma hundreds of kilometers deep. Regardless of whether Earth formed wet or dry, the devastating blow of this moon-forming impact must have cleansed our planet of nearly all its primordial water.

Knowing all this, scientists have long sought a source of water that could be delivered after the formation and cooling of the Earth-moon system. Comets have been known to be ice-rich since the 1950s, and they enter the inner solar system from two vast reservoirs in the outer solar system called the Kuiper belt (which begins around the current orbit of Pluto) and the Oort cloud (which begins far past the Kuiper belt and stretches perhaps halfway to the nearest star). Perhaps, many researchers have thought, comets were the dominant source of Earth's ocean.

But the notion hit some trouble in the 1980s and 1990s, when researchers made the first measurements of deuterium/hydrogen (D/H) ratios on comets from the Oort cloud. Deuterium is a heavier isotope of hydrogen, with a neutron in its nucleus, and its prevalence compared with that of normal hydrogen serves as a useful fingerprint for tracing an object's history. If Earth's ocean was made of melted comets, its D/H ratio should closely match those of comets we observe today. But the Oort cloud comets showed D/H ratios twice as high as that of ordinary seawater. Clearly, most of Earth's water must have come from elsewhere.

In the past few years, though, measurements of comets from the Kuiper belt showed D/H ratios similar to the ocean's, reinvigorating the case for comets delivering Earth's water. But now the pendulum is swinging away from comets once again. Late in 2014 findings from the European Space Agency's Rosetta spacecraft showed that the Kuiper belt–originating comet 67P/Churyumov-Gerasimenko possessed a D/H ratio three times greater than that of the ocean, providing another data point in

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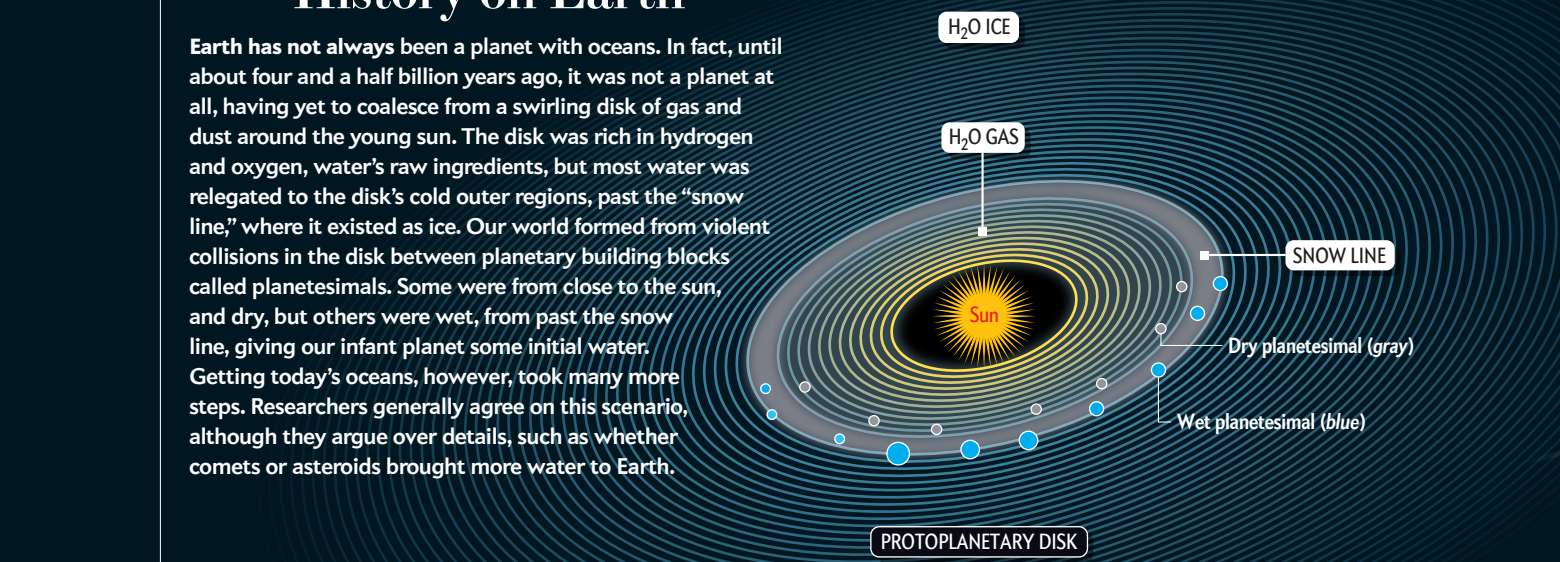
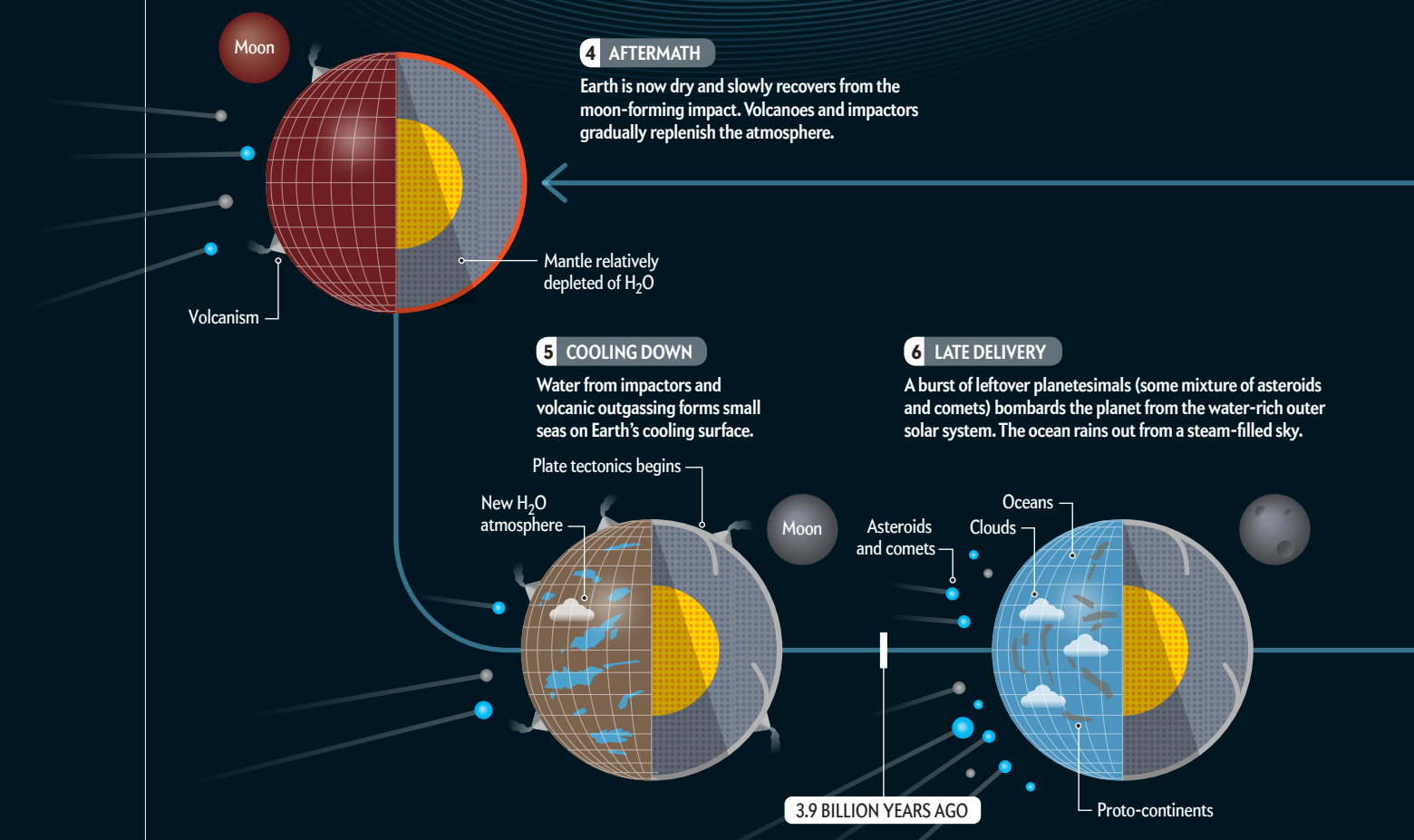
Water's Tumultuous History on Earth

Earth has not always been a planet with oceans. In fact, until about four and a half billion years ago, it was not a planet at all, having yet to coalesce from a swirling disk of gas and dust around the young sun. The disk was rich in hydrogen and oxygen, water's raw ingredients, but most water was relegated to the disk's cold outer regions, past the "snow line," where it existed as ice. Our world formed from violent collisions in the disk between planetary building blocks called planetesimals. Some were from close to the sun, and dry, but others were wet, from past the snow line, giving our infant planet some initial water. Getting today's oceans, however, took many more steps. Researchers generally agree on this scenario, although they argue over details, such as whether comets or asteroids brought more water to Earth.





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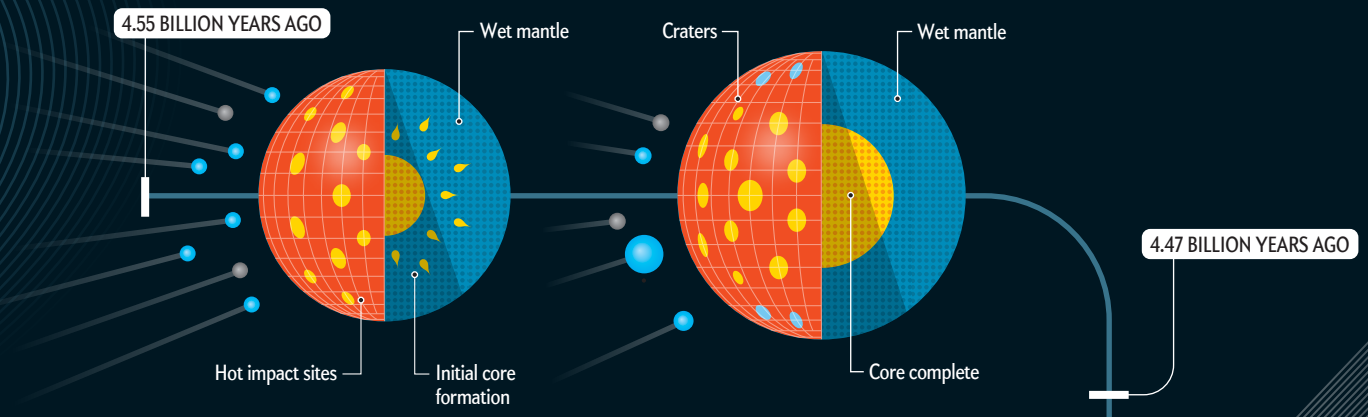
1 HOT START

Our planet is molten from the heat of its formation but retains some moisture in its mantle.

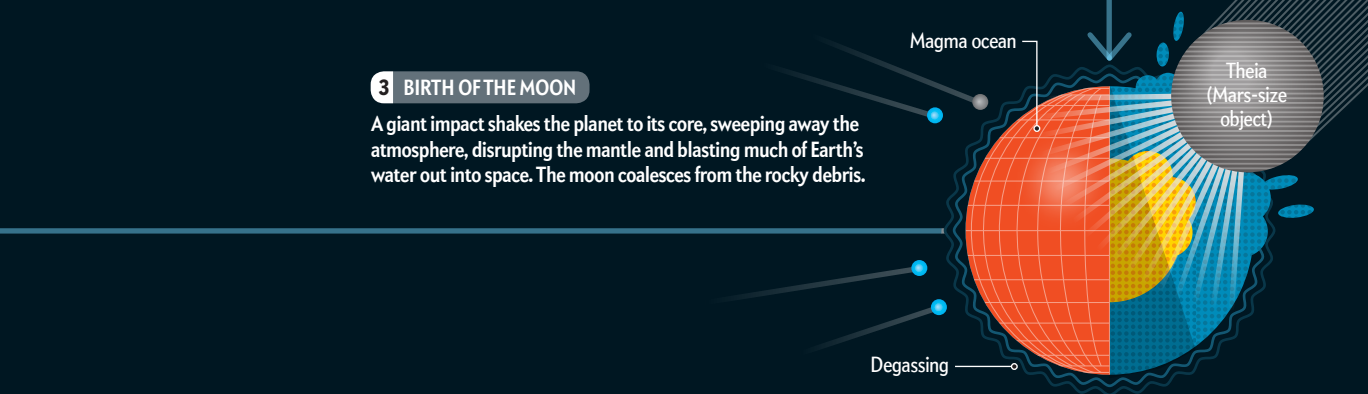
2 PROTO-EARTH

The planet grows as it is bombarded by more planetesimals, and its core forms from sinking heavy elements. Most water is in the mantle as hydrated minerals, although some exists at the surface as the planet cools.



3 BIRTH OF THE MOON

A giant impact shakes the planet to its core, sweeping away the atmosphere, disrupting the mantle and blasting much of Earth's water out into space. The moon coalesces from the rocky debris.

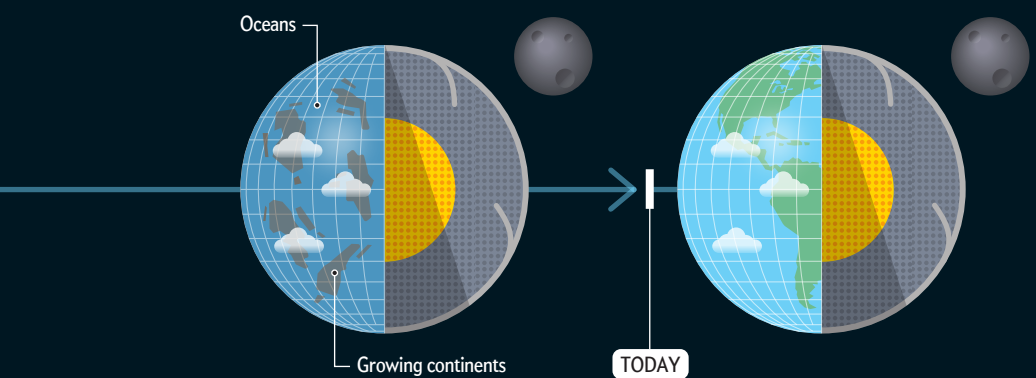


7 FROM PLANET OCEAN …

The world cools from the bombardment, and continents continue to grow from the outpourings of undersea volcanoes.

8 … TO PLANET EARTH

Full-grown continents and oceans now make Earth the familiar world we know today.



VISIBLE EARTH AND NASA (*Earth*)

Illustration by John Grimwade

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favor of some other extraterrestrial source for Earth's water. This result, paired with arguments based on the orbital dynamics of infalling bodies from comet-rich regions, suggests that although occasional comet impacts must have delivered water to Earth, this mechanism is unlikely to be the dominant source.

Asteroids are the obvious alternative, and today they are the consensus favorite for where most of Earth's water came from. Like comets, asteroids are also pieces of small planetesimals from which the planets were built. "Main belt" asteroids orbiting between Mars and Jupiter are far closer to Earth than the Kuiper belt is and, once displaced, have a much better chance than comets of hitting Earth. Proof of this is no farther away than the moon, which is pockmarked by craters from ancient asteroid impacts. Meteorites—rock chips from asteroids that have reached Earth's surface—also fill our science museums as potent reminders that Earth is still steadily bombarded with interplanetary debris. By studying these rare pieces of asteroids, we can glimpse their deeper histories and determine whether or not they might have filled Earth's ocean. Already studies of certain families of meteorites have shown that their D/H ratios align with that of seawater.

In the quest to distinguish between asteroids and comets as the sources for Earth's ocean, there are no easy solutions. The problem may not lie with nature but rather with the questions we ask of it.

Meteorites, like their parent asteroids, exhibit a range of compositions and water contents. Asteroids from the inner edge of the main belt, located out around twice the Earth-sun distance, generate many of the water-depleted rocky meteorites we study on Earth. On the other hand, asteroids from farther-out regions, more than halfway to Jupiter, are relatively wet. They tend to produce meteorites called carbonaceous chondrites—conglomerations of hydrated minerals and carbonates, in which water can make up several percent of the rock's mass. The history of water in these rocks has been a focus of the research of one of us (Young), which draws on observations of water coursing through rocks here on Earth. The water-rich minerals within a carbonaceous chondrite grew by reactions between the rock and either liquid or vaporous water, which take place at comparatively low temperatures of a few hundred degrees Celsius. On Earth, such minerals are produced when water percolates through porous rock. Within meteorites, they attest to a time when water ice melted and flowed through an asteroid's rocky matrix.

The heat source that melted all of this water ice was almost certainly a radioactive isotope of aluminum, ^{26}Al, which existed in abundance in the early solar system. ^{26}Al releases copious energy for a few million years as it decays into an isotope of magnesium, ^{26}Mg. In the cold outer reaches of the young solar system, past the snow line, the heat from decaying ^{26}Al was a potent but brief force shaping the geology and hydrology of volatile-rich asteroids. For a few million years after the sun formed, the water within many asteroids would have been liquid, sustaining hydrothermal circulation systems such as those now found at volcanic vents along Earth's mid-ocean ridges. Hydrated minerals and carbonates would have formed as warm brines percolated through the cracks and fissures within and around an asteroid's radioisotope-heated interior. In the very late stages of planet formation, the gravity of the outer giant planets scattered materials throughout the young solar system, flinging wet asteroids down from beyond the snow line to strike Earth and other rocky planets.

We see evidence for this late-stage reshuffling of material in the chemistry of Earth as well as in that of Mars. For example, the platinum group elements are "iron-loving," or siderophile, meaning they have a chemical affinity for iron and other metals rather than rock. On the newborn molten Earth, these elements should have been dragged down along with the dense, sinking plumes of iron and nickel that formed the planet's core. Instead a surprisingly substantial concentration of siderophile elements exists in the mantle and even the crust today, in amounts that are consistent with chondritelike material contributing approximately 1 percent of Earth's mass after our planet had cooled enough for the core to fully form. This "late veneer" of impactors explains how we have access to enough platinum to make rings for marriage ceremonies and catalytic converters for automobiles. It also could explain how we have enough water to fill Earth's ocean. In all likelihood, all the inner rocky worlds, not just Earth and Mars, were hit with this pulse of material from the asteroid belt during the final stages of planet formation.

There seems to be, however, one key flaw in this tidy picture of asteroids delivering the bulk of Earth's water. The problem becomes evident when investigators look at gaseous elements, such as xenon and argon, which are known as noble gases because they are spectacularly inert, scarcely reacting with any chemical compounds at all. This inertness enables noble gases to serve as a tracer of various physical processes, relatively free from the confusing effects of chemistry. If the rocky planets and the asteroids are closely related, then they should have similar proportions of most noble gases. But researchers studying ratios of xenon to argon in meteorites and planetary materials that have fallen to Earth have found that both Earth and Mars are depleted in these noble gases, relative to meteorites.

Numerous possible answers to this missing xenon problem have been suggested in recent years, including some that may tip the scales back toward comets as the de facto deliverers of water and other volatiles. As of this writing, researchers are eagerly awaiting the first measurements of a comet's noble gases, which should come from the Rosetta spacecraft's exploration of 67P/Churyumov-Gerasimenko. Such measurements may help us at last arrive at a definitive answer for the origin of Earth's ocean, but if past trends are any indication, they may instead only raise more difficult questions that keep the debate raging for decades more.

SCIENTIFIC AMERICAN ONLINE Learn more about a recent breakthrough in the search for the sources of Earth's water at ScientificAmerican.com/mar2015/ocean-origins

WATER'S WELLSPRING: Evidence from Comet 67P/Churyumov-Gerasimenko (*above*) suggests asteroids (*left*) may have delivered most of Earth's water.

COURTESY OF ESA, ROSETTA AND NAVCAM (*Comet 67P/Churyumov-Gerasimenko*); COURTESY OF NASA, JPL AND JOHNS HOPKINS UNIVERSITY (*Eros*)

A FALSE DICHOTOMY?

IN THE QUEST to distinguish between asteroids and comets as the sources for Earth's ocean, it seems there are no easy solutions. It may be that the problem lies not with nature but rather with the questions we ask of it. The dichotomy between asteroids and comets may not be as stark as was previously believed. One of us (Jewitt), along with Henry Hsieh of the Academia Sinica's Institute of Astronomy and Astrophysics in Taiwan, has recently discovered main-belt comets, objects that orbit in the asteroid belt but eject dust periodically in each orbit as ordinary comets do. These objects unexpectedly retain ice even though they orbit inside the sun-soaked, volatile-depleted snow line. Furthermore, as we have shown, the real question is arguably not why Earth has so much water but rather why it has so little. There are numerous pathways by which Earth's relatively small amount of water could have been delivered, and they depend intimately on the exact history of the planet, its impactors and their initial conditions of formation. All these ambiguities leave plenty of room for other, more exotic scenarios of water delivery that, though perhaps unlikely, cannot yet be definitively ruled out.

In theory, for instance, most of Earth's water could have been here almost since the planet's beginning. New research suggests that hydrogen ions from the solar wind could have accumulated to form hydrated minerals on the amorphous rims of interplanetary dust particles, which could then transport this watery material to planets and planetary building blocks early in their formation. Even so, it is difficult to conceive of exactly how such an early reservoir could persist deep in the mantle only to seep up after the great surface-scouring impacts that defined the end of the planet's formation.

Bodies larger than most comets and asteroids have also drawn attention of late. Consider the so-called dwarf planet Ceres, which at 900 kilometers wide is the largest asteroid in our solar system. Up to one half of the mass of Ceres is thought to be water. Early in 2014 researchers witnessed what seemed to be steam venting from the dwarf planet at a rate of some 20,000 kilograms an hour, providing crucial evidence that Ceres is water-rich. The mass of Earth is about 6,000 times that of Ceres. If, as many suspect, half of Ceres's mass is water, then Earth's total water inventory, subterranean and surface alike, corresponds to the water held within only about five Ceres-type bodies.

Such objects were much, much more common in the chaotic early solar system than they are today, and it is not hard to imagine that several Ceres-type bodies found their way into the inner solar system and on to Earth. Only a figurative handful of these objects would have been sufficient to give our planet the gift of the ocean, without a great need for further showers of small asteroids or comets. NASA's Dawn mission will rendezvous with Ceres this month, providing us with a new, up-close glimpse of its ice and outgassing and, undoubtedly, entirely new sets of surprises relating to the history of water both on and off our planet. SA

MORE TO EXPLORE

A Population of Comets in the Main Asteroid Belt. Henry H. Hsieh and David Jewitt in *Science*, Vol. 312, pages 561–563; March 23, 2006.

Water and Astrobiology. Michael J. Mottl, Brian T. Glazer, Ralf I. Kaiser and Karen J. Meech in *Chemie der Erde–Geochemistry*, Vol. 67, No. 4, pages 253–282; December 2007.

Detection of Solar Wind–Produced Water in Irradiated Rims on Silicate Minerals. John P. Bardley et al. in *Proceedings of the National Academy of Sciences USA*, Vol. 111, No. 5, pages 1732–1735; February 4, 2014.

67P/Churyumov-Gerasimenko, a Jupiter Family Comet with a High D/H Ratio. K. Altwegg et al. in *Science*. Published online December 10, 2014.

FROM OUR ARCHIVES

Comets. Fred L. Whipple; July 1951.

Secrets of Primitive Meteorites. Alan E. Rubin; February 2013.

Pluto and Beyond. Michael D. Lemonick; November 2014.

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TECHNOLOGY

SOUND BYTES

Ears are such terrific pattern finders that scientists are using audio data to detect cancer cells and particles from space

By Ron Cowen

Composer Robert L. Alexander was sitting in front of his laptop computer about three years ago, listening to a sound file that would have put most people to sleep: it was a faint flapping, like a distant flag waving in a stiff breeze, repeated over and over, sometimes a little louder, sometimes quieter.

Alexander is a patient man, however. Forty-five minutes into his listening session, the flapping stopped, replaced by a sound like a wind roaring through a forest. It was, he recalls, "the mother of all whooshes."

The sound did, in fact, represent something akin to the wind: the solar wind, a mad rush, across space, of charged particles belched by the sun at the rate of a million tons per second. In 2008 NASA's Wind spacecraft had measured the magnetic field created by these particles as they approached Earth. The field is utterly silent, but it does fluctuate in strength and direction. Alexander, who is also a graduate student at the University of Michigan working on solar data, applied his own algorithm to convert those variations into audible sounds.

This translation is more than a hobby. At 30, Alexander is part of a growing cadre of researchers devoted to the science of sonification: converting data that would ordinarily be displayed visually or numerically into sound. The ear, often more than the eye, has an exceptional ability to pick out subtle differences in a pattern, which is helpful in discovering phenomena not obvious in a visual display. Now it is helping to find hidden astronomical activity and to distinguish cancer cells from normal cells.

Our ears, says neuroscientist Andrew King of the University of Oxford, "can detect changes in a sound that occur after just a few milliseconds." By comparison, the eye's limit for detecting a flickering light is about 50 to 60 times a second. In addition to solar activity and cancer, sonification has been used to examine the eruptions of volcanoes and to discern patterns of changes in particles linked to the cosmic microwave background, the radiation left over from the big bang. Still, many researchers are not aware of the method's power. "I see it as a tool waiting to be exploited," says space scientist Aaron Roberts of the NASA Goddard Space Flight Center.

LISTEN TO THE DATA

TURNING DATA INTO SOUND is not a new idea. The Geiger counter, invented in 1908, emits clicks in the presence of energetic charged particles. And in the 1980s

PHOTOGRAPH BY LYDIA WHITMORE

Illustration by Chrissie Macdonald

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physicist Donald A. Gurnett of the University of Iowa captivated audiences with recordings of a hailstorm near Saturn—he turned data from the Voyager 1 and 2 spacecraft into a "Ping! Ping!" made by bits of icy material striking the probes as they plowed through the planet's rings.

The ear can pick out subtle patterns, suggests neuroscientist Bechara Saab of the Neuroscience Center Zurich, because a mammal's auditory system is faster at transmitting neural signals than most other parts of the brain. This system holds the largest known connection between neurons, a giant synapse called the calyx of Held. This flower-shaped junction transforms sound waves into spikes in neuron activity; to do so, the calyx can release neurotransmitters—the brain's messengers—800 times a second. In contrast, the visual pathway does not have such a speedy neural connection, Saab notes: "In the end, these differences in mechanics mean that stimuli that would be 'invisible' to the eye could be easily picked up by the ear."

To create audio from silent data, scientists can take fluctuations in x-rays and gamma rays—or any other signal that is invisible to the eye—and assign a different sound to each frequency or change in intensity, bringing them within range of human hearing.

The trick is to figure out the meaning behind any changes that scientists hear. When Alexander heard the "whoosh" that day in 2012, he really had no idea what the sound might signify. Neither did space physicist Robert T. Wicks, a research fellow at Goddard, who had given Alexander the raw data.

But when Wicks started sifting through measurements recorded by other instruments on Wind during the same time period, he noticed an odd correlation with Alexander's recording. Nearly every time Alexander's file made a "whoosh" sound, Wick found an upswing in the density of certain charged particles—helium ions—in the solar wind. One possibility is that the influx of ions, which gyrate around the magnetic field lines, sends some of their energy back into the magnetic field, causing it to wiggle.

The interplay reveals one way that energy moves back and forth between the field and the particles. That finding, in turn, may offer new clues about one of the sun's deepest mysteries—why its outer atmosphere is hundreds of times hotter than its roiling surface.

The sound file "has been a revelation," Wicks says, thanks, in part, to audio's ability to compress information. The Wind spacecraft measures the magnetic field carried by the solar wind about 11 times a second. But the audio's CD-like sampling rate packs 44,100 measurements into a second of sound in the range of human hearing. A year's worth of field measurements, which would take months to analyze by eye, thus become just two hours of sound.

These nuanced changes have alerted scientists to important distinctions in the solar wind. Two years ago Alexander made an audio file from measurements of the sun's magnetic particle stream gathered by the Advanced Composition Explorer, another NASA satellite. He converted signals showing the relative abundance of two types of carbon ions in the wind—those stripped of four of their six electrons and others that were entirely denuded, with all six electrons gone—into audible sounds. While listening to the file, Alexander discerned a hum at a frequency of 137.5 cycles per second—a sound close to a C-sharp below middle C.

That there was a hum at all meant that the relative amounts of the two types of carbon ions fluctuated over time. The sounds assigned to the different ions were, every now and then, interfering with each other. Put more musically, they were creating harmony.

"I was digging into the data, listening to 20 to 30 parameters, and I realized that when I got to carbon, there was a very strong harmonic presence," Alexander says. "If I'm hearing carbon, and no one has noticed it, I thought, maybe this is something worth looking into."

The frequency of the hum held a further clue: it corresponded to a time interval in the original spacecraft data of nearly 27 days, the time it takes the sun to revolve once on its axis.

Alexander brought his discovery to University of Michigan space physicist Enrico Landi, who realized that the ratio of the two types of carbon ions changed in sync with the two types of wind produced by the sun. One type, a fast-moving wind, comes from dark, cooler regions in the sun's outer atmosphere (or corona) that are known as coronal holes. Magnetic field lines in these are not tightly packed together, so they let particles escape more quickly. The slow wind, on the other hand, comes from hotter regions, which have denser magnetic fields.

These higher-temperature regions, because they have more energy, strip more carbon atoms of all their electrons than the colder regions can. In 2012 Landi, Alexander and their colleagues published a paper in the *Astrophysical Journal* that argued that the carbon ion differences were the best way to tell the two types of solar wind apart. The method, they contended, should replace what has been the standard diagnostic tool, the ratio of oxygen ions. Advance warning of the type of wind heading toward Earth can be important because each type causes different kinds of space weather, and their magnetic properties can disrupt satellite communications in different ways.

"Just by listening to the data, you could determine the period [of the signal] to a higher accuracy than any other mathematical method," Landi says. That insight has inspired him to explore other features of the sun with audio. Although it is known that the sun's activity cycle, including the number of sunspots, solar flares and other eruptions, waxes and wanes every 11 years, some scientists have suggested that the cycle sometimes lasts longer—19 to 20 years. "We would like to apply auditory analysis to study the 'extended solar cycle' and its relation to the standard 11-year solar cycle," Landi says.

AN UNHEALTHY NOISE

EVEN MORE DOWN-TO-EARTH BENEFITS can be had from turning data into sound. Researchers in England have begun applying sonification to the problem of telling cancer cells from healthy

IN BRIEF

Ears are linked to very fast brain connections, making them excellent data pattern finders.

Signatures of the solar wind, as well as far-off stars, have been discovered by this process of sonification.

Quick diagnosis of cancer cells might also be done by turning their molecular fingerprints into sounds.

SCIENTIFIC AMERICAN ONLINE Listen to audio signals from cancer cells and healthy cells at ScientificAmerican.com/mar2015/science-sounds

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cells while a pathologist is examining biopsy samples from a patient who needs an answer in a hurry.

"In the U.K. health system, there is a very long wait between taking a biopsy from a patient, sending it to a lab, and having it analyzed and sent back," says Ryan Stables, a musician and digital-media technologist at Birmingham City University. In conferring with a colleague, analytical chemist Graeme Clemens of the University of Central Lancashire, Stables got the idea of transforming a visual technique of identifying cancer cells into an audio method.

"We wanted to speed up the process and have someone either in the patient's room or a general practitioner's office" with the data in front of them, determining whether cells are cancerous, Stables says.

In the usual procedure, known as Raman spectroscopy, a pathologist shines infrared laser light on cells sitting on a slide, and the light's energy prompts molecules in the cells to vibrate. Different molecules vibrate in different ways, and the vibrations shift the frequency of photons scattered back from the sample. The spectrum of color in the scattered light coming back from them is a fingerprint that identifies the molecular properties. Some molecules, part of abnormal proteins in cancers, have different fingerprints than normal proteins do. The visual differences are subtle, however, and it takes time and expertise to determine if the cells are healthy or not.

Subtlety, of course, is an auditory specialty. "The human ear is naturally trained in spotting patterns and regularities and is much better than the eye in recognizing them," says Stables's collaborator Domenico Vicinanza, a physicist and musician at DANTE, a European consortium in Cambridge, England, that builds and operates high-speed networks for research and education. For instance, Vicinanza says, the eye cannot tell the difference between a light that blinks 30 and 60 times a second, but the ear can distinguish a source of sound that vibrates 30 and 60 times a second.

Working with Vicinanza, Stables sonified the data, focusing on those parts of the visual spectrum that show differences between cancerous and healthy cells and turning them into distinctive sounds. Stables says he was not surprised that there would be differences between the sonified spectrum of healthy and cancerous cells, but he remarks, "I was surprised by how well we could classify the differences."

In tests, about 150 clinicians were given 300 sound files, each representing a different tissue sample. According to Stables, the clinicians correctly discerned differences between the samples about 90 percent of the time. He and his colleagues reported this work last June at the 20th International Conference on Auditory Display in New York City. Within a year, Stables says, the team expects to begin testing its sonified spectra in doctors' offices.

Stables also believes this method could make its way into the operating room, giving physicians fast feedback during surgery about whether they have removed all cancer cells or whether some remain. To make this work, the spectroscopic analysis has to be done quickly, sonified and broadcast into the operating room. That means Stables and his colleagues not only have to choose tones, pitches and timbres that preserve the character of the original spectrum but also create sounds that are pleasant.

"If you're doing some kind of high-precision surgical procedure, you don't want have this distracting, constant ringing in your ears," Stables says. "It is very difficult to find a balance between making the signal nondistracting and yet preserving the quality of the data that are actually relevant to discerning the differences between two types of tissues or cells." But his tests with clinicians indicate that the sonifiers have found a good balance.

SOUND VS. SIGHT

ALTHOUGH SONIFICATION OFFERS advantages over visual display, Stables, Alexander and other sound specialists face a major hurdle: simply getting researchers to try this new way of exploring data. From elementary school onward, "we're surrounded by visual representations—bar graphs and pie charts," Alexander says. By the time someone becomes a scientist, he adds, "they have a syntax, they have an understanding of how these plots function and a sort of internal logic, whereas when you push 'play' and listen to the data for the first time, you don't have a vocabulary, so you don't really have a basis for comparison."

But recent popularization of some of the research could help highlight the value of the audio approach. An x-ray recording of the violent behavior of a pair of orbiting stars, for example, has been transformed into an album, available on iTunes, of music featuring Afro-Cuban rhythms.

The pair of stars, dubbed EX Hydrae, consists of a white dwarf—an elderly, ultracompact star—locked in a tight gravitational embrace with a puffy ordinary star. As the two stars circle each other, the white dwarf rips matter from its partner, spitting into space x-rays that have been recorded by NASA's Chandra X-ray Observatory. Astrophysicist Wanda Diaz-Merced, who is blind, used an open-source computer program, xSonify, to convert the fluctuating energies of the x-rays into audio. Some musically inclined colleagues saw some of these data printed out as music notes. They strongly resembled a rhythmic pattern, called a clave, found in Afro-Cuban and bossa nova music. German composer Volkmar Studtrucker, a cousin of one of the scientists, took the idea and ran with it, penning an x-ray bossa nova, a fugue, a waltz, a blues composition, a jazz ballad and several other pieces based on different sequences of notes derived from the x-rays. The album, featuring piano, bass and drums, is called *X-ray Hydra*.

The compositions have become quite popular in the astronomy community and among other scientists, and that is music to Alexander's ears: "Part of the challenge is really just getting the data out there, getting more people to listen." He thinks listening will lead to fresh discoveries. This kind of audio "is filled with short, nuanced sounds," Alexander says, "and each one is a physics puzzle waiting to be solved." SA

MORE TO EXPLORE

Assisted Differentiated Stem Cell Classification in Infrared Spectroscopy Using Auditory Feedback. Domenico Vicinanza et al. Presented at the 2014 International Conference on Auditory Display, June 23, 2014.

The Bird's Ear View of Space Physics: Audification as a Tool for the Spectral Analysis of Time Series Data. Robert L. Alexander et al. in *Journal of Geophysical Research: Space Physics*, Vol. 119, No. 7, pages 5259–5271; July 2014.

FROM OUR ARCHIVES

Listening with Your Eyes. Christoph Kayser; *Scientific American Mind*, April/May 2007.

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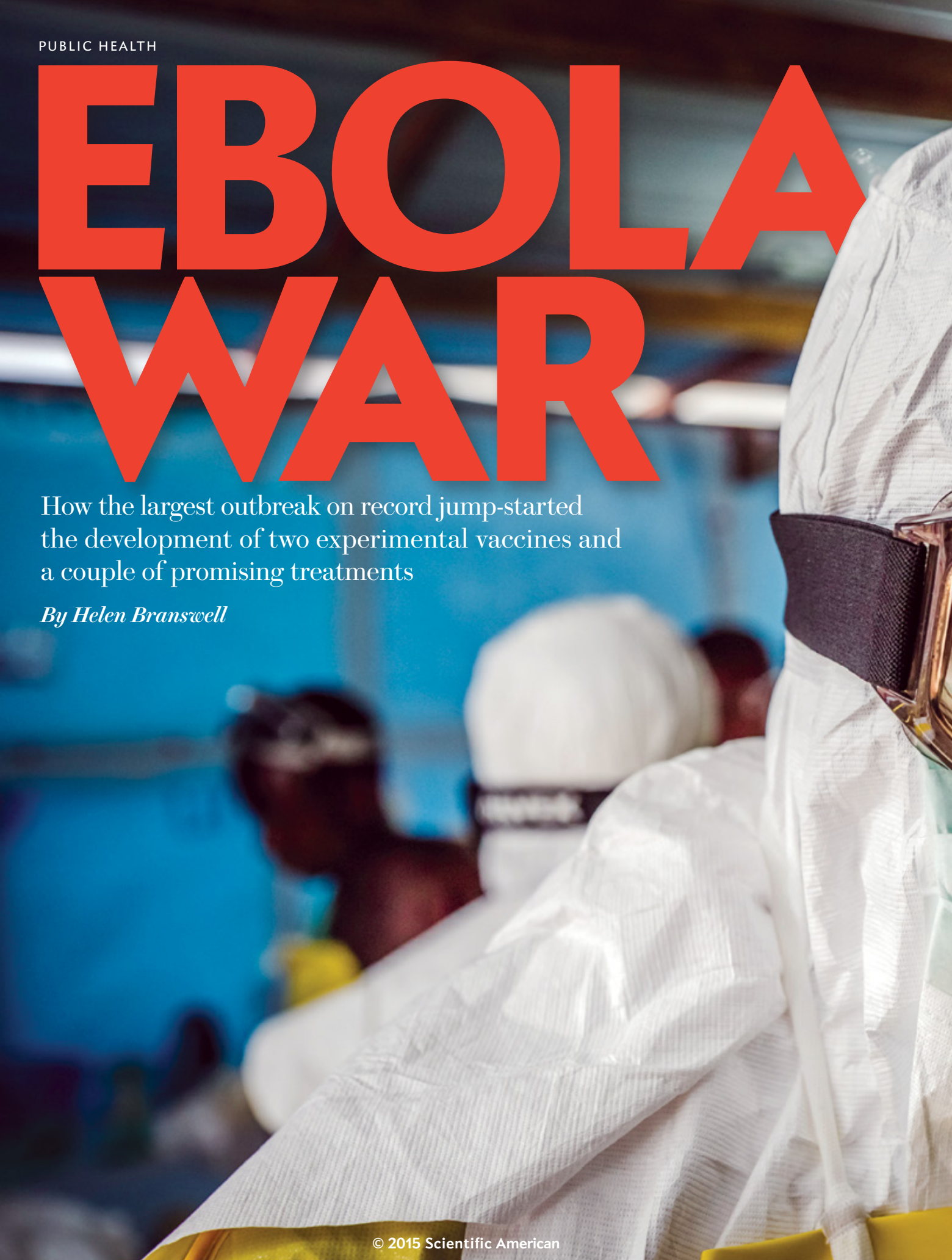
PUBLIC HEALTH

EBOLA WAR

How the largest outbreak on record jump-started the development of two experimental vaccines and a couple of promising treatments

By Helen Branswell



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SUIT OF ARMOR:
Hospital workers don protective gear before entering an Ebola ward in Monrovia, Liberia.

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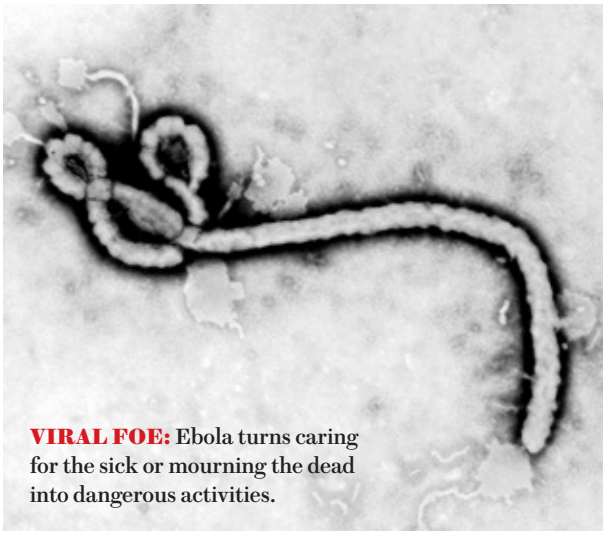
Helen Branswell is the medical reporter for The Canadian Press; her interest in emerging diseases began with her coverage of the 2003 SARS epidemic.

RESEARCHERS OFTEN TALK ABOUT A RACE BETWEEN THE EBOLA VIRUS AND the people it infects. A patient wins the race only if the immune system manages to defeat the virus before it destroys most of his or her organs. A community wins the race if it can isolate the first few patients before the disease spreads. Humanity will win the race if it develops treatments and, ultimately, a vaccine before the virus gains a permanent toehold in the cities of the globe.

For years Ebola held a natural advantage. Outbreaks were too small (typically fewer than 100 people) and too short-lived (less than five months) to give researchers the chance to test potential therapies. By the time they could have put a clinical trial in place, the threat would have passed. Pharmaceutical companies and research groups found it difficult to justify spending money on a disease that, as horrible as it was, had taken 40 years to dispatch its first 1,600 victims. Other diseases seemed far more worrisome: malaria, tuberculosis and HIV killed more than three million people in 2013.

That steely calculus changed with the current, extraordinary Ebola outbreak in West Africa—the largest and longest on record. By mid-January at least 21,000 people had acquired Ebola in Sierra Leone, Liberia and Guinea, and more than 8,500 deaths could be attributed to the disease. International health leaders, realizing that further inaction might allow the virus to spread well beyond the outbreak zone, called for a massive international response to identify and isolate those who might be coming down with Ebola, build and staff dozens of emergency treatment centers to care for the sick, and recruit enough burial teams to safely dispose of the dead.

For the first time ever, scientists had an Ebola outbreak large enough and long enough to allow intensive clinical trials aimed at finding better treatments, one that might be impossible to stop without developing vaccines and new drugs. They also won, for the first time, widespread agreement to test some of these experimental therapies in the field. The unprecedented effort may prove more useful in tackling the next Ebola outbreak than in curtailing the ongoing epidemic. But if researchers are successful this time around, they may ensure that Ebola never has the upper hand for long when it attacks humans again (and it will).



VIRAL FOE: Ebola turns caring for the sick or mourning the dead into dangerous activities.

CUNNING KILLER

AS STARTLING AS IT MIGHT SEEM, given the tsunami of cases over the past 15 months, much remains unknown about the Ebola virus—where it lives, how it comes to occasionally attack humans and why more people do not become infected when it starts spreading. (On average, each individual in this outbreak has transmitted the virus to one or two others, unlike highly contagious illnesses such as measles, where each case typically infects 18 others.)

Although Ebola is not the most contagious of viruses, it is an

IN BRIEF

As long as Ebola outbreaks remained small and sporadic, there was little real chance that researchers could test and distribute vaccines or better treatments.

The current outbreak in West Africa—the largest on record—has changed the odds, focusing new attention and resources to fighting this relentless killer.

Researchers are rushing to test a few experimental treatments and potential vaccines, hoping to prevent thousands more deaths.

PRECEDING PAGES: DANIEL BEREHULAK *Redux Pictures*; THIS PAGE: GETTY IMAGES

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WILL TO LIVE: In Liberia, a worker is sprayed with disinfectant after removing bodies from homes (*1*); a man prepares to clean a patient's house (*2*); and a family welcomes Garmai Sayon (*center*) back into its fold after she survived infection with Ebola (*3*).

DANIEL BEREHULAK *Redux Pictures*

exquisitely effective killer of humans and primates. As of the end of 2014, an estimated 70 percent of the people infected in West Africa had succumbed to the illness, usually within a matter of days—and often beyond the view of health authorities.

How quickly and completely Ebola overwhelms an individual depends on at least two factors: the amount of virus involved and how it first enters the body. After the first few viruses have jumped the species barrier—presumably from fruit bats—to people, it does not take much to keep the chain of transmission going. Many Ebola victims apparently become infected after preparing an infected relative's corpse for burial. Wiping the vomit from a patient's chin or cleaning up after an infected child's bout of diarrhea can also transmit the virus, which gains entry into people's bodies after caregivers touch their own eyes, lips, nose or mouth with their now contaminated hands. And if many viruses are injected directly into the bloodstream, as with an accidental needle stick injury, "I don't think anything's going to save you," says Thomas Geisbert, a microbiologist at the University of Texas Medical Branch at Galveston. "You're just overwhelmed."

Autopsies and pathology reports offer some of the best ways to learn about how viruses spread inside the body, but few have been conducted on Ebola victims because of the high risk of accidental infection to the people performing the necessarily invasive procedures. A recent scientific review identified only 29 human cases where an autopsy or postmortem biopsy had been performed in the disease's nearly 40-year history.

Nevertheless, animal and pathology studies conducted so far show that Ebola viruses make a devastating first strike on the immune system. Like other viruses, Ebola must harness the machinery of cells it infects to make more copies of itself. Among the initial targets are the so-called dendritic cells, which typically act as all-purpose sentries patrolling the tissues of the body, and macrophages, which consume damaged cells. Rather than trying to avoid these first responders, however, Ebola viruses actually seek them out and begin reproducing inside of them. This bold attack accomplishes two things: the viruses disrupt the cells' normal ability to jump-start the rest of the immune system, and they hitch a ride inside the cells, traveling unmolested to the lymph nodes, liver, spleen and other areas of the body.

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As if such guerilla tactics were not enough, Ebola employs another trick to hide its presence: it puts up a decoy to distract the immune system. The virus forces the cells it infects to manufacture and release into the bloodstream large amounts of a substance called secreted glycoprotein, or sGP, which looks a lot like a crucial molecule (known as GP) that sticks out of the viruses' outer covering. Ordinarily the immune system would target the GP—and thereby kill the virus to which it is attached. By fooling the immune system into also attacking the sGP (which, of course, is not attached to the virus), Ebola further undermines the body's ability to mount an effective defense.

NEW TREATMENTS

THE RECENT EBOLA OUTBREAK has taught doctors and health workers some practical ways of overcoming the virus. It has long been known that despite the early setbacks, the immune system can rally to defeat the virus if it is given enough time. Health care workers have confirmed in the current epidemic that they can buy their patients some of that time if they start giving them intravenous fluids soon after the first symptoms appear. The World Health Organization has okayed treating at least some patients with blood from survivors, which, by definition, must include plenty of antibodies, although no one knows whether the treatment works.

The risky decision to support an untested therapy showed how desperate the situation had grown in West Africa. The approach at least makes theoretical sense, however. Convalescent serum was successfully used in response to polio from the 1920s to the 1950s and to flu during the 1918 pandemic. The Bill & Melinda Gates Foundation has begun funding clinical trials of anti-Ebola serums in hard-hit Guinea.

Of course, thanks to the biotech revolution, scientists can now manufacture the necessary antibodies artificially and have done so in a preparation called ZMapp, which is made up of three so-called monoclonal antibodies that target the Ebola virus. ZMapp gained nearly mythical status last summer when Kent Brantly, an American missionary doctor who was infected with Ebola in Liberia, became the first person to receive the treatment. Media reports suggest that Brantly, gravely ill when his first transfusion started, improved rapidly, getting up to shower the next day. There were fewer than a dozen courses of treatment in existence when Brantly was treated (three transfusions equal one course); within a couple of weeks even this small supply was exhausted.

ZMapp was in the early stages of development—undergoing tests in animals—and commercial-scale production had not yet begun when the outbreak began. Manufacturing has since been geared up in the hopes that clinical trials in West Africa can start in the first quarter of 2015. But even if the drug proves to be effective, there is no hope that there will be enough ZMapp for all who might need it in the foreseeable future.

Physicians would not have had even this much material to work with had governments not started spending money trying to develop antidotes in case Ebola was ever turned into a bioweapon. Scientists at Canada's National Microbiology Laboratory and the U.S. National Institute of Allergy and Infectious Diseases (NIAID) researched and

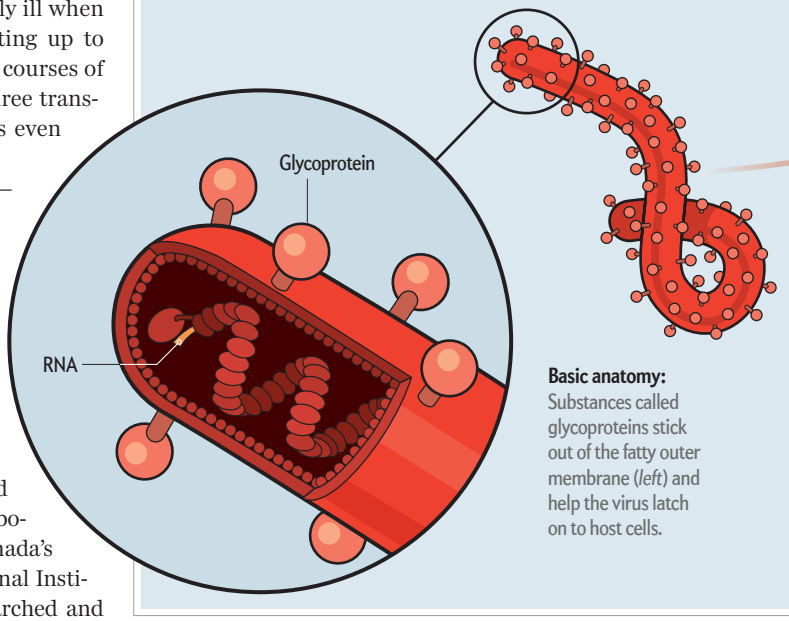
BIOLOGY OF A KILLER

How Ebola Destroys Lives

Early in the course of infection, the virus delivers a lethal one-two punch—targeting key aspects of both the immune system and the circulatory system. The crippling attack on the body's defenses allows the pathogen to reproduce in explosive numbers in other cells throughout the body, while the collapse of the vascular system and subsequent loss of blood provide new opportunities for the pathogen to infect other people.

What Is Ebola?

A member of the Filoviridae family of viruses (so named because the viruses adopt various filamentous shapes), the Ebola virus consists of a single strand of RNA and associated proteins, wrapped in a fatty membrane. Scientists have so far isolated two members of the family—Ebola and Marburg viruses—and grown them in culture. Genes from a third member—Lloviu virus—have been sequenced, but the virus has not yet been fully characterized in a laboratory. Of the five known strains of Ebola (*below*), Reston is the only one that apparently does not cause disease in infected people.



Basic anatomy: Substances called glycoproteins stick out of the fatty outer membrane (*left*) and help the virus latch on to host cells.

Illustration by Jen Christiansen

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Why Is Ebola So Deadly?

Much remains unknown about exactly how the Ebola virus infects cells. But research on non-human primates suggests that the virus targets the immune system's first lines of defensive cells, disabling them and thereby crippling the rest of the immune system. As the viruses reproduce and their numbers mount, they attack the body's blood vessels and various organs as well (*not shown*).

Immune Cells Are Co-opted

Among the first immune cells to be infected by Ebola are the dendritic cells, which patrol the body's tissues looking for microscopic invaders, and the macrophages, which help to spread the alarm about the presence of pathogens by, among other things, producing various inflammatory molecules called cytokines. By targeting cells that travel throughout the body, the Ebola virus quickly spreads to (and reproduces in) the liver, spleen and other major organs. Disabling this early line of defense also triggers an avalanche of problems in the immune system that the virus takes advantage of to rapidly grow and divide.

Once inside a host cell, the viral RNA is duplicated using both viral proteins and the cell's own machinery

The Ebola virus crosses the physical barrier of the skin via cuts, contaminated needles or the mucosal surfaces of the eyes, nose and throat. From this point on, the virus is hard to stop.

Dendritic cell

Infected immune cells transport virus into lymph nodes

Macrophage

Infected immune cells transport virus to blood vessels

Macrophage

Cytokines

Liver and other cells

For complex reasons, the overproduction of cytokines leads, among other things, to the overproduction of clotting factors in the blood. Too many clots form in some areas, and excessive bleeding occurs in others.

Leaky blood vessels cannot supply enough blood to the organs, causing them to fail. Also, the now damaged blood vessels may allow bacteria from the gut to slip into the bloodstream, causing a life-threatening condition known as sepsis.

As chaos reigns throughout the immune system, viral reproduction grows dramatically in liver cells and other tissues.

The overproduction of cytokines prompts the death of many other immune cells, including some of the ones that manufacture antibodies that could ultimately neutralize the Ebola virus.

Immune cells are distracted by decoys

False Targets Are Released

The virus forces infected cells to manufacture substances, called soluble glycoproteins, that look like the glycoproteins found on the virus's outer coat, which help the virus gain entry into host cells. The soluble proteins may act as decoys that fool the immune system into releasing antibodies against the wrong target, further undermining the body's counterattack.

Hijacks the Immune System → **Compromises the Circulatory System** → **Leads to Organ Failure**

Treatment Possibilities

Currently the best line of defense is to prevent infection from happening in the first place: clinicians must wear protective clothing that covers the entire body, including the face; community workers need to identify and—if necessary—isolate anyone who has been exposed to an infected person before they can spread the illness, and burial teams must dispose of infected corpses safely. Providing intravenous fluids early in the course of infection may help some patients survive. More targeted strategies now being developed include the injection of antibodies, from survivors or engineered antibody drugs such as ZMapp (*shown at right*), antiviral drugs and vaccines.

Antibody

The repeated injection of antibodies (either through the transfusion of blood from a survivor or via artificial antibody therapies such as ZMapp) blocks the glycoprotein on Ebola's surface, preventing the virus from infecting host cells.

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developed the antibodies in the cocktail and then licensed their production to Mapp Biopharmaceutical, which in turn depends on Kentucky BioProcessing to grow the antibodies in genetically modified tobacco plants. Kentucky BioProcessing can produce enough antibodies for between 17 and 25 treatment courses per batch; it takes 12 weeks to grow the plants and a couple more to process the material.

Efforts are afoot to try to substantially ramp up ZMapp output. The U.S. government—under its public health emergency authority—is considering bringing another producer onboard in a move that could potentially increase ZMapp output fourfold or fivefold. In addition, researchers are conducting studies in nonhuman primates to determine whether the number or volume of the infusions in a treatment course could be reduced, allowing supplies to be stretched.

VACCINE NEEDED

SO MUCH TIME was lost early on in recognizing the true extent of Ebola's spread through West Africa that the epidemic has now fractured into dozens of different micro outbreaks, with varying epidemiological characteristics. Health care workers, military personnel and local communities are making heroic efforts to save lives and contain the disease. But experts worry that the longer the epidemic continues, the greater the risk that the world could face ongoing transmission of Ebola in pockets of West Africa. In addition, the paralyzing effect the virus has had on the health care systems of the affected countries could open the door to other public health crises, such as outbreaks of measles or even the resurgence of polio.

One of the best ways to forestall this grim future is to develop, test and distribute a successful vaccine—something that was impossible during previous smaller, shorter outbreaks. As case numbers in Guinea, Liberia and Sierra Leone exploded in late summer, the agencies guiding the international response determined that an effective vaccine might be the only way to halt the epidemic.

Safety studies of the two leading experimental vaccines—dubbed cAd3-EBO and rVSV-ZEBOV—were conducted on several hundred volunteers in the U.S., Canada, Europe and various unaffected African countries toward the end of 2014. Larger studies with thousands more people were to begin earlier this year in Liberia and Sierra Leone; trials in Guinea will follow.

The pace is unprecedented: a job that normally takes five to 10 years—the testing and scaled-up production of vaccine—is happening in less than a year. And yet, as the overall rate of new infections started to drop in Liberia toward the end of 2014, another wrinkle cropped up: Would there be enough sick people to determine if the vaccines were working?

No one involved in the Ebola response wants to see more cases. But the reality of vaccine research is that you can only find out if these experimental preparations work in settings where the targeted pathogen is spreading. If infection rates drop too low, the clinical study slated to enroll 27,000 people in Liberia will have to be expanded—adding to the cost, complexity and time it will take to get to the answers.

Organizers are still hoping to avoid that, says Charles Link, Jr., CEO of NewLink Genetics, an Iowa-based biotech company that is developing rVSV-ZEBOV in partnership with pharmaceutical giant Merck. The plan is to focus on the parts of Liberia where the infection rate is greater than average. Nothing is easy about the Ebola vaccines project, Link says: "The complexities are off the chart."

AS THE WORLD WATCHES: Demonstrators in London demand that the British government do more to fight Ebola.

The NewLink vaccine was designed by scientists at the Public Health Agency of Canada. It is composed of a modified live virus (vesicular stomatitis virus, or VSV) that is coupled with a portion of the primary protein found on the Ebola virus's surface. VSV sickens some livestock but is harmless to people; the virus generates a low-grade infection that provokes the immune system to pump out antibodies against the Ebola protein. But the vaccine cannot trigger the disease itself.

The other vaccine, cAd3-EBO, was originally developed by scientists at NIAID. GlaxoSmithKline acquired the rights to it when it bought Swiss vaccine developer Okairos in 2013. It is an inactivated (killed) vaccine that uses a genetically modified chimp adenovirus to present the key surface protein from the Ebola virus to the immune system.

Both experimental vaccines have pros and cons. The GlaxoSmithKline vaccine started off with more advanced testing than the NewLink vaccine. But the VSV vaccine is easier to make, and many more doses were available by late last December. Just how many depends on what preliminary studies show is needed to generate good levels of antibodies.

There are concerns that the GlaxoSmithKline vaccine might not be able to protect with a single dose. A two-dose delivery regimen—especially one that uses different vaccines for priming and boosting—would be phenomenally difficult, given the state

AP PHOTO

SCIENTIFIC AMERICAN ONLINE Scroll through a timeline of Ebola outbreaks and research discoveries at ScientificAmerican.com/mar2015/ebola-timeline

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of the health care infrastructure in the affected countries. It is expected that the NewLink vaccine will require only one shot, but it may induce mild (though nonetheless confusing) side effects such as low-grade fever, chills, muscle aches or headaches—in other words, precisely the same cluster of symptoms that foretell Ebola's arrival. In a world that uses those symptoms to detect Ebola infections, this will make sorting the sick from the well in the outbreak zone more challenging.

The Liberian trial is designed to contain three arms. Some recipients are receiving the GlaxoSmithKline vaccine, some are receiving the NewLink vaccine, and some are getting a placebo, perhaps a flu shot or a hepatitis B vaccine. A number of prominent scientists have argued in the pages of the *Lancet* and elsewhere that placebo-controlled trials in this situation are unethical. But the U.S. Food and Drug Administration, which would need to approve any preparation used by U.S. military or health organizations, has pushed for placebo-controlled trials. "We need to learn what helps and what hurts at the soonest possible time and in the most definitive way," says Luciana Borio, who is leading the FDA's Ebola response. "It's going to be important for generations to come, and we have to get this right."

So much time was lost in recognizing the true extent of Ebola's spread through West Africa that the epidemic has fractured into dozens of different micro outbreaks.

Jeremy Farrar, director of British charity foundation Wellcome Trust, which is funding a number of drug and vaccine trials, had been hoping for more innovative approaches—trials employing what is known as step-wedge and cluster-randomized designs—that allow everyone to get the active vaccine eventually. Still, he can live with a placebo-controlled trial. "I'm not absolutely comfortable with it," he says. "But with a vaccine, which you are giving to healthy people when you don't know its safety profile and you don't know its efficacy, I actually can accept either a cluster-randomized or step-wedge design or a placebo-controlled design."

Meanwhile a step-wedge trial will take place in Sierra Leone. That trial design uses the fact that it is impossible to vaccinate everyone at once to create a control group; you compare the rate of new infections in areas that have already received the vaccine with those in places where rollout has not yet taken place. The benefit: everyone gets vaccine; the disadvantage: it may take longer to determine if a vaccine works.

Guinea, too, will see some type of trial, although it is likely to be less ambitious. The infrastructure of the country is in worse shape than those of its neighbors, making operating clinical trials an even more difficult task. Marie-Paule Kieny, who is the WHO's point person in the international effort to develop Ebola vaccines and drugs, says the Guinean trial will vaccinate health care workers in an observational study that does not include a placebo arm. In addition, the Gates Foundation may fund a trial to see whether ring vaccination—vaccinating around a known case to try to prevent onward transmission—would be effective. (Ring vaccination is what finally vanquished smallpox in the 20th century.)

A series of other experimental vaccines are at different stages of development. Some of them are thought to be at least as promising as the GlaxoSmithKline and NewLink products. One made by Johnson & Johnson started safety trials in early January. But those that are trailing behind the GlaxoSmithKline and NewLink vaccines face a tough economic reality. In the race to defeat the deadly virus, fourth or fifth place is not likely to count. The future market for Ebola vaccines will be limited. Either the WHO or GAVI (the Vaccine Alliance) will most likely stockpile the product for use in future outbreaks. And some affluent countries will surely buy supplies as a shield against bioterrorism. But the market is unlikely to be much bigger. So unless one of the front-runners falters, those at the back of the pack may fall away. "The ones that come after the two first, they have a place only if the first two fail," Kieny says.

Of course, the possibility that the entire vaccine effort might fail is never far from the minds of Ebola researchers and health care workers. Although the epidemic is no longer growing exponentially—as it was last September—the outbreak is still not under control. The number of new cases has fallen in large parts of Liberia, but disease transmission remains intense in the western and northern districts of Sierra Leone. Until the number of new cases drops to zero, however, the possibility of renewed resurgence and spread remains all too real.

Thousands of people died in 2014. Even with the continued efforts of many health care workers, burial teams and other volunteers, hundreds and possibly thousands more will, unfortunately, die in 2015. But the world will have a much better sense in the coming months of just how much farther and faster we need to run to finally outpace this dastardly virus. SA

MORE TO EXPLORE

Ebola: What You Need to Know. In-Depth Reports, ScientificAmerican.com; August 5, 2014.

Camouflage and Misdirection: The Full-On Assault of Ebola Virus Disease. John Misasi and Nancy J. Sullivan in *Cell*, Vol. 159, No. 3, pages 477–486; October 23, 2014. www.cell.com/cell/pdf/S0092-8674(14)01293-8.pdf

Ebola situation reports from the World Health Organization: http://who.int/csr/disease/ebola/situation-reports/en

FROM OUR ARCHIVES

Emerging Viruses. Bernard Le Guenno; October 1995.

scientificamerican.com/magazine/sa

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CLIMATE CHANGE

fantasy

Using the Pacific nation of Kiribati as a poster child for the ravages of rising seas is not only misleading, it may also be harmful *By Simon D. Donner*

TARAWA ATOLL'S narrow, lush islands provide homes and jobs for half of Kiribati's citizens.

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island

IN BRIEF

Countries and international aid organizations are hurriedly building seawalls and taking other steps to try to save impoverished island nations from sea-level rise. **Some islands** are not flooding and could even be rising, as the result of natural ecological processes. **The rush** to do good, a lack of local science and expertise, and a reluctance by native people to say no to outsiders have resulted in bad adaptation projects. **Deeper scientific** and cultural understanding is needed to devise the best solution for island nations battling climate change, including ways to relocate people with dignity.

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Simon D. Donner is an associate professor of climatology at the University of British Columbia who focuses on why climate matters to ecosystems and society. For 10 years, he has studied the impact of climate change on coral reefs and the challenge of human adaptation to climate effects in the Pacific Islands.

With only three days left in a long research trip, I finally witnessed what I had traveled halfway around the world to document. I saw sea-level rise.

A northwest gale blew across the typically calm lagoon of the Tarawa atoll, the capital of the Pacific island nation of Kiribati, now an icon of the places most likely to drown as climate changes and sea levels rise. By high tide that afternoon, waves were breaching seawalls, flooding roads and swamping homes along the crowded islands of South Tarawa.

Like all the other foreigners who arrive at Bonriki International Airport, still clenching their teeth from landing on a runway that extends from coast to coast, I expected that the impacts of climate change would be easy to detect in a remote, developing country that lacks the money and know-how to adapt. The high water appeared to confirm my hypothesis. That month, for the first time ever, the tide gauge read more than three meters above the baseline. The future had come.

That was 2005.

This year marks the 10th anniversary of the first of what have become my regular trips to Kiribati to research how the islands and their people may or may not be adapting to changes in the atmosphere and ocean. In that time the country has gone from a place not listed in my travel agent's database to international fame. Yet the tide gauge has not reached three meters again.

Make no mistake, Kiribati and other island countries such as Tuvalu, the Marshall Islands and the Maldives are threatened by sea-level rise. Global sentiment to "save Kiribati" and funds to that end have soared. Yet I have been on the ground there, and I see that some of the international response to Kiribati's situation has been ill conceived and could do more harm than good.

I can say that because I have worked with the Kiribati people, heard their stories, learned their customs, been blessed by their ancestors, strained to stay cross-legged on a mat during community meetings, consumed all manner of local marine food, channeled the Professor from *Gilligan's Island* to repair scuba equipment without any tools and been nursed to health after dengue fever. These experiences and my analyses of climate patterns and sea levels there have taught me more about the real-world challenges than one can learn from afar. And right now it is clear that no one needs to immediately wall in the islands or evacuate all the inhabitants.

What the people of Kiribati and other low-lying countries need instead are well-thought-out, customized adaptation plans and consistent international aid—not a breathless rush for a quick fix that makes the rest of the world feel good but obliges the island residents to play the part of helpless victim.

INGENIOUS RESIDENTS can adapt to a changing ocean in many ways. A woman and son maintain their own seawall (*top*); a man enjoys his raised house (*bottom*).

PRECEDING PAGES: CLAIRE MARTIN *Institute*; THIS PAGE: JUSTIN McMANUS *Getty Images*

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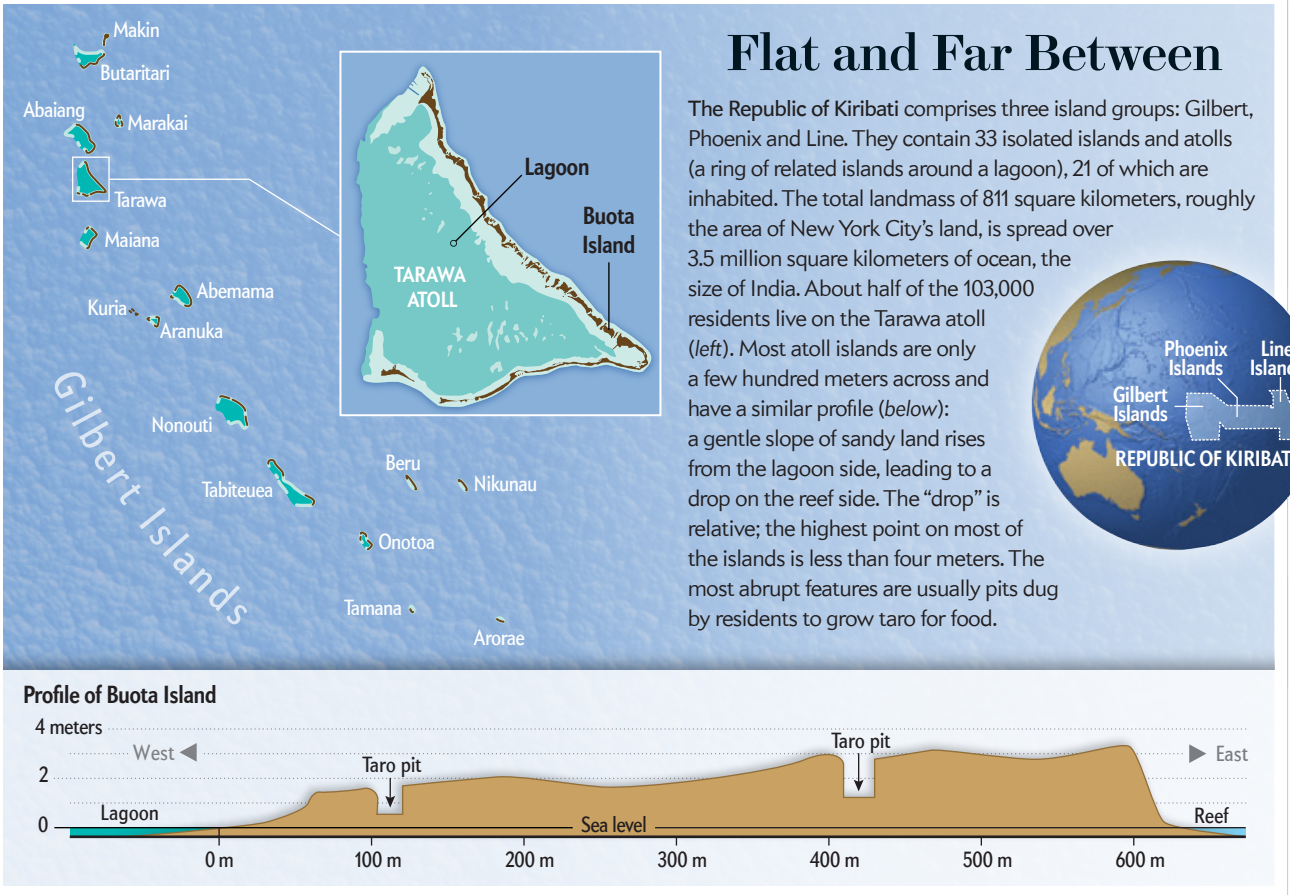

POSTER CHILD

KIRIBATI (PRONOUNCED "KEE-RE-BAS") certainly looks like the poster child for sea-level rise. The country is not simply in the middle of the Pacific Ocean; it *is* the middle of the Pacific Ocean. It is the only country that crosses the equator, the international date line and, to the bewildered first-time visitor, the *Twilight Zone*.

If the islands of Kiribati were mashed together, they would cover only about two thirds of New York City, but they are spread across ocean the size of India. Two thirds of the land in the Gilbert Islands, the main home of the 103,000 Kiribati people, is less than two meters above mean sea level. Much of that land is so narrow that you can stand on the shore of a placid lagoon and hear the waves breaking on the seaward shore behind you.

A high birth rate and the search for jobs have concentrated half of the population on South Tarawa, a string of islands in the Gilbert group that are crammed with homes, government buildings, World War II wreckage, construction debris, garbage dumps, and not nearly enough intact water pipes or toilets. The world's fastest human, Usain Bolt, could sprint the width of most of South Tarawa in less than 20 seconds, although he would likely fall in a taro pit or pigsty, get hit by several speeding, doorless 1990s Japanese minivans that serve as buses, or trip over someone doing his or her business below the high tide line so that it washes out to sea.

It is no wonder that when the World Bank "spun the globe" to choose the most "vulnerable" country for a climate change adaptation demonstration project, the development agency settled on Kiribati. Today the country's Office of the President receives up to five media requests a week from *i-Matang* (foreigners) seeking to tell the story of a country battling sea-level rise, according to communications officer Rimon Rimon.

The islands of Kiribati, however, are not simply yielding to the sea. Predicting the future of coral reef islands is like balancing a bank account. You cannot look only at the withdrawals—the loss of land through inundation and erosion. You also need to look at the deposits. In some areas, the land is expanding. What is more, some of the flooding that occurs there cannot be blamed on sea-level rise, at least not yet.

SHIFTING SANDS

CORAL ATOLLS ARE LIVING ISLANDS; they can grow. These ring-shaped chains of narrow reef islands are among the youngest landforms on the planet. There are giant sequoias on the coast of California older than most of the islands in Kiribati.

Our understanding of coral atolls can be traced back to a remarkable insight by an obsessive 19th-century pigeon breeder named Charles Darwin. Yes, that Darwin. While voyaging on the *Beagle,* Darwin deduced that atolls were the product of sun-loving coral reefs growing on the slopes of sinking volcanoes. The smoking gun for Darwin's theory came more than a century later, in the form of a hydrogen bomb. American scientists drilling into the Eniwetok atoll in the Marshall Islands in advance of 1950s bomb tests uncovered a volcanic foundation thousands of meters below the limestone reef framework.

SOURCE: "REEF-ISLAND TOPOGRAPHY AND THE VULNERABILITY OF ATOLLS TO SEA-LEVEL RISE" BY COLIN D. WOODROFFE. IN *GLOBAL AND PLANETARY CHANGE*, VOL. 62, NOS. 1–2; MAY 2008 (*Buota profile*)

Maps by Emily Cooper

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The reef framework underlying today's atolls was built long ago. During the low sea levels of the last Ice Age, these frameworks formed rocky islands tens of meters high. As the ice melted, rising seas flooded the islands. New corals chased the rising sea by building up the reef rock under them. Segments of the new reefs eventually breached the surface, killing some of the corals. Although these emergent bits of reef were biologically dead, they were geologically alive: they trapped sand and other material that eroded off the surrounding underwater reefs. Beaches expanded. Winds delivered seeds. Plants grew. And over time, atoll islands—collections of gravel and sediment perched atop a long-dead coral reef—were born.

Until recently, scientists assumed that the accretion of land happened after the most recent Ice Age melt ended and sea level began a slow decline. In the past 20 years, however, geologists such as Paul S. Kench of the University of Auckland in New Zealand have found evidence that some atolls grew above the surface while sea level was still rising. As Conrad Neumann of the University of North Carolina at Chapel Hill and Ian MacIntyre of the Smithsonian Institution once pointed out, reef islands do not always "give up" to sea-level rise but may be able to "keep up" or "catch up." It depends on the balance of the rate of sea-level rise and the rate at which the islands collect material.

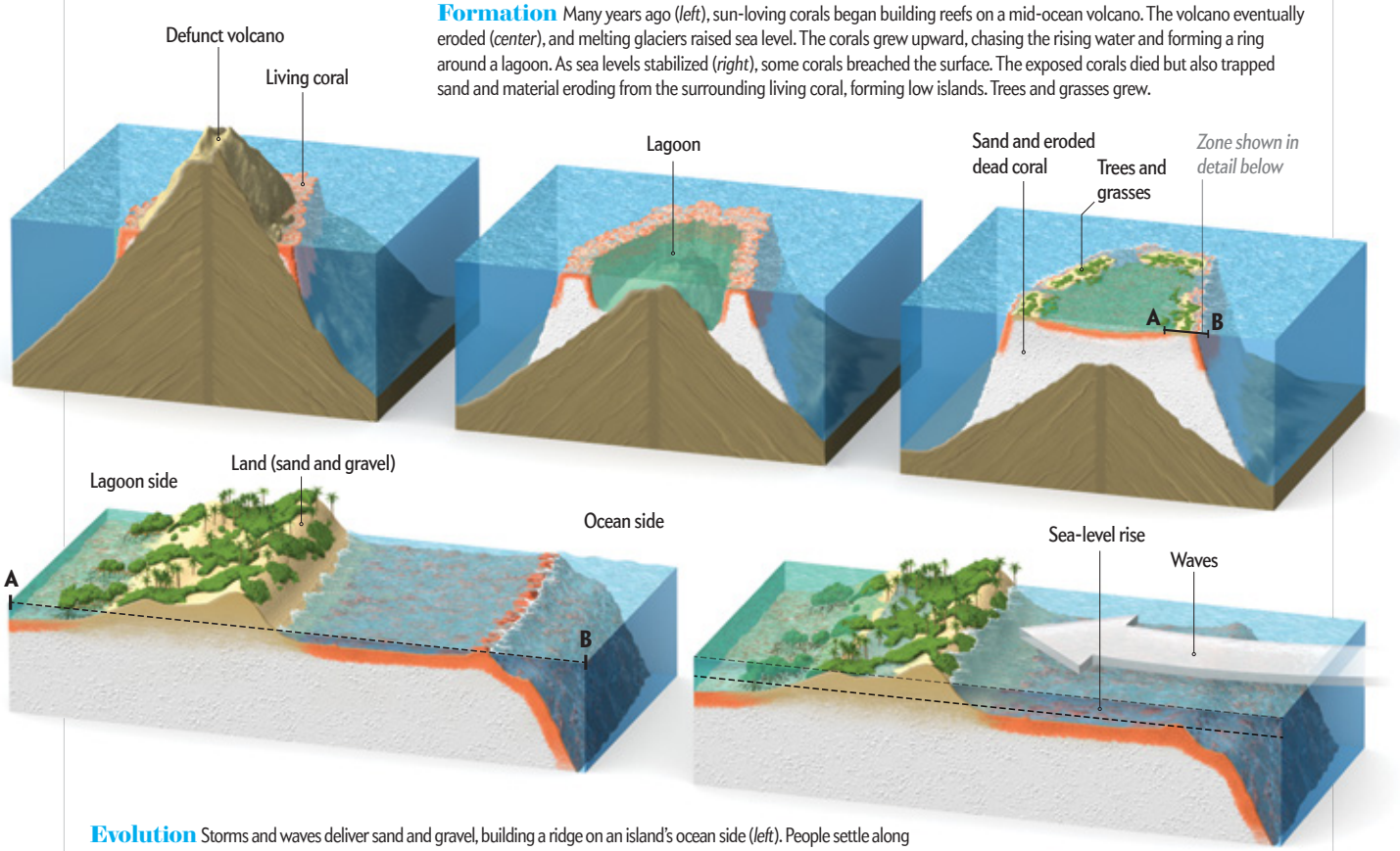
This is where the future gets complicated for Kiribati. Thanks to differences in ocean currents, the extent of surrounding reefs, the angles of various shorelines and the construction of even just a simple pier, one island in an atoll can be eroding while a neighboring island, or even the opposite shore of the same island, is growing. The processes vary from year to year, with the natural ups and downs of the ocean. Some islands in Kiribati are dwindling, but others may be growing.

The potential for islands to grow is not the only circumstance

GEOLOGY

The Rise and Fall of Atolls

The islands in an atoll grow and crumble over time and can change significantly in a few centuries. Some islands evolve in surprising ways as sea level rises. Local ocean currents can build one island while eroding a neighboring island by supplying or stealing sediment. Erecting a simple structure such as a pier or jetty can unwittingly alter the balance.



Formation Many years ago (*left*), sun-loving corals began building reefs on a mid-ocean volcano. The volcano eventually eroded (*center*), and melting glaciers raised sea level. The corals grew upward, chasing the rising water and forming a ring around a lagoon. As sea levels stabilized (*right*), some corals breached the surface. The exposed corals died but also trapped sand and material eroding from the surrounding living coral, forming low islands. Trees and grasses grew.

Evolution Storms and waves deliver sand and gravel, building a ridge on an island's ocean side (*left*). People settle along the middle, protected by the ridge and close to groundwater. Land on the lagoon side remains flatter. As sea level rises (*right*), waves may erode the ridge, flood the lagoon, make groundwater salty and kill vegetation. If the rise is gradual, accumulating sand and gravel might build land fast enough to keep up. If the rise is quick, flooding can carve up and submerge the land.

Illustration by Emily Cooper

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ENCROACHING SEAWATER that infiltrates the sandy ground can kill coconut trees (*1*), make freshwater wells salty (*2*) and harm taro, a staple plant with edible roots and leaves that is grown in pits (*3*).

that suggests there is no need to panic for the region's safety just yet. Despite how it may seem from media coverage, sea-level rise has not created an around-the-clock flood watch in Kiribati, Tuvalu or any other atoll country. Climate change makes extreme events such as floods more likely, but the local height of the ocean at any given time still depends on the natural tidal variations, the weather and the large-scale dynamics of the ocean.

Nowhere is this variability more evident than Kiribati. It is the only country wholly in the path of El Niño, the mischievous interaction between the Pacific Ocean and the atmosphere that disrupts climate every few years. The shift in equatorial winds and currents that characterize El Niño literally raises the ocean in Kiribati. The difference in average sea level at Tarawa between the height of the 1997 El Niño and the low of its contrarian sister La Niña the next year was 45 centimeters—one and a half feet. That is the equivalent of a hill in the flatland of Kiribati.

The record flooding I witnessed during my 2005 visit was a perfect storm of El Niño, a low-pressure weather system driving water toward Tarawa, and the annual high tide. Sea-level rise was complicit in the crime but just as one member of a big cast. El Niño, the weather and the tides make the contribution of sea-level rise to present-day flooding and erosion in Kiribati difficult to detect.

Sea-level rise remains poised to be the star of future sequels to the 2005 floods. Unfortunately, in the world's zest to find examples of people and places being affected by climate change, the line between what *looks like* sea-level rise and what *is* sea-level rise gets blurred.

FALSE STEREOTYPE

THE WORLD HAS THE IMPRESSION that Kiribati is drowning because the true-life situation has not been conveyed accurately. Almost every story about the islands features a photograph or video from the village of Bikenikoura, a marginal strip of sand and coastal mangrove forest that is partially inundated at very high tides. The Kiribati government, flooded with requests to "see" sea-level rise, directs foreign journalists and dignitaries such as United Nations secretary general Ban Ki-moon to Bikenikoura. "It is like our case study," Rimon says. The visitors watch the tide creep into the *maneaba,* the community meeting hut, and return home with the story of a country being swallowed by the sea.

Bikenikoura, or the "golden beach," is not emblematic of the region as a whole, however. When the international church association World Assemblies of God Fellowship looked to create a community for outer islanders moving to South Tarawa in search of work, they had to settle for that bit of land because land is precious in the bustling region. As in many parts of the developing world, overpopulation and economic pressures drive people from safer settlements in outer regions to more vulnerable homes near the population center. The lagoon shoreline of South Tarawa is littered with broken seawalls and flooded swamps, the legacy of failed land-reclamation efforts more than rising seas.

Tebunginako, the other flagship village for sea-level-rise tourists, is a similar case of mistaken identity. The flooding there is the unfortunate consequence of a channel between the lagoon and ocean having been naturally blocked generations ago, most likely by a storm, according to analysis by the South Pacific Applied Geoscience Commission. The old name for the land beside the village is Terawabono, which means "blocked channel."

Flooding in places such as Bikenikoura and Tebunginako winds up being misattributed to sea-level rise because of our expectations. Popular culture, from old, fictionalized tales of European beachcombers to the kitsch of the local tiki bar, has perpetuated a stereotype of idyllic islands inhabited by unsophisticated thatch villages. Visiting for just one week with the explicit purpose of documenting the impacts of sea-level rise

JUSTIN McMANUS *Getty Images (1 and 3);* DAVID GRAY *Corbis (2)*

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triggers a cross-cultural positive feedback loop that only reinforces the image of vulnerable islands.

A North American or European traveling to Kiribati may as well be stepping through a wormhole into another universe. Combine that naïveté with the reserved nature of the Kiribati people, the custom of deferring to outsiders, the legacy of countless past *i-Matang* asking about climate change and the lack of local scientific capacity to verify claims, and a naturally flooding village becomes a victim. Add in the geopolitics—the legitimate need for a tiny country lacking agency on the world stage to raise awareness of a threat to its existence—and the exaggeration about the impacts of sea-level rise can look intentional, whether it is or not. As my friend Claire Anterea of the Kiribati Climate Action Network says, "This is not a story that you will just journalize in one week or two weeks."

RISING DEBATE ABOUT SINKING ISLANDS

EXAGGERATION, WHATEVER ITS IMPETUS, inevitably invites backlash, which is bad because it can prevent the nation from getting the right kind of help.

The reaction began in 2010, when a paper in the journal *Global and Planetary Change* by Kench and his fellow coastal geology expert Arthur Webb, then at the Pacific Islands Applied Geoscience Commission, reported that 23 of 27 atoll islands across Kiribati, Tuvalu and the Federated States of Micronesia for which old aerial photographs were available had either increased in area or remained stable over recent decades. Such historical data are not available for most island nations, although similar results have since been reported for atolls in French Polynesia.

These findings tell us that so far prevailing currents, coastal development and other factors have had more influence on the islands' land area than sea-level rise. The paper by Kench and Webb notes, for example, that the undeveloped North Tarawa island of Buariki has grown by 2 percent since 1943, thanks to natural buildup of the lagoon shore. Much greater expansion has occurred in the developed islands, in many cases as an inadvertent result of human action. In one case, years of linking South Tarawa islands by causeways blocked water flow and redirected sand from the lagoon toward crowded islets such as the government center of Bairiki, which has expanded by 16 percent since 1969.

The findings do not tell us whether the islands have increased in height, whether they will continue to expand under higher rates of sea-level rise, or whether they will continue to store enough freshwater for the people and plants. Of course, islands can erode away, too, which is clear to a visitor looking out from the shore of busy Bairiki at the empty lagoon islet of Bikeman. Robbed of sediment by the same causeway construction that expanded Bairiki, Bikeman went from a green splotch on British colonial maps to a divided sandbar, barely visible at high tide.

Unfortunately, the politicized public discourse on climate change is less nuanced than the science of reef islands. After the Webb and Kench paper was published, headlines mocked previous claims that Kiribati and the other atoll countries are threatened by sea-level rise. The present-day impacts of sea-level rise have since become a political football, with President Anote Tong and some activists claiming the end is nigh, and doubters inside and outside of Kiribati questioning whether the president, along with other politicians or the country as a whole, is merely using talk of sea-level rise for international attention and financial gain.

RUSHING THE WALL

THE GOOD NEWS ABOUT the dynamism of reef islands is that it can buy time for places like Kiribati. That may mean decades or more that can be devoted to adaptation, not evacuation.

The bad news is that the dire talk about rapidly drowning islands makes the already tough task of adaptation even tougher. Once a place is cast as a poster child for climate change, it must continue performing the role for the world, observes my colleague Sophie Webber, a graduate student in geography at the University of British Columbia. Play a role for too long, and you risk becoming the character.

Kiribati is genuinely at risk. Overemphasizing this vulnerability, however, can undermine the resilience of the islands and its people. For example, the drought-prone southern Gilbert Islands are famous in Kiribati for a strong work ethic and community spirit. Yet when the well water in a community on one of those islands, Beru, turned salty a couple of years ago, the community threw up its hands and blamed climate change.

The residents did not suspect, or inspect, the new solar-powered water pumps that had been provided by an aid agency to replace the old fuel-powered pumps and increase resilience to drought. A local consultant later found that the new pumps, not limited by fuel, had been running nonstop and draining the groundwater. The problem was corrected, but the incident highlights the downside of well-meaning foreigners swooping in to rescue people. Rhetoric about a global threat can cause even the most self-sufficient people to blame the world for their problems and question their ability to take action.

The focus on vulnerability also draws the international media, and even the Kiribati government, toward click-worthy sideshows that generate publicity rather than concrete improvements on the ground. One Kiribati man requested refugee status in New Zealand because he claimed climate change threatened his home; in reality, he overstayed his New Zealand visa and did not want to leave. The Kiribati government's recent land purchase in Fiji has been widely reported to be a place for relocating islanders in need of imminent evacuations; in actuality, the deal was a controversial use of limited government funds to secure a former coconut plantation for food supply and other purposes, criticized by opponents of President Tong as a publicity stunt.

The reality is that the next few decades for low-lying reef islands will be defined by an unsexy, expensive slog to adapt. Success will not come from single land purchases or limited-term aid projects. It will come from years of trial and error and a long-term investment by the international community in implementing solutions tailored to specific locales.

One such program, the Kiribati Adaptation Program, funded by the World Bank and others to demonstrate how to do climate change adaptation, has revealed how difficult the task is. It took eight long years of consultation, training, policy development and identifying priorities for the project to finally create something concrete in 2011: seawalls at several places, including the tip of an airport runway, a prominent community and parts of two causeways. Project leaders and the international contractors, under pressure from donors, the Kiribati government and the public to take visible action, settled on a simple design that could be replicated by the local government in the future. But the compromise design lacked expensive measures to reduce wave energy and erosion that are recommended by coastal experts.

SCIENTIFIC AMERICAN ONLINE For more photographs of Kiribati's circumstances, see ScientificAmerican.com/mar2015/donner

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SOLID CAUSEWAY built several decades ago to link the islets of Betio and Bairiki blocked the flow of water and sediment, inadvertently changing the shape of nearby islands.

JUSTIN McMANUS *Getty Images*

Within a few months, the ends of the seawalls were damaged by waves and adjacent beach erosion, in one case dangerously exposing the pipe that carries South Tarawa's freshwater. Fingers were pointed at the contractors for the design, the World Bank and international donors for inflexible procedures and expectations that influenced the decisions, and the project leaders and Kiribati government for not better appreciating the potential adverse effects of seawalls.

The failure could still be turned into a success. Workers for the project are now rehabilitating the seawalls, using a more sloped design and vegetation to absorb some of the incoming wave energy, and project leaders are establishing a new protocol for adaptation projects of the future. Responding to climate change in a place like Kiribati requires a sustained commitment to building local scientific and engineering capacity and learning from mistakes.

A FUTURE WITH DIGNITY

THE FACT THAT REEF ISLANDS can grow in some cases and that adaptation measures can help will not save Kiribati forever, especially if the world fails to reduce greenhouse gas emissions. Climate models project that if we stay on the current emissions path, sea level could be rising at the end of the century at more than five times today's rate. Even in the unlikely case that islands are able to continue, on net, to accumulate material at their current rate, they may become narrower, steeper and possess less freshwater, making them prohibitively expensive to inhabit.

Growing with sea level would also be a mixed blessing for developed islands, whether Tarawa or Male, the crowded capital of the Maldives. In the old days, when homes were made of thatch and wore down roughly every seven years, moving with the islands might have been realistic. But today potential growth from sand and gravel accumulating on the sides or tops of islands occurs where there are homes, roads, hospitals and ports. The infrastructure might inhibit natural island evolution, or the evolution might necessitate expensive or untenable relocation of the infrastructure. And expecting all of the people to move to less populated, less developed outer islands, such as the larger and drier island of Kiritimati thousands of kilometers east of Tarawa, would be nonsensical. Efforts to relocate people would have to counter a force that is possibly even greater than that of climate change: the human development of infrastructure.

Instead Kiribati has launched an initiative that sets an example for other island nations worried about their future. The "Migration with Dignity" initiative is looking to countries such as Australia that have aging populations and would offer Kiribati youth a place that needs their labor. That way, if Kiribati's day of reckoning does come, migrants could join an existing expatriate community rather than be treated as refugees.

The initiative is a reminder that to cope with climate change, the Kiribati people need more than just money and attention. They need respect. That means not using Kiribati as a narrative device in a debate about climate change ("We need to reduce emissions to save these drowning islanders") or as a showcase to prove an institution is helping people deal with climate change. However well intentioned, quickly reported stories and limited-term aid projects lead to time and resources being wasted on futile ideas and duplicated efforts rather than on developing the skills, long-term management strategies and lasting relationships needed to prepare for an uncertain future. In 2005 I traveled to Kiribati thinking three weeks would be long enough to understand how climate change was affecting the country. Ten years later I am still trying to fully wrap my arms around that question.

As you travel out to sea in Kiribati, the flat islands quickly disappear below the horizon. In the old times, fishers navigated home by looking for the reflection of the shallow, greenish lagoon waters in the clouds. One day in the distant future, many of the islands of Kiribati could succumb to the sea. The people may leave, the trees may die and the land may become a submerged reef. The lagoons, still shallow in contrast to the deep open ocean, would remain green as before.

To outsiders, Kiribati would be gone. To the Kiribati people, the ghost of their former homeland would live on in the clouds. SA

MORE TO EXPLORE

Nature and Stability of Atoll Island Shorelines: Gilbert Island Chain, Kiribati, Equatorial Pacific. Eugene C. Rankey in *Sedimentology*, Vol. 58, No. 7, pages 1831–1859; December 2011.

Sea Level Rise and the Ongoing Battle of Tarawa. Simon Donner in *EOS, Transactions of the American Geophysical Union*, Vol. 93, No. 17, pages 169–170; April 20, 2012.

Obstacles to Climate Change Adaptation Decisions: A Case Study of Sea-Level Rise and Coastal Protection Measures in Kiribati. Simon D. Donner and Sophie Webber in *Sustainability Science*, Vol. 9, No. 3, pages 331–345; July 2014.

Developments in Coral Reef and Reef Island Geomorphology. Paul S. Kench in *Geomorphology*, Vol. 222, pages 1–2; October 1, 2014.

FROM OUR ARCHIVES

Storm of the Century Every Two Years. Mark Fischetti; June 2013.

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OUR TRANSPA

No secret is safe in the digital age. The implications for our

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RENT FUTURE

institutions are downright Darwinian

By Daniel C. Dennett and Deb Roy

Illustrations by Zohar Lazar

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Deb Roy is an associate professor at the Massachusetts Institute of Technology, director of the Laboratory for Social Machines, based at the MIT Media Lab, and chief media scientist at Twitter. He also serves on the World Economic Forum's Global Agenda Council on Social Media.

MORE THAN HALF A BILLION YEARS AGO A SPECTACULARLY CREATIVE burst of biological innovation called the Cambrian explosion occurred. In a geologic "instant" of several million years, organisms developed strikingly new body shapes, new organs, and new predation strategies and defenses against them. Evolutionary biologists disagree about what triggered this prodigious wave of novelty, but a particularly compelling hypothesis, advanced by University of Oxford zoologist Andrew Parker, is that light was the trigger. Parker proposes that around 543 million years ago, the chemistry of the shallow oceans and the atmosphere suddenly changed to become much more transparent. At the time, all animal life was confined to the oceans, and as soon as the daylight flooded in, eyesight became the best trick in the sea. As eyes rapidly evolved, so did the behaviors and equipment that responded to them.

Whereas before all perception was proximal—by contact or by sensed differences in chemical concentration or pressure waves—now animals could identify and track things at a distance. Predators could home in on their prey; prey could see the predators coming and take evasive action. Locomotion is a slow and stupid business until you have eyes to guide you, and eyes are useless if you cannot engage in locomotion, so perception and action evolved together in an arms race. This arms race drove much of the basic diversification of the tree of life we have today.

Parker's hypothesis about the Cambrian explosion provides an excellent parallel for understanding a new, seemingly unrelated phenomenon: the spread of digital technology. Although advances in communications technology have transformed our world many times in the past—the invention of writing signaled the end of prehistory; the printing press sent waves of change through all the major institutions of society—digital technology could have a greater impact than anything that has come before. It will enhance the powers of some individuals and organizations while subverting the powers of others, creating both opportunities and risks that could scarcely have been imagined a generation ago.

Through social media, the Internet has put global-scale communications tools in the hands of individuals. A wild new frontier has burst open. Services such as YouTube, Facebook, Twitter, Tumblr, Instagram, WhatsApp and SnapChat generate new media on a par with the telephone or television—and the speed with which these media are emerging is truly disruptive. It took decades for engineers to develop and deploy telephone and television networks, so organizations had some time to adapt. Today a social-media service can be developed in weeks, and hundreds of millions of people can be using it within months. This intense pace of innovation gives organizations no time to adapt to one medium before the arrival of the next.

The tremendous change in our world triggered by this media inundation can be summed up in a word: transparency.

IN BRIEF

Some 540 million years ago the variety of organisms living in the primordial seas skyrocketed. One hypothesis is that the sudden transparency of the oceans drove this evolutionary frenzy.

This Cambrian explosion provides an analogy for understanding how digital technology will transform society. Transparency of information will put pressure on organizations to evolve.

Animals adapted with exoskeletons, camouflage and methods for distracting opponents. With secrets hard to keep, states and corporations will develop analogous armaments.

The new transparency will ultimately lead to the creation of new types of organizations. Natural selection will favor the quickest and most flexible among them.

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We can now see further, faster, and more cheaply and easily than ever before—and we can be seen. And you and I can see that everyone can see what we see, in a recursive hall of mirrors of mutual knowledge that both enables and hobbles. The age-old game of hide-and-seek that has shaped all life on the planet has suddenly shifted its playing field, its equipment and its rules. The players who cannot adjust will not last long.

The impact on our organizations and institutions will be profound. Governments, armies, churches, universities, banks and companies all evolved to thrive in a relatively murky epistemological environment, in which most knowledge was local, secrets were easily kept, and individuals were, if not blind, myopic. When these organizations suddenly find themselves exposed to daylight, they quickly discover that they can no longer rely on old methods; they must respond to the new transparency or go extinct. Just as a living cell needs an effective membrane to protect its internal machinery from the vicissitudes of the outside world, so human organizations need a protective interface between their internal affairs and the public world, and the old interfaces are losing their effectiveness.

When organizations find themselves exposed to daylight, they quickly discover that they can no longer rely on old methods; they must respond to the new transparency or go extinct.

CLAWS, JAWS AND SHELLS

IN HIS 2003 BOOK, *In the Blink of an Eye,* Parker argues that the external, hard body parts of fauna responded most directly to the riot of selection pressures of the Cambrian explosion. The sudden transparency of the seas led to the emergence of camera-style retinas, which in turn drove rapid adaptation of claws, jaws, shells and defensive body parts. Nervous systems evolved, too, as animals developed new predatory behaviors and, in response, methods of evasion and camouflage.

By analogy, we might expect organizations to respond to the pressure of digitally driven social transparency with adaptations in their external body parts. In addition to the organs they use to deliver goods and services, these body parts include information-handling organs of control and self-presentation: public relations, marketing and legal departments, for instance. It is here we can see the impact of transparency most directly. Through social networks, rumors and opinions now propagate across the globe in a matter of days if not hours. Public relations and marketing departments face new demands to "join the conversation"—to respond to individuals on their terms, in an intelligible, honest and conversational way. Organizations that need weeks or months to develop communications strategies gated by slow-moving legal departments will find themselves quickly out of sync. Old habits must be rewired, or else the organization will fail.

Easier access to data has enabled new forms of public commentary grounded in comprehensive empirical observations. Data journalist Nate Silver demonstrated as much during the 2012 U.S. presidential elections. While some news organizations spun why-our-candidate-will-win narratives based on cherry-picked polling data, Silver gave us explanatory narratives grounded in *all* polling data. Not only did Silver predict the elections with uncanny accuracy, but by openly sharing his methodology, he also eliminated any doubt that he merely got lucky. With transparent public polls increasingly available, news organizations and political analysts that spin selectively grounded stories are going to face an increasingly difficult existence.

Consumer goods manufacturers face a closely related challenge. User reviews of products and services are changing the balance of power between customers and companies. A brand's marketing efforts lose influence as the opinions of other consumers become more powerful. Responsive companies are learning to quickly and publicly respond to complaints and negative reviews. And if the reviews are overwhelmingly negative, the only choice is to change or drop the product. Pouring money into marketing mediocre products no longer works.

Small groups of people with shared values, beliefs and goals—particularly those who can coordinate quickly in a crisis using ad hoc channels of internal communication—will be best at the kind of fast, open, responsive communication the new transparency demands. To draw a contrast with large hierarchically organized bureaucracies, we might call these organizations "adhocracies." As the pressures of mutual transparency increase, we will either witness the evolution of novel organizational arrangements that are far more decentralized than today's large organizations, or we will find that Darwinian pressures select for smaller organizations, heralding an era of "too big to succeed."

THE HALF-LIVES OF SECRETS

U.S. SUPREME COURT JUSTICE Louis D. Brandeis, an early champion of transparency, is often quoted on the topic. "Sunlight is said to be the best of disinfectants," he famously wrote. He was right, of course, both metaphorically and literally. But sunlight can be dangerous, too. What if in our zeal for purification, we kill too many friendly cells? What about the risk of destroying the integrity or effectiveness of organizations by exposing too much of their inner workings to the world?

Brandeis was an enemy of secrecy. He apparently thought that the more transparent institutions became, the better they would be. More than a century later we can see that the campaign he helped to initiate has had many successes. But in spite of much political rhetoric about the unalloyed virtues of transparency, secrecy in the halls of power is still maintained—and for good reasons.

A biological perspective helps us see that transparency is a mixed blessing. Animals, even plants, can be seen to be agents with agendas. Informed by their sensory organs, these agents act

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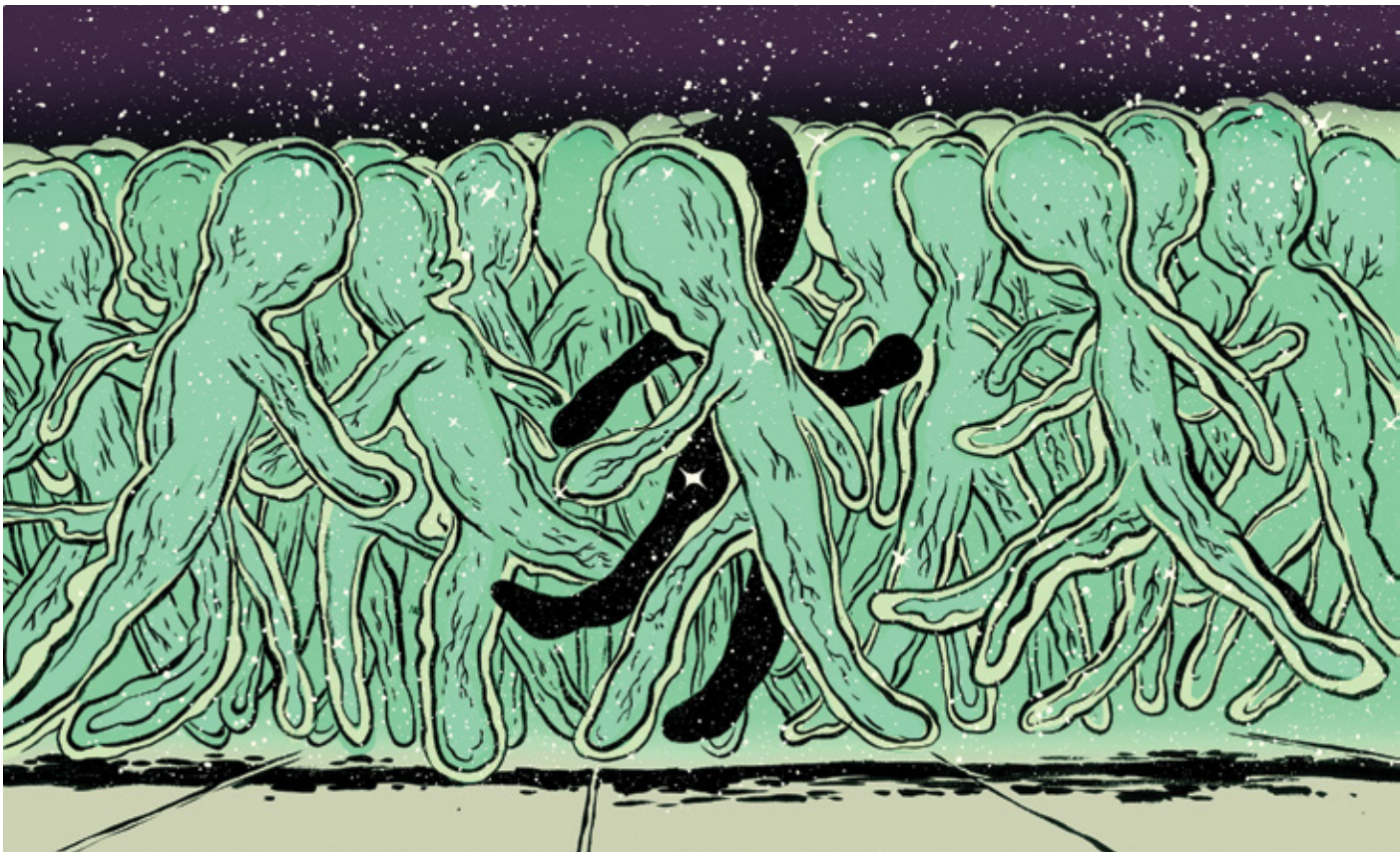

to further their own welfare. A human organization is similar. It is an agent composed of large numbers of working, living parts—people. But unlike the cells that make up plants and animals, people have wide interests and perceptual abilities. An animal or plant does not have to worry about its cells jumping ship or starting a mutiny; except in the case of cancer, the cells composing multicellular life-forms are docile, obedient slaves. People, in contrast, are individually powerful and intensely curious about the wider world.

It was not always so. In earlier times, dictators could rule quite inscrutably from behind high walls, relying on hierarchical organizations composed of functionaries with very limited knowledge of the organization of which they were a part and even less information about the state of the world, near and far. Churches have been particularly adept at thwarting the curiosity of their members, keeping them uninformed or misinformed about the rest of the world while maintaining a fog of mystery around their internal operations, histories, finances and goals. Armies have always benefited from keeping their strategies secret—not just from the enemy but from the troops as well. Soldiers who learn the anticipated casualty rates of an operation will not be as effective as those who remain oblivious about their likely fate. Moreover, if an uninformed soldier is captured, he will have less valuable information to divulge under interrogation.

"Very few things will be secret anymore, and those things which are kept secret won't stay secret very long.... The real goal in security now is to retard the degradation of the half-lives of secrets."

—Joel Brenner, former NSA senior counsel

One of the fundamental insights of game theory is that agents must keep secrets. An agent who reveals "state" to another agent has lost some valuable autonomy and is in danger of being manipulated. To compete fairly in an open market, manufacturers need to protect the recipes for their products, their expansion plans and other proprietary information. Schools and universities need to keep their examinations secret until the students take them. President Barack Obama promised a new era of government transparency, but despite significant improvements, large arenas of secrecy and executive privilege are enforced as vigorously as ever. This is as it should be. Economic statistics, for instance, need to be kept secret until they

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are officially revealed to prevent insider exploitation. A government needs a poker face to conduct its activities, but the new transparency makes this harder than ever before.

Edward Snowden's revelations about the inner workings of the National Security Agency demonstrate how in the era of transparency, a single whistle-blower or mole can disrupt a massive organization. Although Snowden used traditional news organizations to leak information, social-media reaction and amplification assured that the news stories would not die, putting sustained widespread pressure on the NSA and the federal government to act.

The NSA's outer "skin" is adapting dramatically in response. The mere fact that the agency publicly defended itself against Snowden's accusations was unprecedented for an organization that has long resided behind a veil of complete secrecy. Big changes within the organization are inevitable as it sorts out what kinds of secrets it will be able to keep in this more transparent world. As Joel Brenner, former senior counsel at the NSA, reflected on the sudden shift of the agency's operating environment at a December 2013 panel hosted at the MIT Media Lab, "Very few things will be secret anymore, and those things which are kept secret won't stay secret very long.... The real goal in security now is to retard the degradation of the half-lives of secrets. Secrets are like isotopes."

As optimists, we would like to believe that this period of turmoil will push us toward organizations better aligned with the moral codes of civil society and powerful novel ways to correct deviant organizational behavior. But we cannot rule out a permanent weakening of our intelligence organizations that will reduce their abilities to identify threats.

INFORMATION CHAFF

IN THEIR EVOLUTIONARY ARMS RACE, the Cambrian fauna invented a bounty of evasive measures and countermeasures, and this arsenal of tricks has grown ever since. Animals have developed camouflage, alarm calls to warn of approaching threats, bright markings that falsely advertise them to potential predators as being poisonous. The new transparency will lead to a similar proliferation of tools and techniques for information warfare: campaigns to discredit sources, preemptive strikes, stings, and more.

Nature has inspired devious armaments before. The cloud of ink released by cephalopods fleeing a predator was reinvented in aerial warfare as chaff—confusing clouds of radar-reflective metal scraps or dummy warheads that could attract defensive missiles. We can predict the introduction of chaff made of nothing but megabytes of misinformation. It will quickly be penetrated, in turn, by more sophisticated search engines, provoking the generation of ever more convincing chaff. Encryption and decryption schemes will continue to proliferate as well, as organizations and individuals struggle to preserve their privacy and reputations.

SPECIATION OF ORGANIZATIONS

A FINAL IMPLICATION of our Cambrian analogy is that we should soon witness a massive diversification of species of organizations. It has not happened yet, but we can look for early signs. In the U.S., a new class of corporation, the B Corp, was recently created to recognize the need for ventures with double bottom lines optimized for both profit and social purpose. Google and Facebook broke with tradition by enacting unusually powerful voting rights for their founders, yielding publicly traded companies that remain privately controlled, enabling the founders to steer their companies based on their long-term plans with relative indifference to the quarterly whims of Wall Street. The organized protests during the Arab Spring, enabled by social media and unrivaled in their combination of scale and speed of formation, are perhaps also a new kind of (ephemeral) human organization. Time will tell, but it appears that we might be at the cusp of a radical branching of the organizational tree of life.

The speed with which transparency will shape an organization depends on its competitive niche. Commercial companies are most exposed to the effects of public opinion because customers can easily switch to alternatives. If left untended, a consumer brand built over decades can unravel in months. Churches and sports leagues are somewhat more protected because of the deep-rooted cultural habits and network effects of faithful churchgoers and sports fans. But when child abuse or head injuries that quietly persisted through the pre-Internet ages surface under the glare of mutual transparency, even the mightiest churches and sports leagues must adapt or perish.

Most sheltered from immediate evolutionary pressures are systems of government. Protests fueled by social media can topple rulers and ruling parties, but the underlying organs of the state tend to continue relatively unperturbed by changes in political leadership. State machinery faces little competitive pressure and is thus the slowest to evolve. Yet even here we should anticipate significant change, because the power of individuals and outsiders to watch organizations will only increase. Under popular pressure, governments are opening access to vast new streams of raw data produced by their internal operations. Coupled with advances in large-scale pattern analysis, data visualization, and data-grounded professional and citizen journalism, we are creating powerful social feedback loops that will accelerate transparency of organizations.

There is a self-limiting aspect to this emerging new human order. Just as ant colonies can do things that individual ants cannot, human organizations can also transcend the abilities of individuals, giving rise to superhuman memories, beliefs, plans, actions—perhaps even superhuman values. For better or for worse, however, we are on an evolutionary course to rein in our superhuman organizations by holding them accountable to individual human standards. This self-regulating dynamic, enabled by accelerating human-machine communicative capabilities, is as unique to our species as human language itself. SA

MORE TO EXPLORE

In the Blink of an Eye: How Vision Sparked the Big Bang of Evolution. Andrew Parker. Basic Books, 2003.

The Social Cell: What Do Debutante Balls, the Japanese Tea Ceremony, Ponzi Schemes and Doubting Clergy All Have in Common? Daniel Dennett in *New Statesman*, Vol. 140, No. 5084, pages 48–53; December 19, 2011.

No Place to Hide: Edward Snowden, the NSA, and the U.S. Surveillance State. Glenn Greenwald. Metropolitan Books, 2014.

The Coming Entanglement: Bill Joy and Danny Hillis. Interview by Steve Mirsky in ScientificAmerican.com; February 15, 2012. www.scientificamerican.com/podcast/episode/the-coming-entanglement-bill-joy-an-12-02-15

FROM OUR ARCHIVES

How Should We Think about Privacy? Jaron Lanier; November 2013.

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Innovations IN

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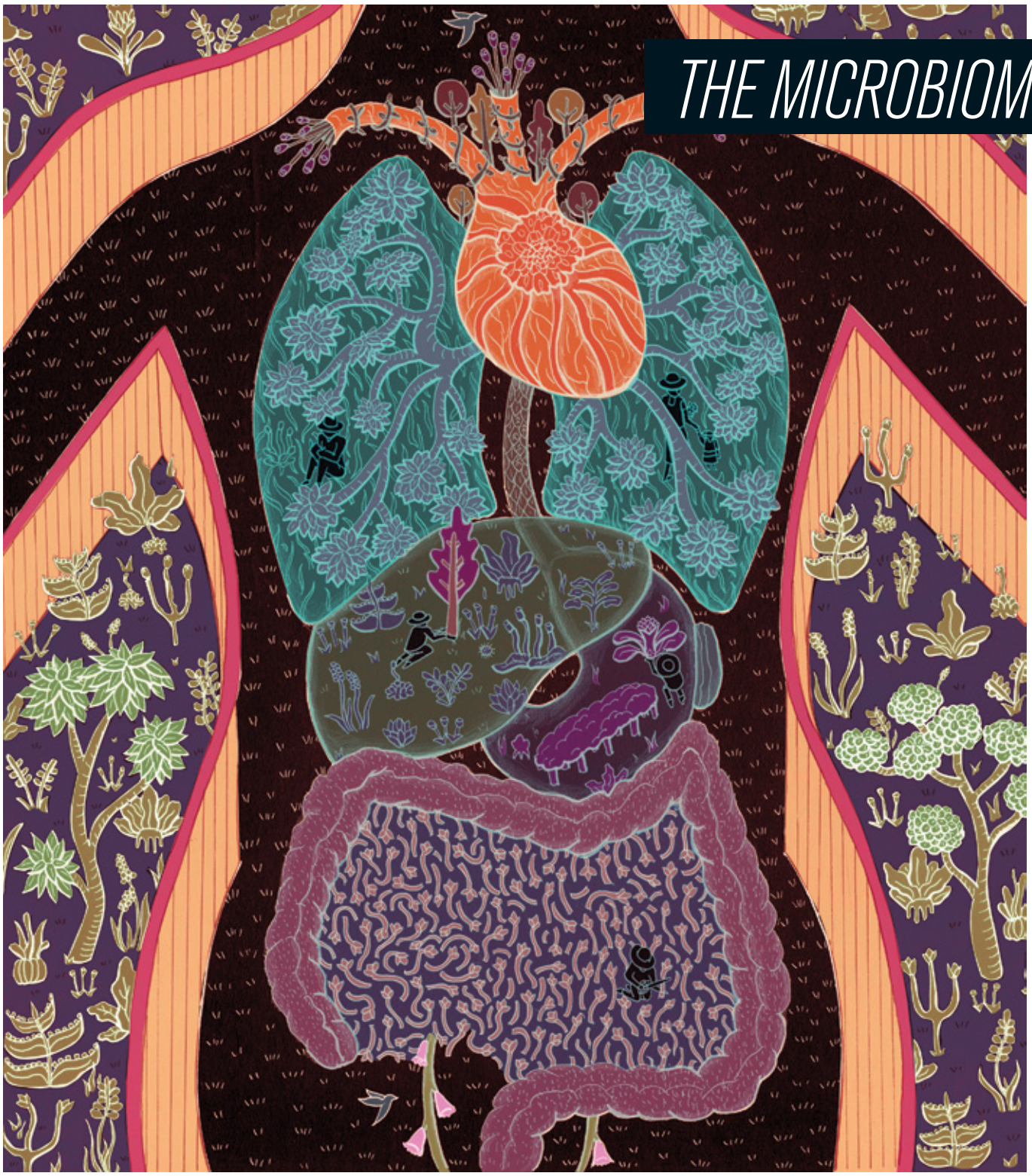

THE MICROBIOME

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The Microbes Within

ANTONY VAN LEEUWENHOEK WROTE TO the Royal Society of London in a letter dated September 17, 1683, describing "very little animalcules, very prettily a-moving," which he had seen under a microscope in plaque scraped from his teeth. For more than three centuries after van Leeuwenhoek's observation, the human "microbiome"—the 100 trillion or so microbes that live in various nooks and crannies of the human body—remained largely unstudied, mainly because it is not so easy to extract and culture them in a laboratory. A decade ago the advent of sequencing technologies finally opened up this microbiological frontier. The Human Microbiome Project reference database, established in 2012, revealed in unprecedented detail the diverse microbial community that inhabits our bodies.

Most live in the gut. They are not freeloaders but rather perform many functions vital to health and survival: they digest food, produce anti-inflammatory chemicals and compounds, and train the immune system to distinguish friend from foe. Revelations about the role of the human microbiome in our lives have begun to shake the foundations of medicine and nutrition. Leading scientists, including those whose work and opinions are featured in the pages that follow, now think of humans not as self-sufficient organisms but as complex ecosystems colonized by numerous collaborating and competing microbial species. From this perspective, human health is a form of ecology in which care for the body also involves tending its teeming population of resident animalcules.

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GUT MICROBIOME

The Peace-keepers

Amid the trillions of microbes that live in the intestines, scientists have found a few species that seem to play a key role in keeping us healthy

By Moises Velasquez-Manoff

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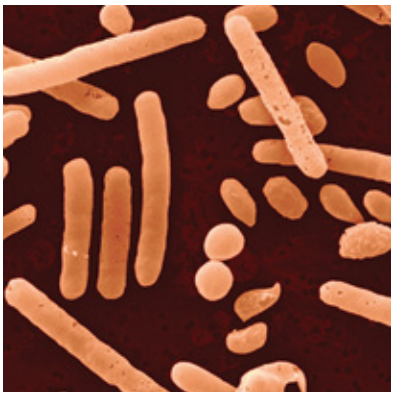
IN THE MID-2000s Harry Sokol, a gastroenterologist at Saint Antoine Hospital in Paris, was surprised by what he found when he ran some laboratory tests on tissue samples from his patients with Crohn's disease, a chronic inflammatory disorder of the gut. The exact cause of inflammatory bowel disease remains a mystery. Some have argued that it results from a hidden infection; others suspect a proliferation of certain bacteria among the trillions of microbes that inhabit the human gut. But when Sokol did a comparative DNA analysis of diseased sections of intestine surgically removed from the patients, he observed a relative depletion of just one common bacterium, *Faecalibacterium prausnitzii.* Rather than "bad" microbes prompting disease, he wondered, could a single "good" microbe prevent disease?

Sokol transferred the bacterium to mice and found it protected them against experimentally induced intestinal inflammation. And when he subsequently mixed *F. prausnitzii* with human immune cells in a test tube, he noted a strong anti-inflammatory response. Sokol seemed to have identified a powerfully anti-inflammatory member of the human microbiota.



UNRULY NAMESAKE: Clostridium difficile, *a bacterial scourge in hospitals, is a distant relative of benign "clostridial cluster" microbes that seem to play a key role in gut health.*

Each of us harbors a teeming ecosystem of microbes that outnumbers the total number of cells in the human body by a factor of 10 to one and whose collective genome is at least 150 times larger than our own. In 2012 the National Institutes of Health completed the first phase of the Human Microbiome Project, a multimillion-dollar effort to catalogue and understand the microbes that inhabit our bodies. The microbiome varies dramatically from one individual to the next and can change quickly over time in a single individual. The great majority of the microbes live in the gut, particularly the large intestine, which serves as an anaerobic digestion chamber. Scientists are still in the early stages of exploring the gut microbiome, but a burgeoning body of research suggests that the makeup of this complex microbial ecosystem is closely linked with our immune function. Some researchers now suspect that, aside from protecting us from infection, one of the immune system's jobs is to cultivate, or "farm," the friendly microbes that we rely on to keep us healthy. This "farming" goes both ways, though. Our resident microbes seem to control aspects of our immune function in a way that suggests they are farming us, too.

Independent researchers around the world have identified a select group of microbes that seem important for gut health and a balanced immune system. They belong to several clustered branches of the clostridial group. Dubbed "clostridial clusters," these microbes are distantly related to *Clostridium difficile,* a scourge of hospitals and an all too frequent cause of death by diarrhea. But where *C. difficile* prompts endless inflammation, bleeding and potentially catastrophic loss of fluids, the clostridial clusters do just the opposite—they keep the gut barrier tight and healthy, and they soothe the immune system. Scientists are now exploring whether these microbes can be used to treat a bevy of the autoimmune, allergic and inflammatory disorders that have increased in recent decades, including Crohn's and maybe even obesity.

F. prausnitzii was one of the first clostridial microbes to be identified. In Sokol's patients those with higher counts of *F. prausnitzii* consistently fared best six months after surgery. After he published his initial findings in 2008, scientists in India and Japan also found *F. prausnitzii* to be depleted in patients with inflammatory bowel disease. Sokol was particularly intrigued by the results from Japan. In East Asian populations the gene variants associated with inflammatory bowel disease differ from the gene variants in European populations. Yet the same bacterial species—*F. prausnitzii*—was reduced in the guts of those in whom the disease developed. This suggested that whereas different genetic vulnerabilities might underlie the disorder, the path to disease was similar: a loss of anti-inflammatory microbes from the gut. And although Sokol suspects that other good bacteria besides *F. prausnitzii* exist, this similarity hinted at a potential one-size-fits-all remedy for Crohn's and possibly other inflammatory disorders: restoration of peacekeeping microbes.

MICROBIAL ECOSYSTEMS

ONE OF THE QUESTIONS central to microbiome research is why people in modern society, who are relatively free of infectious diseases, a major cause of inflammation, are so prone to inflammatory, autoimmune and allergic diseases. Many now suspect that society-wide shifts in our microbial communities have contributed to our seemingly hyperreactive immune systems. Drivers of these changes might include antibiotics; sanitary practices that are aimed at limiting infectious disease but that also hinder the transmission of symbiotic microbes; and, of course, our high-sugar, high-fat modern diet. Our microbes

SCIENCE SOURCE

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Why Microbiome Treatments Could Pay Off Soon

Effective interventions may come before all the research is in *By Rob Knight*

Today we are at an exciting threshold of biology. Advances in DNA sequencing, coupled with high-end computation, are opening a frontier in new knowledge. Obtaining genetic information and obtaining insight from it have never been cheaper. The potential for curing previously incurable diseases, including chronic ones, seems immense. If this sounds familiar, you might be thinking that you heard it 15 years ago, when the Human Genome Project was in full swing. Many feel that genomic medicine has not yet delivered on its promise. So what is different this time with the microbiome? For one thing, you cannot really change your genome, but each of us has changed our microbiome profoundly throughout our lives. We have the potential not just to read out our microbiome and look at predispositions but to change it for the better.

What is most exciting at this stage is that we have mouse models that let us establish whether changes in the microbiome are causes or effects of disease. For example, we showed in collaborative work with Jeffrey I. Gordon's laboratory at Washington University in St. Louis last year that transferring the microbes from an obese person into mice raised in a bubble with no microbes of their own resulted in fatter mice. Normally, germ-free mice exposed to a mouse with microbial-based obesity would themselves become obese, but we could design a microbial community taken from lean people that protected against this weight gain. Similarly, we could take microbes from Malawian children with kwashiorkor, a profound nutritional deficiency, transplant them into germ-free mice and transfer the malnutrition, although the mice that received the microbes from the healthy identical twins of the sick children did fine. Remarkably, the mice that got the kwashiorkor microbiome, which lost 30 percent of their body weight in three weeks and died if untreated, recovered when given the same peanut butter–based supplement that is used to treat children in the clinic.

We have the potential not just to read out our microbiome and look at predispositions but to change it for the better.

The germ-free mice are far too expensive to deploy in Malawi, Bangladesh and the other sites in the Mal-ED (pronounced "mal-a-dee") global network for the study of malnutrition and enteric diseases collaboration with which we work. Thus, we are trying to move from the mouse model to a test-tube model and ultimately to a primarily computational model based on DNA sequencing that is so inexpensive, it is effectively free.

With crowdfunded projects such as American Gut, which already has thousands of participants who have had their microbiomes sequenced, and studies of people whose lives are very different from modern Western civilization, such as the Hadza of Tanzania, Yanomami of Venezuela and Matsés of Peru, we may be able to replenish our ancestral microbes and discover new ones that help to maintain health for individuals or entire populations. A good analogy is iodizing salt: Instead of understanding in detail why some people but not others were susceptible to cretinism and goiter, adding a nutrient to the food supply greatly reduced incidences of these diseases. Perhaps the same type of intervention is possible using some of the microbes that we are now discovering Westerners lack.

Rob Knight *is a computational biology pioneer, co-founder of the American Gut Project and director of the new Microbiome Initiative at the University of California, San Diego.*

Illustrations by Gluekit

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eat what we eat, after all. Moreover, our particular surroundings may seed us with unique microbes, "localizing" our microbiota.

The tremendous microbial variation now evident among people has forced scientists to rethink how these communities work. Whereas a few years ago they imagined a core set of human-adapted microbes common to us all, they are now more likely to discuss core functions—specific jobs fulfilled by any number of microbes.

Faced with the many instances of a misbehaving immune system, it is tempting to imagine that rather than having developed a greater vulnerability to many diseases, we actually suffer from just one problem: a hyperreactive immune system. Maybe that tendency has been enabled, in part, by a decline or loss of key anti-inflammatory microbes and a weakening of their peacekeeping function.

Antibiotics may deplete the bacteria that favorably calibrate the immune system, leaving it prone to overreaction.

In ecosystem science, "keystone species" have an outsize role in shaping the greater ecosystem. Elephants, for example, help to maintain the African savanna by knocking down trees, thus benefiting all grazing animals. The concept may not apply perfectly to our inner microbial ecosystems—keystone species tend to be few in number, whereas peacekeeping microbes such as *F. prausnitzii* are quite numerous. Yet it provides a useful framework to think about those clostridial microbes.

They seem to occupy a particular ecological niche, sidled right up against the gut lining, which allows them to interface more closely with us, their hosts, than other members of the gut microbiota. They often specialize in fermenting dietary fiber that we cannot digest and produce by-products, or metabolites, that appear to be important for gut health. Some of the cells that line our colon derive nourishment directly from these metabolites, not from the bloodstream. And when no fiber comes down the hatch, the clostridial microbes and others can switch to sugars in the intestinal mucous layer—sugars we produce, apparently, to keep them happy. In fact, they seem to stimulate mucus production.

Kenya Honda, a microbiologist at Keio University in Tokyo, was among the first to uncover the critical role of clostridial microbes in maintaining a balanced immune system. To study how native microbes affect animals, scientists decades ago developed the germ-free mouse: an animal without any microbiota whatsoever. These rodents, delivered by cesarean section and raised in sterile plastic bubbles, can exist only in labs. Of the many oddities they present—including shrunken heart and lungs and abnormalities in the large intestine—Honda was particularly intrigued by their lack of cells that prevented immune overreaction, called regulatory T cells, or Tregs. Without these cells, the mice were unusually prone to inflammatory disease.

Honda wanted to know which of the many intestinal species might induce these suppressor cells. Soon after Sokol identified the anti-inflammatory effects of *F. prausnitzii,* Honda began whittling away at the gut microbiota of mice by treating them with narrow-spectrum antibiotics. The animals' Tregs declined after a course of vancomycin. With their ability to restrain their immune reaction hobbled, the mice became highly susceptible to colitis, the rodent version of inflammatory bowel disease and allergic diarrhea. Honda found he could restore the Tregs and immune equilibrium of the mice just by reinstating 46 native clostridial strains.

Honda repeated the exercise with human-adapted microbes obtained from a healthy lab member. He extracted just 17 clostridial species this time that, in mice, could induce a full repertoire of Tregs and prevent inflammation. These human-adapted microbes specialized in nudging the immune system away from inflammatory disease. They came from branches of the clostridial group labeled clusters IV, XIVa and XVIII. *F. prausnitzii* belongs to cluster IV.

Vedanta Biosciences recently formed to try to turn Honda's 17-strain "clostridial cocktail" into a treatment for inflammatory disease. If the company's efforts are successful, it could signal the arrival of the next generation of probiotics—human-adapted microbes to treat immune-mediated disease—and all derived from one member of Honda's lab. As always, it is unclear if what works in lab mice will translate to humans. Sokol has his doubts. He recently identified a type of regulatory T cell that is unique to humans and that is deficient in people with inflammatory bowel disease. He questions if Honda's cocktail, which has been developed in mice, will activate these cells in people.

TROUBLE WITH ANTIBIOTICS

EVEN IF THE COCKTAIL falls short, Honda's meticulous demonstration of a link between antibiotics and vulnerability to inflammatory disease has raised a troubling question. A number of studies have found a small but significant correlation between the early-life use of antibiotics and the later development of inflammatory disorders, including asthma, inflammatory bowel disease and, more recently, colorectal cancer and childhood obesity. One explanation for this association might be that sickly people take more antibiotics. Antibiotics are not the cause, in other words, but the result of preexisting ill health.

Honda's studies suggest another explanation: antibiotics may deplete the very bacteria that favorably calibrate the immune system, leaving it prone to overreaction. Brett Finlay, a microbiologist at the University of British Columbia, has explored this possibility explicitly. Early-life vancomycin treatment of mice increased the animals' risk of asthma later, he found, in part by depleting those very same clostridial bacteria identified by Honda. The corresponding population of suppressor cells collapsed. And the animals became less able to restrain their immune responses when encountering allergens later.

These dynamics may also apply to other diseases. Earlier this year Cathryn Nagler, an immunologist at the University of Chica-

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The Gene–Microbe Link

Evidence that genes shape the microbiome may point to new treatments for common diseases *By Ruth E. Ley*

The ecology of the gut microbiome may trigger or contribute to a variety of diseases, including autoimmune disorders and obesity, research suggests. Factors such as early environment, diet and antibiotic exposure have a lot to do with why people differ from one another in the composition of their microbiomes. But specific gene variants are also linked to greater risks of developing many of these diseases. Do your genes act on your microbiome, which in turn promotes disease?

One way researchers have addressed this question is to pick specific genes that are good candidates—for instance, those with a strong link to a disease that also has a microbiome link—and examine whether people who carry mutations that are known to increase the risk of a certain disease also have microbiomes that differ from those who do not have the mutations. A team led by Dan Frank at the University of Colorado Denver took this approach and revealed that specific variants of the *NOD2* gene that confer a high risk of developing inflammatory bowel disease to their carriers are also associated with an altered intestinal microbiome.

A powerful and broader way to look for an effect of human genetic variation on the microbiome is to compare twins. Identical twins share nearly 100 percent of their genes; fraternal twins, 50 percent. Co-twins are raised together, so the environmental effects on their microbiomes should be about the same. If the microbiomes of the identical twins are more alike within a twinship than those of the fraternal twins, we can conclude that genes have played a role. If variation within twinships of each kind is about the same, we can say a shared genome has had no additional effect.

A powerful way to look for an effect of human genetic variation on the microbiome is to compare twins.

Early twins studies were based on fewer than 50 twin pairs and could not detect any greater similarities in the microbiomes of identical twins compared with those of fraternal twins. But recent work my laboratory at Cornell University conducted with researchers at King's College London compared nearly 500 twin pairs, a sample size sufficient to show a marked genetic effect on the relative abundance of a specific set of gut microbes. Furthermore, so-called heritable microbes—the bacteria most influenced by host genetics—were more abundant in lean twins than obese ones.

Experiments in germ-free mice showed that one gut bacterium in particular, *Christensenella minuta,* can influence the phenotype—the composite of observable characteristics or traits—of the host. Germ-free mice live in sterile bubbles—and they are very skinny. When they are given a microbiome in the form of a fecal transplant from a human donor, however, they plump up within a day or two because the bacteria help them digest their food and develop a proper metabolism. We found that if *C. minuta* was added to the feces of an obese human donor, the recipient mice were thinner than when *C. minuta* was not added. Results showing *C. minuta* has an effect of controlling fat gain in the mouse match data that reveal lean people have a greater abundance of *C. minuta* in their gut than obese people.

This is evidence that a person's genes can influence the gut microbiome's composition and in turn can shape the individual's phenotype. Further work will show what specific genes are involved as well as how the microbiome may be reshaped to reduce risk of developing chronic inflammatory diseases within the context of a person's genotype, suggesting potential new approaches to treating obesity-related diseases.

Ruth E. Ley *is an associate professor of molecular biology and genetics at Cornell University.*

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go, knocked out the clostridial bacteria with antibiotics and then fed the animals peanut protein. Without those microbes and their corresponding Tregs present, the protein leaked through the gut barrier into circulation, prompting the rodent version of a food allergy. She could prevent the sensitization just by introducing those clostridial bacteria.

One key difference between mice with and without the clostridial clusters was how many mucus-secreting cells they possessed. Animals that harbored the clostridial clusters had more. That may have far-reaching consequences. Mucus, scientists are finding, contains compounds that repel certain microbes, maintaining a tiny distance between them and us. But it also carries food for other bacteria—complex, fermentable sugars that resemble those found in breast milk. Lora Hooper, a microbiologist at the University of Texas Southwestern Medical Center in Dallas, calls this dual function the "carrot" and the "stick." Mucus serves both as an antimicrobial repellent and a growth medium for friendly bacteria.

This phenomenon matters for several reasons. As Nagler's experiments suggest, one way these clostridial clusters may promote gut health and a balanced immune system is by ensuring a healthy flow of mucus. Just as those elephants help to maintain the African savanna, these microbes may favorably shape the greater gut ecosystem by stimulating secretion of the sugars other friendly microbes graze on.

Conversely, scientists observe defects in the mucous layer in other disorders, particularly inflammatory bowel disease, where these clostridial bacteria are often depleted. The question has always been which comes first: defects in mucus secretion and the selection of an aberrant community of microbes or acquisition of an aberrant community of microbes that thins the mucous layer and increases vulnerability to disease? Both factors may work together.

In 2011 scientists at the University of Colorado Boulder sampled people with variants of a gene called *NOD2* associated with inflammatory bowel disease. No one quite understands how these variants of the gene, which codes for a microbial sensor, increase the risk of disease. Study participants included people both with and without disease. Those suffering from inflammatory bowel disease had reduced counts of clostridial bacteria, the scientists found. But more surprising, people who did not have disease but who carried the predisposing *NOD2* variants also had a relative depletion of clostridial clusters. Their microbial communities seemed positioned closer to a diseaselike state.

The study seems to highlight the role of genes in determining the composition of gut microbiota and the vulnerability to Crohn's. But epidemiological surveys complicate the picture. A number of studies over the years have linked having fewer sanitary amenities in childhood with a lower risk of inflammatory bowel disease in adulthood. And a 2014 study from Aarhus University in Denmark found that among northern Europeans, growing up on a farm with livestock—another microbially enriched environment—halved the risk of being stricken with inflammatory bowel disease in adulthood.

These patterns suggest that perhaps by seeding the gut microbiota early in life or by direct modification of the immune system the environment can affect our risk of inflammatory bowel disease despite the genes we carry. And they raise the question of what proactive steps those of us who do not live on farms can take to increase our chances of harboring a healthy mix of microbes.

THE IMPORTANCE OF FIBER

ONE OF THE MORE SURPRISING discoveries in recent years is how much the gut microbiota of people living in North America differs from those of people living in rural conditions in Africa and South America. The microbial mix in North America is geared to digesting protein, simple sugars and fats, whereas the mix in rural African and Amazonian environments is far more diverse and geared to fermenting plant fiber. Some think that our hunter-gatherer ancestors harbored even greater microbial diversity in their guts. If we accept the gut microbiota of people in rural Africa and South America as proxies for those that prevailed before the industrial revolution, then, says Justin L. Sonnenburg, a microbiologist at Stanford University, the observed differences suggest North Americans and other Westernized populations have veered into evolutionarily novel territory.

What troubles Sonnenburg about this shift is that the bacteria that seem most anti-inflammatory—including the clostridial clusters—often specialize in fermenting soluble fiber. Fermentation produces various metabolites, including butyrate, acetate and propionate—some of the substances that produce underarm odor. Various rodent studies suggest that these metabolites, called short-chain fatty acids, can induce Tregs and calibrate immune function in ways that, over a lifetime, may prevent inflammatory disease. Fermentation by-products may be one way our gut microbes communicate with our bodies. One takeaway is to "feed your Tregs more fiber," as University of Oxford immunologist Fiona Powrie put it last year in the journal *Science.*

Yet the seeming importance of these metabolites has others puzzled. Many bacteria produce these short-chain fatty acids, and yet only a few microbes seem potently anti-inflammatory. So although production of these metabolites may be a prerequisite for microbes that favorably tweak the immune system, says Sarkis Mazmanian, a microbiologist at the California Institute of Technology, it is insufficient to explain why some bacteria are more anti-inflammatory than others. Other characteristics, such as how close they live to the gut lining or the molecules they use to prod the host immune system, must also play a role, he says.

There is, however, an issue of sheer quantity. Some hunter-gatherers consumed up to 10 times as much soluble fiber as modern populations, and their bodies likely were flooded with far more fermentation by-products. Our fiber-poor modern diet may have weakened that signal, producing a state of "simmering hyperreactivity," Sonnenburg says, and predisposing us to the "plagues" of civilization. He calls this problem "starving our microbial self." We may not be adequately feeding some of the most important members of our microbiota.

Mouse experiments support the idea. Diets high in certain fats and sugars deplete anti-inflammatory bacteria, thin the mucous layer and foster systemic inflammation. Potentially dangerous opportunists bloom. In one intervention on human volunteers, University of California, San Francisco, microbiologist Peter Turnbaugh found that switching to a high-fat, high-protein diet spurred an expansion of bile-tolerant bacteria, one of which, *Bilophila wadsworthia,* has been

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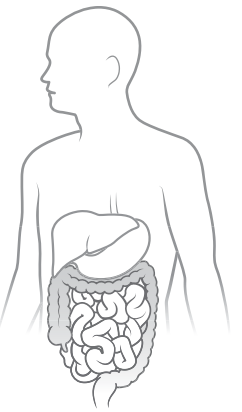
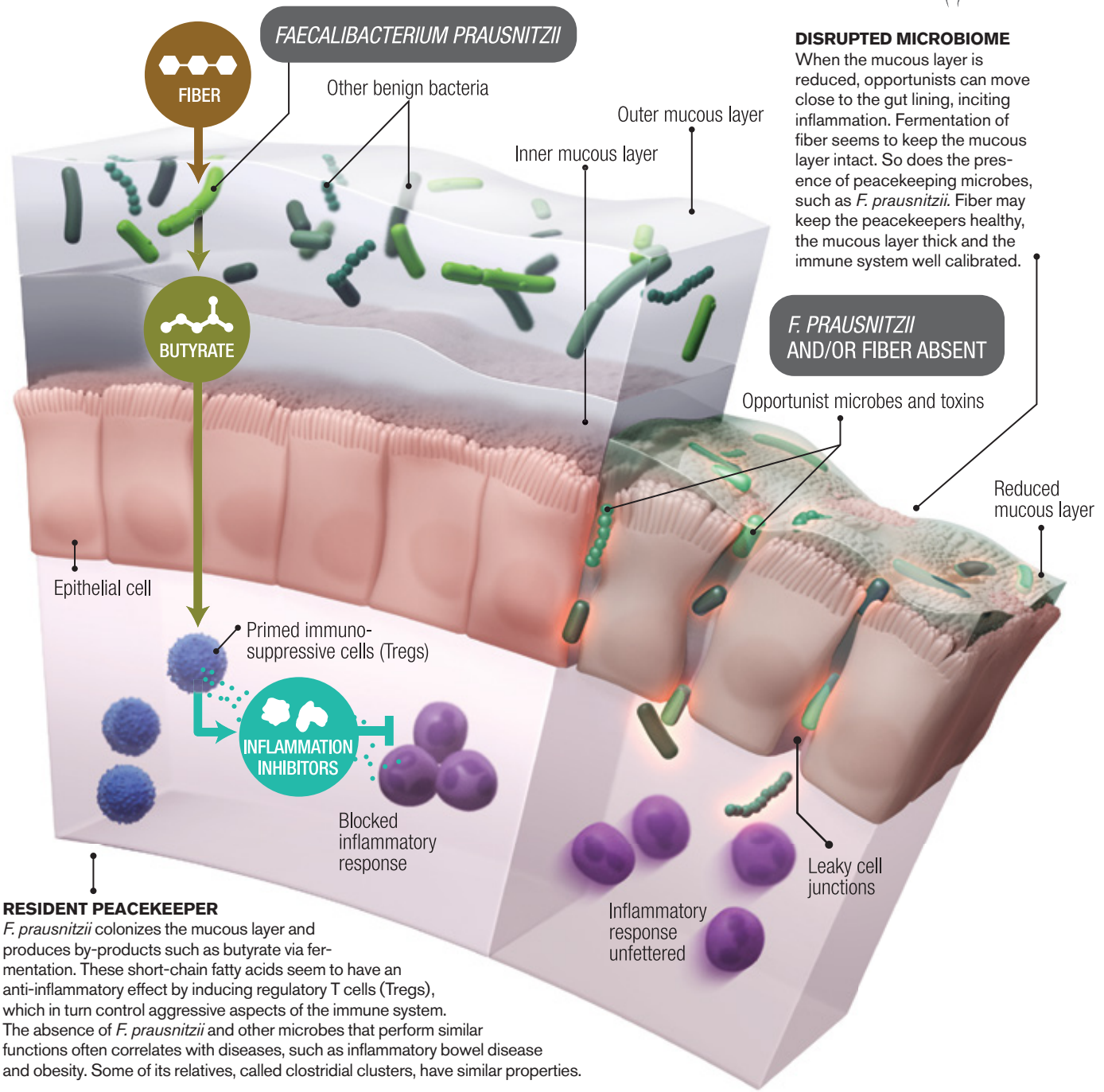
Your Microbes at Work: Fiber Fermenters Keep Us Healthy

The gut houses trillions of microbes. They eat what you eat. Many specialize in fermenting the soluble fiber in legumes, grains, fruits and vegetables. Certain microbial species are adept at colonizing the mucous layer of the gut. Mucus contains antimicrobial substances that keep the microbiota at a slight distance. But it also contains sugars such as those found in breast milk. Some microbes, often the same ones that specialize in fermenting fiber, can use these sugars as sustenance when other food is not available. The by-products of fiber fermentation nourish cells lining the colon. Some by-products pass into the circulation and may calibrate our immune system in a way that prevents inflammatory disorders such as asthma and Crohn's disease.





DISRUPTED MICROBIOME
When the mucous layer is reduced, opportunists can move close to the gut lining, inciting inflammation. Fermentation of fiber seems to keep the mucous layer intact. So does the presence of peacekeeping microbes, such as *F. prausnitzii*. Fiber may keep the peacekeepers healthy, the mucous layer thick and the immune system well calibrated.

RESIDENT PEACEKEEPER
F. prausnitzii colonizes the mucous layer and produces by-products such as butyrate via fermentation. These short-chain fatty acids seem to have an anti-inflammatory effect by inducing regulatory T cells (Tregs), which in turn control aggressive aspects of the immune system. The absence of *F. prausnitzii* and other microbes that perform similar functions often correlates with diseases, such as inflammatory bowel disease and obesity. Some of its relatives, called clostridial clusters, have similar properties.

SOURCE: "FEED YOUR TREGS MORE FIBER," BY JULIA BOLLRATH AND FIONA POWRIE, IN *SCIENCE*, VOL. 341; AUGUST 2, 2013

Illustration by AXS Biomedical Animation Studio

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Microbiome Engineering

Synthetic biology may lead to the creation of smart microbes that can detect and treat disease

By Justin L. Sonnenburg

In the not too distant future each of us will be able to colonize our gut with genetically modified "smart" bacteria that detect and stamp out disease at the earliest possible moment. This scenario may sound like the premise for a sci-fi flick, but it is a very real possibility. Microbiome engineering holds great promise because of advances in the field of synthetic biology, which strives to create and rewire biological organisms so they perform desired tasks. Synthetic biologists are attempting to turn bacterial cells into the biological equivalent of the silicon wafer. These principles have been primarily applied to organisms for biofuel production, but the resulting techniques and genetic tool kit, when applied to our resident microbes, will have profound consequences for human health.

These resident microbes are adept at sensing what food is present, whether any pathogens are lurking and what the inflammatory state of the gut is—their survival depends on it. The model gut-resident bacterial species that we are using in our laboratory for initial tests, *Bacteroides thetaiotaomicron,* possesses more than 100 genetic circuits, each responsive to a different cue within the gut. If *B. thetaiotaomicron* "sees" pectin from an apple you recently ate, one circuit is triggered. If you eat a poached egg teeming with *Salmonella,* the resulting intestinal damage triggers a different circuit in *B. thetaiotaomicron.* Each of these circuits can be rewired so that the environmental cue elicits a designed response. Our early tests are focused on optimizing a DNA memory device for *B. thetaiotaomicron* so that we can record this bacterium's experiences as it transits through the gut. Invertible pieces of DNA are designed to flip, like switches, depending on what the bacterium detects. The two possible orientations (forward or flipped) of the DNA piece are akin to binary computer bits, which record a 1 or 0. Reading a genetic memory chip of a bacterium after it exits the gut will reveal fundamental principles about a single cell's journey through the digestive tract.

We are also working to design bacteria that secrete anti-inflammatory molecules when inflammation is detected, providing site-specific drug delivery within the intestine that automatically shuts off when the inflammation is eliminated. In addition to recording memories and treating inflammation, these smart bacteria may ultimately help combat invading pathogens, diagnose early stages of cancer, correct diarrhea or constipation, and regulate mood or behavior.

It is also important to develop safety mechanisms that ensure these organisms can be controlled. We are working to engineer a "kill switch" for eliminating engineered microbes if necessary.

The gut microbiota guides our immune system, metabolism, and even our moods and behavior. As we learn more about the specifics of our relationship with our resident microbes, we will be able to genetically manipulate them in a variety of ways to improve human health.

Justin L. Sonnenburg *is an assistant professor in the department of microbiology and immunology at the Stanford University School of Medicine.*

We are working to design bacteria that secrete anti-inflammatory molecules and provide site-specific drug delivery within the intestine.

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linked to inflammatory bowel disease. On the other hand, preventing this skewing of the microbial self does not seem that difficult. In rodents, adding fermentable fiber to a diet otherwise high in fat keeps the "good" microbes happy, the mucous layer healthy and the gut barrier intact, and it prevents systemic inflammation. Taken together, these studies suggest that it is not only what is in your food that matters for your health but also what is missing.

The human studies are even more intriguing. Mounting evidence suggests that the systemic inflammation observed in obesity does not just result from the accumulation of fat but contributes to it. Scientists at Catholic University of Louvain in Belgium recently showed that adding inulin, a fermentable fiber, to the diet of obese women increased counts of *F. prausnitzii* and other clostridial bacteria and reduced that dangerous systemic inflammation. Weight loss was minor, but later analysis of this and two similar studies revealed that the intervention worked best on patients who, at the outset, already harbored clostridial clusters IV, IX and XIVa—some of the same clusters represented in Honda's cocktail. Those without the bacteria did not benefit, which suggests that once species disappear from the "microbial organ," the associated functions might also vanish. These individuals might not require ecosystem engineering so much as an ecosystem restoration.

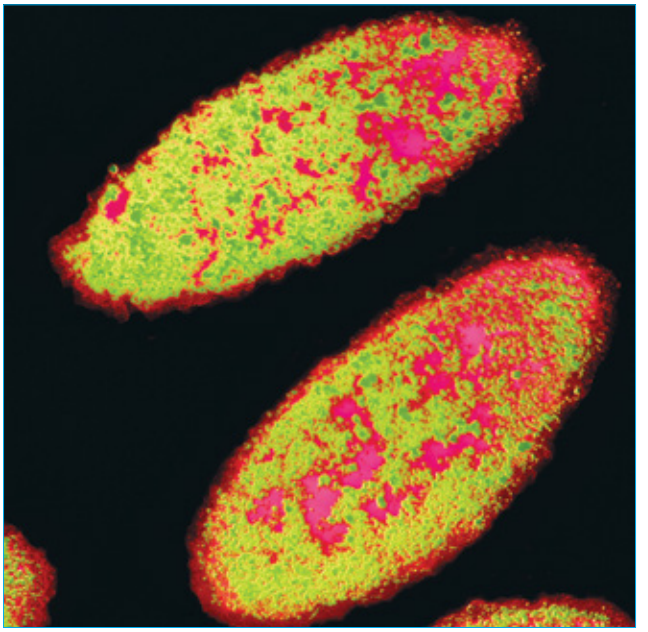
That possibility has also been tested. Several years ago Max Nieuwdorp, a gastroenterologist at the Academic Medical Center in Amsterdam, transplanted microbes from lean donors to patients recently diagnosed with metabolic syndrome, a cluster of symptoms that often predicts type 2 diabetes. The recipients saw improvements in insulin sensitivity and an enrichment of their microbiota, including among those clostridial species. But six months after the transplant the patients had relapsed, metabolic improvements had faded and their microbes had reverted to their original states.

To Sonnenburg, this outcome suggests that the dance between human host and microbial community has considerable momentum. Removing the "diseased" ecosystem and installing a new one may not overcome the inertia. The gut immune system may simply mold the new community in the image of the old. That may explain why fecal transplants, which effectively vanquish *C. difficile*–associated diarrhea, have so far failed to treat inflammatory bowel disease. The former is caused by a single opportunist; the latter may be driven by an out-of-whack ecosystem and our response to the microbial derangement.

To overcome the inertia, Sonnenburg foresees treating the host *and* the microbiota simultaneously. The idea has not been tested, but he imagines clearing out the microbiota, perhaps with antibiotics, followed by immunosuppressants to quiet the patient's immune system and allow healing. Only then might the new community of microbes stick and successfully recalibrate the immune system.

EVOLUTION OF MOBILITY

WHEN ANIMAL LIFE EXPLODED some 800 million years ago, microbes had already existed on Earth for maybe three billion years. A major innovation in animal evolution was the gut—a tube that takes nutrients in one end and expels waste from the other. It is even possible, argues Margaret McFall-Ngai, a microbiologist at the University of Wisconsin–Madison, that microbes drove the evolution of the gut directly. Plants only succeeded in colonizing land when they had developed relationships with microbes that helped them extract vital nutrients from soil. Perhaps one evolutionary innovation of animals was to scoop up the microbial communities necessary for survival and to take them along for the ride, achieving mobility.



KARI LOUNATMAA *Science Source*

DANGEROUS OPPORTUNIST: Bilophila wadsworthia, *a species of bacterium linked to inflammatory bowel disease, bloomed in the microbiota of human volunteers fed a high-fat, high-protein diet in a recent experiment.*

Mucus may be one way the human gut selects for these microbes. Only co-adapted bacteria, Sonnenburg thinks, can metabolize the complex sugars it contains. A cornerstone of this symbiosis may be the simple imperative of acquiring nutrients in a world of scarcity. We hunt and gather the goods; the microbes ferment what we cannot digest, taking a cut in the process and keeping pathogens at bay. Our immune systems quiet down when they receive signals, conveyed partly in microbial metabolites, indicating that the right microbes are in place.

The field of gut microbiome research has already moved from the idea of describing the core species to identifying the core ecological functions various microbes perform. Many potential species may fulfill any given role. Now another concept may be emerging, which might be called the keystone relationship. "The interaction between fiber and microbes that consume it," Sonnenburg says, "is the fundamental keystone interaction that everything else is built on in the gut." It may lie at the heart of the symbiotic pact between microbes and humans.

Moises Velasquez-Manoff *is author of* An Epidemic of Absence: A New Way of Understanding Allergies and Autoimmune Diseases. *His work has appeared in the* New York Times, Mother Jones *and* Nautilus.

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THE NOTION THAT THE STATE of our gut governs our state of mind dates back more than 100 years. Many 19th- and early 20th-century scientists believed that accumulating wastes in the colon triggered a state of "auto-intoxication," whereby poisons emanating from the gut produced infections that were in turn linked with depression, anxiety and psychosis. Patients were treated with colonic purges and even bowel surgeries until these practices were dismissed as quackery.

MENTAL HEALTH

Thinking from the Gut

The microbiome may yield a new class of psychobiotics for the treatment of anxiety, depression and other mood disorders

By Charles Schmidt

The ongoing exploration of the human microbiome promises to bring the link between the gut and the brain into clearer focus. Scientists are increasingly convinced that the vast assemblage of microfauna in our intestines may have a major impact on our state of mind. The gut-brain axis seems to be bidirectional—the brain acts on gastrointestinal and immune functions that help to shape the gut's microbial makeup, and gut microbes make neuroactive compounds, including neurotransmitters and metabolites that also act on the brain. These interactions could occur in various ways: microbial compounds communicate via the vagus nerve, which connects the brain and the digestive tract, and microbially derived metabolites interact with the immune system, which maintains its own communication with the brain. Sven Pettersson, a microbiologist at the Karolinska Institute in Stockholm, has recently shown that gut microbes help to control leakage through both the intestinal lining and the blood-brain barrier, which ordinarily protects the brain from potentially harmful agents.

Microbes may have their own evolutionary reasons for communicating with the brain. They need us to be social, says John Cryan, a neuroscientist at University College Cork in Ireland, so that they can spread through the human population. Cryan's research shows that when bred in sterile conditions, germ-free mice lacking in intestinal microbes also lack an ability to recognize other mice with whom they interact. In other studies, disruptions of the microbiome induced mice behavior that mimics human anxiety, depression and even autism. In some cases, scientists restored more normal behavior by treating their test subjects with certain strains of benign bacteria. Nearly all the data so far are limited to mice, but Cryan believes the findings provide fertile ground for developing analogous compounds, which he calls psychobiotics, for humans. "That dietary treatments could be used as either adjunct or sole therapy for mood disorders is not beyond the realm of possibility," he says.

PERSONALITY SHIFTS

SCIENTISTS USE germ-free mice to study how the lack of a microbiome—or selective dosing with particular bacteria—alters behavior and brain function, "which is something we could never do in people," Cryan says. Entire colonies of germ-free mice are bred and kept in isolation chambers, and the technicians who handle them wear full bodysuits, as if they were in a biohazard facility. As with all mice research, extrapolating results to humans is a big step. That is especially true with germ-free mice because their brains and immune systems are underdeveloped, and they tend to be more hyperactive and daring than normal mice.

A decade ago a research team led by Nobuyuki Sudo, now a professor of internal medicine at Kyushu University in Japan, restrained germ-free mice in a narrow tube for up to an hour and then measured their stress hormone output. The amounts detected in the germ-free animals were far higher than those measured in normal control mice exposed to the same restraint. These hormones are released by the hypothalamic-pituitary-adrenal axis, which in the germ-free mice was clearly dysfunctional. But more important, the scientists also found they could induce more normal hormonal responses simply by pretreating the animals with a single microbe: a bacterium called *Bifidobacterium infantis*. This finding showed for the first time that intestinal microbes could influence stress responses in the brain and hinted at the possibility of using probiotic treatments to affect brain function in beneficial ways. "It really got the field off the ground," says Emeran Mayer, a gastroenterologist and director of the Center for Neurobiology of Stress at the University of California, Los Angeles.

Meanwhile a research team at McMaster University in Ontario led by microbiologist Premsyl Bercik and gastroenterologist Stephen Collins discovered that if they colonized the intestines of one strain of

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The Diverse Microbiome of the Hunter-Gatherer

The Hadza of Tanzania offer a snapshot of the co-adaptive capacity of the gut ecosystem

By Stephanie L. Schnorr

We tend to forget that modern humanity is largely sheltered from the last vestiges of wild untamed Earth and that our way of life bears little resemblance to how our ancestors lived during 90 percent of human history. We have lost nearly all trace of these former selves—and, worse, have marginalized the few remaining humans who retain their hunter-gatherer identity. In Tanzania, tribes of wandering foragers called the Hadza, who have lived for thousands of years in the East African Rift Valley ecosystem, tell us an immense and precious story about how humans, together with their microbial evolutionary partners, are adapted to live and thrive in a complex natural environment.

Ongoing research with the Hadza to characterize the hunter-gatherer-microbiome relationship has yielded not only insight into the co-adaptive capacity of this microbial ecosystem but also a profound appreciation for how versatile human life can be. The microbiome is central to our biology. It mediates the interaction and exchange of information across host-environment thresholds such as the mouth, skin and gut.

The strength and importance of this mediation are borne out in the Hadza gut microbiota. Their microbiome harbors incredibly high taxonomic diversity, indicating great ecosystem stability and flexibility. It is capable of withstanding the perpetual presence of parasites and pathogens and can respond to fluctuations in diet caused by an unpredictable and seasonally dependent food supply. Interestingly, bacterial taxonomic abundance is different in Hadza men and women. Because of the sexual division of labor in Hadza society, men and women tend to consume more of their respective foraged food resources. The women primarily collect and eat tubers and other plant foods. As a result, it appears that women carry more bacteria to help process the plant fiber in their diets. This difference has direct implications for how the gut microbiota may enable Hadza

germ-free mice with bacteria taken from the intestines of another mouse strain, the recipient animals would take on aspects of the donor's personality. Naturally timid mice would become more exploratory, whereas more daring mice would become apprehensive and shy. These tendencies suggested that microbial interactions with the brain could induce anxiety and mood disorders.

Bercik and Collins segued into gut-brain research from their initial focus on how the microbiome influences intestinal illnesses. People who suffer from these conditions often have co-occurring psychiatric problems such as anxiety and depression that cannot be fully explained as an emotional reaction to being sick. By colonizing germ-free mice with the bowel contents of people with irritable bowel syndrome, which induces constipation, diarrhea, pain and low-grade inflammation but has no known cause, the McMaster's team reproduced many of the same gastrointestinal symptoms. The animals developed leaky intestines, their immune systems activated, and they produced a barrage of pro-inflammatory metabolites, many with known nervous system effects. Moreover, the mice also displayed anxious behavior, as indicated in a test of their willingness to step down from a short raised platform.

AUTISM CONNECTION?

SCIENTISTS HAVE ALSO BEGUN to explore the microbiome's potential role in autism. In 2007 the late Paul Patterson, a neuroscientist and developmental biologist at the California Institute of Technology, was intrigued by epidemiological data showing that women who suffer from a high, prolonged fever during pregnancy are up to seven times more likely to have a child with autism. These data suggested an alternative cause for autism besides genetics. To investigate, Patterson induced flu-like symptoms in pregnant mice with a viral mimic: an immunostimulant called polyinosinic:polycytidylic acid, or poly(I:C). He called this the maternal immune activation (MIA) model.

The offspring of Patterson's MIA mice displayed all three of the core features of human autism: limited social interactions, a tendency toward repetitive behavior and reduced communication, which he assessed by using a special microphone to measure the length and duration of their ultrasonic vocalizations. In addition, the mice had leaky intestines, which was important because anywhere from 40 to 90 percent of all children with autism suffer from gastrointestinal symptoms.

Then Caltech microbiologist Sarkis Mazmanian and his doctoral student Elaine Hsiao discovered that MIA mice also have abnormal microbiomes. Specifically, two bacterial classes—Clostridia and Bacteroidia—were far more abundant in the MIA offspring than in normal mice. Mazmanian acknowledges that these imbalances may not be the same as those in humans with autism. But the finding was compelling, he says, because it suggested that the behavioral state of the MIA mice—and perhaps by extension autistic behavior in humans—might be rooted in the gut rather than the brain. "That raised a provocative question," Mazmanian says. "If we treated gastrointesti-

BEN PORTER (*reference photograph*)

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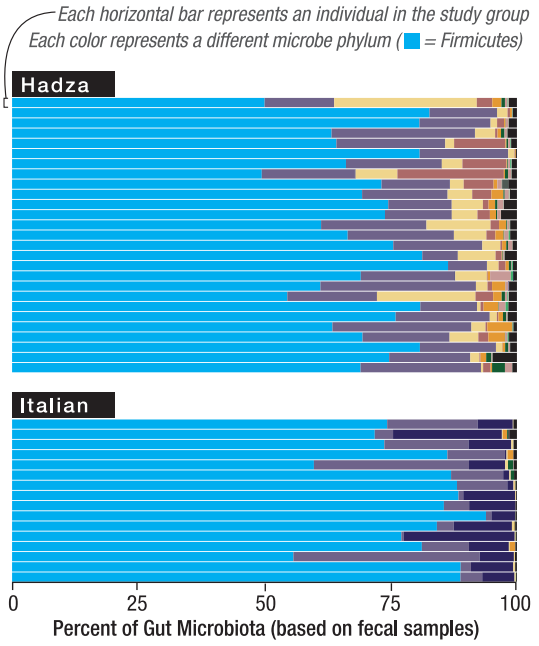
women to obtain adequate nutrition for fertility and reproductive success, despite a resource-limited environment. Through our work with the Hadza, we have been able to contribute to mounting evidence that human microbiota exerts a powerful influence on host health and survival, especially in natural fertility- and subsistence-based populations.

Comparative analysis of the gut microbiota of hunter-gatherers with that of Westernized industrial populations is also beginning to yield important insights. The microbial diversity in industrial groups is far below that of the Hadza, as well as those of other rural farming communities in Burkina Faso, Malawi and South Africa. Whereas a reduction in diversity may not seem ideal, it is the predictable response of an ecosystem facing a narrow range of selective pressures and is therefore no less adaptive. Some technological interventions, such as hypersanitation, consumption of refined foods and habitual use of antibiotics, have had a dramatic impact over time on the functional role of the microbiome in industrial populations. These aspects of a Westernized way of life have to a large extent displaced much of the original mutualistic functions of the microbiome in stabilizing our bodies against foreign microorganisms, allowing us to digest unprocessed foods and helping train our immune system to effectively fight disease.

We are just beginning to understand how the microbiome evolves over our lifetimes as a dynamic and mutualistic ecosystem that helps to facilitate human health. Thanks to the Hadza, we know that ancient human hunter-gatherers must have maintained a direct and persistent interface with the natural environment. As a result, the ancestral human microbiome was almost certainly a taxonomically diverse community, providing the functional flexibility that accompanied global colonization and is our adaptive legacy.

Stephanie L. Schnorr *is a Ph.D. candidate in the Research Group on Plant Foods in Hominin Dietary Ecology at the Max Planck Institute for Evolutionary Anthropology in Leipzig, Germany.*



TAXONOMIC TREASURE TROVE:
A survey of fecal microbiota of 43 subjects revealed a more varied mix of gut bacteria phyla among Hadza hunter-gatherers compared with urban Italians.

nal symptoms in the mice, would we see changes in their behavior?"

Mazmanian and Hsiao investigated by dosing the animals with a microbe known for its anti-inflammatory properties, *Bacteroides fragilis,* which also protects mice from experimentally induced colitis. Results showed that the treatment fixed intestinal leaks and restored a more normal microbiota. It also mitigated the tendency toward repetitive behavior and reduced communication. Mazmanian subsequently found that *B. fragilis* reverses MIA deficits even in adult mice. "So, at least in this mouse model, it suggests features of autism aren't hardwired—they're reversible—and that's a huge advance," he says.

LIMITS OF RESEARCH

THE HUMAN GUT MICROBIOME evolved to help us in myriad ways: Gut microbes make vitamins, break dietary fiber into digestible short-chain fatty acids and govern normal functions in the immune system. Probiotic treatments such as yogurt supplemented with beneficial strains of bacteria are already being used to help treat some gastrointestinal disorders, such as antibiotic-induced diarrhea. But there are little data about probiotic effects on the human brain.

In a proof-of-concept study Mayer and his colleagues at U.C.L.A. uncovered the first evidence that probiotics ingested in food can alter human brain function. The researchers gave healthy women yogurt twice a day for a month. Then brain scans using functional magnetic resonance imaging were taken as the women were shown pictures of actors with frightened or angry facial expressions. Normally, such images trigger increased activity in emotion-processing areas of the brain that leap into action when someone is in a state of heightened alert. Anxious people may be uniquely sensitive to these visceral reactions. But the women on the yogurt diet exhibited a less "reflexive" response, "which shows that bacteria in our intestines really do affect how we interpret the world," says gastroenterologist Kirsten Tillisch, the study's principal investigator. Mayer cautions that the results are rudimentary. "We simply don't know yet if probiotics will help with human anxiety," he says. "But our research is moving in that direction."

Strains of *Bifidobacterium,* which is common in the gut flora of many mammals, including humans, have generated the best results so far. Cryan recently published a study in which two varieties of *Bifidobacterium* produced by his lab were more effective than escitalopram (Lexapro) at treating anxious and depressive behavior in a lab mouse strain known for pathological anxiety. Although Cryan is optimistic that such findings may point the way to the development of psychobiotics, he is wary of hype. "We still need a lot more research into the mechanisms by which gut bacteria interact with the brain," he says.

Charles Schmidt *is a recipient of the National Association of Science Writers' Science in Society Journalism Award. His work has appeared in* Science, Nature Biotechnology, Nature Medicine *and the* Washington Post.

SOURCE: "GUT MICROBIOME OF THE HADZA HUNTER-GATHERERS," BY STEPHANIE L. SCHNORR ET AL., IN *NATURE COMMUNICATIONS,* VOL. 5, ARTICLE NO. 3654; APRIL 15, 2014

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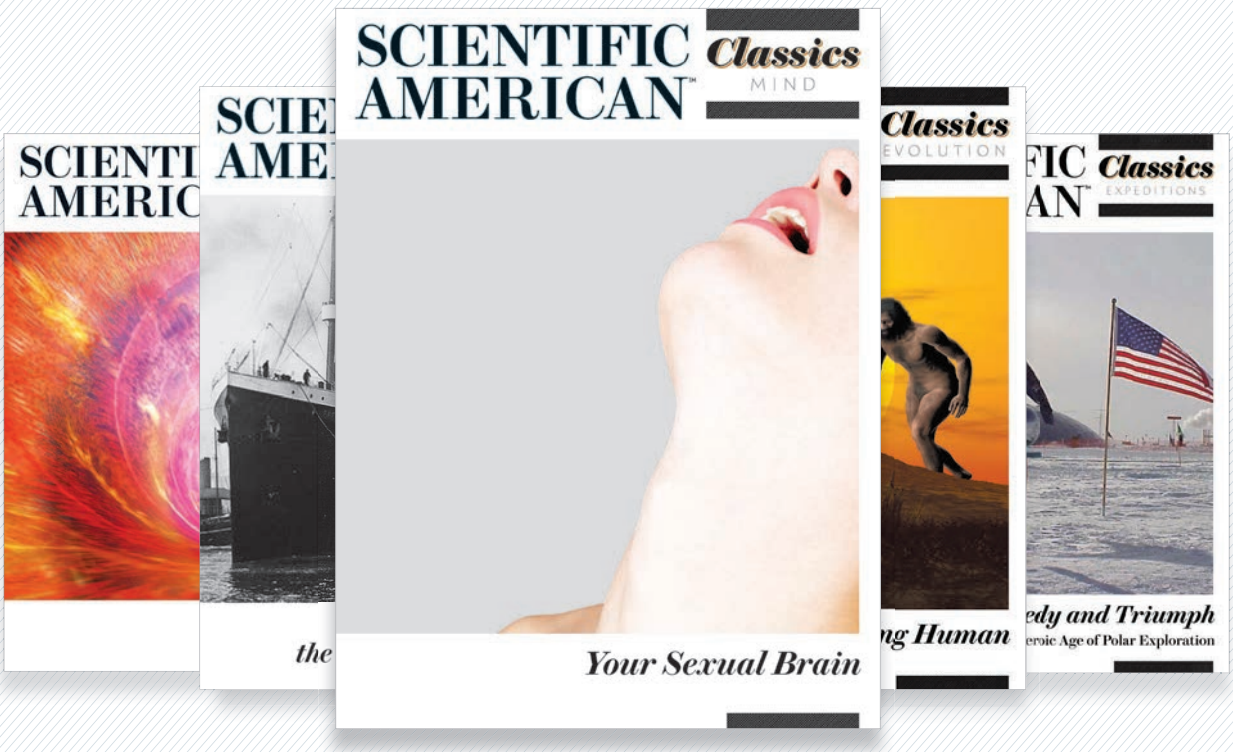

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Beneath the Surface: Killer Whales, SeaWorld, and the Truth Beyond *Blackfish*

by John Hargrove, with Howard Chua-Eoan. Palgrave Macmillan,* 2015 ($26)

Since his first visit to SeaWorld as a young boy, Hargrove dreamed of working with orcas. Eventually he got his wish and became a senior trainer there, caring for killer whales over 14 years. As Hargrove's love for and knowledge of the creatures increased, however, he gradually concluded that the work he was part of at SeaWorld was harming them and was unacceptably dangerous to himself and the other human trainers. Orcas are too big and too intelligent to be kept in captivity, Hargrove argues, and he came to see the daily "Shamu Stadium" shows where the whales perform tricks as "part of a rapacious corporate scheme that exploited both the orcas and their human trainers." He resigned from SeaWorld in 2012 and appeared in the documentary *Blackfish,* which criticized the park's practices after its trainer Dawn Brancheau was killed by a whale in 2010. Here Hargrove covers both the joy of his own experiences with orcas as well as the case for why such interactions in captivity should end.

Rust: The Longest War

by Jonathan Waldman. Simon & Schuster, 2015 ($26.95)

Of all the environmental challenges threatening worldwide infrastructure, rust, journalist Waldman admits, is not "sexy." It creeps in gradually and seems like more of an aesthetic blight than a dire danger to the modern machinery our society depends on. Yet rust is costlier than all other natural disasters combined, Waldman explains, and the science of corrosion, along with the ingenious engineering strategies humans have devised to fight it, is fascinating. Rust "seizes up weapons, manhandles mufflers, destroys highway guardrails, and spreads like a cancer in concrete," he writes. Waldman attends "Can School," interviews rust experts and visits the Alaska pipeline, among other adventures, to illuminate the myriad attacks rust makes on our daily lives. In doing so, he adds luster to a substance considered synonymous with dullness.

Neuroscience: A Historical Introduction

by Mitchell Glickstein. MIT Press, 2014 ($50)

Neuroscientists sometimes say, with a mix of awe and whimsy, that the brain is the most complex machine in the universe. Because the topic is such a weighty one, some of the books that introduce this discipline arrive with more heft than a 1988 laptop. Glickstein, a professor emeritus of neuroscience at University College London, takes a less daunting approach by conveying the stories of the scientific discoveries that have given us an understanding of the basics of vision, reflexes, learning and memory. He succeeds by relating the way scientists and clinicians have derived new insights from contemplating disease and injury in humans while probing the workings of the nervous systems of rats, flies and sea slugs. This approach provides understanding of neurons and the way pain, heat and taste are processed by the brain—and much more. —*Gary Stix*

Junk DNA: A Journey through the Dark Matter of the Genome

by Nessa Carey. Columbia University Press, 2015 ($29.95)

When the human genome was first sequenced, 98 percent of it was dismissed as "junk" because it did not code for proteins and thus seemingly lacked purpose. Yet in recent years researchers have realized that these stretches of DNA are also important: for one thing, changes to them can lead to serious diseases. In chronicling what we know and what we wonder about junk DNA, biologist Carey makes an apt comparison to dark matter. Just as the universe appears to contain mass that we cannot see or understand and yet nonetheless exerts a pull on normal matter, the mysterious parts of our genome have a vital effect on the workings of more straightforward elements of DNA. In fact, far from being useless, genetic rubbish may be what differentiates humans from less advanced species.

NIGEL WORRALL *Corbis*

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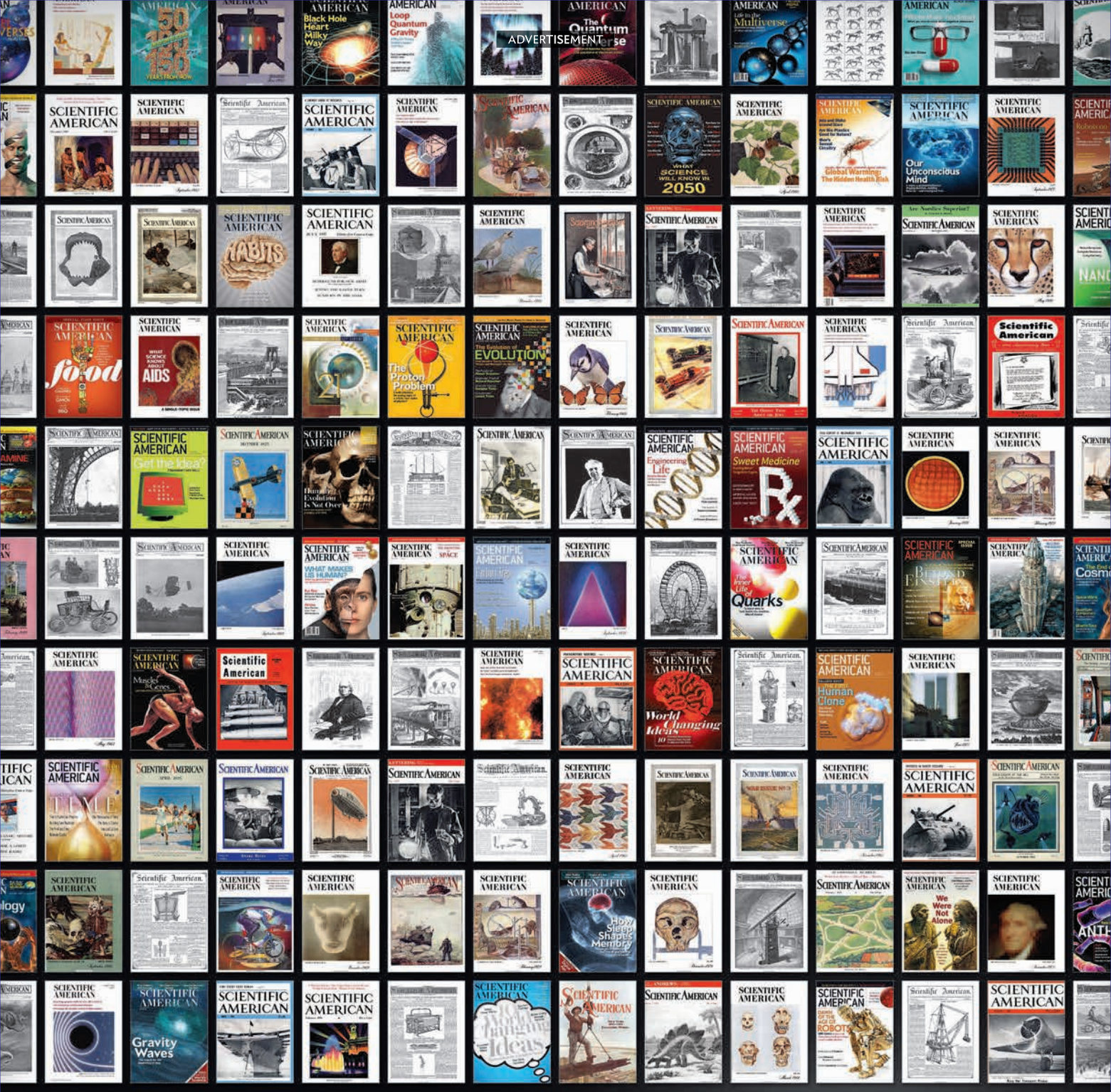

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Michael Shermer is publisher of *Skeptic* magazine (www.skeptic.com). His new book, *The Moral Arc*, is out now (Henry Holt, 2015). Follow him on Twitter @michaelshermer

Forging Doubt

Just because we don't know everything doesn't mean we know nothing

What do tobacco, food additives, chemical flame retardants and carbon emissions all have in common? The industries associated with them and their ill effects have been remarkably consistent and disturbingly effective at planting doubt in the mind of the public in the teeth of scientific evidence. Call it pseudoskepticism.

It began with the tobacco industry when scientific evidence began to mount that cigarettes cause lung cancer. A 1969 memo included this statement from an executive at the Brown & Williamson tobacco company: "Doubt is our product since it is the best means of competing with the 'body of fact' that exists in the minds of the general public." In one example among many of how to create doubt, a Philip Morris tobacco executive told a congressional committee: "Anything can be considered harmful. Applesauce is harmful if you get too much of it."

The tobacco model was subsequently mimicked by other industries. As Peter Sparber, a veteran tobacco lobbyist said, "If you can 'do tobacco,' you can do just about anything in public relations." It was as if they were all working from the same playbook, employing such tactics as: deny the problem, minimize the problem, call for more evidence, shift the blame, cherry-pick the data, shoot the messenger, attack alternatives, hire industry-friendly scientists, create front groups.

Documentary filmmaker Robert Kenner encountered this last strategy while shooting his 2008 film *Food, Inc.* He has said that he "kept bumping into groups like the Center for Consumer Freedom that were doing everything in their power to keep us from knowing what's in our food." Kenner has called them "Orwellian" because such front groups sound like neutral nonprofit think tanks in search of scientific truth but are, in fact, funded by the for-profit industries associated with the problems they investigate.

Consider "Citizens for Fire Safety," a front group created and financed in part by chemical and tobacco companies to address the problem of home fires started by cigarettes. Kenner found it while making his 2014 film *Merchants of Doubt,* based on the 2010 book of the same title by historians of science Naomi Oreskes and Erik Conway. (I appear in an interview in the film.) To misdirect regulators and the public away from the link between cigarettes and home fires, the tobacco industry hired Sparber to work with the National Association of State Fire Marshals to promote the use of chemical flame retardants in furniture. As another memo reads: "You have to fireproof the world around the cigarette." Suddenly Americans' furniture was awash in toxic chemicals.

Climate change is the latest arena for pseudoskepticism, and the front group du jour is ClimateDepot.com, financed in part by Chevron and Exxon and headed by a colorful character named Marc Morano, who told Kenner: "I'm not a scientist, but I do play one on TV occasionally … hell, more than occasionally." Morano's motto to challenge climate science, about which he admits he has no scientific training, is "keep it short, keep it simple, keep it funny." That includes ridiculing climate scientists such as James E. Hansen of Columbia University. "You can't be afraid of the absolute hand-to-hand combat metaphorically. And you've got to name names, and you've got to go after individuals," he says, adding with a wry smile, "I think that's what I enjoy the most."

Manufacturing doubt is not difficult, because in science all conclusions are provisional, and skepticism is intrinsic to the process. But as Oreskes notes, "Just because we don't know *everything,* that doesn't mean we know *nothing*." We know a lot, in fact, and it is what we know that some people don't want us to know that is at the heart of the problem. What can we do about this pseudoskepticism?

In *Merchants of Doubt,* close-up prestidigitator extraordinaire Jamy Ian Swiss offers an answer: "Once revealed, never concealed." He demonstrates it with a card trick in which a selected card that goes back into the deck ends up underneath a drinking glass on the table. It is virtually impossible to see how it is done, but once the move is highlighted in a second viewing, it is virtually impossible not to see it thereafter. The goal of proper skepticism is to reveal the secrets of dubious doubters so that the magic behind their tricks disappears. SA

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Nestlé
Good Food, Good Life

Nestlé's research on nutrition and the human gut microbiome

NESTLÉ IS COMMITTED TO ENHANCING THE QUALITY OF CONSUMERS' LIVES THROUGH nutritional products that promote health and wellness. It is with this mindset that the company actively pursues research on the human microbiome (the collection of microorganisms that inhabit specific parts of the human body) with the aim to develop functional products that provide microbial-mediated health benefits (see Fig. 1). Nestlé pioneered research on beneficial microorganisms – so called 'probiotics', i.e. "live microorganisms that, when administered in adequate amount, confer a health benefit to the host" (WHO expert group, 2011) – identifying lead *Lactobacillus* sp. and *Bifidobacterium* sp. strains to be included in a variety of food products such as infant formulae. This approach was further enriched by the development of nutritional products containing blends of microbiome-modulatory substances such as short-chain oligosaccharides (i.e. prebiotics), tailored to promote health through promotion of endogenous beneficial bacteria.

ADVERTISER FEATURE

The association between multicellular organisms and prokaryotic microorganisms is not the exception, it is the rule. All organisms – from simple nematodes to complex humans – coexist with a population of microorganisms. These associations might be parasitic, commensalistic or mutualistic. The nature of the interaction might change over time, depending upon host or environmental factors. The dynamics of host–microbe interactions raises interesting questions. Did these associations impart an evolutionary advantage to the host or to the microbe? Can an existing interaction between a host and a microbial system be modulated in a way beneficial to the host? What are the predominant factors that influence the equilibrium between the host and the microbiome? These questions may remain at least partially unanswered for the next few years, but based on data accumulated so far it is already generally accepted that nutrition plays a major part in influencing this dynamic equilibrium.

The spectrum of biological activities that are affected by host-associated microorganisms is currently the subject of extensive investigation among the scientific community. In mammals, data accumulated so far indicate that the microbiome influences a wide range of physiological processes, including digestion, the innate and adaptive immune response, the gastrointestinal endocrine system, or even the central nervous system – to name a few. In humans, nutrition plays a significant part in all of these aspects and over recent years much research has been directed to this area.

From calories to bioactives: Increasing expectations from nutrition

PUBLIC AWARENESS OF the importance of nutrition to maintain health and prevent disease has significantly increased over the past few decades, paralleled by a significant expansion of research activities in nutritional sciences. In response to these social developments, and sometimes preceding them, the food industry has changed as well. The concept that appetizing food can also be good for your health is at the same time visionary and simple. Instead of treating disease with

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drugs alone, the nutrition and health industry is providing an increasing range of food-based products with the appropriate nutritional composition to help decrease the risk of developing diseases or improve recovery from illness. With the introduction of food-based nutritional approaches the health sector has more access to diversified solutions spanning from preventative to therapeutic approaches. Growing scientific consensus converges on the idea that contemporary nutritional habits in developed countries, sometimes loosely defined as a 'Western diet', characterized by an overconsumption of refined sugars, salt and saturated fat, together with lifestyle changes that include reduced physical activity, contribute to major diseases such as obesity, diabetes and cardiovascular disease. Public health scientists and health economists also argue for prevention as a complementary strategy to treatment with the benefit of reducing healthcare costs.

In view of the constantly increasing interest in the microbiome, the state of the science of nutrition and the human gut microbiome was reviewed and discussed by leading scientists in the field at the 11th Nestlé International Nutrition Symposium in Lausanne in October 2014.

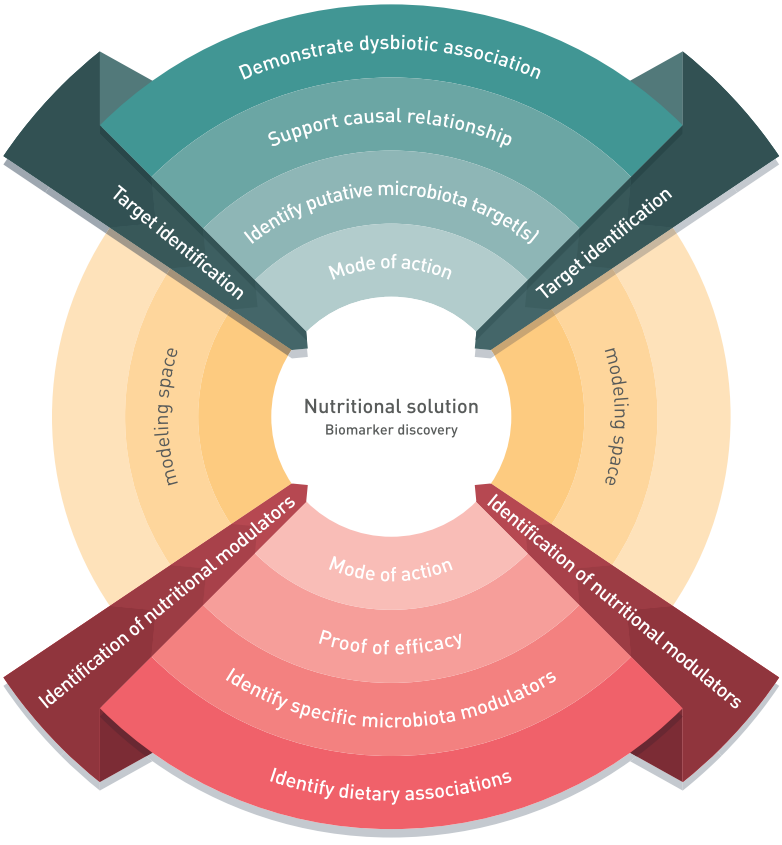

FIGURE 1 Nestlé approach to microbiome research: from hypothesis generation to development of targeted nutritional interventions.

Beneficial gut microbes

DIETARY FIBRES ARE known to be beneficial to human health, particularly plant fibres that humans cannot digest. Scientists realized that the reason for this perplexing observation is because part of our food is also food for bacteria colonizing the human gut. The complex microbial world living in us (some researchers refer to the 2kg bacterial mass as a major human organ) had until recently defied explanation. However, thanks to new analytical developments largely based on characterization of nucleic acid sequences, the scientific community was able to study the totality of the gut microbes and these organisms have become a new target for the development of beneficial dietary interventions.

The original hypothesis that host-associated microbes play an important part in our health is more than 100 years old and dates back to Elie Metchnikoff (1908 Nobel Prize in Medicine), who described it in his book "The Prolongation of Life: Optimistic Studies." Metchnikoff's hypothesis started with an epidemiological observation of his time: Bulgarian people live longer than other Europeans; and Bulgarians eat more yoghurt. Hence one might search for a life-prolonging principle in yoghurt. However, Metchnikoff went a step further and offered a visionary concept that tried to explain the effects of nutrition on health. He defined two main types of gut bacteria, which digest food in the colon in two fundamentally different ways. The first category includes saccharolytic bacteria, which can digest carbohydrates from plant sources into small organic acids. Among those, the lactic acid bacteria, which ferment lactose into lactic acid during yoghurt production, were for Metchnikoff the main bacteria responsible for the above epidemiological observations. Short-chain fatty acids such as acetate, propionate and butyrate – the metabolic end products of the majority of saccharolytic colonic bacteria – are the focus of much current research linking the gut to other organs[1]. In the second category he classified bacteria that digest animal proteins which leads to harmful metabolic waste products in a process he called "putrefaction". These products in his hypothesis accelerate the aging process.

A 2014 Nature paper analyzing gut microbiome in the faeces of human volunteers fed alternatively with a carbohydrate-rich, plant-derived diet or a protein-rich, animal-derived diet came essentially to the same conclusions when using an impressive battery of contemporary 'omics' analytical approaches, based on state-of-the-art nucleic acid sequencing technologies[2].

Nestlé's interest in probiotics

NESTLÉ RESEARCH SCIENTISTS build on Metchnikoff's hypothesis for several reasons. Nestlé manufactures a large quantity of dairy products. For the production of yoghurt, our scientists and technologists have a sound knowledge of industrial milk fermentation by lactic acid bacteria; they curate large collections of bacterial starter strains, many of which are close relatives of gut bacteria.

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Nestlé is also a leading producer of infant formula – our paediatricians and nutritionists strive to develop formulae that are close to human breast milk. For more than fifty years it has been known that breast milk contains factors that facilitate the establishment of the *Bifidobacterium*-dominated gut microbiome typically observed in breastfed babies. By association ('breast is best') beneficial health effects were attributed to bifidobacteria.

The next goal became to find candidates for promising probiotic ('health-promoting') bacteria. With the pioneering work of Minoru Shirota, a Japanese microbiologist who took Metchnikoff's ideas at face value, the first commercial developments took place with a probiotic drink that was introduced to the market in 1935, kick-starting the search for health-promoting bacteria. A few decades later, Nestlé and a handful of other companies that became interested in this area of research screened bacterial strains for candidate probiotic strains with specific properties using a panel of preclinical tests. Nestlé scientists published the first *Bifidobacterium* sp.[3] and the second *Lactobacillus* sp.[4] genome sequence, which allowed genome-based insights into the potential mechanisms of action of beneficial microbes. Genomic comparisons between bacterial strains of the same species that displayed different characteristics were conducted on microarrays, enabling scientists to make preliminary associations linking genes with phenotypes (i.e. bacterial characteristics). In collaboration with the Karolinska Institute in Sweden, we linked only hypothetical open reading frames of the sequenced *Bifidobacterium longum* strain NCC2705 with protection against rotavirus diarrhoea in a mouse model (unpublished data). Japanese researchers succeeded in linking carbohydrate transporter genes of the same NCC2705 strain with protection against toxigenic *Escherichia coli* infection[5]. Comprehensive analyses of bacterial metabolic products revealed that acetic acid excreted by the NCC2705 strain in the gut inhibited the activity of a toxin produced by the pathogenic *E. coli* (Shiga toxin). This validated the concept proposed by Metchnikoff that metabolic end products of the gut microbiome may be beneficial to the mammal host.

The identification of bacterial genes that encode health-promoting properties is necessary to build greater insight into the mechanisms underlying probiotic functions. However, for the food industry it is even more important to explore the range of health effects that can be achieved with probiotics and the ecosystems they influence.

A Nestlé-sponsored clinical trial published 20 years ago demonstrated that feeding a blend of bifidobacteria and lactic streptococci protected children against rotavirus diarrhoea[6]. In a randomized controlled trial at the International Center for Diarrhoeal Diseases Research in Bangladesh (ICDDR,B), Nestlé scientists demonstrated that *Lactobacillus paracasei* strain NCC2461 (also named ST11) had a significant therapeutic effect on children hospitalized with bacterial, but not with viral, diarrhoea[7]. Notably, the same strain also mediated a lower nasal congestion in adults with allergic grass-pollen rhinitis in a small proof of concept trial. The effect was attributed to a decrease in allergen-specific antibodies[8]. In a different clinical setting, *Bifidobacterium lactis* NCC2818 (see Fig. 2) was also shown to reduce allergic reactions in patients suffering from allergic rhinitis[9]. Moreover, *L. paracasei* NCC2461 was shown to decrease skin sensitivity to environmental stresses by increasing the skin barrier function[10]. Thus, one probiotic strain can have effects on more than one organ system (in this example NCC2461, on gut and nasal mucosa and skin), and different probiotics can affect the same organ while using different effector pathways. While these results provide further evidence that the described health benefits may be attributed to the introduction of a given probiotic strain, much remains to be investigated about their mechanism of action especially with respect to their direct and or indirect roles in biological outcomes.

Nestlé's research to understand mechanisms of action: The case of IBS

A RATIONALIZATION OF the differential effects mentioned is complicated by a limited understanding of the mechanisms of interaction between the gut-associated microbes and our physiology. As part of its efforts to fill this knowledge gap, Nestlé collaborated with scientists at McMaster University in Ontario, Canada, to characterize the role of gut microbes in an experimental model of irritable bowel syndrome (IBS). Oral supplementation of a probiotic *B. longum* strain (NCC3001) led to a reduction of anxiety-like behaviours, such as fear to explore the environment[11]. This was paralleled by normalization in the level of brain signalling molecules involved in the response to environmental stimuli. Those data, together with several independent studies reporting an alteration of the intestinal microbiome composition in IBS patients as compared to healthy subjects, suggest a role for the gut-associated microbes in the pathophysiology of this disease.

This hypothesis is further supported by recently obtained results (unpublished) demonstrating transfer of several IBS-related intestinal and behavioural characteristics to germ-free mice after colonization with faecal microbiome from IBS patients, which was not observed in germ-free mice colonized with healthy volunteers' faecal microbiome.

Nestlé's research on prebiotics

AS AN ALTERNATIVE to providing beneficial microbes directly by means of the probiotic approach, food compounds can be introduced that specifically support the growth of intestinal health-associated bacteria. These substances are called prebiotics. Many plant-derived materials have been explored, including inulin (fructo-polysaccharides present in fibers from many fruits and vegetables), fructo-oligosaccharides (FOS, derived from chicory root) and galacto-oligosaccharides (GOS from soybeans or synthesized from milk sugar). A recent Nestlé clinical trial in children demonstrated that prebiotic supplementation of infant formula with FOS/GOS led to an increase in faecal bifidobacteria, which was also associated with increased faecal acetate, butyrate and propionate, and decreased concentration of pathogenic *Clostridium difficile*[12].

Recent technological developments in analytical sugar chemistry have identified new and potentially bioactive

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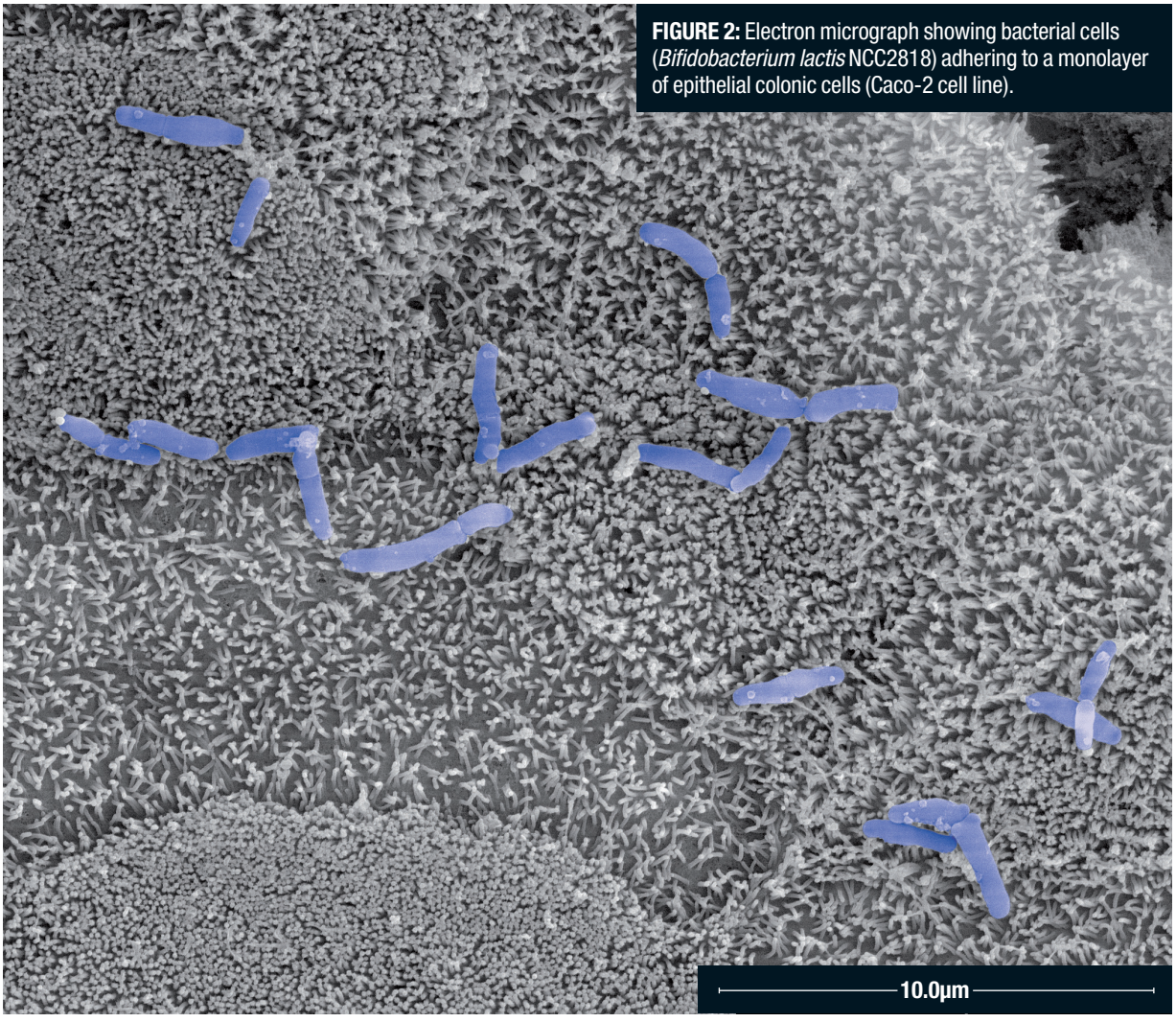

FIGURE 2: Electron micrograph showing bacterial cells (*Bifidobacterium lactis* NCC2818) adhering to a monolayer of epithelial colonic cells (Caco-2 cell line).

compounds in human breast milk. Advances in synthetic chemistry enabling large-scale production of these compounds have opened up opportunities to improve the nutritional quality of infant formulae. These innovations are based on a very intriguing concept: the "glycan code" in breast milk. In short, this concept tries to explain why oligosaccharides – which are indigestible to babies – are the third-most prominent component in milk, are complex in structure and are variable between species. The hypothesis states that lactating mothers produce breast milk sugar components that help an optimal gut microbiome to develop in the intestines of the newborn soon after birth. Babies acquire gut microbes from their mother and the environment, and it is important for the health of the infant that the correct microbiome establishes itself in early life. Nestlé is conducting controlled nutritional intervention trials with uniquely supplemented infant formula to test the hypothesis.

Short-chain fatty acids and the human gut microbiome

WHAT ELSE CAN human gut microbes do? Several studies have shown that soluble dietary fibers such as fructooligosaccharides (FOS) can have beneficial effects on body weight and glucose control. FOS is a prebiotic, indigestible by the gut enzymes, but metabolized by bacteria in the colon, i.e. food to our gut commensals. These bacteria produce acetate, propionate and butyrate as metabolic endpoints. Butyrate feeds the colon and induces glucose synthesis in the intestine (intestinal gluconeogenesis), which enters the circulation. Propionate activates receptors (more precisely FFAR3, free fatty acid receptor 3) on the nerves surrounding the portal vein, which transports the nutrients absorbed in the gut to the liver[13]. The peripheral nerves connect to the brain, which regulates gluconeogenesis in the intestine, illustrating the existence of an active bi-directional gut–brain axis making a positive contribution to our energy balance. Notably, feeding propionate instead of FOS induced similar effects, illustrating the importance of metabolites produced by the gut microbiome.

However, our connection with gut bacteria is more intricate than just providing extra calories. Metabolites of gut bacteria have other important physiological functions, as revealed by a collaborative study between Lausanne

University, Novartis, CHUV, EPFL and Nestlé[14]. Using a mouse model of allergic airway inflammation, it was demonstrated that a diet rich in plant fibers reduced the pathological manifestations in the lung, while these were increased upon feeding mice with a diet low in fiber content. Also in this case, propionate ingestion reproduced the protective effects of a high-fibre diet on the lung, linking health beneficial effects of diets rich in plant fibres to metabolic products of gut bacteria. Similarities in the two systems described above go even further: the first relay in the gut–lung axis is the same as in the gut–brain axis: propionate activates FFAR3. Then, however, the pathways deviate: FFAR3 activation leads to glucose regulation in one case, yet it reduces the capacity of immune cells to mount pro-allergenic properties in the second case. It could be argued that high-fibre diets may produce multiple physiological benefits on both glucose regulation and immune function.

Nestlé's initiative to unravel the microbial metabolome

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IN COLLABORATION WITH Imperial College London, Nestlé research has initiated a series of comprehensive metabolite profiling studies (metabolome studies) to identify key functional molecules produced by the gut microbiome. In one of these studies the metabolome of germfree mice was compared with the metabolome from mice colonized with a bacterial community isolated from the stools of a human baby. Colonized mice showed higher gut concentrations of tauro-conjugated bile acids and reduced plasma levels of lipoproteins[15], suggesting that the energy harvest from the diet depended on the presence and the type of gut microbiome. It was subsequently investigated how the bacterial-host interaction was influenced after feeding pre-, pro- or symbiotics to mice. Differential effects could be assigned to pre- or probiotic modulation of the gut microbial metabolism, some features being exacerbated upon symbiotic (probiotic + prebiotic) administration. For instance, prebiotic galacto-oligosaccharides (GOS) reduced lipogenesis and triglyceride concentrations, while the probiotic *L. rhamnosus* NCC4007 strain induced decreased plasma lipoprotein levels[16]. Interestingly, germ free mice are resistant to weight gain when on a high fat diet. Compared to conventional mice, germ-free mice on a high-fat diet consumed fewer calories, excreted more faecal lipids, weighed less, showed enhanced insulin sensitivity and an altered cholesterol metabolism[17]. The metabolic events were also studied shortly after the establishment of gut bacteria in germ-free mice. The acquisition of a gut microbiome resulted in rapid increase of body weight; it stimulated glycogenesis and then triglyceride synthesis in the liver. Encouraged by these metabolomics results, we asked whether the knowledge acquired in animal experiments could be applied to humans. The data acquired in human subjects indicate interesting parallels. A 2014 study published by Nestlé scientists reported different urine and stool metabolome profiles between breastfed and milk formula-fed infants, revealing a relationship between processing of dietary proteins by intestinal bacteria and host protein metabolism[18]. At the other extreme of the lifespan, centenarians showed an increased urinary excretion of bacterial metabolites, suggesting links between gut microbiome composition and longevity[19].

Developing tangible perspectives

WHERE IS THE future of microbiome research leading? Some microbiologists now see humans as a multi-organism consortium. For more doubtful scientists it remains to be proven to what extent our phenotype is co-determined by the microorganisms that inhabit our gut. Skeptics have already voiced their opinions. William P. Hanage is a Harvard epidemiologist who, in a 2014 Nature comment, called for a good dose of caution towards the conclusions of many published microbiome studies, underlining that association is not causation[20]. It is safe to predict that the microbiome field will be progressively integrated into established health research and applications. As molecular mechanisms start to be identified in the context of human disease, the field will probably move away from having its own identity and be incorporated by scientists and clinicians who can associate the findings in their areas of expertise.

Experimental therapies such as faecal transplants, which have been effective in fighting recurrent *Clostridium difficile* intestinal infections, demonstrate the importance of gut microbiome equilibrium for human health. Microbial transplantation is still in an experimental stage and clinicians would benefit from a better understanding of the mechanisms involved, which might allow future interventions with defined microbial communities or microbiome-derived compounds. Perhaps the best way to summarize the future for microbiome research is that there will be a progressive integration into the mainstream of epidemiological and medical research while concentrating on microbiome function rather than its composition. The challenge will be the application of new analytical tools to couple patient populations with treatments or clinical decision-making. Therefore, the microbiome has the potential to play a part in the evolution of personalized medicine. In the future, microbiome characteristics may be used to indicate whether a subject might react positively to a medical or dietary intervention, or which treatment might be best adapted to a person's physiology.

The microbiome is currently being associated with a range of conditions, including anxiety, autism, inflammation and obesity. How can we intervene to change microbial ecology in a way that would provide a therapeutic benefit? If we consider the human microbiome as an ecosystem, there will be underlying principles defined in ecosystems such as soil, lakes, rivers, and oceans that will serve as guides. It seems certain that as our understanding of human microbial ecology develops, we will be able to identify the molecular mechanisms underlying associations, determine key points of intervention and demonstrate efficacy in randomized clinical trials.

Overall, the field of microbiome research and its impact on human health is too important for scientists interested in nutrition and health to be ignored. At Nestlé we have selected two approaches. Scientists at the Nestlé Research Center in Lausanne are conducting prospective

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nutritional and health studies with frequent sampling of diverse microbiome together with a detailed documentation of health outcome (selected studies to be found in ClinicalTrials.gov under the following registration identifiers: NCT01276626, NCT01715246, NCT01581957, NCT01983072, NCT02031887, NCT01880970, NCT01971671, NCT02021058, NCT02223585). In partnership with the Epigen consortium, Nestlé participates in a large, long-term birth cohort study in Singapore, to characterize how delivery mode and gestational age influence infant gut microbiome and health-related parameters (ClinicalTrials.gov identified: NCT01174875). In parallel, we organized a smaller birth cohort study in Bangladesh with ICDDR,B, an institution that has a significant database on nutrition, health and disease in its population. ICDDR,B is renowned for translating research into interventions that lead to a measurable health improvement in their population. With these prospective data and by taking advantage of existing cohorts in Europe and beyond, we will test predictions of the literature concerning microbiome-health associations. For those associations, which we can confirm for the investigated population, we will design nutritional intervention trials targeting microbiome changes and test for predicted health benefits.

At the Nestlé Institute of Health Sciences Lausanne, which is the bioanalytical arm of Nestlé Research, we are investigating microbe–host interactions for the promising microbiome–health associations with respect to their mechanisms of action by deploying state-of-the-art 'omics' technologies and informatics systems approaches for multiple data analytics integration. With this double-pronged approach, we are excited by the prospect of delivering new knowledge in food compositions and nutritional interventions that promote human health by working in concert with host-associated microbes.

References

1. Brussow,H. & Parkinson,S.J. You are what you eat. Nat. Biotechnol. 32, 243-245 (2014).
2. David,L.A. et al. Diet rapidly and reproducibly alters the human gut microbiome. Nature 505, 559-563 (2014).
3. Schell,M.A. et al. The genome sequence of Bifidobacterium longum reflects its adaptation to the human gastrointestinal tract. Proc. Natl. Acad. Sci. U. S. A 99, 14422-14427 (2002).
4. Pridmore,R.D. et al. The genome sequence of the probiotic intestinal bacterium Lactobacillus johnsonii NCC 533. Proc. Natl. Acad. Sci. U. S. A 101, 2512-2517 (2004).
5. Fukuda,S. et al. Bifidobacteria can protect from enteropathogenic infection through production of acetate. Nature 469, 543–547 (2011).
6. Saavedra,J.M., Bauman,N.A., Oung,I., Perman,J.A., & Yolken,R.H. Feeding of Bifidobacterium bifidum and Streptococcus thermophilus to infants in hospital for prevention of diarrhoea and shedding of rotavirus. Lancet 344, 1046–1049 (1994).
7. Sarker,S.A. et al. Lactobacillus paracasei strain ST11 has no effect on rotavirus but ameliorates the outcome of nonrotavirus diarrhea in children from Bangladesh. Pediatrics 116, e221-e228 (2005).
8. Wassenberg,J. et al. Effect of Lactobacillus paracasei ST11 on a nasal provocation test with grass pollen in allergic rhinitis. Clin. Exp. Allergy 41, 565-573 (2011).
9. Singh,A. et al. Immune-modulatory effect of probiotic Bifidobacterium lactis NCC2818 in individuals suffering from seasonal allergic rhinitis to grass pollen: an exploratory, randomized, placebo-controlled clinical trial. Eur. J. Clin. Nutr. 67, 161-167 (2013).
10. Gueniche,A. et al. Randomised double-blind placebo-controlled study of the effect of Lactobacillus paracasei NCC 2461 on skin reactivity. Benef. Microbes. 5, 137-145 (2014).
11. Bercik,P. et al. Chronic gastrointestinal inflammation induces anxiety-like behavior and alters central nervous system biochemistry in mice. Gastroenterology. 139, 2102-2112 (2010).
12. Holscher,H.D. et al. Effects of prebiotic-containing infant formula on gastrointestinal tolerance and fecal microbiota in a randomized controlled trial. JPEN J. Parenter. Enteral Nutr. 36, 95S-105S (2012).
13. De Vadder,F. et al. Microbiota-generated metabolites promote metabolic benefits via gut-brain neural circuits. Cell 156, 84-96 (2014).
14. Trompette,A. et al. Gut microbiota metabolism of dietary fiber influences allergic airway disease and hematopoiesis. Nat. Med. 20, 159-166 (2014).
15. Martin,F.P. et al. A top-down systems biology view of microbiome-mammalian metabolic interactions in a mouse model. Mol. Syst. Biol. 3, 112 (2007).
16. Martin,F.P. et al. Panorganismal gut microbiome-host metabolic crosstalk. J. Proteome. Res. 8, 2090-2105 (2009).
17. Rabot,S. et al. Germ-free C57BL/6J mice are resistant to high-fat-diet-induced insulin resistance and have altered cholesterol metabolism. FASEB J. 24, 4948-4959 (2010).
18. Martin,F.P. et al. Impact of breast-feeding and high- and low-protein formula on the metabolism and growth of infants from overweight and obese mothers. Pediatr. Res. 75, 535-543 (2014).
19. Collino,S. et al. Metabolic signatures of extreme longevity in northern Italian centenarians reveal a complex remodeling of lipids, amino acids, and gut microbiota metabolism. PLoS. One. 8, e56564 (2013).
20. Hanage,W.P. Microbiology: Microbiome science needs a healthy dose of scepticism. Nature 512, 247-248 (2014).

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.

Translation Frustration

Sticks and stones may break your bones, but poorly translated words may also hurt you

This magazine has various foreign-language editions. As such, I occasionally get requests from overseas translators tasked with trying to make sense of some of my more idiomatic constructions. For example, my January 2014 column discussed Jesse Bering's book *Perv: The Sexual Deviant in All of Us*. The book's dedication reads: "For you, you pervert, you." So I wrote, "Bering was kind enough to dedicate *Perv* to me. And to you. And, well, to any reader brave enough to crack the binding." Which prompted this response from a translator: "I guess the phrase 'crack the binding' has some special meaning about abnormal sex, but I couldn't find it. Could you enlighten me?"

Indeed, translation can be a minefield. If I tried to tell my colleague in his language that I would indeed enlighten him, I could inadvertently say that I was helping him lose weight or setting him on fire. Best leave translation to the pros.

Of course, occasions arise in which no pro is available and the clock is going ticktock (or *tic-tac* in Italy or even *kachi kachi* in Japan). One place where time is of the essence is, of course, a hospital. When health care workers and patients speak different languages, the best available option may be to turn to various Web-based automated translation tools.

And so, in the notorious Christmas issue (because it's long been home to offbeat research) of the journal now officially known as the *BMJ* (shortened from *British Medical Journal* to save space for them and to take up more space for the rest of us who have to explain what *BMJ* stands for every time we cite it), Sumant Patil and Patrick Davies of the Nottingham Children's Hospital in England set out to, as they wrote, "evaluate the accuracy and usefulness of Google Translate in translating common English medical statements."

The two intrepid Internet interpreters tested Google Translate's talents using 10 common English medical phrases, such as "your wife is stable" and "your husband had a heart attack." They asked the Web-based program to turn each phrase into 26 different languages. The system performed best when turning English into other western European languages (74 percent accuracy, according to the researchers' own metric). It had the most problems attempting to make sense in Asian (46 percent) and African (45 percent) languages. So we are still a long way from a Star Trekian universal translator that does not cause an unfortunate interplanetary incident every time representatives from two cultures start yapping at each other.

For example, the news that "your wife needs to be ventilated" often became "your wife needs to be aired," which just adds insult to injury. Besides, I've worked in hospitals, and pretty much everybody needs to be aired, especially doctors who've been on call for 36 hours straight. The aforementioned and positive "your wife is stable" was commonly translated as "your wife cannot fall over," which is great in a raging storm at sea but could fail to offer the necessary comfort to a concerned husband in an emergency room.

A typical error for "your husband had a heart attack" was to have it come out as "your husband's heart was attacked." That rendering has things exactly backward because the husband in question was in fact attacked *by* his heart, which is clearly trying to kill him. The phrase "we will need your consent for operation" was sometimes mangled into "we need your consent for operating (such as machinery)," which implies that, as you wait for an OR to open up, the management would appreciate it if you could put in a shift at the loading dock.

The researchers admit that, whereas computerized translation seems problematic, "we have, however, not assessed the accuracy of human translators, who cannot be assumed to be perfect and may be subject to confidentiality breaches." Then again, digital data can also get loose. In a hospital setting, however, a hack that leads to the release of privileged information is less dangerous than a hack who's performing an appendectomy. SA

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Illustration by Matt Collins

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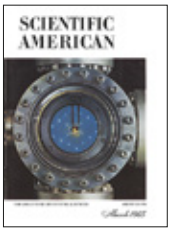

March 1965

Magnet Earth

"Since 1958 direct measurements of the outer reaches of the earth's field by means of artificial satellites and rocket probes have convinced many geophysicists that the simple picture of that magnetic field must be drastically revised. Far from being free of external influences, the geomagnetic field is continuously buffeted by a 'wind' of electrically charged particles emanating from the sun, distorted by electric currents circulating in the radiation belts that girdle the earth. The net result of all these influences is a geomagnetic field shaped somewhat like a teardrop with a tremendously elongated tail. Analysis of the data provided by the satellite measurements has progressed to the stage at which the broad outlines of the magnetosphere can now be mapped with reasonable accuracy."

March 1915

Hookworm in School

"Only recently have educators turned their attention to the physical condition of the average school child, and in the south they have done so largely because of the discovery of the enormously important part played by hookworm. Pupils at school become infected, with the school as a site of exchange. In a comparatively short time the premises around the homes of all the schoolchildren are polluted, and we have the change (which anemia produces) coming over the community. Progress of the children in school is retarded; the daily attendance is poor; the health of the community is below normal; the crops are not so well cultivated; the houses are not so well provided for or kept; the whole community is sick and doesn't know it. The economic loss is tremendous."

Saturn

"For the next few months Saturn will be in a favorable position for observation, and the attention of astronomers throughout the world will be attracted to this most beautiful and most wonderful of all the planets. That which especially distinguishes Saturn from the other planets is a most peculiar system of thin rings, surrounding it in the plane of its equator. As seen from the equator of the planet, the ring rises into the heavens like a luminous arch, perpendicular to the horizon on each side. It would appear as a thin band of gold dividing the celestial vault. From Titan, the planet would appear as a disk ten times as large as the sun looks to us. Our design pictures the planet as it would appear if it could be seen from its moon Titan. —Abbé Th. Moreux, Director of the Observatory of Bourges"

More images, old and new, of Saturn and its moons are at www.ScientificAmerican.com/mar2015/saturn

SATURN, as seen from Titan, in an artist's impression, 1915

March 1865

Rubidium

"According to the latest experiments of Prof. Bunsen in connection with the preparation and properties of this metal, it appears that it may be reduced from carbonated aciferous tartrite of oxide of rubidium (in a manner similar to the reduction of kalium [potassium]). It is very light, like silver, its color is white, with a yellowish *nuance,* hardly perceptible. In contact with air it covers itself immediately with a bluish gray coating of suboxyd, and is inflamed (even when in large lumps) after a few seconds, much quicker than kalium."

Scientific (but Fearful)

"There is a proposition afloat to build a railway from Siam to China; and the King of Siam, if an engineer is sent to examine the route, 'will furnish elephants and give protection from Bangkok, through his dominions to Luang Prabang; but he cannot furnish the means to pay passage and salary, and fears it will be wasting all his money. He is also fearful that the engineer will get intoxicated and fall into the river and be drowned, or on account of change of climate die of dysentery, or from traveling in the jungle may die of jungle fever, the same as many others have done, and thus the business prove a failure, and the money wasted.'"

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Dust Up

What would happen if the Yellowstone supervolcano erupted?

Simmering below the geysers and hot springs of Yellowstone National Park in Wyoming is a gigantic reservoir of magma that someday could erupt. To find out how much ash such an explosion would generate, the U.S. Geological Survey gathered data and ran a simulation about the distribution of ash from prior supervolcano eruptions, including those that happened at Yellowstone 2.1 million, 1.3 million and 640,000 years ago. A January eruption lasting one month would bury nearby states in a meter or more of the thin, abrasive debris. It would also cast a blanket of at least a few millimeters over the entire U.S. and much of Canada—enough, according to the USGS, to damage airplanes and cars, shutting down transportation. A supervolcano has erupted somewhere on the planet every 100,000 years or so, but USGS experts say that current geologic activity at Yellowstone "provides no signs that a supereruption will occur in the near future." —*Mark Fischetti*

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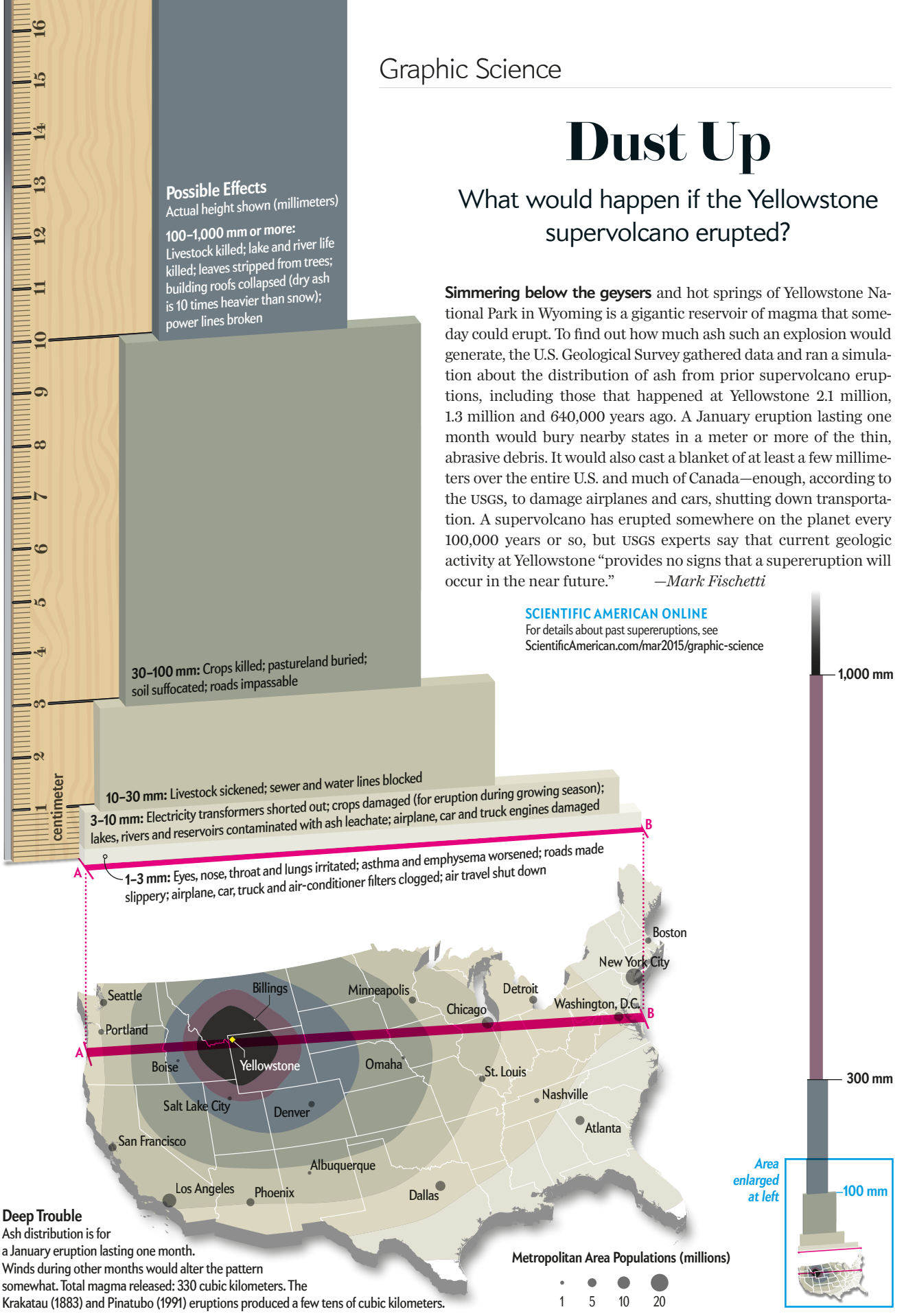
For details about past supereruptions, see
ScientificAmerican.com/mar2015/graphic-science



Deep Trouble
Ash distribution is for a January eruption lasting one month. Winds during other months would alter the pattern somewhat. Total magma released: 330 cubic kilometers. The Krakatau (1883) and Pinatubo (1991) eruptions produced a few tens of cubic kilometers.

SOURCES: "MODELING ASH FALL DISTRIBUTION FROM A YELLOWSTONE SUPERERUPTION," BY LARRY G. MASTIN ET AL., IN *GEOCHEMISTRY, GEOPHYSICS, GEOSYSTEMS*, VOL. 15, NO. 8; AUGUST 2014 (*maps and graphs*); U.S. GEOLOGICAL SURVEY AND GNS SCIENCE (*effects*)

Map by XNR Productions, Graphic by Jen Christiansen

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When it comes to annuities, remember these two words: "Watch out!"

That's right. Annuities are sold as completely safe, secure investments that deliver dependable, predictable returns no matter how the wildly volatile stock market performs. Sounds good, doesn't it?

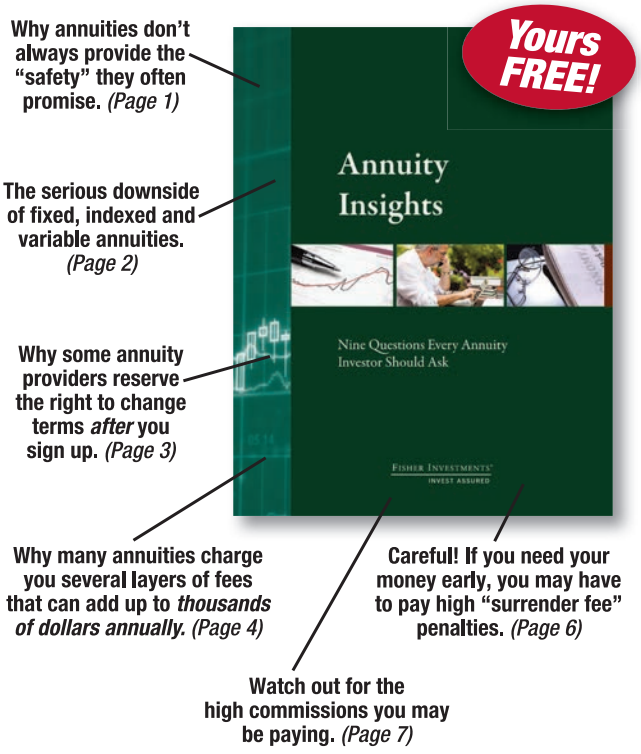
But . . . what's never mentioned by the salesperson is the fact that *the vast majority of annuities are nothing but extremely complicated insurance policies.* And when it comes to insurance policies, you should never rely solely on a glitzy sales guide which may obscure an annuity's true costs and restrictions.

The devil is in the details.

With annuities, the *really* important details are buried in the contract and prospectus which can amount to *hundreds of pages*. And remember, annuity providers often reserve the right to change terms *after* you've bought the annuity which can cause huge problems.

Before you sign on the dotted line, *please* read our FREE report.

The information you'll find there could save you from making one of the biggest investment mistakes of your life.



Locked up in annuity jail? *Perhaps we can help you escape.*

Want out of your annuity? Have a portfolio of $500,000 or more? We may rebate some or all of your annuity surrender penalties. Rebates average over $13,000.* Call **1-800-695-5929 Ext. AC88** for details, plus a free analysis of your annuity.

About Fisher Investments — Fisher Investments is a money-management firm that serves both successful individuals and large institutional investors. We currently have over $58 billion** in assets under management and are proud of our over 35-year track record.

Please hurry! This offer contains time-sensitive information.

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*Rebates are for investors who liquidate an annuity with surrender penalties and fund a Fisher Investments Private Client Group account. Average rebates from August 2011 to September 2013 were $13,227. Terms and conditions apply. See www.AnnuityAssist.com/Terms-and-Conditions for further information.
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